European Medicines Agency
Evaluation of Medicines for Human Use

EMA/522704/2009

ASSESSMENT REPORT

FOR

Eporatio

International Non-proprietary Name: epoetin theta

Procedure No. EMEA/H/C/001033

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant ratiopharm GmbH submitted on 04 June 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Eporatio, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 13 December 2007.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The Applicant applied for the following indications:

- Treatment of symptomatic anaemia associated with chronic renal failure.
- Treatment of symptomatic anaemia in cancer patients with non-myeloid malignancies receiving chemotherapy.
- Increasing the yield of autologous blood from patients in a predonation programme.

Scientific Advice:
The applicant received Scientific Advice from the CHMP on two occasions (23 June 2004 and 18 November 2004). The Scientific Advice pertained to the clinical aspects of the dossier.

Licensing status:
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: **Pierre Demolis** Co-Rapporteur: **Harald Enzmann**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 04 June 2008.
- The procedure started on 25 June 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 26 Sep 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 Sep 2008.
- During the meeting on 20 – 23 Oct 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 Oct 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 Feb 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 9 Apr 2009.
- During the CHMP meeting on 20 – 23 April 2009, the CHMP agreed on a List of Outstanding issues to be addressed in writing and by the applicant.
- Applicant submitted the responses to the CHMP List of Outstanding issues on 17 June 2009.
- The Rapporteurs circulated an updated Responses Assessment Report on 6 July 2009.
- During the meeting on 20 - 23 July 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Eporatio on 23 July 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 21 July 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Human endogenous erythropoietin is a glycoprotein produced in the kidney in response to the oxygen tension of the blood. Erythropoietin then circulates to the bone marrow where it stimulates the proliferation and differentiation of red blood cell progenitors, leading to more red blood cells and increased oxygen-carrying capacity. Epoetin for clinical use is produced by recombinant DNA technology using mammalian cells as expression systems. All Epoetins in clinical use have a similar amino acid sequence as endogenous erythropoetin but differ in their glycosylation pattern. Glycosylation influences pharmacokinetics and may affect efficacy and safety.

Eporatio containing the active substance epoetin theta, is obtained by recombinant DNA technology and has the same biological effects as endogenous epoetin. It is produced by mammalian cells into which the human epoetin gene has been introduced. It contains r-HuEPO as the active substance and is structurally similar to Epoetin alfa, Epoetin beta, and Epoetin delta. Epoetin theta belongs to the pharmacological class of chemically defined anti-anaemic drugs.

Eporatio has been developed as a stand alone product. The Applicant is seeking approval for the indication treatment of symptomatic anaemia associated with chronic renal failure as well as treatment of symptomatic anaemia in cancer patients with non-myeloid malignancies receiving chemotherapy.

Chronic renal failure or chronic kidney disease (CKD) is the progressive loss of kidney function. The kidneys attempt to compensate for renal damage by hyperfiltration (excessive straining of the blood) within the remaining functional nephrons (filtering units that consist of a glomerulus and corresponding tubule). Over time, hyperfiltration causes loss of function.

Anaemia, defined as a deficiency in the concentration of haemoglobin-containing red blood cells, is very common in patients with chronic kidney disease or chronic renal failure and can have a significant impact on patient morbidity and mortality. This is predominantly caused by inadequate epoetin production of the kidneys, resulting in inappropriately low circulating epoetin levels. Replacement therapy with recombinant human epoetin has provided an effective treatment for patients with renal anaemia and has been shown to increase red blood cell (RBC) mass, reduce the need for RBC transfusions, and alleviate symptoms in this population.

Patients with solid malignancies may develop anaemia as a result of disease characteristics, chemotherapy, or due to decreased endogenous erythropoietin production. The pathophysiology of tumour anaemia is multi-factorial. In advanced stages of haematological malignancies bone marrow involvement with malignant cells often leads to progressive anaemia. It is characterised by a close interaction between the tumour cell population and the immune system, leading to the activation of macrophages and increased expression of various cytokines, especially Interferon-g, Interleukin-1 and TNF. This is followed by an insufficient endogenous erythropoietin synthesis, suppressed differentiation of erythroid precursor cells the bone marrow and alterations of iron metabolism.

The chronic tumour anaemia is the most common type in patients with malignant disease, though it is often aggravated by chemo- or radiotherapy. This is a major clinical problem in particular as platinum-based chemotherapy regimens may diminish the endogenous erythropoietin production by damaging renal tubular cells.

The development of chemotherapy-associated anaemia is typically insidious, and a later complication of treatment, while newer chemotherapeutic agents and drug combinations have amplified the problem. Transfusion is the traditional approach to the management of anaemia. The aims of management of this condition are to eliminate symptoms arising from anaemia, to improve quality of life, to minimise secondary effects of anaemia on other systems such as the cardiovascular system, mental function and endocrine function, and to minimise the possible side effects of anaemia therapy.

2.2 Quality aspects

Introduction

Epoetin theta is obtained by recombinant DNA technology as it is produced by mammalian cells into which the human epoetin gene has been introduced. It contains recombinant human erythropoietin as the active substance. Its amino acid sequence corresponds to the sequence of Epoetin alfa, Epoetin beta, and Epoetin delta whereas minor differences in glycosylation are likely to exist between these Epoetins.

Epoetin theta is formulated as a liquid ready-to-use formulation presented as single-dose pre-filled syringes. Eight different strengths are intended for the market from 1 000 IU/ syringe up to 30 000 IU/ syringe. The filling volumes are either 0.5 mL (1 000/ 2 000/ 3 000/ 4 000/ 5 000 IU/ syringe) or 1.0 mL (10 000/ 20 000/ 30 000 IU/ syringe).

Active Substance

Epoetin theta is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. The first 27 amino acids (signal peptide) and the last amino acid (terminal arginine) are cleaved during translation to result in the 165 amino acid polypeptide. Three N-linked oligosaccharide chains are linked to amino acid positions Asn-24, Asn-38 and Asn-83 and one O-linked oligosaccharide chain is linked to Ser-126. Disulfide bridges between cysteines Cys-7 and Cys-161 as well as between Cys-29 and Cys-33 stabilise the higher order protein structure (secondary, tertiary).

The oligosaccharide chains are subject to post-translational modifications and display heterogeneity to a certain extent. The molecular weight of the glycosylated protein is 30.6 kDa according to the Ph. Eur. monograph, 40% of which are carbohydrate structures. The purification strategy of produced erythropoietin is aimed to make the resulting protein solution conformant to the Ph. Eur. monograph (01/2006:1316) and to achieve a high sialylation grade.

- Manufacture

The Active Substance is manufactured and released by Merckle Biotec GmbH, Ulm, Germany.

After a series of sub cultivations, the cells are seeded into the production fermenter. The production is based on a perfusion process, whereby the individual harvests are collected at regular intervals and each harvest is stored frozen until further processing.

The Active Substance is recovered from the thawed harvests by a conventional purification process comprising orthogonal chromatography steps and a viral filtration step. The manufacturing steps are monitored by process controls that include operational parameters, acceptance criteria and specifications.

The Master Cell Bank (MCB) was established using foetal calf serum from a certified source. The Working Cell Bank (WCB) was established without the use of materials of human or animal origin. The cultivation and all subsequent manufacturing steps are also performed without the use of materials from human or animal origin. The cell culture medium is animal component free. Insulin provided in the medium is produced in a recombinant yeast cell line. Characterisation of both cell banks in terms of genetic stability and viral safety is satisfactorily achieved by analysis of genotypic and phenotypic tests as well as virus testing

Process validation data demonstrate that the process steps from thawing the WCB vial, to harvesting the production process and purification are consistent. All parameters for the fermentation process and the purification process were maintained within defined ranges.

- Adventitious Agents

The viral safety of the medicinal product Epoetin theta has been satisfactorily addressed by the Applicant. The viral safety is confirmed by the experimental finding that the CHO cell substrates (MCB, WCB and Post Production Cells) show no biological evidence of any productive viral infection. To minimize the risk of contamination of the Medicinal Product by adventitious viruses the process is monitored batch wise and the purification includes validated viral removal and inactivation steps.
A risk assessment with regard to TSE according to the "Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 Rev.2) has been done.

- Characterisation

An extensive characterisation programme has been conducted for the drugs substance with respect to the protein backbone, carbohydrate moiety and biological properties.

State of the art analytical methods, in particular the combination of mass spectrometric detection with liquid chromatography separation were established to evaluate the integrity of the primary structure of epoetin theta including correct N- and C-termini as well as correctly linked disulphide bridges. Based on peptide maps by trypsin and Endo LysC sequence coverage of 99% was achieved while the presence of the missing peptide (Leu153-Lys154) was verified by correct mass calculations of the complete de-N-glycosylated epoetin theta. Circular dichroism (CD) measurements in the far UV-range indicated the typical four helix bundle architecture of EPO. Additional CD-measurements in the near UV-range and by fluorescence spectroscopy confirmed a unique location of particular amino acids within the three-dimensional structure.

For a thorough characterisation of the carbohydrate moiety a variety of complementary analytical techniques was applied to address various aspects of structural diversity. The total N-glycan pool released from the protein backbone was subjected to chromatographic separation according to charge followed by subsequent chromatographic separation according to antennarity and LacNAc-repeats. This strategy enabled a more detailed analysis and identification of separated glycan fractions by HPAEC-PAD as well as by mass spectrometric methods (ESI-MS and MALDI-TOF MS). Confirmation of particular structures of isolated peaks was achieved by ^{1}H-NMR analysis.
Quantitative characterisation of glycosylation was performed by HPAEC-PAD and an additional method, CGE-LIF, the detection of which is based on fluorescence labelling of glycans.

As a result of the overall methodological strategy, N-glycans of epoetin theta are found to be di- to tetrasialylated, di- to tetraantennary oligosaccharides that may be partly elongated by LacNAc repeats. The major portion is represented by tetraantennary tetrasialylated structures. A low proportion of oligosaccharides are phosphorylated oligomannosidic structures. N-glycans are found to be O-acetylated in their terminally linked sialic acids to various extents rising from a low level at glycosylation site Asn24 via an intermediate level at Asn38 to a considerable level at Asn83. All N-glycosylation sites are found fully occupied.
The majority of O-glycan structures are the mono- and disialylated GalNAcGal. A considerable degree of O-acetylation of sialic acids was also detected for the O-glycan. The O-glycosylation site was found fully occupied.
The batches analysed were found to be essentially free of unusual potentially immunogenic glycan structures. The level of N-glycolyl neuraminic acid is found to be consistently at acceptable low levels.

The various isoforms of epoetin theta – its molecular mass heterogeneity - evolving from carrying three heterogeneously structured N-glycans and one O-glycan are visualised by ES-MS of the desialylated molecule. The expanded mass profile allows identifying the particular N-glycan and O-glycan structures attached to the EPO-molecule and thus bridges the analytical work performed on the isolated N-glycan pool and the protein backbone.

Dimers and higher molecular weight species of epoetin theta were investigated by SE-HPLC particularly developed for that purpose. SDS-PAGE with or without subsequent Western Blotting or analytical ultracentrifugation were alternative approaches to characterise aggregates and their tendency to develop over time. Epoetin theta is practically free from aggregates over time. For epoetin theta low amounts of Met54 oxidation and Asn47 and Asn147 deamidation were determined but remained within the given ranges over time. None of the potential N- or C-terminal variants could be detected in epoetin theta.

The biological activity of epoetin theta is determined by the normocythaemic mouse bioassay. In addition the in vitro biological activity studied in a TF-1 cell-proliferation assay is considered to support the correct three-dimensional structure of epoetin theta.

- Comparability

Epoetin theta has initially been developed at a development service provider and been transferred to a development contract manufacturer for scale-up and adaptation. The manufacturing process was finally transferred to Merckle Biotec where epoetin theta is manufactured at commercial scale. In order to support comparability of batches manufactured at all sites and particularly to support that Merckle Biotec batches are representative of the clinical batches manufactured at the development contract manufacturer a comprehensive comparability programme was conducted covering tests typically performed at release tests and during extended characterisation.
Comparison of batches manufactured at pilot scale (development service provider) and batches produced at full scale (development contract manufacturer and Merckle Biotec) revealed consistent and comparable results with respect to all routine tests conducted. Considering extended characterisation the same picture was obtained and no deviation was observed between results from the sites within the scope of natural variability.

Comparability of commercial batches from both sites and representativeness of Merckle Biotec batches for batches used in clinical trials is therefore supported by the data provided.

- Specification

Appropriate specifications have been set for analysis of the active substance at release and at the end of shelf life. The proposed active substance specifications include tests and acceptance criteria for physicochemical properties, identity by CZE and SDS-PAGE, N-terminal amino acid sequence, trypsin peptide mapping, sialic acid by colorimetry/VIS spectrometry, ratio NGNA/NANA by RP-HPLC, N-linked Oligosaccharides by Capillary Gel electrophoresis /LIF, Higher Molecular Mass species by SE-HPLC, Oxidised epoetin theta by EndoGlu-C Digestion/RP-HPLC, Host Cell Protein, total DNA, Bioactivity assay, Protein concentration by A280, Bioburden and Endotoxin.

The proposed active substance specification was generally considered acceptable, although some tests and acceptance criteria were revised, taking into account the results obtained with batches used in pivotal clinical trials. The Applicant has agreed to review the acceptance criteria and commits to reconsider them after a total of 20 commercial scale batches have been manufactured at Merckle Biotec. A corresponding commitment has been obtained from the Applicant.

- Stability

The claimed shelf life of the active substance is supported by batch data. Stability of epoetin theta Active Substance has been evaluated on the basis of batches manufactured at full scale by Merckle Biotec reflecting the pivotal data, and at pilot scale by development service provider and full scale by a contract manufacturer (clinical phase III material) reflecting the supportive data.
Epoetin theta active substance is stored long term at ≤-70°C. Accelerated and stress stability studies were performed. Suitable containers have been applied for the stability studies. In conclusion no

changes or trends relating to the quality and consistency of the batches over this period at ≤-70°C were observed. Thus based on the real time data provided, an 18-month shelf-life at ≤-70°C can be granted.

Medicinal Product

The epoetin theta Medicinal Product is a liquid ready-to-use formulation presented as single-dose pre-filled syringes. Eight different strengths are intended for the market from 1 000 IU/ syringe up to 30 000 IU/ syringe. The filling volumes are either 0.5 mL (1 000/ 2 000/ 3 000/ 4 000/ 5 000 IU/ syringe) or 1.0 mL (10 000/ 20 000/ 30 000 IU/ syringe).
The Medicinal Product solutions are filled into sterilised type I glass syringes having a Luer conus. The syringes are closed with a laminated chlorobutyl rubber plunger stopper and a non-laminated bromobutyl rubber tip cap. The needle is provided separately.

In terms of the excipients, the composition per 0.5 mL or per 1 mL is the same for all dosage strengths of Eporatio Medicinal Product. They differ only with respect to the concentration of the active substance. The excipients are water for injection, sodium dihydrogen phosphate dihydrate, sodium chloride, polysorbate 20, trometamol and hydrochloric acid for pH adjustment.

- Pharmaceutical Development and Manufacture of the Product

The Medicinal Product manufacturing process mainly consists of compounding steps, sterile filtration and aseptic filling of the product. Each step was appropriately described and is validated.

A liquid formulation was developed, which did not change between preclinical and clinical trials and the Medicinal Product intended for the market.

Eporatio pre-filled syringes are manufactured and packed by Merckle GmbH and released by Merckle Biotec GmbH, both in Germany. Release and stability testing takes place either at Merckle Biotec GmbH or at contract testing laboratories.

Manufacture of Eporatio Medicinal Product is carried out using dedicated sterilised equipment starting with preparation and 0.2µm filtration of the excipient solution, then adding thawed Eporatio active substance. After 0.2µm filtration the bulk Medicinal Product solution is aseptically filled into siliconised and pre-sterilised glass syringes. Following packaging and labelling the Medicinal Product is stored at 2 to 8°C. Shipping is performed under controlled temperature conditions (2-8°C).

Eporatio Medicinal Product is presented as ready-to-use solution in 1 mL prefilled syringes, a separate sterilised injection needle is added for the application of the Medicinal Product. The following components come into contact to the liquid formulation:

- 1 mL syringe made of borosilicate glass type I which is siliconised on the inner barrel surface by baked silicone.
- FluoroTec®-laminated syringe stopper from chlorobutyl rubber (type I) with B2-40 coating
- Tip cap made of non-laminated bromobutyl rubber (type I).

The plunger rod is made of polypropylene. The 0.4x12 mm, 27G x ½″ steel needle with Luer adapter is packed separately. A needle shield is optionally added as safety device. The syringe barrels are siliconised, sterilised and depyrogenised. The stoppers and needles are sterilised. A respective validation protocol has been provided, which confirms acceptable sterility. In conclusion the primary packaging components are considered to be in accordance to Ph. Eur. and ISO requirements.

- Product Specification

The Medicinal Product release specification includes tests for identity, purity and content, as well as pharmaceutical and microbiological tests. Some minor issues regarding the Medicinal Product shelf life specifications, which have no impact on the overall risk-benefit of the product, remain to be fully resolved by the Applicant. A corresponding commitment has been obtained by the Applicant.

- Stability of the Product

The applicant claims a 18 months shelf-life for the Medicinal Product when stored at 2 to 8°C Pivotal stability studies have been initiated with batches manufactured by the commercial process covering the complete range of dose strengths. Most batches have been produced at pilot scale. Data are available after storage at long-term conditions, intermediate and stress conditions and support the claimed shelf life. Extension of the shelf-life will be sought once further data will be available.
The shelf-life specification includes all parameters measured for release.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and Medicinal Product have been presented in a satisfactory manner. The results of the tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

At the time of CHMP opinion, there were few minor unresolved quality issues, which have no impact on the Risk-benefit balance of the product. The applicant provided a Letter of Undertaking and committed to resolve these as follow-up measures after the opinion, within an agreed timeframe.

2.3 Non-clinical aspects

Introduction

Non-clinical studies were performed in mouse, rat, rabbit and dog as detailed in the following sections. The studies (local tolerance, safety pharmacology, repeat-dose toxicity and PD/PK study, see below) are claimed to be GLP compliant.

Pharmacology

- Primary pharmacodynamics

In *in vitro* pharmacology experiments, the human erythroleukemic cell line TF-1, a human erythroleukaemia cell line known to proliferate in response to epoetin stimuli, was used for the characterization of the biological activity of epoetin theta. A bioassay for the analysis of the activity of erythropoietins was developed based on two detection systems, which yielded similar EC_{50} values (data not shown). Several erythropoietin samples, among them 8 Epoetin theta batches, epoetin beta and epoetin alfa were compared for their activity to induce proliferation in TF-1 cells. Erythropoietin BRP from the European Directorate for the Quality of Medicines served as reference standard and was tested in parallel to the test items. The Epoetin theta batches tested showed the expected biological activity and no difference to the reference standard was observed (data not shown).
The primary *in vivo* pharmacology was studied by the normocythemic mouse assay. The study was performed in 72 male B6D2F1 mice with 8 animals per dose group (single dose of 10, 20 and 40 IU per animal, respectively, for two batches of Epoetin theta or for the BRP reference standard). All mice were of similar age and body weight. Four days after injection, blood was sampled to measure the reticulocyte count, and body weight was recorded. No differences for reticulocyte counts and body weights were observed between Epoetin theta and the reference standard in all doses tested (data not shown).
Moreover, a combined pharmacokinetic and pharmacodynamic study was performed in the albino rat. Epoetin theta was administered once or repeatedly for 21 days to rats of both genders at a dose of 2500 IU/kg/day by the subcutaneous and by the intravenous route. The pharmacodynamic action of

Epoetin theta was assessed by monitoring the haematology parameters haematocrit and reticulocytes. Blood was sampled pre-treatment and at regular intervals. Assessment of haematology parameters did not reveal marked differences between the two routes of administration or between males and females. After a single administration, haematocrit and reticulocyte count increased up to 96 hours post dose. After repeat dosing, haematocrit levels remained at significantly raised levels during the 96 h postdose observation period, whereas reticulocyte counts declined after cessation of administration (data not shown).

- Secondary pharmacodynamics

Determination of the growth promoting effects on human malignant cells

The ability of Epoetin theta and Epoetin beta to induce cell proliferation was studied in the human malignant cell lines TF-1 (erythroblast, erythroleukaemia), MCF-7 (breast epithelial, adenocarcinoma), 786-O (renal epithelial, adenocarcinoma), K-562 (bone marrow lymphoblast, myelogenous leukaemia), RT112/84 (epithelial, bladder carcinoma), and FaDu (pharynx, head and neck squamous cell carcinoma). The five non-erythroid tumour cell lines used in the study are all reported to express the EPOR, which has been identified in tumour cell lines. Proliferative effects of Epoetin theta were confined to TF-1 cells. Furthermore, the qualitative nature of the dose-response characteristics was identical between Epoetin theta and Epoetin beta.

Scientific literature further suggested that rhEPO was able to increase the mean tumour oxygen pressure irrespective of anaemia indicating an improvement of tumour oxygenation following rhEPO treatment. In addition, rhEPO treatment did not enhance tumour growth in DS-sarcoma bearing anaemic and non-anaemic rats. Moreover, anaemia resulted in a worsening of tumour oxygenation in DS-sarcoma bearing rats which could partially be reversed by rhEPO administration or by transfusion with red blood cells in small tumours. In larger tumours, neither method of anaemia correction resulted in significant changes in tumour oxygenation

- Safety pharmacology programme

The effects of a single intravenous dose of 30000 IU/kg Epoetin theta (concentration of 15000 IU/ml) on the central nervous system were assessed in male Sprague-Dawley albino rats. Epoetin theta was administered by a single intravenous injection into the tail vein of 6 animals. Control animals (n=6) received the vehicle (diluent alone) only. There were no biologically significant effects on functional observation battery parameters (e.g. grip strength, hind limb splay and body temperature) or motor activity (data not shown).

Effects of Epoetin theta on the respiratory system were examined in male Sprague-Dawley CD® (Crl:CD®(SD)BR) albino rats. Epoetin theta was administered by a single intravenous injection into the tail vein (2 mL/kg dose volume) of 6 animals. Control animals (n=6) received the vehicle (diluent alone, 2 mL/kg dose volume) only. There were no treatment-related effects on tidal volume, or respiratory rate, or respiratory minute volume compared to both the concurrent controls and the pre-study data (data not shown).

Effects of Epoetin theta on the renal system were examined in male Sprague-Dawley CD® (Crl:CD®(SD)BR) albino rats. Epoetin theta was administered by a single intravenous injection into the tail vein (in 2 ml/kg dose volume) of 6 animals. Control animals (n=6) received the vehicle (diluent alone) only. There was no apparent effect on water consumption, creatinine clearance or any of the clinical chemistry or urinalysis parameters examined in rats. There were no macroscopic changes or kidney weight modifications indicative of a test article related effect (data not shown).

The haemodynamic effects of Epoetin theta were evaluated when administered by intravenous injection in the conscious unrestrained male Beagle dog. Two groups of two conscious instrumented male beagle dogs were given a single i.v. injection of vehicle or Epoetin theta (2 ml/kg). The Epoetin theta dose administered was approximately 25000 IU/kg. All 4 dogs that received an intravenous bolus dose of the vehicle with or without Epoetin theta exhibited changes in the hemodynamic profile including: transient reductions in blood pressure (systemic, left ventricular and pulmonary artery) and concurrent reductions and/or elevations in heart rate. These histamine-like reactions observed in all four animals were attributed to a detergent (Tween-20) in the vehicle formulation. An additional animal was instrumented separately and treated at a lower dose volume (0,3 ml/kg), proposed for use in a subsequent 6-week toxicity study. The additional animal did not exhibit a similar reaction (data not shown).

- Pharmacodynamic drug interactions

No studies were submitted.

Pharmacokinetics

No specific pharmacokinetic studies were submitted. The pharmacokinetics of Epoetin theta was studied following single and repeated subcutaneous and intravenous administration of Epoetin theta for 21 days to the albino rat in the pharmacology/pharmacokinetic study described under primary pharmacology above. Toxicokinetics was assessed as part of the 6-weeks s.c and i.v repeat dose toxicity study in dogs.
Two ELISA methods were validated and used for measurement of Epoetin theta and anti- Epoetin theta antibodies, respectively, in plasma and serum of rat and dog.
The measurement of pharmacokinetic parameters (AUC, C_{max}, T_{max} and $T_{½}$) and of bioavailability yielded values within the expected range. No differences between gendres or routes of administration were noted (data not shown).
No studies on distribution, metabolism, excretion and pharmacodynamic drug interactions were submitted.

Toxicology

- Single dose toxicity

No studies were submitted.

- Repeat dose toxicity (with toxicokinetics)

The types of studies conducted and their design are summarised in the following table 4.

Table 4: Repeat-dose toxicity studies

Species/Sex/ Number/Group	**Dose/Route/Duration**	**NOAEL (IU/kg/day)**
Sprague Dawley CD rat/ 12/ sex/group	0, 100, 500, 2500 IU/ kg/day **Intravenous/ 6 weeks**	100
Sprague Dawley CD rat / 12/ sex/ group	0, 100, 500, 2500 IU/ kg/day **Subcutaneous/ 6 weeks**	100
Sprague Dawley CD rat / Main study: 20/ sex/ group Recovery-period: 12/sex/group (vehicle and high dose group)	0, 100, 500, 2500 IU/ kg/day **Subcutaneous/** up to **13 weeks** * with a 4-week recovery period	Not determined
Beagle dog / 3/ sex/ group	0, 100, 500, 2500 IU/ kg/day **Subcutaneous/ Intravenous/ 6 weeks**	100
Beagle dog / Main study: 3/sex/group (0 and 500) 4/sex/group (100, 2500) Recovery-period: 2/sex/group (0 and 2500)	0, 100, 500, 2500 IU/ kg/day/ **Subcutaneous/** **13 weeks** with a 4-week recovery period	100

Toxicokinetic parameters and antigenicity were evaluated in these studies in addition to toxicity.
Rat studies. In the 13 weeks study, there were numerous unscheduled deaths from all Epoetin theta dose groups (euthanised because of poor and/or deteriorating condition or found dead) during the study. A total of 45 animals across all test article dose groups in the duration of the study were euthanised or found dead. There was a clear dose-dependency noted, with 3 deaths in low-dose, 17 deaths in mid-dose and 25 deaths in high-dose groups.
Histopathological changes were seen in the bones and bone marrow, spleen, liver, gastrointestinal system, thymus, heart and kidney. The changes described in the bones (hyperostosis), bone marrow, spleen and heart were considered related to the pharmacological activity of Epoetin theta. Changes noted in the stomach, duodenum and thymus were believed to possibly to stress related and as such, secondary to the administration of Epoetin theta.
In Epoetin theta treated rats surviving until the scheduled termination of the recovery period (day 99) in the 13 weeks study, the predominant macroscopic finding was splenic enlargement due to

congestion. In these animals, the bone marrow was either hypocellular (male rats) or remained hypercellular (female rats).
Following subcutaneous or intravenous administration up to 6 weeks, the NOAEL was established as 100 IU/kg. In the 13 weeks study, dose-related effects with mortality, observed in this study were all considered to be a direct effect and/or indirect effect of the pharmacological activity of Epoetin theta, and as a result a NOAEL cannot be established.
Antibodies against Epoetin theta were not detected in the 6-week intravenous study in rats. In the study performed with the subcutaneous route, no antibodies were detected against Epoetin theta for any animals with the exception of one high-dose male. In the 13-week study, antibodies produced against Epoetin theta were detected in 47/526 samples. Measured concentrations (expressed as rabbit IgG equivalents) were detected in 26 samples of 17 different animals. It should be noted that only a subset of animals (50%) were investigated for antibodies. There was no dose-relationship in the formation of antibodies. 13 of the 17 animals with antibodies also showed skin pallor suggesting that the antibodies were neutralising.
Dog studies. Histamine-like reactions were observed in all groups (including the control group) in the 6 weeks study, but at a higher incidence among test article-treated animals. In the 13 weeks study, histamine-like reactions were observed in all dogs. Polysorbate 20, which is one of the constituents of the vehicle was reported to cause histamine-like reactions in dogs. However, it was found to be difficult to separate putatively pharmacological effects (reddening) from histamine-like effects, because they induce similar clinical signs.
Histopathological changes were present in the bone marrow, bones (hyperostosis) and liver in the 6 weeks study. In the 13 weeks study the same histological findings were reported with also in kidneys, congestion, tubular haemorrhage and degeneration and regeneration, which were not observed in the shorter term study. Full recovery of these changes could not be demonstrated during the 4 weeks period off treatment in the 13 weeks study. Bone marrow haematopoiesis had decreased, but secondary effects in the marrow (fibrosis), bone (hyperostosis), and kidney (tubular degeneration/ regeneration, interstitial fibrosis, dilation of Bowman's capsule) did not resolve completely during the recovery period.
The NOAEL after subcutaneous or intravenous administration was considered to be 100 IU/kg in the 6 and 13 weeks studies. At higher dose levels, bone marrow fibrosis and bone endosteal and trabecular hyperostosis were observed.
In the 6-week study, there was no antibody formation noted against Epoetin theta in most of the samples. Antibodies were detected for one control female and one mid-dose male (500 IU/kg/day), but the titres were slightly above the lower detection limit of the assay. In the 13 week study, there was no antibody formation noted against Epoetin theta in any of the samples but one, for which the measured value was slightly above the lower detection limit. No antibodies produced against Epoetin theta were detected in all other samples with sufficient blood for analysis.

- Genotoxicity

No studies were submitted.

- Carcinogenicity

No studies were submitted.

- Reproduction Toxicity

No studies were submitted.

- Toxicokinetic data

Toxicokinetic parameters were evaluated as part of the repeat dose toxicity studies (data not shown).

- Local tolerance

Local tolerance was assessed in male Himalayan rabbits using the two clinical routes (intravenous and subcutaneous) and three routes of potential concern in case of miss-administration (intramuscular, paravenous and intra-arterial). The doses tested were 1,000 IU, 5,000 IU and 15,000 IU Epoetin theta.
No Epoetin theta-related changes were noted. Intravenous, intramuscular, intraarterial, paravenous and subcutaneous injections did not reveal any Epoetin theta-related changes. There were no

morphological differences between test and control sites. All minimal to moderate changes observed represented non-specific reactions to the administration (data not shown).
Repeat-dose toxicity studies in rats and dogs for up to 13 weeks revealed that Epoetin theta is slightly well tolerated locally when administered intravenously than when administered subcutaneously and that local tolerance of Epoetin theta is slightly greater in dogs than in rats, but not sex-related (data not shown).

- Other toxicity studies

No other toxicity studies (dependence, metabolites, impurities) were submitted.

Ecotoxicity/environmental risk assessment

No environmental risk assessment was submitted.

Discussion on the non-clinical aspects

The biological activity of epoetin theta has been characterized in an *in vitro* cell proliferation study. Moreover, the biological efficacy of epoetin theta has been demonstrated after intravenous and subcutaneous administration in various animal models *in vivo* (mice, rats, dogs). After administration of epoetin theta, the number of erythrocytes, the haematocrit values and reticulocyte counts increase.
In safety pharmacology studies, epoetin theta did not reveal adverse effects regarding central nervous, renal or respiratory systems. Cardiovascular safety pharmacology study performed in beagle dogs following an intravenous bolus showed transient reductions in blood pressure, elevations in heart rate and clinical signs consistent with histamine release in all dogs receiving the vehicle with or without epoetin theta. Polysorbate 20 (Tween-20), which is a component of the vehicle, has been reported to induce transient histamine release in the dog and haemodynamic effects observed in the safety pharmacology study could be considered to be due to the presence of polysorbate 20.
The pharmacokinetics programme was only conducted within the frame of PD and toxicology studies and it encompassed determination of Epoetin theta plasma levels after single and repeated administration in rats and dogs, with the aim to calculate plasma exposure parameters (AUC, C_{max} etc.), bioavailability and exposure margins as compared to human therapeutic exposure. No other experiments were performed in respect to absorption; this is considered acceptable since Epoetin theta is intended for injection only and not for application via the oral route.
No information was provided on organ distribution, metabolism, excretion and pharmacokinetic drug-drug interactions, but this is considered acceptable.
No single dose toxicity studies were performed on the justification that exceptionally high single doses were investigated in safety pharmacology studies. The CHMP considered the lack of single dose toxicity studies as acceptable. Based on the known actions of epoetins no relevant acute toxicity is expected.
In repeat dose toxicity studies, the pharmacological activity of Epoetin theta resulted in an increase in haematological parameters of haemoglobin, red blood cell count, reticulocyte count and haematocrit. The main signs of toxicity observed were attributed to the pharmacological activity and were related to an adaptive response of the organism to the erythropoietic stimulus. There were haematopoietic hypercellularity of the bone marrow with fibrosis at high doses, extramedullary haematopoiesis and bone hyperostosis. Associated lesions were observed in the thymus, kidney, stomach, heart with congestion and haemorrhage.
Reddening reactions were observed in rats and dogs receiving Epoetin theta. Moreover, reddening to a lesser extent was noted in dogs only receiving the vehicle. Published data have reported that polysorbate 20 caused histamine-like reactions in dogs. Given that histamine-like reactions and pharmacological effects of the drug give similar clinical signs it is difficult to distinguish the origin of the reddening in dogs.
Antibody formation against Epoetin theta was clearly demonstrated in the rats; the neutralising capacity of the antibodies was not determined but could be inferred from the fact that there was a sudden decline in reticulocyte and RBC count (and related parameters such as hematocrit) in some rats after several weeks of treatment.
In general, non-clinical data with epoetin theta reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated-dose toxicity.

Genotoxicity and carcinogenicity studies with epoetin theta were not submitted, which is acceptable given the nature of the drug.
No reproductive toxicity studies with epoetin theta were submitted. Animal studies with other epoetins do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women. It is unknown whether epoetin theta is excreted in human breast milk, but data in neonates show no absorption or pharmacological activity of erythropoietin when given together with breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with epoetin theta should be made taking into account the benefit of breast-feeding to the child and the benefit of epoetin theta therapy for the woman.
The absence of an Environmental Risk Assessment is considered acceptable.

2.4 Clinical aspects

Introduction
The Applicant provided 6 phase I pharmacodynamic/pharmacokinetic studies, 6 phase II/III studies supporting the indication anaemia in chronic renal failure patients and 3 phase III studies supporting the indication anaemia in cancer patients (see tables 5, 6 and 13). The following indications were initially claimed:

- Treatment of symptomatic anaemia associated with chronic renal failure.
- Treatment of symptomatic anaemia in cancer patients with non-myeloid malignancies receiving chemotherapy.
- Increasing the yield of autologous blood from patients in a predonation programme. Its use in this indication must be balanced against the reported increased risk of thromboembolic events. Treatment should only be given to patients with moderate anaemia (haemoglobin 10-13 g/dl [6.21-8.07 mmol/l]), no iron deficiency), if blood conserving procedures are not available or insufficient when the scheduled major elective surgery requires a large volume of blood (4 or more units of blood for females or 5 or more units for males).

No studies supporting the indication 'Increasing the yield of autologous blood from patients in a predonation programme' were submitted and the Applicant withdrew this indication during the evaluation procedure.

Scientific advice was provided by the Committee of Human Medicinal Products (CHMP) on 2 occasions (23 June 04 and 18 November 2004). The advice consisted of recommendations regarding the type of studies to be performed, choice of comparator, inclusion criteria, primary efficacy endpoints and the analysis thereof, secondary efficacy endpoints, duration of treatment, and the size of the safety database. This advice was taken into consideration in the current clinical development programme.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

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

Pharmacokinetics
Six PK studies were submitted, two of them performed in healthy volunteers, two performed in patients with end-stage renal disease treated with haemodialysis, one in patients with chronic renal failure not yet receiving dialysis and one in patients with non-myeloid malignancies on cyclic chemotherapy. Pharmacokinetic information is available for 102 subjects in 6 studies: 45 healthy volunteers (studies XM01-12 and XM01-20); 31 subjects with end-stage renal disease treated by haemodialysis (studies XM01-01 and XM01-11); 14 subjects with chronic renal failure not yet receiving dialysis (study XM01-10); and in 12 anaemic subjects with non-myeloid malignancies on

cyclic chemotherapy (study XM01-24). An overview of all Phase I clinical studies submitted is shown in table 5 below.

Table 5: Phase I pharmacokinetic/pharmacodynamic studies with Epoetin theta

Name	Study design and type of control	Route	N	Diagnosis of subjects	duration of treatment
XM01-12	Phase I, open, randomised, three-way crossover study	s.c.	18	Healthy subjects	3 single doses
XM01-20	Phase I, randomised, double-blind, placebo-controlled, parallel-group	s.c. single doses	40	Healthy subjects	1 single dose
XM01-01	Phase I, open, study with sequential design.	i.v. followed by s.c. doses	18	End-stage renal disease	2 single doses
XM01-11	Phase I, open, single group study	i.v. 3 times weekly	14	End-stage renal disease	7 doses of Epoetin theta over 2 weeks
XM01-10	Phase I, open, single group study	s.c. 3 times weekly	14	Chronic renal failure	7 doses of Epoetin theta over 2 weeks
XM01-24	Phase I, open, single group study	s.c. once weekly 20,000 IU Epoetin theta over 3 weeks	14	non-myeloid malignancies	3 doses of Epoetin theta over 3 weeks

In terms of analytical methods, a validated double sandwich ELISA method was used for quantitation of Epoetin plasma values and standard PK data analysis was performed (data not shown).

- Absorption

No specific studies were submitted.

- Distribution

No specific studies were submitted.

- Elimination

No studies were submitted.

The pharmacokinetics of Epoetin theta in healthy subjects was investigated in studies **XM01-12** and **XM01-20.**

Study XM01-12 was a single centre, open label, randomised, three-way crossover phase I study in 18 healthy subjects. The primary objective of this study was to compare single-dose pharmacokinetics (C_{max} and AUC_{0-120h}) of s.c. Epoetin theta between different administration sites (upper arm, abdomen, and thigh). Secondary objectives were to further investigate pharmacokinetics, pharmacodynamics, safety, and tolerability. Each subject was to receive 3 administrations of Epoetin theta 40 IU/kgBW s.c., separated by a washout period of 14 days, at separate body sites: upper arm, abdomen, and thigh.
The 40 IU/kg BW dose for Epoetin theta was chosen on the basis of the data collected during the development of epoetin beta.
The subjects were randomised to 1 of the 6 possible treatment sequences. 18 subjects were analysed for safety and 17 and 16 (for C_{max} and AUC_{0-120h}, respectively) for the pharmacokinetic evaluation.

Results: All administration sites had somewhat different PK profiles. The results indicate that absorption was most rapid and peak plasma levels highest at the abdominal site, followed by the thigh

and then upper arm. Bioequivalence according to the predefined criteria could not be proven for the three sites of administration. Relevant PK parameters did not reach the predefined acceptance criteria.

Study XM01-20 was a single centre, double-blind, placebo-controlled, phase I study in 40 healthy subjects. The primary objectives of the study were to characterise safety, tolerability, and pharmacokinetics of a single dose of Epoetin theta following s.c. administration to healthy male subjects. Secondary objectives were investigation of the dose-linearity of Epoetin theta after s.c. administration and efficacy. Subjects were randomised to receive one s.c. administration of either 450 or 900 IU/kgBW Epoetin theta, or respective placebo.
Of the 40 subjects included in the study 28 subjects treated with Epoetin theta (14 with 450 and 14 with 900 IU/kgBW) were analysed for pharmacokinetics and 40 were analysed for safety and pharmacodynamics.
Results: For the primary endpoints mean $AUC_{0-\infty}$ and mean Cmax, the results for the 900 IU/kg BW dose were 2.6-2.7 times higher than the results obtained for the 450 IU/kg BW dose. T_{max} was similar for the 2 doses, while CL/f declined with increasing dose (data not shown).

The pharmacokinetics of Epoetin theta in subjects with chronic renal failure was investigated in studies **XM01-01** (haemodialysis), **XM01-11** (haemodialysis), and **XM01-10** (pre-dialysis).

Study XM01-01 was a multicentre, open, phase I study in 18 subjects with endstage renal disease treated by haemodialysis. The primary objective of the study was to characterise the pharmacokinetics of a single dose of Epoetin theta following i.v. and s.c. administration to subjects with end-stage renal disease treated 3 times weekly with haemodialysis. Secondary objectives were safety, bioavailability and efficacy. Subjects were to receive single doses of 40 IU/kgBW Epoetin theta on study days 13 (i.v.) and 20 (s.c.). The dose of 40 IU/kgBW was chosen on the basis of the data collected during the development of Epoetin beta. 18 subjects were analysed for safety and 17 for pharmacokinetics. They each received a single dose of 40 IU/kgBW Epoetin theta on study days 13 (i.v.) and 20 (s.c.).
Results: The results indicate that for a single s.c. compared to a single i.v. dose of 40 IU/kg (low therapeutic dose), exposure is reduced to about 30% and peak plasma concentrations to about 6%, whereas terminal half-life is increased about 2.5-fold (13.9 h compared with 5.7 h following i.v. administration) and clearance rate about 3-fold (data not shown).

Study XM01-10 was a single centre, open, phase I study in 14 subjects with chronic renal failure not yet receiving dialysis. The primary objective of the study was to compare steady state pharmacokinetics of Epoetin theta (40 IU/kgBW s.c.) after multiple dosing over 2 weeks with the pharmacokinetics of the first dose (40 IU/kgBW s.c.). Secondary objectives were comparison of the steady-state pharmacokinetics of s.c. Epoetin theta after multiple dosing with the pharmacokinetics of the first dose, safety, and tolerability. Subjects were to receive Epoetin theta 40 IU/kgBW s.c. three times weekly over 2 weeks. All 14 subjects included in the study were analysed for safety and pharmacokinetics.
Results: The pre-dose corrected concentrations time profiles of Epoetin theta after s.c. single and s.c. multiple dose were slightly different. The comparison of the PK parameters $C_{max,ss}/C_{max}$, AUC0-72h,ss/AUC0-72h, and t1/2,ss/t1/2 gave no statistical evidence for a difference between single and multiple dose. The point estimates for C_{max},ss/C_{max}, AUC0-72h,ss/AUC0-72h are close to 100% and the 90% CIs inside the predefined equivalence range (data not shown).

Study XM01-11 was a single centre, open, phase I study in 14 subjects with endstage renal disease treated by haemodialysis. The primary objective was to compare steady state pharmacokinetics of i.v. Epoetin theta after multiple dosing over 2 weeks with the pharmacokinetics of the first dose. Secondary objectives were to compare steady-state pharmacokinetics of i.v. Epoetin theta after multiple dosing with the pharmacokinetics of the first dose, safety, and tolerability. Subjects were to receive Epoetin theta 40 IU/kgBW i.v. 3 times weekly over 2 weeks. All 14 subjects included in the study were analysed for safety and pharmacokinetics.
Results: The pre-dose corrected concentrations time profiles of Epoetin theta after single and multiple i.v. doses differed. After reaching C_{max}, Epoetin theta concentrations declined faster for multiple dose than for single dose. Consequently, $AUC_{0-48h,ss}$ for multiple dose was lower compared to single dose (data not shown).

The pharmacokinetics of Epoetin theta in subjects with non-myeloid malignancies on cyclic chemotherapy was investigated in study **XM01-24**. This was a single centre, open, phase I study in 14 anaemic subjects with non-myeloid malignancies on cyclic chemotherapy. The primary objective of this study was to investigate steady state pharmacokinetics of Epoetin theta after multiple dosing over 3 weeks in subjects with non-myeloid malignancies on cyclic chemotherapy in comparison to the pharmacokinetics of the first dose. Secondary objectives were further evaluation of pharmacokinetics, safety and pharmacodynamics. Subjects were to receive three s.c administrations of 20,000 IU Epoetin theta at weekly intervals. The weekly dose of 20,000 IU chosen for this study is lower than the currently recommended dose for Epoetin beta in this indication which is 30,000 IU. Pharmacokinetic parameters for Day 15 could not be derived for 2 subjects; thus the pharmacokinetic population consisted of 12 subjects.
Results: The PK profiles after single dose and multiple dose administration were markedly different. All parameters were extremely variable. Mean C_{max} and $AUC_{0\text{-}168h}$ were higher for single dose compared to steady state. Correspondingly, C_{max} and $AUC_{0\text{-}168h}$ on Day 15 were lower than on Day 1 and the difference was statistically significant. Geometric mean t1/2 and t_{max} was statistically not significantly different on the two days due to the high variability. In 10 of the 14 subjects pre-dose plasma concentrations of Epoetin theta on Day 15 were below the pre-dose concentration on Day 1 (data not shown).

- Dose proportionality and time dependencies

No studies addressing dose proportionality and time dependencies were submitted.

- Special populations

No studies in patients with hepatic impairment, different weights, in elderly or children were submitted. No studies addressing gender or ethnic differences were submitted.

- Pharmacokinetic interaction studies

No studies were submitted.

- Pharmacokinetics using human biomaterials

No studies were submitted.

Pharmacodynamics

- Mechanism of action

No studies were submitted.

- Primary and Secondary pharmacology

No separate pharmacodynamic studies have been performed. Pharmacodynamics of epoetin theta have been analysed within all pharmacokinetic studies. Pharmacodynamic information is available for 116 subjects including 12 placebo-treated subjects in study XM01-20. Haemoglobin, haematocrit, and reticulocyte values were the pharmacodynamic parameters mainly studied. These were further investigated in phase II and III studies in the target patient populations.

Single-dose administration: Haemoglobin, haematocrit, and reticulocytes parameters did not differ remarkably between pre- and post-dose measurements (day 1 and 8) during treatments A (upper arm), B (abdomen), and C (thigh). Subcutaneous injection of of 40 IU/kgBW Epoetin theta in healthy subjects at the different injection sites had no influence on haemoglobin, haematocrit, and reticulocytes values. Only slight increases were observed on day 8 compared to baseline for all three pharmacodynamic parameters after each type of application (data not shown). Similar results were observed for end-stage renal disease (ESRD) subjects treated by haemodialysis (study XM01-01, s.c. and i.v, data not shown).
Single s.c. administration of Epoetin theta at doses of 450 and 900 IU/kgBW in healthy subjects (study XM01-20) caused a significant increase in the level of reticulocytes, peaking on Day 8 after administration and almost returning to baseline on Day 22. Erythrocyte count increased significantly,

peaking on Day 10 after administration at the higher dose level of 900 IU/kg. Significant increases in haematocrit, haemoglobin and mean corpuscular volume (MCV) were also observed (data not shown).

Multiple i.v. administrations: Multiple i.v. administrations of 40 IU/kgBW three times weekly over 2 weeks in ESRD subjects treated by haemodialysis (study XM01-11) resulted in slight increases in mean values for haemoglobin, haematocrit, and erythrocytes between Day 0 and Day 16 and Day 21, respectively (data not shown).

Multiple s.c. administrations: Multiple s.c. administrations of 40 IU/kgBW three times weekly over 2 weeks in ESRD subjects not yet treated by dialysis (study XM01-10) resulted in slight increases in mean values for haemoglobin, haematocrit, and erythrocytes between Day 0 and Day 16.
Multiple s.c. administrations of 20,000 IU Epoetin theta once per week over three weeks in anaemic subjects with non-myeloid malignancies on cyclic chemotherapy (study XM01-24) resulted in an increase in the percentage of reticulocytes during the course of the study compared to baseline, indicating an increase in red blood cell production. The increase was statistically significant on Days 15 and 24. After a transient decrease in haemoglobin and haematocrit on Day 8 (after the first dose with Epoetin theta), no statistically significant differences from baseline were detected for both parameters at the following visits (data not shown).

In terms of secondary pharmacology, heart rate, blood pressure, and body weight were measured at regular intervals in the 6 phase I studies. Oral body temperature was also measured in study XM01-01.
Mean and median values of heart rate, body weight and oral body temperature did not show any clinically relevant changes over time. There were no clinically relevant differences to baseline in individual subjects except in study XM01-11. Values above the reference range were observed in this study on patients with end-stage renal disease but it was concluded that the values originated from the underlying hypertension (data not shown).
Physical examination and 12-lead ECGs were performed at several timepoints in all of the phase I studies. There were no clinically significant findings for the physical examination apart from reddened and warmed skin in the area of the arteriovenous fistula in 1 patient in study XM01-01. Although abnormal ECG measurements were reported in some subjects none of them were considered to be clinically significant (data not shown).

Discussion on clinical pharmacology
The absence of absorption, distribution , metabolism and elimination studies is acceptable because the properties of epoetins in general regarding absorption and distribution are known and there are no specific metabolites besides proteolytic fragments (as for proteins in general).
Pharmacokinetic differences between administration sites, observed in study XM01-12, are reflected in section 5.2 of the SPC as follows:
"Following subcutaneous injection at three different sites (upper arm, abdomen, thigh) in healthy volunteers, similar plasma level profiles were observed. The extent of absorption (AUC) was slightly greater after injection in the abdomen in comparison to the other sites."
In study XM01-20, a certain dose-response relationship could be shown, although this was not strictly linear. This may be due to the small sample size which was not powered to demonstrate a linear dose-response relationship. Moreover, the observed phenomenon of a greater than proportional increase in AUC and a descreased clearance with increased doses is known from historical clinical trials and has already been described in the literature (see P. Veng-Pedersen, J Pharmaceut. Sciences, 1995 ; W.K. Cheung et al., Clin. Pharmacol. Therapeutics, 1998; R. Ramakrishan, J. Clin. Pharmacol. 2004).
In renal anaemia studies, the pharmacokinetic profile in study XM01-01 is in agreement with those of other epoetins. Moreover, the XM01-10 study results suggest that the PK profiles of s.c. administered epoetin theta at a low therapeutic dose are very similar after single and multiple dose administration. There was no trend for an accumulation after multiple s.c. administration of Epoetin theta. On the contrary, the XM01-11 results show that i.v. administered epoetin theta at a low therapeutic dose was eliminated faster after multiple injections compared to the first injection resulting in reduced exposure at steady state. Accumulation after multiple dose administration of epoetin theta compared to a single dose after i.v. administration was not observed. The same has been described for other epoetin-containing medicinal products.

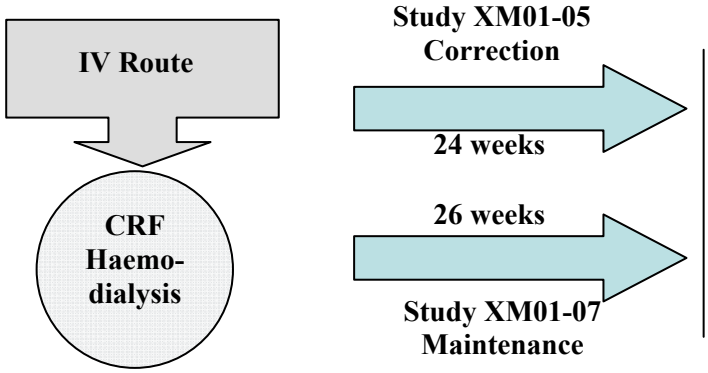
Concerning the cancer treatment anaemia studies, it is accepted that the factors influencing the pharmacokinetics of Epoetin theta /erythropoetin in the target population of patients with chemotherapy are numerous, e.g. chemotherapy is known to increase the concentration of endogenous erythropoietin, explaining the generally high baseline levels (although considerable differences between subjects were observed). Therefore a simple comparison of single dose/steady state pharmacokinetics is not possible.
No accumulation of epoetin theta was observed.
The observed pharmacodynamic effects were within the expected effects of the action of erythropoetin. The transient decrease in haemoglobin and haematocrit after the initial Epoetin theta dose in study XM01-24 was possibly related to the preceding chemotherapy cycle or blood loss for pharmacokinetic sampling, while the recovery of both parameters after consequent doses reflects the pharmacodynamic effect of Epoetin theta.

Clinical efficacy

Anaemia in Chronic Renal Failure (CRF) patients
Six studies have been performed to support the application for the use of Epoetin theta in the treatment of anaemia in chronic renal failure patients, an overview of which is given in table 6. All but two (**XM01-08** and **XM01-09**) were double blind, randomised, multicentre phase II (2) or phase III (4). Study **XM01-05** was a correction phase study designed to demonstrate the efficacy of Epoetin theta with respect to the dose-dependent average increase of haemoglobin per week within the fixed-dose phase in CRF patients receiving dialysis. Study **XM01-07** was a maintenance phase study designed to demonstrate the non-inferiority of Epoetin theta compared with Epoetin beta in terms of efficacy in similar patients. The correction phase study **XM01-04** and the maintenance phase **XM01-06** study enrolled CRF patients not yet under dialysis and their objectives were similar to those of XM01-05 and XM01-07, respectively. Patients not on hemodialysis received their treatments via the subcutaneous route as opposed to patients receiving dialysis, who received treatment intravenously. Study **XM01-08** was a long-term follow up study to XM01-04 and XM01-06 and its objective was to demonstrate therapeutic equivalence between once-weekly administration of Epoetin theta and three times-weekly administration of Epoetin theta. Finally, study **XM01-09** was a long-term follow up study to XM01-05, in which patients were primarily followed for long-term safety. A schematic representation of efficacy study designs is given in figure 1 below.

Figure 1: *Overall study designs*

(i) Renal insufficiency, intravenous route



(ii) Renal insufficiency, subcutaneous route

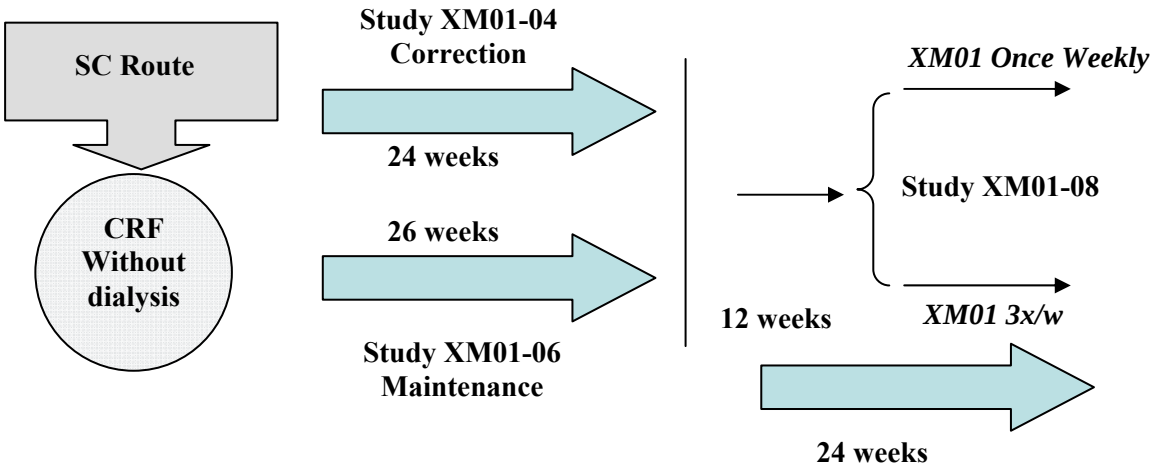


Table 6 Phase II and III studies in renal anaemia patients

Study & patient number	Type of study	Study design and type of control	Test products; Dosage regimen; Route of administration
XM01-04 N=133	Efficacy and safety Patients with anaemia associated with chronic renal failure, not yet receiving dialysis Correction phase study - sc	Phase II, multinational, multicentre, randomised, controlled, double-blind, parallel group, correction phase study	Fixed dose phase: Group 1: 20 IU/kg$_{BW}$ Epoetin theta Group 2: 30 IU/kg$_{BW}$ Epoetin theta Group 3: 40 IU/kg$_{BW}$ Epoetin theta Group 4: 80 IU/kg$_{BW}$ Epoetin theta Group 5: 120 IU/kg$_{BW}$ Epoetin theta Group 6: 20 IU/kg$_{BW}$ Epoetin beta; Subcutaneous, three times weekly
XM01-05 N=150	Efficacy and safety Patients with anaemia associated with chronic renal failure, receiving haemodialysis Correction phase study - iv	Phase II, multinational, multicentre, randomised, controlled, double-blind, parallel-group, correction phase study	Fixed dose phase: Group 1: 40 IU/kg$_{BW}$ Epoetin theta Group 2: 60 IU/kg$_{BW}$ Epoetin theta Group 3: 80 IU/kg$_{BW}$ Epoetin theta Group 4: 120 IU/kg$_{BW}$ Epoetin theta Group 5: 40 IU/kg$_{BW}$ Epoetin beta; Intravenous, three times weekly
XM01-06 N=288	Efficacy and safety Patients with anaemia associated with chronic renal failure, not yet receiving dialysis Maintenance phase study - sc	Phase III, multinational, multicentre, randomised, controlled, double-blind, comparative, parallel group, maintenance phase study	During baseline period, treatment with s.c. Epoetin beta with same dose and frequency as before entering the study. During the treatment period (Epoetin theta or Epoetin beta) dose was adjusted when required*
XM01-07 N=270	Efficacy and safety Patients with anaemia associated with chronic renal failure, receiving haemodialysis Maintenance phase study - iv	Phase III, multinational, multicentre, randomised, controlled, double-blind, comparative, parallel-group, maintenance-phase study	During baseline period, treatment with i.v. Epoetin beta with same dose and frequency as before entering the study. During the treatment period (Epoetin theta or Epoetin beta) dose was adjusted when required*
XM01-08 N=289	Long-term efficacy and safety Patients with anaemia associated with chronic renal failure, not yet receiving dialysis Follow-up study to studies XM01-04 and XM01-06	Phase III, multinational, multicentre, randomised, open, parallel-group study	First 12 weeks: Epoetin theta s.c. at the same dose and frequency at which either Epoetin theta or Epoetin beta was received before entering the study. In the subsequent 24 weeks: Epoetin theta at the same dose either once weekly, or equally divided over 3 doses per week. Dose was adjusted when required*

Study & patient number	Type of study	Study design and type of control	Test products; Dosage regimen; Route of administration
XM01-09 N=124	Long-term safety Patients with anaemia associated with chronic renal failure, receiving haemodialysis Follow-up study to study XM01-05	Phase III, multinational, multicentre, open study	Intravenous Epoetin theta at the same weekly dose and frequency as given at the end of study XM01-05. Dose was adjusted to maintain haemoglobin within the target range of 9.5 to 12 g/dL.
Dose was adjusted to maintain the haemoglobin level within ± 1g/dL of the baseline value and within the target range of 9.5 to 12.0 g/dL.			

- Dose response studies

The correction phase studies XM01-05 and XM01-04 in patients receiving haemodialysis and in patients not yet on haemodialysis, respectively, contained an initial dose-response phase. These are described in the main studies section below.

- Main studies

Study CSR XM01-04: Safety and efficacy of Epoetin theta in chronic renal failure-associated anaemia patients not yet receiving dialysis (correction phase, subcutaneous route) and,
Study CSR XM01-05: Safety and efficacy of Epoetin theta in chronic renal failure-associated anaemia patients receiving haemodialysis (correction phase, intravenous route)

METHODS

Studies CSR XM01-04 and XM01-05 were multinational, multicentre, randomised, active controlled, double-blind ("third party blinding"), parallel-group phase II studies. XM01-04 was conducted in 34 centres based in 9 countries. XM01-05 was conducted in 25 centres based in 4 countries.

Study Participants

Study XM01-04 included adult patients with chronic renal failure not yet treated with dialysis, with a glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2. Study XM01-05 included adult patients with chronic renal failure who had been treated with haemodialysis for at least 12 weeks, receiving haemodialysis twice or three times a week and having adequate quality of haemodialysis defined as Kt/Vurea ≥ 1.2 (within the last 8 weeks prior to enrolment).

In both studies, patients should not have received epoetin within the last 12 weeks prior to enrolment or epoetins with a longer half-life within the last 6 months. Patients had to have stable haemoglobin values ≤ 10.0 g/dL. Female patients of childbearing potential and patients requiring red blood cell transfusions or with red blood cell transfusion within the last 8 weeks were notably not included in the study.

Treatments

Both studies comprised 3 parts:

- Screening period (up to 2 weeks, no treatment with study drug),
- Fixed-dose phase (in XM01-04: 4 weeks of subcutaneous tiw treatment with 20, 30, 40, 80, and 120 IU/kgBW Epoetin theta, or 20 IU/kgBW Epoetin beta; in XM01-05: 4 weeks of intravenous tiw treatment with 40, 60, 80, 120 IU/kgBW Epoetin theta, or 40 IU/kgBW Epoetin beta). No dose changes were allowed during this phase apart from reductions in case of very high haemoglobin values above 12 g/dL for safety reasons,
- Adaptation phase in which the epoetin dose for each patient was adjusted based on haemoglobin levels. The adaptation (correction) phase lasted until the patient reached the haemoglobin response, with a maximum duration of 20 weeks if a response was not achieved.

The aim in both treatment phases was to increase haemoglobin levels to between 11.0 and 12 g/dL.

Objectives

The objectives of the study included examination of the efficacy of Epoetin theta in achieving dose-dependent correction of anaemia, examination of the safety and tolerability of Epoetin theta and comparison to Epoetin beta in terms of both efficacy and safety.

Outcomes/endpoints

Primary efficacy endpoint

Dose-dependent average increase of Hb per week within the fixed-dose phase. Epoetin theta was to be regarded as effective if there was a statistically significant difference in the increase of Hb levels after treatment with 20 (XM01-04) or 40 (XM01-05) compared to 120 IU/kgBW Epoetin theta given tiw.

Secondary efficacy endpoints

- Number of patients reaching Hb response: i.e. Hb level > 11.0 g/dL on 2 consecutive measurements in the adaptation phase without blood transfusions within the preceding 3 months
- Time required to achieve Hb response
- Dose-response relationship of Epoetin theta in the fixed-dose phase (average Hb increase per week)
- Doses of Epoetin theta or Epoetin beta at time of Hb response
- Number of patients with blood transfusions and blood units per patient
- Measured haemoglobin, haematocrit and reticulocyte counts and their changes from baseline.

Sample size

XM01-04: Based on information from other epoetins, the determination of the sample size was based on the assumption that average Hb increases of 0.35 and 0.61 g/dL per week could be expected in the two Epoetin theta groups (20 and 120 IU/kg). The common SD was assumed to be $\sigma = 0.23$. A sample size of 25 patients in each of the 6 dose groups would have 97% power to detect a difference of 0.26 g/dL/week between the contrasted groups (α=0.05 level). As the statistical analysis of the primary endpoint was to be performed on the ITT population (i.e. all randomised patients), drop-outs were not taken into consideration for the sample size calculation. Thus, atotal of 150 patients were to be randomised into the 6 treatment groups.

XM01-05: Based on the information from other epoetins, the determination of the sample size was based on the assumption that average Hb increases of 0.28 and 0.50 g/dL per week could be expected in the two Epoetin theta groups (40 and 120 IU/kgBW). The common SD was assumed to be $\sigma = 0.23$. A sample size of 25 patients in each of the 5 dose groups would have 91% power to detect a difference of 0.22 g/dL/week between the contrasted groups (α=0.05 level). As the statistical analysis of the primary endpoint was to be performed on the ITT population (i.e. all randomised patients), drop-outs were not taken into consideration for the sample size calculation. Thus, a total of 125 patients were to be randomised.

Randomisation

Patients were randomised in a 1:1:1:1:1:1 ratio to the six treatment groups (XM01-04) or in a 1:1:1:1:1 ratio to the five treatment groups (XM01-05). Randomisation was stratified by country as country was considered an important factor influencing study outcome. Three patients were erroneously randomised in Study XM01-05 but were not treated with any of the study medications and regarded as 'screen failures' by the respective investigators. The Blinded Review Committee also decided to treat these patients as included not randomised patients.

Blinding (masking)

A double-blind design was chosen for this study to minimise bias but a true double blinding was not technically feasible because Epoetin theta was provided in vials and the reference drug (NeoRecormon®) as a solution in pre-filled syringes. Third party blinding was therefore used.

Statistical methods

The intent-to-treat (ITT) population was the primary population for efficacy analyses and consisted of all randomised patients. The safety population consisted of all randomized patients who received at least 1 dose of study treatment. The according to protocol (ATP) population consisted of all patients of the ITT population who did not have any major protocol violations. The ATP population was the secondary population for analyses of the primary efficacy variable.

In terms of the primary efficacy endpoint: A stepwise-rejecting-multiple-test procedure for a priori ordered hypotheses was used to compare the lowest dose Epoetin theta group with the other Epoetin

theta groups (starting with the highest dose group and followed by the others in descending dose order). The ANCOVA model included a term for treatment as fixed class variables and Hb at baseline as covariate. Exploratory comparisons of the Epoetin theta dose groups versus Epoetin beta were also performed. Concerning the secondary efficacy endpoints, treatment groups were compared using descriptive statistics. No adjustments of the significance level for multiple testing were made.

RESULTS

Participant flow
In XM01-04, 320 patients were screened, 134 of whom were randomised and 133 were treated. 131 (97.8%) patients completed the fixed dose phase and 112 (83.6%) patients completed the study.
In XM01-05, 263 patients were enrolled and 150 (57.0%) patients were randomised. 148 (98.7%) patients completed the fixed-dose phase and 138 (92.0%) patients completed the adaptation phase.

Recruitment
XM01-04: first patient enrolled: 29 July 2005; last patient completed the study: 20 March 2007
XM01-05: first patient enrolled: 18 August 2005; last patient completed the study: 02 August 2006

Conduct of the study
XM01-04: There was one protocol amendment (dated 22 March 2005) that did not have a substantial impact on the study outcome. Concerning the statistical analysis the most important deviation from the planned statistical analysis was that the factor "country" was not included in any of the two statistical models as explanatory variable. This was not feasible due to the imbalanced number of patients in the participating countries.
XM01-05: The original protocol (issued on 21 March 2005) was modified by 1 local and 2 global amendments which did not have a substantial impact on the study conduct.

Baseline data
In study XM01-04, baseline demographic characteristics were similar across treatment groups, with the exception of the proportion of women in the Epoetin theta 20 IU/kgBW group, which was higher compared to the other groups, but this was not considered to be clinically relevant. The history of chronic renal failure varied across groups. Time since diagnosis of renal anaemia was similar across groups. Baseline haemoglobin values were similar across the 6 treatment groups. With some minor exceptions, the most common causes of renal insufficiency were similar across groups.
In XM01-05, baseline demographic characteristics were similar across treatment groups, with the exception of the proportion of men in the Epoetin theta 60 IU/kgBW group, which was higher than in the 4 other treatment groups, but this was not considered to be clinically relevant. The history of chronic renal failure, the time since diagnosis of renal anaemia and the time since first dialysis were comparable across the 5 treatment groups. In terms of blood transfusions prior to study entry there was some imbalance between treatment groups: of the 9 patients having received blood transfusions in the 3 months prior to study entry, 5 were in the Epoetin theta 120 IU/kgBW group, but due to the small number this was not considered significant. Of the same 9 patients, 3 had received transfusions less than 8 weeks prior to study entry, contrary to study protocol. These had been considered as minor protocol violations.

Numbers analysed
The analysis was performed on the ITT population as planned. In XM01-04, the ITT comprised 134 patients. One patient in the ITT population was not treated and was therefore not included in the Safety population (comprising 133). In total, 12 patients with major protocol violations were excluded from the ATP population which thus comprised 122 patients. In XM01-05, the ITT and SP populations were identical because all randomised patients were treated at least once with the study medication. They comprised 150 patients. 15 patients with major protocol violations were excluded from the ATP population which thus comprised 135 patients.

Outcomes and estimation

Primary efficacy endpoint:

XM01-04: Results of the ANCOVA analysis showed that the mean (± SD) weekly increase of haemoglobin in the Epoetin theta 120 IU/kgBW group was significantly higher than in the Epoetin theta 20 IU/kgBW group: 0.73 ± 0.33 g/dL vs. 0.20 ± 0.28 g/dL, p < 0.0001. The primary endpoint was thus met.

Table 7: *Weekly increase of haemoglobin in the fixed-dose phase (ITT population)*

Statistic	EpoTheta 20 IU/kg (N=21)	EpoTheta 30 IU/kg (N=23)	EpoTheta 40 IU/kg (N=25)	EpoTheta 80 IU/kg (N=22)	EpoTheta 120 IU/kg (N=22)	EpoB 20 IU/kg (N=21)
Mean weekly increase (g/dL)						
Mean	**0.20**	**0.39**	**0.45**	**0.52**	**0.73**	**0.30**
SD	0.28	0.30	0.22	0.19	0.33	0.28
Median	0.20	0.48	0.41	0.50	0.65	0.22
Range	-0.50 to 0.75	-0.30 to 1.11	-0.05 to 0.76	0.14 to 0.83	0.17 to 1.63	0.00 to 1.05
Comparison vs. EpoTheta 20 IU/kgBW						
Mean difference		-0.20	-0.24	-0.32	-0.52	-0.10
95% CI		-0.35, -0.04	-0.40, -0.09	-0.48, -0.16	-0.68, -0.36	-0.26, 0.06
p value *		0.0150	0.0023	0.0001	<0.0001	0.2074

* All statistical comparisons are against the lowest dose of Epoetin theta (20 IU/kgBW).

XM01-05: Results of the ANCOVA analysis showed that the mean (± SD) weekly increase of haemoglobin in the Epoetin theta 120 IU/kgBW group was significantly higher than in the Epoetin theta 40 IU/kgBW group: 0.58 ± 0.27 g/dL vs 0.26 ± 0.26 g/dL, p < 0.0001. The primary endpoint of the study was thus met.

Table 8: *Weekly increase of haemoglobin (g/dL) in the fixed-dose phase (ITT population)*

	EpoTheta 40 IU/kg (N=29)	EpoTheta 60 IU/kg (N=30)	EpoTheta 80 IU/kg (N=32)	EpoTheta 120 IU/kg (N=30)	EpoB 40 IU/kg (N=29)
Mean	0.26	0.29	0.46	0.58	0.33
SD	0.26	0.25	0.27	0.27	0.26
Median	0.27	0.30	0.45	0.58	0.35
Range	–0.27 to 0.76	–0.15 to 0.85	–0.02 to 1.15	–0.07 to 1.01	–0.40 to 1.05
Comparison vs EpoTheta 40 IU/kg					
Mean difference		–0.06	–0.20	–0.32	–0.07
95%CI		–0.19, 0.07	–0.33, –0.07	–0.45, –0.18	–0.20, 0.07
p value		0.3852	0.0028	<0.0001	0.3349

There were no statistically significant interactions between country and treatment or between baseline reading and treatment (data not shown).

Secondary efficacy endpoints

***Dose-response relationship of weekly haemoglobin increase in the fixed-dose phase*:** There was a statistically significant linear relationship between the mean weekly haemoglobin values in the fixed-

dose phase and the dose of Epoetin theta over the range of doses administered in both studies (data not shown).

***Haemoglobin response rate*:** The majority of patients had a haemoglobin response (i.e. a haemoglobin level > 11.0 g/dL on 2 consecutive measurements in the adaptation phase without blood transfusions within the preceding 3 months) and similar response rates were found across treatment groups in both studies. The response rates of numerically corresponding Epoetin beta and Epoetin theta groups were identical in both studies. There were no statistically significant differences of the response rates between the treatment groups (or between countries in study XM01-05, data not shown).

***Time to achieve haemoglobin response*:** The mean time to response generally showed a dose-dependent decrease with increasing doses of Epoetin theta in both studies and the log-rank test indicated a statistically significant difference among treatment groups in time to achieve haemoglobin response. Numerically corresponding doses of Epoetin theta and Epoetin beta showed generally similar mean times to haemoglobin response in the two studies (data not shown). In study XM01-05, country-stratified results showed similar results in terms of time to achieve haemoglobin response (data not shown).

***Dose of epoetin in the week before the haemoglobin response*:** In both studies, the mean single doses of epoetin in the week before the response were similar between numerically corresponding Epoetin theta and Epoetin beta treatment groups. It should be noted that the patients received these single doses three times each week (data not shown).

***Blood transfusions*:** Blood transfusions were administered on a case by case basis at the discretion of the investigator. In study XM01-05, a total of 5 patients received blood transfusions. There were no statistically significant differences between the treatment groups with regard to number of blood transfusions. In study XM01-04, only three patients received blood transfusions (data not shown).

Measured values of haemoglobin, haematocrit, and reticulocytes

Haemoglobin: In both studies, baseline haemoglobin values were similar across all treatment groups. In accordance with the study design, values gradually increased during the fixed-dose phase and reached a plateau during the adaptation phase. As expected, the magnitude of the increases in the Epoetin theta groups was dose dependent (data not shown).

Haematocrit: In both studies, the changes of haematocrit values were very similar to the changes of haemoglobin values over time and across the treatment groups (data not shown).

Reticulocyte: Values showed a high degree of variability in all treatment groups and at all timepoints and were thus difficult to interpret.

Study CSR XM01-06: Safety and efficacy of Epoetin theta in chronic renal failure-associated anaemia patients not yet receiving dialysis (maintenance phase, subcutaneous route)

Study CSR XM01-07: Safety and efficacy of Epoetin theta in chronic renal failure-associated anaemia patients receiving haemodialysis (maintenance phase, intravenous route)

METHODS

Studies XM01-06 and XM01-07 were multinational, multicenter, randomised, controlled, double-blind ("third party blinding"), comparative, parallel-group phase III studies. XM01-06 was conducted in 50 centres based in 10 countries. XM01-07 was conducted in 34 centres based in 5 countries.

Study Participants

Study XM01-06 included adult patients with chronic renal failure being treated for renal anaemia, not yet on dialysis and having a GFR < 60 mL/min/1.73 m2 within the last three months. In study XM01-07, participants were adults with chronic renal failure being treated for renal anaemia and on haemodialysis for at least 6 months.

In both studies, patients should have been maintained on s.c. therapy with Epoetin beta and having stable Hb levels within the previous 8 weeks (within the target range ≥ 9.5 g/dL and < 12.0 g/dL and the difference between the highest and lowest values < 2 g/dL, based on at least 4 Hb measurements). Female patients of childbearing potential, patients with active bleeding or with red blood cell transfusion within the last 3 months were notably not included in the studies.

Treatments

Both studies comprised four parts:

- Screening visit
- Baseline period (2 weeks, patients treated with intravenous or subcutaneous epoetin beta at the same dose and frequency as prior to the study)
- Treatment period (24 weeks; patients randomised 1:2 to Epoetin beta or an equivalent dose of Epoetin theta; the EVP Weeks 15 to 26). During the randomised treatment period, the epoetin dose could be adjusted according to a protocol-defined dosing algorithm to maintain Hb values within the target interval (I=[baseline-1.0, baseline+1.0]∩[9.5, 12.0])
- Follow-up period (up to 30 days after last dose of study medication)

Objectives

Objectives of the study included demonstration of non-inferiority of Epoetin theta compared to Epoetin beta in terms of efficacy, safety and tolerability, as well as immunogenicity.

Outcomes/endpoints

Primary efficacy endpoint

The primary endpoint was the change of Hb level from baseline (mean of Visits 1, 2, and 3) to end of treatment (mean of Weeks 15-26; the EVP).

Secondary efficacy endpoints

The following efficacy parameters were assessed during the EVP only (Visits 11 to 17; Weeks 15 to 26)

─ Mean weekly dose of epoetin required to maintain Hb levels during the EVP within the target interval. The target interval for haemoglobin values was defined as I=[baseline-1.0, baseline+1.0]∩[9.5, 12.0], where the baseline value was the mean of Visits 1, 2 and 3.

─ Percentage of patients with dose changes. The percentage of patients with dose changes during the EVP was calculated by treatment group within country, treatment group and overall.

─ Number of dose changes per patient. The number of dose changes per patient within the EVP were analysed descriptively.

─ Percentage of Hb values per patient within the target interval (defined above). Results of Hb assessments were used to monitor if patients had Hb levels within the target interval during the EVP.

─ Percentage of patients with Hb values within the target interval (defined above) at each week during the EVP. Results of Hb assessments were used to monitor if patients had Hb levels within the target interval at each week during the EVP.

─ Within-patient variance in Hb levels. For each patient the within-variance in Hb levels during the EVP was calculated.

─ Hb changes from baseline. The Hb changes from baseline were analysed at each week during the EVP.

Sample size
Assuming a 2:1 randomisation for Epoetin theta and Epoetin beta and a difference of 1.0 g/dL in Hb as greatest clinically acceptable difference, a sample sizes of 128 (Epoetin theta) and 64 (Epoetin beta) would have 90% power to show that Epoetin theta was not inferior to Epoetin beta (α=0.05). In this calculation it was assumed that the expected difference in means was 0.5 g/dL in favour of Epoetin beta and that the common SD was 1.0 g/dL. Assuming a drop-out rate of 25%, 170 patients had to be treated with Epoetin theta and 85 patients with Epoetin beta, giving a total of 255 patients to be randomised. The estimated drop-out rate was based on results from recently published clinical trials with Darbepoetin alfa.

Randomisation
At the randomisation visit at the end of the baseline period, patients were randomised in a ratio of 2:1 to Epoetin theta: Epoetin beta. The randomisation was stratified by country, using blocks with length of 3 and an assignment ratio of Epoetin theta to Epoetin beta of 2:1. The size of the randomisation blocks was not disclosed to the study centres. Patients were not randomised if the mean of the Hb levels at Visit 1 and Visit 2 was < 9.5 g/dL or ≥ 12.0 g/dL.

Blinding
A true double-blind design was not technically feasible for this study because the test drug (Epoetin theta) was provided as a solution in vials and the reference drug (NeoRecormon®) as a solution in pre-filled syringes. The investigator, any sub-investigators or study nurses, and the patient were blinded to the study medication.

Statistical methods
The full analysis set (ITT population) comprised all randomised patients. The per protocol set (ATP population) was the primary population for efficacy analyses and comprised all patients of the ITT population who were treated with study medication and who did not have any major protocol violations. The safety population was the population for the safety analyses and comprised all patients of the ITT population who received at least 1 dose of study treatment. The primary analysis was based on the ATP population, as a per protocol analysis is considered a more conservative approach for non-inferiority analyses.
In terms of the primary efficacy endpoint, a difference of 1.0 g/dL was considered the greatest clinically acceptable difference; therefore the limit of non-inferiority was defined as a difference between the 2 treatment groups of -1.0 g/dL. The analysis of covariance (ANCOVA) model for non inferiority testing included a term for treatment and country as fixed class variables and haemoglobin at baseline as covariate. Concerning the secondary efficacy endpoints, treatment groups were compared using descriptive statistics. No adjustments of the significance level for multiple testing were made.

RESULTS

Participant flow
In XM01-06, 373 patients were enrolled and screened. 288 patients were randomised and treated. 255 (88.5%) patients completed the study; 167 (86.5%) patients in Epoetin theta group and 88 (92.6%) patients in the Epoetin beta group.
In XM01-07, 347 patients were screened. 270 patients were randomised and treated. 233 (86.3%) patients completed the study; 156 (86.7%) patients in Epoetin theta group and 77 (85.6%) patients in the Epoetin beta group.

Recruitment
XM01-06: first patient enrolled: 17 August 2005; last patient completed the study: 10 May 2007
XM01-07: first patient enrolled: 22 August 2005; last patient completed the study: 09 November 2006

Conduct of the study
For XM01-06, no protocol amendments were made. For XM01-07, the original protocol (issued on 22 February 2005) was modified by 1 amendment that did not have a substantial impact on the study conduct. In both studies, changes and clarifications concerning statistical analyses were only minor.

Baseline data
In XM01-06, demographic and baseline characteristics were comparable across the 2 treatment groups with minor exceptions (slightly higher percentage of men in the Epoetin beta group and slightly higher percentage of patients aged ≥ 65 years in the Epoetin theta group) of little clinical relevance. Time since diagnosis of renal failure and renal anaemia did not differ between treatment groups. Time since initiation of epoetin treatment was similar and differences in the most common causes of renal failure were not clinically relevant.
In XM01-07, demographic and baseline characteristics were comparable across the 2 treatment groups and across the 5 countries. Time since diagnosis of renal failure and renal anaemia were also comparable between treatment groups. Differences in the most common causes of renal insufficiency between treatment groups were not clinically relevant.

Numbers analysed
The analysis was performed on the ATP population as planned. In XM01-06, the ITT population comprised 288 patients (193 receiving Epoetin theta and 95 receiving Epoetin beta). The ATP population comprised 240 patients (159 Epoetin theta; 81 Epoetin beta). The SP was identical to the ITT population (288 patients). In XM01-07, the ITT population comprised 270 patients (180 receiving Epoetin theta and 90 receiving Epoetin beta). 46 patients with major protocol violations were excluded from the ATP population which thus comprised 224 patients (150 and 74 respectively). The SP was identical to the ITT population (270 patients).

Outcomes and estimation

Primary efficacy endpoint: Analysis of non-inferiority in the ATP population
XM01-06: Mean Hb values were similar in both treatment groups at baseline and during the EVP for the ATP population. The primary endpoint was thus met and Epoetin theta was considered as non-inferior to Epoetin beta.

Table 9 : *Primary analysis of non-inferiority – change in Hb levels from baseline to the end of treatment (EVP) (ATP population)*

Haemoglobin values	Epoetin theta N=159	Epoetin beta N=81	Total N=240
Baseline (g/dL)			
Mean	10.88	10.93	10.90
SD	0.59	0.61	0.60
Range	9.50 to 12.00	9.50 to 11.90	9.50 to 12.00
Mean EVP (g/dL)			
Mean	11.07	11.08	11.08
SD	0.94	0.82	0.90
Range	8.29 to 14.06	9.34 to 13.79	8.29 to 14.06
Change from baseline to mean EVP (g/dL)			
Mean	0.19	0.15	0.18
SD	0.80	0.73	0.78
Range	-1.59 to 2.86	-1.85 to 1.89	-1.85 to 2.86
ANCOVA comparison*			

Haemoglobin values	Epoetin theta N=159	Epoetin beta N=81	Total N=240
Epo theta – Epo beta Estimated difference (SE)		0.01 (0.11)	
95% CI		-0.20, 0.22	
p value		0.9207	

The ANCOVA model of the primary efficacy endpoint included country as fixed effect and Hb baseline reading as covariable. Baseline Hb values had an effect on the outcome of the primary endpoint, with a p value of 0.0076; country had no effect on the outcome of the primary analysis (p=0.2820). For the baseline term, the estimated effect on the primary analysis was -0.24 (SE 0.09).
Exploratory ANCOVA models with interaction effects for country and baseline readings by treatment group were performed. These analyses revealed no statistically significant interaction between baseline and treatment (p=0.2767), and between country and treatment (p=0.7820).
The findings for the ITT population supported the primary analysis of non-inferiority in the ATP population. The estimated treatment difference was 0.00 (SE 0.10) g/dL (95% CI: -0.20, 0.20), p=0.9983, indicating that the difference between groups was less than 1.0 g/dL and it was not statistically significant.

XM01-07: Mean Hb values were similar in both treatment groups at baseline and during the EVP. The primary aim of the study was met and Epoetin theta was considered as non-inferior to Epoetin beta.

Table 10: *Primary analysis of non-inferiority – change in Hb levels from baseline to the end of treatment (EVP) (ATP population)*

Haemoglobin values	Epoetin theta N=150	Epoetin beta N=74	Total N=224
Baseline (g/dL)			
Mean	10.86	10.83	10.85
SD	0.62	0.59	0.61
Range	9.70 to 11.90	9.60 to 11.90	9.60 to 11.90
Mean EVP (g/dL)			
Mean	10.66	10.66	10.66
SD	0.89	0.92	0.90
Range	8.53 to 13.20	8.36 to 14.50	8.36 to 14.50
Change from baseline to mean EVP (g/dL)			
Mean	-0.21	-0.17	-0.19
SD	0.82	0.96	0.87
Range	-1.98 to 2.51	-2.31 to 4.30	-2.31 to 4.30
ANCOVA comparison*			
EpoTheta – EpoB Estimated difference (SE)		-0.01 (0.11)	
95% CI		-0.24, 0.21	
p value		0.9021	

The ANCOVA model of the primary efficacy endpoint included country as fixed effect and Hb baseline reading as covariable. Both terms had an effect on the outcome of the primary endpoint, with p values of 0.0020 for country and < 0.0001 for baseline values. For the baseline term, the estimated effect on the primary analysis was -0.49 (SE 0.09), indicating that the higher the baseline Hb value, the lower the mean change from baseline.

The findings for the ITT population supported the ATP analysis of non-inferiority: the estimated treatment difference was -0.08 (SE 0.11) g/dL (95% CI: -0.30, 0.14), p=0.4636.

Secondary efficacy endpoints:

Mean weekly dose of epoetin
During the EVP, the mean weekly dose of epoetin was similar in the Epoetin theta group and the Epoetin beta group for the ATP population in both studies. Slight differences in doses of epoetin between groups were not statistically significant; notably, there was wide variation in dosing values for both groups. Similar results were obtained in the ITT population in both studies.
In study XM01-06, there was a decrease from baseline in mean weekly dose of epoetin during the EVP for both Epoetin theta and Epoetin beta (data not shown).
Percentage of patients with dose changes during the EVP: In both studies, dose changes during the EVP were required by about half of the patients in both the ATP and the ITT. The majority of patients with dose changes required only 1 or 2 dose changes during the EVP (data not shown).
Rate of dose changes during the EVP: The rate of dose change was the number of dose changes observed divided by the number of possible dose changes for each patient (including patients with no dose changes during the study). In both studies, there was no relevant difference in the mean rate of dose change during the EVP for the Epoetin theta and Epoetin beta groups (ATP and ITT population, data not shown).
Percentage of haemoglobin values within the target interval during the EVP: For this endpoint, individual percentages of Hb values within the target interval during the EVP were described; i.e. for each patient the percentage of Hb values within the target interval out of all their observed Hb values in the EVP was calculated.
In both studies, the individual mean percentage of Hb values within the target interval during the EVP was similar in both groups; the range was 0 to 100% for both groups, indicating that for some patients all Hb levels were within the target interval (ATP and ITT population, data not shown).
Percentage of patients with haemoglobin values within the target interval during the EVP: In study XM01-06, the percentage of patients with Hb values within the target interval during the EVP was higher for the Epoetin beta group than for the Epoetin theta group at all time points except Weeks 17, 19, 24, and 26, when the difference between groups was < 5%. However, percentages at each week varied markedly, depending on the numbers of patients included in the analysis; a difference of only 1 or 2 patients in the analysis population had a marked effect on the percentages of patients within the target interval (ATP population, data not shown). In study XM01-07, the percentage of patients with Hb values within the target interval was similar in both groups at almost all weeks during the EVP. The percentage was slightly higher for the Epoetin beta group than for the Epoetin theta group at Weeks 16 and 20; at all other time points, the difference between groups was < 5%. (ATP population, data not shown).
Within-patient standard deviation and variability in haemoglobin levels during the EVP: In both studies and for both ATP and ITT populations, the within patient standard deviation and variability in Hb levels during the EVP was similar for the Epoetin theta and the Epoetin beta groups (data not shown).
Haemoglobin changes from baseline during the EVP: In both studies, the time courses of mean Hb values during the study for the Epoetin theta and Epoetin beta groups were almost superimposable. The mean changes from baseline to each visit were also almost identical between groups, showing that minor fluctuations in Hb values were normal in patients under stable maintenance therapy. Findings for the time course of Hb values and mean changes from baseline were similar across countries. Results were similar for the ATP and ITT populations (data not shown).
Blood transfusions: In both studies and for both ATP and ITT populations, the difference between Epoetin theta and Epoetin beta groups in terms of blood transfusions administered during the study as well as during the EVP was not clinically meaningful or statistically significant. Blood transfusion during the EVP would have resulted in exclusion from the ATP population.

Study CSR XM01-08: Long-term efficacy and safety of Epoetin theta in chronic renal failure-associated anaemia patients not yet receiving dialysis (comparison of once- and thrice-weekly administration of Epoetin theta, subcutaneous route)

METHODS

This was a multinational, multicentre, randomised, open, parallel-group Phase III follow-up study for the subcutaneous application in patients with anaemia associated with chronic renal failure. It was conducted in 50 centres based in 11 countries.

Study Participants

Patients successfully treated for renal anaemia with Epoetin theta or Epoetin beta in the previous studies XM01-04 (Correction phase study - subcutaneous) or XM01-06 (Maintenance phase study - subcutaneous) were eligible for enrolment into this study. All eligible patients who completed study XM01-04 or XM01-06 regularly and who had signed and dated written informed consent for this follow-up study could be included.

There were no formal exclusion criteria at visit 1. At visit 7 (week 13), patients presenting with any of the following were not eligible for randomisation:

- Serum ferritin ≤ 100 µg/L or transferrin saturation (TSAT) ≤ 20%
- Active bleeding
- Red blood cell transfusion within the last four weeks
- Known positive test for human immunodeficiency virus (HIV) antibodies
- Concomitant therapy with immunosuppressive drugs, steroids (oral or intravenous) or androgens
- Resistance to epoetin (more than 300 IU/kgBW/week)

Treatments

Patients previously treated with Epoetin theta continued their individual s.c. therapy with Epoetin theta. Patients who were previously treated with Epoetin beta started s.c. treatment with Epoetin theta with the same dose and frequency they had been treated with Epoetin beta in the previous study. The planned complete study participation time was 36 weeks. For the first 12 weeks of the study (the pre-randomisation period), all patients were to receive Epoetin theta at the same individual dose and frequency of administration of epoetin treatment (Epoetin theta or Epoetin beta) that they were receiving at the end of study XM01-04 or XM01-06. It should be noted that in the parent study XM01-04 a thrice weekly dosing frequency was predefined in the protocol, whereas in the parent study XM01-06 the dosing frequency could be adapted and the majority of patients were treated once weekly with epoetin. At week 13, patients who met all the eligibility criteria were randomised 1:1 to receive either Epoetin theta once-weekly s.c. or Epoetin theta three times-weekly s.c. during the following 24 weeks (the evaluation period). The total weekly dose was based on their previous therapy. Dose adaptations were to be made throughout the study to maintain haemoglobin levels within the therapeutic range (9.5, 12.0 g/dL) and, in addition, during the evaluation period, to maintain haemoglobin levels within ± 1 g/dL of the individual baseline value (determined prior to randomisation).

Objectives

To demonstrate therapeutic equivalence in terms of efficacy, safety and tolerability between once-weekly and three times-weekly administration of Epoetin theta (by injecting the same total weekly dose).

Outcomes/endpoints

Primary efficacy endpoint

Time-adjusted area under the curve for haemoglobin (AUC-Hb) during the efficacy evaluation period (EEP) (weeks 25 to 36, 12 weeks) (primary endpoint) and mean weekly Epoetin theta dose per kg of body weight during the efficacy evaluation period (weeks 25 to 36, 12 weeks) (co-primary endpoint).

Secondary efficacy endpoints

- Percentage of patients with dose changes (increases, decreases)
- Number of dose changes per patient (increases, decreases)
- Percentage of haemoglobin values per patient within the target interval (both, 9.5 to 12.0 g/dL and individual baseline value ± 1.0 g/dL, determined prior to randomisation)
- Percentage of patients with haemoglobin values within the therapeutic range (9.5 to 12.0 g/dL)

– Within-patient variance in haemoglobin levels, measured values of haemoglobin, haematocrit and reticulocytes
– Number of patients with blood transfusions

Sample size
The determination of the sample size was based on the primary efficacy endpoints, i.e. AUC 25-37 and Dose 25-36. The sample size was determined to provide a power of at least 0.8 for the rejection of the null hypothesis for each of the primary variables at a two-sided level of α=0.05. Assuming a drop-out rate of 15%, in total at least 266 patients were to be randomised at the end of week 12. Recruiting 266 patients into the study would result in a power of 0.8 for the hierarchical test procedure (power of 0.96 for the test concerning the primary variable AUC 25-37) in the ATP population.

Randomisation
At week 13, patients who met all the eligibility criteria were randomised 1:1 to receive either Epoetin theta once-weekly s.c. or Epoetin theta three times-weekly s.c. during the following 24 weeks (the evaluation period).

Blinding (masking)
This was an open study. To make sure that the prior study XM01-04 or XM01-06 was kept blinded, the drug administrator in study XM01-04 or XM01-06 informed the investigator only about the initial Epoetin theta dose that had to be administered at visit 1 (which was also the final visit of study XM01-04 or XM01-06).

Statistical methods
Four analysis populations were evaluated:
– Followed-up not randomised (FNR): All patients who were treated at least once with Epoetin theta in study XM01-08 but were not randomised.
– Full analysis set (intent-to-treat [ITT] population): All patients who were randomised to one of the study treatments at the start of week 13 (all randomised patients) including patients with major protocol violations. This set was the secondary population for the efficacy analyses.
– Per-protocol set (according to protocol [ATP] population): All patients of the full analysis set who did not have any major protocol violations. This was the primary population for efficacy analyses.
– Safety set (safety population [SP]): All patients of the full analysis set (all randomised patients) who received at least 1 dose of study treatment. This population was used for the analyses of safety data.
To show equivalence between once-weekly and thrice-weekly administration regarding the AUC, a two-sided 95% confidence interval for the difference in the AUC had to lie entirely within the equivalence range of -1.0 to +1.0 g/dL. A difference of maximal 1.0 g/dL was considered to be without clinical relevance. To show equivalence between once-weekly and thrice-weekly administration regarding the total weekly dose a two-sided 95% confidence interval for the ratio had to lie entirely within the equivalence range of 0.8 to 1.25. For evaluation of secondary efficacy endpoints the treatment groups were compared using descriptive statistics. Descriptive p-values were calculated with appropriate statistical tests but were regarded as supportive only. No adjustments of the significance level for multiple testing were made.

RESULTS

Participant flow
209 of the 289 patients enrolled in this study were previously treated with Epoetin theta and continued their treatment. 80 of the 289 patients enrolled in this study were previously treated with Epoetin beta and were switched to treatment with Epoetin theta at the same dose and frequency. In total, 177 (61.2%) patients completed the study; 95 (85.6%) patients in the once weekly group and 82 (73.2%) patients in the thrice weekly group.

Recruitment
First patient enrolled: 2 February 2006; last patient completed the study: 21 January 2008

Conduct of the study
There were no amendments to the study protocol. There were two changes of the statistical analysis and some clarifications of the calculation of the efficacy endpoints which did not have a substantial impact on study conduct.

Baseline data
Baseline demographic characteristics were similar across treatment groups. Time since first diagnosis of renal failure and of renal anaemia was similar among treatment groups. Differences between groups in causes of renal failure were not clinically relevant.

Numbers analysed
289 patients were enrolled. 66 patients were followed-up but not randomised (FNR). 223 patients were randomised at the end of week 12 (once weekly group:111, thrice weekly group:112). 7 and 15 patients discontinued before the efficacy evaluation period, respectively, so that 95 in the once-weekly group and 82 in the thrice-weekly group had a regular study end. The ATP population comprised 188 patients (99 once weekly; 89 thrice weekly) and the Safety population comprised 223 patients (111 and 112, respectively).

Outcomes and estimation
Primary efficacy endpoint

To show equivalence between once-weekly and thrice-weekly administration regarding the AUC, a two-sided 95% confidence interval for the difference in the AUC had to lie entirely within the equivalence range of -1.0 to +1.0 g/dL. A difference of maximal 1.0 g/dL was considered to be without clinical relevance.

Table 11: Time-adjusted area under the curve for haemoglobin during the EEP (ATP population)

Parameter	EpoTheta once weekly (N=99)	EpoTheta thrice weekly (N=89)
Time-adjusted AUC (g/dL) at baseline		
Mean ± SD	11.012 ± 0.902	11.039 ± 0.878
Time-adjusted AUC (g/dL) during the EEP		
Mean ± SD	10.728 ± 0.829	10.908 ± 0.960
	ANCOVA analysis	
Epoetin theta once weekly vs thrice weekly		
Mean difference	-0.17	
95% CI	-0.40, 0.06	
Parent study (XM01-04 – XM01-06)		
Mean difference	-0.03	
95% CI	-0.31, 0.25	
p value	0.8429	
Baseline Hb		
Effect estimate	0.45	
p value	< 0.0001	

The parent study from which patients entered the current study did not have a statistically significant effect on AUC-Hb ($p = 0.8429$); the mean difference of the AUC between patients coming from XM01-04 and XM01-06 (XM01- 04 minus XM01-06) is estimated to be –0.03 g/dL. Baseline Hb did have a statistically relevant effect on AUC-Hb ($p < 0.0001$), with an effect estimate of 0.45 g/dL, indicating a positive correlation between baseline Hb and AUC-Hb. Exploratory analyses of the interaction effects between treatment and baseline Hb and between treatment and parent study were performed and no important interactions were identified. Patients from each of the two parent studies were equally distributed between the once weekly and the thrice weekly regimen (data not shown).

The mean weekly Epoetin theta dose per kg of body weight in the ATP population during the efficacy evaluation period (weeks 25 to 36, 12 weeks) is presented in Table 12. To show equivalence between once-weekly and thrice-weekly administration regarding the total weekly dose a two- sided 95% confidence interval for the ratio had to lie entirely within the equivalence range of 0.8 to 1.25.

Table 12: Mean weekly Epoetin theta dose per kg of body weight during the EEP (ATP population)

Mean weekly dose	**EpoTheta once weekly (N=99)**	**EpoTheta thrice weekly (N=89)**
Baseline (IU/kgBW)		
Mean ± SD	35.706 ± 35.967	39.051 ± 30.265
Median	27.826	29.116
EEP (IU/kgBW)		
Mean ± SD	37.091 ± 35.904	49.539 ± 50.240
Median	27.397	29.508
	ANCOVA analysis	
Epoetin theta once weekly vs thrice weekly		
Mean ratio	0.7453	
95% CI	0.6145, 0.9038	

Results of the ANCOVA analysis showed that the mean (± SD) weekly Epoetin theta dose during the EEP were not equivalent, as the 95% CI of 0.6145, 0.9038 does not lie entirely within the predefined equivalence range of 0.8 to 1.25. Although two interaction analyses demonstrated that there is no interaction between parent study and treatment effect or between baseline dose and treatment effect, exploratory analyses showed that the parent study from which patients entered the current study had a statistically significant effect on the mean weekly Epoetin theta dose during the EEP ($p = 0.0005$). Patients from parent study XM01-04 had higher mean weekly doses at baseline, as starting doses of up to 120 IU/kgBW Epoetin theta thrice weekly had been used during the fixed-dose phase of the study. In addition, there was an imbalance between the once and thrice weekly treatment groups in patients from parent study XM01-04. Patients randomised to the once weekly regimen had a remarkably lower mean dose at study start than patients randomised to the thrice weekly regimen (data not shown). Variability of epoetin dose during the EEP was also associated with study XM01-04, because patients coming from study XM01-04 had received higher predetermined epoetin doses during the fixed-dose phase and they also had higher and less stable haemoglobin levels at study entry. Finally, variability was again almost exclusively attributed to patients randomised to the thrice weekly regimen (data not shown).
These differences had a statistically significant influence on the study results of the whole follow-up study despite the fact that the number of patients from parent study XM01-06 included into the follow-up study was twice as high as patients included from parent study XM01-04 (151 patients versus 72 patients, respectively, ITT population).
Results in the ITT population were in the same line as the ones for the ATP population in both co-primary endpoints and in subsequent exploratory analyses.

Secondary efficacy endpoints

Percentage of patients with dose changes during the EEP: In the ATP population, similar percentages of patients in the two treatment groups required doses changes (increases and decreases). Findings were similar for the ITT population (data not shown).
Rate of dose changes per patient during the EEP: The rate of dose change was the number of dose changes observed divided by the number of possible dose changes for each patient (including patients with no dose changes during the study). There was no relevant difference in the mean rate of dose change during the EEP for the once weekly and thrice weekly groups in both ATP and ITT population (data not shown).
Percentage of haemoglobin values within the target interval during the EEP: The target interval for Hb values in this study was defined as $I=[9.5, 12.0] \cap [\text{baseline}-1.0, \text{baseline}+1.0]$. The individual mean percentage of Hb values within the target interval during the EEP was similar in both groups. Values were higher in patients from parent study XM01-06 compared to XM01-04. Findings were similar for the ITT population (data not shown).

Percentage of patients with haemoglobin values within the therapeutic range during the EEP: In both groups, in the ATP population the percentage of patients with Hb values within the therapeutic range (9.5 to 12.0 g/dL) during the EEP was similar. The percentage of patients with Hb values within the therapeutic range during the EEP was in most cases higher in patients from parent study XM01-06 compared to patients from XM01-04. Findings were similar for the ITT population (data not shown).
Within-patient variance in haemoglobin levels during the EEP: Within patient standard deviation and variability in Hb levels during the EEP was similar for the once weekly and thrice weekly groups. Findings were similar for the ITT population (data not shown).
Measured values of haemoglobin: A slight decrease in Hb values was observed in both groups during the first 12 weeks on-study. The mean Hb at study entry was higher in patients from study XM01-04 compared to patients from study XM01-06 (12.2 vs 11.0 g/dL, respectively). Patients who entered this study from the parent study XM01-04 had higher Hb values at study entry due to the high starting doses of up to 120 IU/kgBW Epoetin theta thrice weekly. Furthermore, patients from study XM01-04 had achieved a haemoglobin response just prior to entering this study (inclusion requirement), which was defined as haemoglobin values > 11.0 g/dL on 2 consecutive measurements. It was thus expected that the Hb values in patients from study XM01-04 would decrease in study XM01-08 in order to reach the target Hb range of ≤ 12 g/dL. The time course for the ITT population was comparable to that for the ATP population.
Blood transfusions: Two (2.0%) Epoetin theta once weekly patients and two (2.2%) patients in the thrice weekly group required blood transfusions during the study (ATP population). Both of the Epoetin theta once weekly patients and no thrice weekly patient required blood transfusions during the EEP. All 4 patients who received blood transfusions had entered this study from parent study XM01-06. In the analysis of the ITT population, a total of 3 (2.7%) once weekly patients and 3 (2.7%) thrice weekly patients required blood transfusions during the study. Two Epoetin theta once weekly patients and no thrice weekly patient required blood transfusions during the EEP.

Study CSR XM01-09: Long-term safety Epoetin theta in chronic renal failure-associated anaemia patients receiving haemodialysis (intravenous route)

METHODS
This was a multinational, multicentre, open study in patients with chronic renal failure who had completed the "Correction phase study - intravenous" (XM01-05) according to protocol. It was conducted in 22 centres in 4 countries.

Study Participants
All eligible patients who completed study XM01-05 as per protocol and who had signed and dated written informed consent for this safety follow-up study could be included.

Treatments
Epoetin theta was initially administered intravenously three times a week. All patients enrolled were to receive Epoetin theta intravenously at the dose of their epoetin treatment (Epoetin theta or Epoetin beta) they were receiving at the end of study XM01-05. Dose adaptations were to be made if haemoglobin levels left the therapeutic range [9.5, 12.0 g/dL]. The dose could be adjusted based on haemoglobin levels. The investigator had the option to reduce the frequency of administration from three times a week to two times per week if four consecutive, weekly-measured haemoglobin values showed a stable haemoglobin level (difference ≤ 2 g/dL between minimal and maximal value).The study participation time for patients was 36 weeks. Thereafter the patient was observed for adverse events for 30 days after the last administration of study medication (Epoetin theta).

Objectives
To demonstrate long-term safety of intravenously administered Epoetin theta based on adverse events and immunogenicity. Secondary objective was to demonstrate long-term efficacy of intravenously administered Epoetin theta.

Outcomes/endpoints
Primary endpoint

The adverse events (AEs) were based on frequency and quality as well as frequency of study discontinuation due to AEs. Immunogenicity of Epoetin theta was evaluated by analysis of antibodies to Epoetin theta every 12 weeks during the whole study.

Secondary endpoints :
- time adjusted-area under the curve (AUC) for haemoglobin during the treatment period
- percentage of haemoglobin values per patient within the therapeutic range [9.5, 12.0 g/dL]
- percentage of patients with haemoglobin values within the therapeutic range
- within-patient variance in haemoglobin levels
- mean weekly Epoetin theta dose in IU/kgBW of patients within therapeutic range
- percentage of patients with dose changes (increase/decrease)
- number of dose changes per patient,
- number of patients with blood transfusions.

Sample size
As no formal statistical hypothesis testing had to be done in this study, no exact sample size calculation was given. In the protocol it was planned that about 125 patients could enter this study, but as 138 patients completed the study "Correction phase study – intravenous" (XM01- 05) according to protocol, all of these patients had the possibility to enter this study
Randomisation
Not applicable.

Blinding (masking)
This study was an open study. To make sure that the prior study XM01-05 was kept blinded, the drug administrator in study XM01-05 informed the investigator only about the initial Epoetin theta dose that has to be administered at visit 1 (which was also the final visit of study XM01-05).

Statistical methods
The intent-to-treat (ITT) population was the primary population for efficacy analyses and consisted of all included patients. The safety population was the population for the safety analyses and consisted of all patients of the ITT population who received at least 1 dose of study treatment. These 2 populations were identical because all included patients were treated at least once with study medication. The according to protocol population (ATP) consisted of all patients of the ITT population who were treated with study medication and who did not have any major protocol violations. The ATP population was the secondary population for efficacy analyses. Demographic and baseline characteristics, secondary efficacy endpoints, AEs and other safety endpoints were presented as descriptive statistics (continuous variables) or frequency tables (categorical variables).

RESULTS

Participant flow
Of 138 patients having completed study XM01-05, 124 patients were enrolled and treated in this study. 109 (87.9%) patients completed the study as planned; 15 patients prematurely discontinued the study. The primary reason for discontinuation was adverse event in 5 patients, renal transplantation in 4 patients, patient's request in 2 patients, loss to follow-up in 1 patient, other reasons in 3 patients. All patients who discontinued the study were followed up for AEs during a period of 30 days after their last visit, except for a single patient who was lost to follow-up.

Recruitment
First patient enrolled: 08 February 2006; last patient completed the study: 11 April 2007

Conduct of the study
The original protocol (issued on 12 July 2005) was modified by 1 global amendment that did not have a substantial impact on the study conduct. Some minor changes to the statistical analysis were made and some clarifications concerning the efficacy evaluation were made.

Numbers analysed
A total of 124 patients were enrolled and treated in this study, 99 patients previously treated with Epoetin theta and 25 previously treated with Epoetin beta.

Outcomes and estimation
Efficacy secondary endpoints

Time-adjusted area under the curve of haemoglobin: The mean (± SD) time-adjusted AUC of haemoglobin remained generally stable and within the therapeutic range [9.5, 12.0 g/dL] during the treatment period (data not shown).
Percentage of haemoglobin values per patient within the therapeutic range: The mean percentage of haemoglobin values per patient within the therapeutic range generally increased during the treatment period, thus reflecting patients with very high haemoglobin levels caused by the high starting doses of up to 120 IU/kgBW Epoetin theta tiw administered during the previous study XM01-05. Similar results were observed in the by country analysis (data not shown).
Mean weekly Epoetin theta dose per kg of body weight: The mean dose of Epoetin decreased after the initial phase of the treatment period and remained stable during the rest of the treatment period. Variability was high. The majority of patients received Epoetin theta three times weekly and the number of patients treated with less than thrice weekly administrations is very small for comparison of treatment regimens (data not shown).
The time course and the change from baseline of haemoglobin values: Mean haemoglobin values were high during the initial phase of the treatment period and then they decreased to a lower level and remained stable thereafter (data not shown).
Percentage of patients with dose changes: More patients had a tendency towards dose decrease than dose increase during the initial phase of the treatment period. The proportion of patients having a tendency towards dose decrease was similar to the proportion with a tendency to dose increase in subsequent treatment phases (data not shown).
Number of dose changes per patient (increases, decreases): The mean rate of dose changes, i.e. the number of dose changes observed divided by the number of possible dose changes for each patient, over the course of the study was low. The mean rate of dose changes was higher in the initial period compared to subsequent periods (data not shown).
Patients receiving blood transfusions: Blood transfusions were administered on a case-by-case basis at the discretion of the investigator. In total, 4 (3.2%) patients received blood transfusions over the course of the study. Single transfusions were received by 3 patients (in week 9, 17 and 26), whereas one patient received 2 transfusions in weeks 2 and 3.

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

No efficacy cross-trial analyses for renal anaemia were submitted.

- Clinical studies in special populations

No clinical studies for renal anaemia in special populations were submitted.

- Supportive study(ies)

No supportive clinical studies for renal anaemia were submitted.

Anemia in cancer patients

Three studies (all phase III) have been submitted in support for the use of Epoetin theta in the treatment of anaemia in cancer patients receiving chemotherapy. Study **XM01-21** was designed to assess the efficacy and safety of Epoetin theta compared to placebo and Epoetin beta in patients with solid tumours receiving platinum-containing therapy whereas study **XM01-22** included only patients with solid tumours or non-myeloid haematological tumours receiving non-platinum chemotherapy. Finally, study **XM01-23** included patients with multiple myeloma, low-grade non-Hodgkin's lymphoma or chronic lymphocytic leukaemia and with endogenous erythropoietin deficiency. However, this indication has since been removed from the list of possible oncological indications for

epoetins. This study therefore became supportive for the efficacy and safety assessment of Epoetin theta in anaemic cancer patients receiving chemotherapy. As this had become a supportive study and because recruitment was slow, recruitment stopped in December 2007. Table 13 gives an overview of the cancer anaemia studies:

Table 13: Phase II and III studies in cancer anaemia patients

Study & patient number	Type of study	Study design and type of control	Test products; Dosage regimen; Route of administration
XM01-21 N=223	Patients with solid tumours receiving platinum-containing chemotherapy and having a haemoglobin level ≤ 11 g/dL	Phase III , multinational, multicentre, randomised, placebo- and active-controlled, double-blind, parallel-group study	Epoetin theta:Starting dose s.c. 20,000 IU once weekly and two weekly placebo injections Adjustment up to 40,000 and to a maximum of 60,000 IU once weekly and two weekly placebo injections Placebo: s.c. thrice weekly Epoetin beta: Starting dose s.c.150 IU/kg_{BW} thrice weekly. Adjustment up to 300 IU/ kg_{BW} thrice weekly
XM01-22 N=186	Patients with solid tumours or non-myeloid haematological malignancies receiving nonplatinum chemotherapy and having a haemoglobin level of ≤ 11 g/dL.	Phase III multinational, multicentre, randomised, placebo-controlled, double-blind, parallel-group study	Epoetin theta or placebo: Starting dose s.c. 20,000 IU once weekly Adjustment up to 40,000 and to a maximum of 60,000 IU once weekly
XM01-23 N=177	Patients with low grade non-Hodgkin's lymphoma, chronic lymphocytic leukaemia or multiple myeloma with endogenous erythropoietin deficiency receiving anticancer therapy and having a haemoglobin level of ≤ 10 g/dL (amended to ≤ 11g/dL).	Phase III multinational, multicentre, randomised, placebo-controlled, double-blind, parallel-group study	Epoetin theta or placebo: Starting dose s.c. 20,000 IU once weekly Adjustment up to 40,000 and to a maximum of 60,000 IU once weekly

- Dose response study(ies)

No formal dose-response studies were performed. However, dose escalation occurred in all studies submitted in support of the cancer anemia indication (see *Treatments* under main studies below).

- **Main study(ies)**

Study XM01-21: Efficacy and safety of Epoetin theta in patients with solid tumours, receiving platinum-containing chemotherapy and having a haemoglobin level of ≤ 11 g/dL
Study XM01-22: Efficacy and safety of Epoetin theta in patients with solid tumours or non-myeloid haematological tumours, receiving nonplatinum chemotherapy and having a haemoglobin level of ≤ 11 g/dL
Study XM01-23: Efficacy and safety of Epoetin theta in patients with low grade Non-Hodgkin´s lymphoma, chronic lymphocytic leukaemia or multiple myeloma, with endogenous erythropoietin deficiency, receiving anticancer-therapy and having a haemoglobin level of ≤ 10 g/dL (amended to ≤ 11 g/dL)

METHODS
All three studies were multinational, multicentre, randomised, placebo-controlled, double-blind, parallel-group, Phase III studies. XM01-21 had in addition an active control. XM01-21 was conducted in 54 centres in 10 countries, XM01-22 was conducted in 72 centres in 10 countries and XM01-23 was conducted in 12 countries.

Study Participants

Patients were to have anaemia with a haemoglobin level of ≤ 11 g/dL at baseline. In XM01-21, patients were to have solid tumours and to be receiving platinum-containing chemotherapy. At least 3 (amended to 2) additional platinum-based chemotherapy cycles or 2 months of platinum based chemotherapy were to be scheduled at the time of inclusion. In XM01-22, patients were to have solid tumours or non-myeloid haematological malignancies and to be receiving non-platinum-containing chemotherapy. At least 3 (amended to 2) additional non-platinum-based chemotherapy cycles, or 2 months of non-platinum based chemotherapy were to be scheduled at the time of inclusion. In XM01-23, patients were to have low grade non-Hodgkin´s lymphoma (NHL), chronic lymphocytic leukaemia (CLL) or multiple myeloma (MM) and to be receiving anticancer therapy.
Main exclusion criteria were as follows: any erythropoietin given during the last 4 weeks or ongoing treatment with other erythropoietins, known presence of antibodies to epoetin, more than two red blood cell transfusions within 4 weeks before inclusion or any red blood cell transfusions within the last 2 weeks, life expectancy less than 6 months (this was amended to 3 months), chemotherapy during the last 7 days before study start, radiotherapy affecting bone marrow or surgery during the last 14 days before inclusion or planned during the conduct of the study. Additional exclusion criteria for XM01-21 included any other primary haematologic disorder that would cause anaemia (e.g. sickle cell anaemia) and malignancy of head and neck. For XM01-22, additional exclusion criteria included acute leukaemia (acute lymphocytic leukaemia or acute myeloid leukaemia), myeloid malignancies and malignancies of the head and neck. For XM01-23, additional exclusion criteria were anaemia of unknown origin, acute or chronic bleeding and any other malignancy (except for NHL, CLL or MM).

Treatments
Patients were randomised to receive Epoetin theta or placebo. In study XM01-21 an additional treatment group received Epoetin beta as an active comparator. The starting dose was 20,000 IU/week delivered as a subcutaneous injection. This dose was increased to 40,000 IU/week in patients who did not partially respond after 4 weeks of treatment, and again to 60,000 IU/week if the haemoglobin level did not reach the designated increase after the second 4-week period of treatment. Dose reductions could be made according to protocol-defined algorithms. Patients randomised to placebo were to receive injections of placebo according to the same schedule as patients randomised to Epoetin theta. Dose adjustments were to be implemented as for Epoetin theta. The duration of treatment was 12 weeks in studies XM01-21 and XM01-22 and it was 16 weeks in study XM01-23.
Patients randomised to Epoetin beta in XM01-21 received Epoetin beta subcutaneously according to the label, with a starting dose of 450 IU/kgBW per week to be injected in 3 equal aliquots. The weekly dose of Epoetin beta was not to exceed 900 IU/kgBW. Dose increases could only be made after 4 weeks of treatment. Dose reductions followed the protocol-defined algorithm.

Objectives
The primary objective was to demonstrate superiority of Epoetin theta versus placebo in terms of efficacy. The secondary objectives were to compare efficacy, safety and tolerability of Epoetin theta versus placebo (and Epoetin beta only in XM01-21).

Outcomes/endpoints
Primary endpoints
The primary efficacy endpoint is the number of patients with a complete haemoglobin response which was defined as an increase in the haemoglobin level of ≥ 2 g/dL from baseline without the benefit of a transfusion within the previous 4 weeks before laboratory sampling. Haemoglobin was measured weekly throughout the study at a central laboratory. The baseline haemoglobin level was defined as the mean of the values resulting from measurements at visits 1 and 2.

Secondary endpoints
– Number of patients having a partial haemoglobin response defined as an increase in haemoglobin levels of ≥ 1 g/dL from baseline without the benefit of a transfusion in the 4 weeks before laboratory sampling.
– Number of patients having a complete haemoglobin response with the initial dose, defined as an increase in haemoglobin levels of ≥ 2 g/dL from baseline without the benefit of a transfusion within the previous 4 weeks, and without requiring any dose adjustment (i.e. the dose remained at 20,000 IU/week in the case of Epoetin theta [or 450 IU /kgBW in the case of Epoetin beta]).

– Number of patients having a partial haemoglobin response with the initial dose, defined as an increase in haemoglobin levels of ≥ 1 g/dL from baseline without the benefit of a transfusion within the previous 4 weeks and without requiring any dose adjustment (i.e. the dose remained at 20,000 IU/week for Epoetin theta [or 450 IU /kgBW in the case of Epoetin beta]).
– Number of patients receiving one or more transfusions and number of blood units transfused.
– Time course of haemoglobin, haematocrit and reticulocytes. Change from baseline of haemoglobin, haematocrit and reticulocytes was analysed each week during the treatment period.
– Quality of life. Validated translations of the FACT-An questionnaire were used. The questionnaire was to be completed by the patient at visit 2 (baseline), at visit 8 (after 6 weeks, or visit 10 at 8 weeks specifically in the longer treatment duration study XM01-23) and at the end of study.
– Dose of Epoetin theta (and Epoetin beta, XM01-21) at time of partial or complete haemoglobin response.

Sample size
XM01-21: It was calculated that 58 patients per treatment group would give the study 90% power to detect a statistically significant difference assuming a response rate of 0.5 in the Epoetin theta group and 0.2 in the placebo group. It was planned to recruit 72 patients per group for a total of 216 patients because dropouts and protocol violations related to cancer therapy were anticipated to result in a slight decrease in the difference between treatment effects. Furthermore, 216 patients would provide a better base to evaluate the safety of the study treatments.
XM01-22: It was calculated that 80 patients per treatment group would give the study 90% power to detect a statistically significant difference assuming a response rate of 0.45 in the Epoetin theta group and 0.2 in the placebo group. It was planned to recruit 88 patients per group for a total of 176 patients because dropouts and protocol violations related to cancer therapy were anticipated to result in a slight decrease in the difference between treatment effects.
XM01-23: It was concluded, that when the sample size in the treatment groups are 97 (116), a $\chi 2$-test with a two-sided significance level $\alpha=0.05$ will have a power of 0.9 (0.95) to detect the difference between the proportions p(Epoetin theta)=0.6 and p(Placebo)=0.36.
Although 97 patients per treatment group (i.e. 194 patients in total) were considered enough to achieve a power of 0.9 for the confirmatory test of the main endpoint, it was recommended to include a total of 232 patients (i.e. 116 per treatment group) because possible dropouts and protocol violations related to the cancer therapy might result in a slight decrease of the treatment effect difference.

Randomisation
Patients were randomised in a 1:1 ratio to Epoetin theta or placebo (or a 1:1:1 ratio to Epoetin theta, Epoetin beta, or placebo specifically in study XM01-21). The randomisation was stratified by country except in study XM01-23 for which recruitment was slow and the study was stopped prematurely.

Blinding (masking)
All persons involved in the conduct of the study were blinded to the study medication. The investigator performed all assessments of the patient (e.g. evaluation of clinical observations, AEs) without knowledge of treatment. The syringes used for Epoetin theta and placebo were identical and the solutions of Epoetin theta and placebo were colourless and contained in identical vials; therefore they were indistinguishable from each other.
In study XM01-21, a true double-blinding was only technically feasible between Epoetin theta and placebo. Epoetin beta was provided as a solution in pre-filled syringes. The dosing scheme was also different between Epoetin theta and Epoetin beta.

Statistical methods
The intent-to-treat (ITT) population (full analysis set) was the primary population for efficacy analyses and consisted of all randomised patients. The safety population was the primary population for the safety analyses and consisted of all patients of the full analysis set who received at least 1 dose of study treatment. These 2 populations were identical because all randomised patients were treated at least once with study medication. The per protocol set (according to protocol population [ATP]) consisted of all patients of the full analysis set who were treated with study medication and who did not have any major protocol violations. The ATP was the secondary population for efficacy analyses.

For the primary efficacy endpoint a logistic regression was used to test the difference in the proportion of responders between Epoetin theta and placebo. The logistic regression model included the qualitative explanatory variable 'treatment' (and 'type of cancer' in studies XM01-22 and XM01-23), and the continuous variable 'haemoglobin at baseline'. Secondary efficacy endpoints: Treatment groups were compared using descriptive statistics. No adjustments of the significance level for multiple testing were made.

RESULTS

Participant flow
In XM01-21, 350 patients were screened, of which 223 were randomised. 76 patients were treated with Epoetin theta, 73 with Epoetin beta and 74 with placebo. 181 (81.2%) patients completed the study according to protocol. Of the 42 patients who prematurely discontinued study medication, 9 were in the Epoetin beta group, 12 in the Epoetin theta group and 21 in the placebo group. The most common reason for discontinuation was patient's request (21 patients) followed by other reasons (8 patients) and AEs (7 patients).
In XM01-22, 306 patients were screened, of which 186 were randomised. 95 patients received Epoetin theta and 91 patients received placebo. 161 (86.6%) patients completed the study according to protocol. Of the 25 patients who prematurely discontinued study medication, 15 were in the placebo group and 10 were in the Epoetin theta group. The most common reason for discontinuation was the occurrence of an AE (10 patients), followed by patient's request (9 patients) and lack of efficacy, patient lost to follow-up, and other reasons (2 patients each). All patients who discontinued the study were followed up for AEs during a period of 30 days after their last visit.
In XM01-23, 274 patients were screened and 177 patients were randomised. 90 patients were treated with Epoetin theta and 87 with placebo. 146 (82.5%) patients completed the study according to protocol. Of the 31 patients who prematurely discontinued study medication, 18 were in the placebo group and 13 were in the Epoetin theta group. The most common reasons for discontinuation were patient's request (12 patients, 7 in the placebo group and 5 in the Epoetin theta group) and the occurrence of an AE (8 patients, 4 in each group).

Recruitment
XM01-21: first patient enrolled: 10 October 2005; last patient completed the study: 23 July 2007
XM01-22: first patient enrolled: 17 November 2005; last patient completed the study: 11 May 2007
XM01-23: first patient enrolled: 17 November 2005; last patient completed the study: 21 April 2008

Conduct of the study
The original protocol (issued on 1 April 2005) was amended by 4 global amendments and 1 local amendment. These amendments did not adversely affect the conduct of the study. Of most importance, amendment 2 concerned the upper Hb target limit and amendment 4 concerned the inclusion criteria. The original protocol specified that dose adjustment and withholding of treatment was to occur if total haemoglobin exceeded 14 g/dL. Based on EMEA CHMP recommendations, amendment 2 reduced the threshold for dose adjustment or withholding of treatment to 13 g/dL. Furthermore, the original protocol specified treatment interruption for exceeding 14 g/dL, whereas the amendment indicated a 50% reduction of the last dose for exceeding the new threshold of 13 g/dL, followed by interruption of treatment if required. Under amendment 4, patients with ECOG performance status 3 were also permitted to be included. Patients with a life expectancy less than 3 months (formerly 6 months) were not permitted to be included. In studies XM01-21 and XM01-22, inclusion and exclusion criteria were also amended to permit the participation of patients with at least two (formerly three) additional (non)platinum-based chemotherapy cycles or two months of (non)platinum-based chemotherapy planned. In study XM01-23, the inclusion and exclusion criteria were amended to change the upper limit of the baseline Hb value from 10 to 11 g/dL.

Baseline data
There were no important imbalances in demographic characteristics, nature of primary malignancy and previous anticancer therapy between the treatment groups in the three studies.
In study XM01-21, ovarian epithelial cancer was the primary malignant disease in 55 (24.7%) patients. The next most common malignant diseases were gastric cancer in 18 (8.1%) patients, lung

squamous cell carcinoma stage unspecified in 16 (7.2%) patients and breast cancer and ovarian epithelial cancer metastatic in 15 (6.7%) patients each.
In study XM01-22, haematological malignancies were the primary malignant disease in 102 (54.8%) patients. The most common haematological malignancies were multiple myeloma (39 patients) and Non-Hodgkin's lymphoma (31 patients). Solid tumours were the primary malignant disease in 84 (45.2%) patients. The most common solid tumour types were breast cancer (33 patients) and gastric cancer (9 patients).
In study XM01-23, the primary malignant disease was multiple myeloma in 139 (78.5%) patients, low-grade NHL in 19 (10.7%) patients, and chronic lymphocytic leukaemia in 19 (10.7%) patients.

Numbers analysed
In study XM01-21, the ITT population comprised 223 patients (76 for Epoetin theta, 73 for Epoetin beta and 74 for placebo), the ATP population 196 patients and the safety population (SP) 223 patients.
In study XM01-22, the ITT population comprised 186 patients (95 for Epoetin theta and 91 for placebo), the ATP population 171 patients (88 for Epoetin theta and 83 for placebo) and the SP 186 patients.
In study XM01-23, the ITT population comprised 177 patients (90 for Epoetin theta and 87 for placebo), the ATP population 157 patients (81 for Epoetin theta and 76 for placebo) and the SP 177 patients.
In all studies, ITT and SP were identical as all patients in the ITT received at least one dose of the study medication. Patients with major protocol violations were in each study excluded from the ITT to yield the ATP.

Outcomes and estimation

Primary efficacy endpoint
In all studies, a higher proportion of patients in the Epoetin theta group than in the placebo group had a complete haemoglobin response without blood transfusion and differences between the treatment groups were statistically significant ($p < 0.0001$). Baseline haemoglobin levels had no statistically significant effects on response rate and neither had the tumour type in studies XM01-22 and XM01-23.
Table 14: Study XM01-21-Complete Hb response without blood transfusion within the previous 4 weeks (ITT)

Characteristic	**Placebo (N=74)**	**Epoetin theta (N=76)**
Non-responders	59 (79.7%)	26 (34.2%)
Responders	15 (20.3%)	50 (65.8%)
Logistic regression		
Treatment (Epoetin theta vs placebo)		
p value	**< 0.0001**	
Odds ratio (95% CI)	**8.063 (3.886, 17.626)**	
Baseline Hb (1 unit of change)		
p value	**0.1408**	
Odds ratio (95% CI)	**0.802 (0.596, 1.074)**	

In study XM01-21, the proportion of patients in the Epoetin beta group who achieved a complete haemoglobin response without blood transfusion was 71.2%.

Table 15: Study XM01-22-*Complete Hb response without blood transfusion within the previous 4 weeks (ITT)*

Characteristic	**Placebo (N=91)**	**Epoetin theta (N=95)**
Non-responders	68 (74.7%)	26 (27.4%)
Responders	23 (25.3%)	69 (72.6%)
Logistic regression		

Treatment (Epoetin theta vs placebo)	
p value	**< 0.0001**
Odds ratio (95% CI)	**7.944 (4.182, 15.632)**
Type of cancer (haemato. vs solid)	
p value	0.7058
Odds ratio (95% CI)	0.877 (0.443, 1.734)
Baseline Hb (1 unit of change)	
p value	0.3619
Odds ratio (95% CI)	0.888 (0.684, 1.146)

Table 16: Study XM01-23-*Complete Hb response without blood transfusion within the previous 4 weeks (ITT)*

Characteristic	**Placebo (N=87)**	**Epoetin theta (N=90)**
Non-responders	64 (73.6%)	32 (35.6%)
Responders	23 (26.4%)	58 (64.4%)
Logistic regression		
Treatment (Epoetin theta vs placebo)		
p value	**< 0.0001**	
Odds ratio (95% CI)	**5.277 (2.736. 10.532)**	
Type of cancer (Low grade NHL vs CLL vs MM)		
p value	0.5045	
Baseline Hb (1 unit of change)		
p value	0.0757	
Odds ratio (95% CI)	1.291 (0.979, 1.725)	

In studies XM01-22 and XM01-23, stratified analyses according to malignancy type showed that the overall difference between Epoetin theta vs placebo and placebo was statistically significant. Only within two strata with low patient numbers (CLL and NHL) the difference did not reach significance but the results across strata are consistent as in all strata Epoetin theta vs placebo is superior to placebo.

Table 17: Studies XM01-22 and XM01-23-*Complete Hb response without blood transfusion within the previous 4 weeks, by type of cancer (ITT)*

Stratum (Tumour)	**P lacebo**		**Epoetin theta**		**Odds ratio: Epoetin theta vs Placebo**
	N total	**Responder rate**	**N total**	**Responder rate**	**Chi2 p-value**
XM01-22 - CLL	7	0.4286	6	1.0000	0.0261
XM01-23 - CLL	8	0.3750	11	0.4545	0.7288
XM01-22 - NHL	16	0.5000	15	0.6000	0.5761
XM01-23 - NHL	14	0.4286	5	0.6000	0.5099
XM01-22 - MM	18	0.1111	21	0.6667	0.0004
XM01-23 - MM	65	0.2154	74	0.6757	<.0001

Secondary efficacy endpoints

Number of patients having a partial haemoglobin response/ a complete haemoglobin response with the initial dose/ a partial haemoglobin response with the initial dose: A higher proportion of

patients in the Epoetin theta groups than in the placebo groups achieved partial haemoglobin responses with or without dose adjustments and without blood transfusion or complete haemoglobin responses without dose adjustments and without blood transfusion. Differences between treatment groups were statistically significant. Baseline haemoglobin levels had no statistically significant effects on response rate. In study XM01-21, similar results were found for Epoetin beta compared to placebo, while no differences we detected between Epoetin theta and Epoetin beta. In studies XM01-22 and XM01-23, type of cancer had no statistically significant effect on response rate (data not shown).

Number of patients receiving blood transfusions and number of blood units transfused: A higher proportion of patients in the placebo groups than in the Epoetin theta groups received blood transfusions after randomisation. The difference between the treatment groups was statistically significant (except in study XM01-23 in which significance was not reached). Baseline haemoglobin levels had a statistically significant effect on the rate of blood transfusion. In study XM01-21, the proportion of patients receiving blood transfusions in the Epoetin beta group was lower than in the placebo group; however this difference was not statistically significant. Neither was the difference in the proportion of patients receiving blood transfusions between the Epoetin beta and Epoetin theta groups. In studies XM01-22 and XM01-23, the type of cancer had no statistically significant effect on the rate of blood transfusion (data not shown).

Time course of haemoglobin, haematocrit and reticulocytes

Haemoglobin: Baseline haemoglobin values were similar between treatment groups. Over the course of the studies mean haemoglobin levels rose steadily in the Epoetin theta groups. In the placebo groups, there were no consistent changes in haemoglobin levels. Treatment with Epoetin theta resulted in statistically significant increases in mean haemoglobin levels compared to placebo. Similar results were observed for Epoetin beta in study XM01-21. The difference between treatment with Epoetin beta and Epoetin theta in the same study was not statistically significant (data not shown).

Haematocrit: Overall, the changes of haematocrit values were very similar to the changes of haemoglobin values over time (data not shown).

Rticulocytes: Absolute reticulocyte values showed a high degree of variability in all 3 treatment groups and at all timepoints and were thus difficult to interpret (data not shown).

Quality of life: In study XM01-21, all FACT scores and subscores but one showed higher mean changes from baseline in the Epoetin theta group and Epoetin beta group compared to placebo, but the differences were not statistically significant. Similar mean results were observed for all FACT scores and subscores between Epoetin theta and placebo in study XM01-22. A subsequent analysis comparing FACT scores before and after treatment in studies XM01-21 and XM01-22 showed that the Fact-F (fatigue) score had changed significantly in the course of the treatment in the Epoetin theta and Epoetin beta group, but not in the placebo group. In study XM01-23, FACT scores and subscores showed lower mean changes from baseline in the Epoetin theta group compared to placebo and some of the differences were statistically significant; however, baseline values for all scores and subscores were markedly higher in the Epoetin theta group than in the placebo group in this study (data not shown).

Dose of Epoetin theta or Epoetin beta at the time of partial or complete haemoglobin response:

Table 18: Mean±SD of Epoetin theta (and Epoetin beta) dose at the time of response

Study	Type of response	Epoetin theta (IU)	Epoetin beta (IU)
XM01-21	Complete response	30,000.0±12,936.3	42,230.8±23,455.9
	Partial response	27,826.1±12,469.9	39,827.3±21,831.5
XM01-22	Complete response	27,681.2±14,260.7	n/a
	Partial response	24,871.8±10,659.3	n/a
XM01-23	Complete response	30,517.2±15,151.0	n/a
	Partial response	25,144.9±11,179.4	n/a

For study XM01-21, it should be noted that the mean dose at baseline was higher for Epoetin beta (31050 IU) compared to Epoetin theta (20000 IU).

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

A cross-study meta-analysis of Quality of Life and blood transfusion data was submitted for all three cancer anaemia studies (XM01-21, XM01-22 and XM01-23). For the Quality of Life endpoint, in

addition to comparisons between treatment groups, changes from baseline within each treatment group were examined. The results of this meta-analysis were in line with those of the individual studies (see above, data not shown).

- Clinical studies in special populations

No clinical studies in special populations were submitted for cancer anaemia.

- Supportive study(ies)

Study XM01-23 was stopped prematurely due to slow recruitment and because the specific indication targeted with this study was removed from the list of possible oncological indications for epoetins. Study XM01-23 is therefore considered supportive although described together with the main cancer anaemia studies due to similar design and results.

- Discussion on clinical efficacy

Efficacy results from eight double blind (except one study), randomised, multicentre phase II (2) or phase III (6) studies and from a single arm, multicentre phase III study were provided.

Renal anaemia

Study **XM01-05** was a correction phase study designed to demonstrate the efficacy of Epoetin theta with respect to the dose-dependent average increase of haemoglobin per week within the fixed-dose phase in CRF patients. Study **XM01-07** was a maintenance phase study designed to demonstrate the non-inferiority of Epoetin theta compared with Epoetin beta in terms of efficacy. All patients received their treatments via the intravenous route. The correction phase study **XM01-04** and the maintenance phase **XM01-06** study enrolled CRF patients not yet under dialysis and had similar design and objectives as studies XM01-05 and XM01-07, respectively. All patients received their treatments via the subcutaneous route. The primary objective of follow-up study **XM01-08** was to demonstrate therapeutic equivalence between once-weekly s.c. administration of Epoetin theta and three times-weekly s.c. administration of Epoetin theta. Finally, follow-up study **XM01-09** was primarily a safety study and only included secondary efficacy endpoints.

Separate studies were submitted to demonstrate the efficacy and safety of epoetin theta using the subcutaneous and the intravenous routes of administration. The correction phase, maintenance-phase and safety follow-up components of the clinical trial were considered separately for the subcutaneous and intravenous routes of administration.

The primary objective of correction phase studies was to demonstrate the efficacy of Epoetin theta with respect to the dose-dependent average increase of haemoglobin per week within the fixed-dose phase. The aim in both treatment phases was to increase haemoglobin levels to between 11.0 and 12 g/dL. Results showed that the mean weekly increase of haemoglobin in the highest Epoetin theta dose group was significantly higher than in the lowest Epoetin theta dose group. The primary objective of both studies was therefore met.

In both maintenance phase studies, the primary efficacy endpoint was the same, namely: “change of haemoglobin from baseline to the end of treatment. Although the chosen delta of 1.0 g/dL was very permissive, results indicated that mean Hb values were similar in both treatment groups at baseline and during the evaluation period and the ANCOVA comparison of change in Hb from baseline to treatment end showed much tighter control of Hb values than the chosen delta permitted. The difference between groups was < 1.0 g/dL and was not statistically significant. Consequently, the primary aim of both studies was met and Epoetin theta was considered as non-inferior to Epoetin beta.

The primary objective of follow-up study XM01-08 was to demonstrate therapeutic equivalence between once-weekly administration of Epoetin theta and three times-weekly administration of Epoetin theta. Patients treated for renal anaemia in studies XM01-04 and XM01-06 with Epoetin theta or Epoetin beta were eligible. The primary endpoint was the time-adjusted area under the curve for haemoglobin (AUC-Hb) during the efficacy evaluation period and the co-primary endpoint was the mean weekly Epoetin theta dose per kg of body weight during the same period. The primary endpoint was met; the equivalence range of -1.0 to +1.0 g/dL was again considered as very permissive, but the observed difference fell well within this margin, hence it was acceptable. The co-primary endpoint was not met due to reasons delineated in exploratory analyses described under the study results.

Nevertheless, the SPC contains a statement that if the frequency of administration is changed, haemoglobin level should be monitored closely and dose adjustments may be necessary.
Although overall a safety study, XM01-09 included secondary efficacy endpoints. Patients treated for renal anaemia in study XM01-05 were enrolled and results showed that treatment with Epoetin theta is able to maintain Hb levels long-term within the target range.

Anemia in cancer patients
In cancer studies, epoetin theta was administered via the subcutaneous route. All three studies had parallel designs. Study **XM01-21** was designed to assess the efficacy and safety of Epoetin theta compared to placebo and Epoetin beta in patients with solid tumours receiving platinum-containing therapy. Study **XM01-22** included patients with solid tumours or non-myeloid haematological tumours receiving non-platinum chemotherapy and study **XM01-23** included patients on anticancer chemotherapy with low grade Non-Hodgkin´s lymphoma, chronic lymphocytic leukaemia or multiple myeloma and with endogenous erythropoietin deficiency. In studies XM01-22 and XM01-23, Epoetin theta was compared to placebo only.
Results in all three studies indicated that a higher proportion of patients in the Epoetin theta group than in the placebo group had a complete haemoglobin response without blood transfusion. The difference between the treatment groups was statistically significant. In studies XM01-22 and XM01-23, stratified analyses according to malignancy type showed that the overall difference between Epoetin theta and placebo was statistically significant. Only within two strata with low patient numbers (CLL and NHL) the difference did not reach significance but the results across strata are consistent as in all strata Epoetin theta is superior to placebo. In study XM01-21, the difference between the epoetin theta and placebo group in the number of blood transfusions was also statistically significant. This difference was however not statistically significant between the epoetin beta and the placebo group.

The original applied indication included a claim for “Increasing the yield of autologous blood from patients in a predonation programme”. No studies were submitted for this indication. The CHMP raised a major objection, as the product had been accompanied by a complete and independent application and not by an application for a ‘similar biological medicinal product’ (according to Article 10 (4), Directive 2001/83/EC), as initially intended. Therefore, the CHMP considered that no extrapolation from the indications of other authorised epoetins was acceptable. The Applicant subsequently withdrew this indication from the list of claimed indications.

No studies in paediatric patients were submitted. As a result, the CHMP restricted the indications to the treatment of adults only.

Clinical safety

- Patient exposure

The evaluation of safety focuses on findings from 9 completed phase II/III studies (XM01-04, 05, 06, 07, 08, 09, 21, 22, 23). Supportive data come from 6 completed phase I studies (XM01-01, 10, 11, 12, 20, 24). The studies are listed in tables 5, 6 and 13.
The evaluations for the phase II/III studies were performed on the respective safety populations, which were defined as patients treated at least once with the randomised study medication in the controlled phase II/III studies (XM01-04, 05, 06, 07, 21, 22, 23) and as patients treated at least once with Epoetin theta in the renal anaemia follow-up studies (XM01-09 and 08). In the follow-up studies XM01-08 (for XM01-04 and 06) and XM01-09 (for XM01-05) all patients received Epoetin theta, irrespective of whether they received Epoetin theta or Epoetin beta in the predecessor study.
In the phase I studies no analysis populations were defined and all patients included in the individual studies were included.
The types and numbers of patients as well as the type of medications administered in all phase I/II/III studies are listed in the following table 19.

Table 19: Overall exposure in completed clinical studies

Study category	Study number	Number of patients		
		EpoTheta	EpoB	Placebo
Controlled phase II/III RA studies				
Intravenous	XM01-05	121	29	–
Intravenous	XM01-07	180	90	–
Subcutaneous	XM01-04	112	21	–
Subcutaneous	XM01-06	193	95	–
Sub-total		*606*	*235*	–
Controlled phase III CT studies				
Subcutaneous	XM01-21	76	73	74
Subcutaneous	XM01-22	95	–	91
Subcutaneous	XM01-23	90	–	87
Sub-total		*261*	*73*	*252*
Total for controlled phase II/III studies		**867**	**308**	**252**
Follow-up phase III RA study (for XM01-05)				
Intravenous	XM01-09	25/99 (EpoB / EpoTheta in XM01-05) *	–	–
Sub-total		*25*	–	–
Follow-up phase III RA study (for XM01-04 & XM01-06)				
Subcutaneous	XM01-08	80/209 (EpoB / EpoTheta in XM01-04 & XM01-06)**	–	–
Sub-total		*80*	–	–
Total for controlled phase II/III studies and follow-up studies		**972***	**308***	**252**
Phase I studies				
End-stage renal disease treated by haemodialysis, subcutaneous + intravenous	XM01-01	18	–	–
End-stage renal disease treated by haemodialysis, intravenous	XM01-11	14	–	–
Chronic renal failure not yet receiving dialysis, subcutaneous	XM01-10	14	–	–
CT, subcutaneous	XM01-24	14	–	–
Healthy subjects, subcutaneous	XM01-12	18	–	–
Healthy subjects, subcutaneous	XM01-20	28	–	12
Total for phase I studies		**106**	**–**	**12**
OVERALL TOTAL *		**1078*/****	**308*/****	**264**

* 124 patients who completed study XM01-05 (99 treated with Epoetin theta, 25 with Epoetin beta) all received Epoetin theta in study XM01-09. The 25 patients who switched from Epoetin beta to Epoetin theta are counted twice in these

totals, i.e. once in the overall total for Epoetin beta and once in the overall total for Epoetin theta. However, patients who were continuously treated with Epoetin theta in both studies are counted only once in the totals for Epoetin theta.

** 289 patients who completed study XM01-04 or XM01-06 (209 treated with Epoetin theta, 80 with Epoetin beta; 95 from study XM01-04, 194 from study XM01-06) all received Epoetin theta in study XM01-08. The 80 patients who switched from Epoetin beta to Epoetin theta are counted twice in these totals, i.e. once in the overall total for Epoetin beta and once in the overall total for Epoetin theta. However, patients who were continuously treated with Epoetin theta in both studies are counted only once in the totals for Epoetin theta.

NA=not applicable

The duration of exposure in all phase I/II/III studies is listed in the following table 20.

Table 20: Overall exposure duration in completed clinical studies

Duration of exposure (days)	Persons	Person years
1 to 30	27	1.03
31 to 90	245	48.86
91 to 180	328	133.16
181 to 270	136	90.57
271 to 360	95	84.72
> 360	141	158.86

The number and size of administered doses of Epoetin theta and Epoetin beta in the controlled phase II/III studies is listed in the following table 21. Further exposure to Epoetin theta in patients continuing into the follow-up renal anaemia studies XM01-08 and XM01-09 is not shown.

Table 21: Dosing exposure in controlled phase II/III studies

Indication and studies	**Renal anaemia studies (XM01-04, -05, -06, -07)**		**Cancer treatment anaemia studies (XM01-21, -22, -23)**		
Treatment type	**EpoTheta N=606**	**EpoB N=235**	**EpoTheta N=261**	**Placebo N=252**	**EpoB N=73**
Number of doses					
Total	23823	9324	3132	2222	2201
Mean, no./patient	39.3	39.7	12.0	12.5	30.2
SD, no./patient	19.0	19.1	3.1	3.6	8.4
Median, no.	35.5	41	12	12	35
Range	1 to 73	1 to 72	1 to 16	1 to16	3 to 36
Weekly dose, IU/kg_{BW}					
Mean	108.7	72.1	422.4	-	535.7
SD	89.9	55.8	172.3	-	159.7
Median	82.2	58.0	401.6	-	564.5
Range	8.3 to 490.2	8.8 to 382.1	139.7 to 1014.1	-	257.8 to 981.5

Baseline demographic data by study treatment are listed for the pooled controlled phase II/III studies in the following table 22.

Table 22: Basic demographic characteristics in controlled phase II/III studies

Indication and studies	**Renal anaemia studies (XM01-04, -05, -06, -07)**		**Cancer treatment anaemia studies (XM01-21, -22, -23)**		
Treatment type	**EpoTheta N=606**	**EpoB N=235**	**EpoTheta N=261**	**Placebo N=252**	**EpoB* N=73**
Age					

Indication and studies	Renal anaemia studies (XM01-04, -05, -06, -07)		Cancer treatment anaemia studies (XM01-21, -22, -23)		
Treatment type	EpoTheta N=606	EpoB N=235	EpoTheta N=261	Placebo N=252	EpoB* N=73
Mean, yrs	61.3	61.7	58.1	58.5	57.3
SD, yrs	14.0	13.8	12.5	12.6	10.5
≤ 64 yrs, n (%)	326 (53.8)	127 (54.0)	170 (65.1)	154 (61.1)	53 (72.6)
65-74 yrs, n (%)	172 (28.4)	59 (25.1)	75 (28.7)	77 (30.6)	16 (21.9)
≥ 75 yrs, n (%)	108 (17.8)	49 (20.9)	16 (6.1)	21 (8.3)	4 (5.5)
Gender					
Male, n (%)	313 (51.7)	140 (59.6)	109 (41.8)	91 (36.1)	22 (30.1)
Female, n (%)	293 (48.3)	95 (40.4)	152 (58.2)	161 (63.9)	51 (69.9)
Weight, kg					
Mean	71.2	72.8	67.0	66.1	69.0
SD	14.5	14.9	14.4	13.2	14.6
Race					
White, n (%)	603 (99.5)	233 (99.1)	226 (86.6)	219 (86.9)	66 (90.4)
Other, n (%)	3 (0.5)	2 (0.9)	35 (13.4)	33 (13.1)	7 (9.6)

- Adverse events

Analyses of all types of adverse events were performed separately for renal anaemia (RA) and cancer therapy anaemia (CT) studies. Within the RA group of studies, the controlled (XM01-04, -05, -06 and -07) studies were analysed separately from the follow-up (XM01-08 and -09) studies. Within the same group additional analyses of adverse events comparing correction vs maintenance phase studies and subcutaneous vs intravenous Epoetin theta administration were conducted.

Table 23: Overall frequencies of TEAEs, TEADRs, severe TEAEs, and severe TEADRs in all controlled phase II/III studies

	Renal anaemia studies (XM01-04, -05, -06, -07)				Cancer treatment anaemia studies (XM01-21, -22, -23)					
Category	**EpoTheta N=606**		**EpoB N=235**		**EpoTheta N=261**		**Placebo N=252**		**EpoB N=73**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
TEAEs	421	69.5	155	66.0	200	76.6	190	75.4	63	86.3
TEADRs	139	22.9	43	18.3	60	23.0	50	19.8	16	21.9
Severe TEAEs	57	9.4	24	10.2	44	16.9	45	17.9	13	17.8
Severe TEADRs	14	2.3	3	1.3	3	1.1	2	0.8	1	1.4

The majority of the TEAEs in all phase II/III studies were assessed as unrelated to the study medication.

The most common adverse events across all renal anaemia patients treated with Epoetin theta in the 4 controlled studies were hypertension (10.2%), headache (8.7%), muscle spasms (6.4%) and chronic renal failure (5.3%). These adverse events are also most common under treatment with Epoetin beta in these studies. There are no clinically relevant differences between the TEAE profiles of the Epoetin theta groups and the Epoetin beta groups across or within the studies. In the correction phase studies XM01-04 and 05, the proportion of patients with TEAEs was higher for patients treated with Epoetin theta compared to those treated with Epoetin beta (70.4 vs 56.0%). In the maintenance phase studies XM01-06 and 07, the percentages of patients who experienced TEAEs were similar for the two

treatment groups: Epoetin theta 257 (68.9%) patients, Epoetin beta 127 (68.6 %). Some differences were found in event frequencies between the studies with intravenous administration of study drug (XM01-05, 07) and those with subcutaneous administration (XM01-04, 06). The frequencies of adverse events and serious adverse events and discontinuations were somewhat higher in the i.v. treated patients.
The most common adverse events in the cancer therapy studies were asthenia (17.6%), neutropenia (16.9%), nausea (14.9%) and leukopenia (11.1%). The frequency of TEAEs in the Epoetin theta and placebo group was similar (76.6% vs 75.4 %, respectively), while the frequency of TEAEs in the Epoetin beta group was slightly higher (86.3%).

Most frequent treatment emergent adverse drug reactions (TEADRs) in controlled phase II/III studies.
In renal anaemia studies, TEADRs were reported in 139 (22.9%) patients treated with Epoetin theta and 43 (18.3%) patients treated with Epoetin beta.

Table 24: Most frequent SOCs for TEADRs in controlled phase III RA studies XM01-04, -05, -06 and -07

MedDRA SOC	EpoTheta N=606		EpoB N=235	
	n	%	n	%
Vascular disorders	48	7.9	9	3.8
Investigations	25	4.1	9	3.8
Injury, poisoning and procedural complications	21	3.5	9	3.8
Nervous system disorders	21	3.5	8	3.4
General disorders and administration site conditions	20	3.3	8	3.4
Gastrointestinal disorders	17	2.8	2	0.9
Musculoskeletal and connective tissue disorders	7	1.2	6	2.6
Infections and infestations	5	0.8	5	2.1

NOTE: This table contains all SOCs with TEADR frequencies ≥ 2% in either treatment group. SOCs are sorted by decreasing frequency in the Epoetin theta group.

Frequencies of SOCs were low and comparable between treatment groups except for the SOC vascular disorders that was more common in the Epoetin theta group (difference ≥ 3%).
Frequencies of TEADRs were also low and comparable between treatment groups. Hypertension was the only TEADR that occurred in ≥ 3% of patients in either treatment group and was more common in the Epoetin theta group than the Epoetin beta group: 41 (6.8%) Epoetin theta patients vs 7 (3.0%) Epoetin beta patients. Other TEADRs that occurred in ≥ 1% patients of the Epoetin theta group were headache 12 (2.0%) vs 5 (2.1%), arteriovenous fistula thrombosis 9 (1.5%) vs 2 (0.9%), and blood pressure increased 6 (1.0%) vs 4 (1.7%). Hypertension and headache are known side effects of epoetins. Arteriovenous fistula thrombosis is a common complication in patients undergoing haemodialysis and was only observed in the studies with intravenous administration of study drugs.
In cancer treatment anaemia studies, TEADRs were more common in patients treated with Epoetin theta than those treated with placebo: 60 (23.0%) vs 50 (19.8%).

Table 25: Most frequent SOCs for TEADRs in controlled phase III CT studies XM01-21, 22 and 23

MedDRA SOC	EpoTheta N=261		Placebo N=252		EpoB N=73	
	n	%	n	%	n	%
General disorders and administration site conditions	26	10.0	16	6.3	4	5.5
Gastrointestinal disorders	18	6.9	19	7.5	11	15.1
Nervous system disorders	11	4.2	8	3.2	6	8.2
Vascular disorders	8	3.1	6	2.4	4	5.5
Musculoskeletal and connective tissue disorders	7	2.7	3	1.2	2	2.7
Infections and infestation	4	1.5	5	2.0	0	-
Investigations	3	1.1	6	2.4	3	4.1
NOTE: This table contains all SOCs (preferred terms) with frequencies ≥ 2% (≥ 3%) in the Epoetin theta or placebo group. SOCs and preferred terms within each SOC are sorted alphabetically.						

Frequencies of TEADRs in most SOCs were low and comparable between treatment groups. General disorders and administration site conditions were more common (difference ≥ 3%) in the Epoetin theta group than the placebo group (10.0 vs 6.3%) and this was largely due to an imbalance in asthenia (Epoetin theta 6.5%, placebo 3.6%).
The most common TEADRs in the Epoetin theta group were asthenia (6.5%), nausea (4.6%), headache (3.4%) and vomiting (3.1%). The most common TEADRs in the placebo group were nausea (5.6%) and asthenia (3.6%).

Severe TEAEs and TEADRs in controlled phase II/III studies. The majority of TEAEs were assessed as mild or moderate. In renal anaemia studies, severe TEAEs occurred in 57 (9.4%) patients treated with Epoetin theta and 24 (10.2%) patients treated with Epoetin beta. Frequencies in all SOCs were low and comparable between treatment groups.

Table 26: Most frequent SOCs for severe TEAEs in controlled phase III RA studies XM01-04, -05, -06 and -07

MedDRA SOC	EpoTheta N=606		EpoB N=235	
	n	%	n	%
Cardiac disorders	19	3.1	5	2.1
Renal and urinary disorders	15	2.5	6	2.6
Metabolism and nutrition disorders	6	1.0	1	0.4
Nervous system disorders	6	1.0	4	1.7
Infections and infestations	5	0.8	3	1.3
General disorders and administration site conditions	3	0.5	4	1.7
NOTE: This table contains all SOCs with severe TEAE frequencies ≥ 1% in either treatment group. SOCs are sorted by decreasing frequency in the Epoetin theta group.				

The only severe TEAE that occurred in ≥ 1% of patients of the Epoetin theta group was “worsening” of chronic renal failure in 11 (1.8%) Epoetin theta patients vs 5 (2.1%) Epoetin beta patients. Severe TEADRs were reported in 14 (2.3%) Epoetin theta patients and 3 (1.3%) Epoetin beta patients.

In cancer treatment anaemia studies, severe TEAEs occurred in 44 (16.9%) patients treated with Epoetin theta and 45 (17.9%) patients treated with Epoetin beta. Frequencies in most SOCs were low and comparable between treatment groups.

Table 27: Most frequent SOCs for severe TEAEs in controlled phase III CT studies XM01-21, 22 and 23

MedDRA SOC	EpoTheta N=261		Placebo N=252		EpoB N=73	
	n	%	n	%	n	%
Blood and lymphatic system disorders	21	8.0	15	6.0	7	9.6
Neoplasms benign, malignant, unspec.	10	3.8	11	4.4	1	1.4
Gastrointestinal disorders	6	2.3	9	3.6	0	-
Infections and infestations	8	3.1	6	2.4	0	-
General disorders and administration site conditions	5	1.9	15	6.0	2	2.7
Respiratory, thoracic and mediastinal disorders	4	1.5	6	2.4	0	-
NOTE: This table contains all SOCs (preferred terms) with frequencies ≥ 2% (≥ 3%) in the Epoetin theta or placebo group.						

Severe TEADRs were reported in 3 Epoetin theta patients, 2 placebo patients, and 1 Epoetin beta patient.

Adverse events in follow-up RA studies XM01-09 and -08

In study XM01-09, the most common TEAEs were headache (34.7%), muscle spasms (30.6%), hypotension (19.4%), abdominal pain (17.7%), procedural hypotension (16.9%), hypertension (11.3%), and back pain (10.5%). In XM01-08, these were hypertension (15.9%) and chronic renal failure (14.9%). The incidence of TEAEs was higher in the follow-up studies XM01-08 and -09 than in the predecessor studies XM01-04/06 and -05, respectively. The majority of the TEAEs were assessed as unrelated to the study medication in both studies. In study XM01-08, the adverse event profile was comparable in once-weekly and thrice-weekly treated patients.

In study XM01-09, the most common TEADRs were headache in 6 (4.8%) patients and hypertension in 5 (4.0%) patients. In study XM01-08 (pre-dialysis patients), the most common TEADR was hypertension, in 15 (5.2%) patients.

In both studies, the majority of the TEAEs were mild or moderate. In study XM01-09, severe TEADRs occurred in 3 patients: convulsion, hypertension and arteriovenous fistula thrombosis each in 1 patient. In study XM01-08, one patient had two severe adverse events (epistaxis and hypertensive crisis) that were assessed as TEADR.

Immunogenicity

In phase I studies, no anti-Epoetin theta antibodies could be detected in 120 blood samples from 60 subjects treated with Epoetin theta: 14 from study XM01-10, 14 from XM01-11, 18 from XM01-12, and 14 from XM01-24.

In phase II/III RA studies, antibody testing for the phase II/III RA studies was performed on 3329 samples from 946 patients in studies XM01-04, 05, 06, 07, 08, and 09. Only 2 patients with potentially positive anti-Epoetin theta antibody results were identified. One tested positive on a single occasion and the other tested positive twice. In both cases, there was no indication of lack of Epoetin theta efficacy or of PRCA development. Given the absence of seroconversion, the possibility of specific neutralising anti-Epoetin theta /anti-erythropoietin reactivity development was dismissed.

Antibody analysis results for patients with long-term observation (>360 days) who were treated with Epoetin theta was available for 141 patients (97 patients s.c. and 44 patients i.v. treatment). The antibody analysis for patients with long-term s.c. observation (>360 days) from 97 patients showed that most patients were consistently negative for the screening assays. Isolated positive screening

results were negative in the confirmation assays. Antibody analysis for patients with long-term i.v. observation (>360 days) from 44 patients showed that most patients were consistently negative for the screening assays. Isolated screening results were positive for a single patient in one confirmation assay: this was the same patient who tested positive twice in the earlier RA studies, as described above.
In phase III CT studies, antibody testing for the phase III CT studies was performed on 1174 blood samples from 579 patients. Only 1 patient (22-10-503-3) treated wtih placebo in study XM01-22 was identified with one solitary positive result at baseline (visit 2). A cellular assay to detect neutralisation was negative. A blood sample taken from this placebo-treated patient at visit 14 was negative.

- Serious adverse event/deaths/other significant events

Table 28: Most frequent serious TEAEs in controlled RA studies XM01-04, 05, 06, and 07 (≥ 1% patients in either group)

MedDRA SOC/preferred term	EpoTheta N=606		EpoB N=235	
	n	%	n	%
Any serious TEAE	116	19.1	44	18.7
Cardiac disorders	29	4.8	7	3.0
Cardiac failure	6	1.0	1	0.4
Gastrointestinal disorders	9	1.5	4	1.7
General disorders and administration site conditions	12	2.0	8	3.4
Condition aggravated	8	1.3	3	1.3
Infections and infestations	24	4.0	5	2.1
Pneumonia	8	1.3	4	1.7
Injury, poisoning and procedural complications	11	1.8	5	2.1
Arteriovenous fistula thrombosis	8	1.3	1	0.4
Metabolism and nutrition disorders	10	1.7	4	1.7
Nervous system disorders	7	1.2	7	3.0
Renal and urinary disorders	23	3.8	7	3.0
Renal failure chronic	19	3.1	6	2.6
Vascular disorders	11	1.8	4	1.7

Table 29: Most frequent serious TEAEs in CT studies XM01-21, 22 and 23 (≥ 1% patients in either group)

MedDRA SOC / preferred term	Epoetin theta N=261		Placebo N=252		EpoB N=73	
	n	%	n	%	n	%
Any serious TEAE	42	16.1	46	18.3	9	12.3
Blood and lymphatic system disorders	13	5.0	4	1.6	3	4.1
Febrile neutropenia	6	2.3	1	0.4	2	2.7
Neutropenia	3	1.1	0	-	1	1.4
Gastrointestinal disorders	7	2.7	11	4.4	1	1.4
General disorders and administration site conditions	4	1.5	9	3.6	1	1.4
Pyrexia	0	-	3	1.2	0	-
Infections and infestations	13	5.0	10	4.0	0	–

MedDRA SOC / preferred term	Epoetin theta N=261		Placebo N=252		EpoB N=73	
	n	%	n	%	n	%
Pneumonia	8	3.1	2	0.8	0	–
Neoplasms benign, malignant and unspecified	9	3.4	14	5.6	1	1.4
Malignant neoplasm progression	6	2.3	11	4.4	1	1.4
Renal and urinary disorders	4	1.5	0	-	1	1.4
Renal failure	3	1.1	0	-	0	-

The majority of the serious TEAEs were assessed as unrelated to the study medication. In renal anaemia studies, serious TEADRs occurred in 26 (4.3%) patients treated with Epoetin theta and 8 (3.4%) patients treated with Epoetin beta. Most of the serious TEADRs only occurred in 1 or 2 patients of one or both treatment groups. The only serious TEADR with a frequency ≥ 1% was arteriovenous fistula thrombosis that occurred in 8 (1.3%) patients in the Epoetin theta group and 1 (0.4%) patient in the Epoetin beta group. In the cancer treatment anaemia studies, serious TEADRs were only reported in 7 patients (Epoetin theta 3, 1.1%; placebo 3, 1.2%; Epoetin beta 1, 1.4%).

Deaths. A total of 29/841 (3.4%) patients died in the controlled phase II/III RA studies: 21/606 (3.5%) patients treated with Epoetin theta and 8/235 (3.4%) patients treated with Epoetin beta. In study XM01-07 the causal relationship to the study medication was assessed as unlikely in 2 patients (1 Epoetin theta, 1 Epoetin beta). All other deaths were considered to be unrelated to study medication. In the follow-up study XM01-09, 4 patients who completed study XM01-05 died. In the follow-up study XM01-08, 7 patients who had completed study XM01-04 or 06 died. The majority of the deaths were due to cardiac disorders (SOC): 20 of the 32 deaths (21 in the controlled studies, 11 in the follow-up studies in Epoetin theta patients and 4 of the 8 deaths in Epoetin beta patients.
A total of 48/586 (8.2%) patients died in the controlled phase III CT studies: 18/261 (6.9%) patients treated with Epoetin theta, 26/252 (10.3%) with placebo, and 4/73 (5.5%) patients treated with Epoetin beta. In 1 patient treated with Epoetin beta in study XM01-21, the causal relationship of the death to study medication was assessed as unclassifiable by the investigator. All other deaths were considered to be unrelated to study medication. All of the deaths could be attributed to the underlying or concomitant disease or concomitant cancer treatment.

- Laboratory findings

Coagulation variables. The observed changes in coagulation variables did not raise concerns. The various treatment groups exhibited similar changes in coagulation variables (data not shown).
Clinical chemistry variables. Baseline values of clinical chemistry variables as well as changes of these variables on study were expected, based on the nature of the underlying diseases (renal failure, cancer), of concomitant diseases and of the administered treatment (anaemia correction, chemotherapy). No imbalances between treatment arms were detected (data not shown).
Transient increases in serum potassium and phosphate levels in isolated cases have been described for Epoetin beta. In the renal anaemia studies, similar elevations were observed in patients treated with Epoetin theta. No patient had an elevation for potassium or phosphate to above 3 times the upper limit of reference range (data not shown).
Haematology variables. Values of haematology variables and changes in these variables on study were expected, based on the nature of underlying diseases (renal failure, cancer under chemotherapy treatment) and the pharmacodynamic action of epoetin. No imbalances between treatment groups were detected unless expected, e.g. changes due to the pharmacodynamic action of epoetin in the Epoetin theta but not the placebo group. Of note, dose-dependent rises in platelet counts within the reference range, which are known for Epoetin beta, may also occur in Epoetin theta-treated patients (data not shown, see SPC section 4.4).

- Safety in special populations

Analyses of TEAEs in patient subpopulations of the pooled controlled phase II/III RA studies and the pooled controlled phase III CT studies on the following intrinsic factors at study baseline were provided:
Age: ≤ 64, 65-74, ≥ 75 years for RA studies; ≤ 64, ≥ 65 years for CT studies
Gender: male, female
Hypertension at baseline: yes, no
Diabetes mellitus at baseline: yes, no
Analyses based on race were not performed due to the small numbers of non-white patients enrolled in the studies.
Analyses for patients with or without cardiac impairment were not performed. Furthermore, the impact of hepatic impairment could not be assessed as patients with known liver disease or markedly elevated transaminase values were excluded from the studies.
A higher incidence of serious and severe adverse events and deaths was observed in patients 75 years and older treated with Epoetin theta in clinical trials. Moreover, certain adverse events were more frequent in female patients than in males (data not shown).

- Safety related to drug-drug interactions and other interactions

No drug-drug interaction studies were submitted and hence related safety has not been addressed.

- Discontinuation due to adverse events

Overall in phase II/III clinical studies, 19 (6.3%) of patients receiving Epoetin theta i.v. and 46 (8.1%) of patients receiving Epoetin theta s.c. discontinued treatment due to adverse events. This compares to 6 patients (5%) having received Epoetin beta i.v. and 10 patients (5.3%) having received Epoetin beta s.c., respectively. 19 patients (7.5%) that received placebo discontinued treatment due to adverse events.
In the controlled RA studies, the following TEAEs led to study discontinuation and occured in more than 2 patients: “worsening” of chronic renal failure (18 (3.0%) Epoetin theta patients vs 5 (2.1%) Epoetin beta patients), renal impairment (3 (0.5%) Epoetin theta patients vs 2 (0.9%) Epoetin beta patients) and cardiac failure (3 (0.5%) Epoetin theta vs 1 (0.4%) Epoetin beta patients).
In the controlled CT studies, frequencies of TEAEs leading to premature discontinuation of study medication were low. The only TEAEs leading to study discontinuation in more than two patients were: neoplasm progression (2 (0.8%) patients in the Epoetin theta group, 6 (2.4%) patients in the placebo group and 1 (1.4%) patient in the Epoetin beta group) and pneumonia (1 (0.4%) patient in the Epoetin theta group and 2 (0.8%) patients in the placebo group).
In study XM01-09, TEAEs leading to premature discontinuation of the study were reported in 6 (4.8%) patients: none occurred in more than two patients.
In study XM01-08, TEAEs that lead to premature discontinuation of the study and occurred in more than two patient were: chronic renal failure (28, 9.7%), renal impairment (7, 2.4%), renal failure (3, 1.0%), and condition aggravated (3, 1.0%).

- Post marketing experience

N/A

- Discussion on clinical safety

Overall the safety profile of Epoetin theta is consistent with the known safety profile of epoetins and as expected for the investigated (patient) populations. There were no new or unexpected findings.
The most common adverse events in renal anaemia patients treated with Epoetin theta are well known side effects of marketed epoetins and well known symptoms of the underlying chronic kidney disease. There were no clinically relevant differences between the TEAE profiles of the Epoetin theta groups and the Epoetin beta groups across or within the studies.
In the correction phase studies XM01-04 and 05, the proportion of patients with TEAEs was higher for patients treated with Epoetin theta compared to those treated with Epoetin beta. This may be explained by the higher starting doses of Epoetin theta (up to 120 IU/kgBW) compared to Epoetin beta in these studies. More patients with higher doses of Epoetin theta (60 IU/kg BW and above) had serious

adverse events and study discontinuations, whereas in the Epoetin beta group with the dose identical to the lowest dose of Epoetin theta less adverse events were seen. Particularly cardiac disorders occurred more frequently in the Epoetin theta treatment groups with the higher doses. For these adverse events, a dose-dependency was seen.
In the maintenance phase studies XM01-06 and 07, the percentages of patients who experienced TEAEs were similar for the two treatment groups. Some differences were found in event frequencies between the studies with intravenous administration of study drug (XM01-05, 07) and those with subcutaneous administration (XM01-04, 06). The frequencies of adverse events and serious adverse events and discontinuations were somewhat higher in the i.v. treated patients. These imbalances can probably be explained by the fact that patients in the studies with i.v. administration were already receiving dialysis and had a more advanced stage of renal anaemia.
Secondary analyses were performed on adverse events of special interest in the randomised renal anaemia studies. Such adverse events included renal failure, tumour progression, pure red cell aplasia (PRCA), hypertension, thromboembolic events, arteriovenous shunt thrombosis, cardiac disorders, skin reactions/injection site disorders and infections/infestations.
In studies XM01-09 (intravenous administration) and -08 (subcutaneous administration), the profile of the most frequent TEAEs can be expected in the rather elderly study population having chronic renal failure for several years accompanied by renal anaemia that had already been treated with epoetin. The higher incidence of adverse events in the follow-up studies XM01-08 and -09 than in the predecessor studies XM01-04/06 and -05 can be expected due to the longer treatment duration in the follow-up studies. The higher incidence of adverse events in study XM01-09 compared to XM01-08 can be explained in the same way as in their respective predecessor studies (see above).
In cancer studies, the overall TEAE profiles were consistent with those expected for rather elderly cancer patients who had been treated with epoetin for anaemia resulting from administration of CT. The observed TEAEs were typical for the underlying cancer (e.g. asthenia) or known side effect of either epoetins (e.g. hypertension and headache) or CT (e.g. nausea, vomiting, leukopenia, neutropenia, and thrombocytopenia).
The CHMP raised a major objection with regards to immunogenicity due to the different glycosylation pattern of Epoetin theta compared to other licensed epoetins. The applicant claimed that the glycosylation pattern of Epoetin theta had been characterised and shown to be similar to that of other epoetins and that no indication for immunogenic potential of Epoetin theta had been detected in the clinical studies (in the phase II/III efficacy studies one patient of the renal anaemia studies and one patient with cancer indication were detected to have anti-epoetin antibodies in a single occasion each, and no patient had neutralizing antibodies). The CHMP considered the issue to be resolved.
Patients over 75 years of age had a higher incidence of serious and severe adverse events irrespective of a causal relationship to treatment with epoetin theta. Furthermore, deaths were more frequent in this patient group compared to younger patients.
No drug-drug interaction studies were submitted and hence related safety has not been addressed. However, given the protein nature of the product, no drug-drug interactions are expected.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

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

Risk Management Plan

The MAA submitted a risk management plan.

Summary of the EU Risk Management Plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Hypertensive disorders	**Routine** Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR	**Routine** An increase in blood pressure, hypertension and its aggravation and hypertensive crisis are mentioned in section 4.8 of the SPC. Detailed information concerning the close monitoring of blood pressure, symptoms and warning signals of hypertensive crisis and recommended measures in case of increased blood pressure are included in the warning section 4.4 of the SPC. Uncontrolled hypertension is included in section 4.3 (contraindications).
Shunt thrombosis in haemodialysis patients	**Routine** Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR	**Routine** Shunt thrombosis is mentioned in section 4.8 of the SPC. In the warning section 4.4 it is mentioned that during haemodialysis, patients treated with Eporatio may require increased anticoagulation treatment to prevent clotting of the arterio-venous shunt.
Thromboembolic events in cancer patients	**Routine** Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR	**Routine** Thromboembolic events are mentioned in section 4.8 of the SPC. Section 5.1 of the SPC mentions that, in a systematic review of 57 clinical trials involving more than 9000 cancer patients, an increased relative risk of thromboembolic events was observed in cancer patients under chemotherapy and treated with recombinant human erythropoietin. The risk for patients treated to achieve haemoglobin concentrations less than 13 g/dl is unclear, as few such patients were included in the data reviewed.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Pure red cell aplasia (PRCA) caused by neutralising anti-erythropoetin antibodies	**Routine** Signal detection procedure for all incoming spontaneous ADR reports, and offering of antibody testing in case of a suspected anti-erythropoietin antibody-mediated PRCA. Presentation of collated data in the corresponding chapter of the PSUR.	**Routine** Neutralising anti-erythropoietin antibody mediated pure red cell aplasia (PRCA) and the demand to discontine therapy with epoetin theta in case of its diagnosis is mentioned in section 4.8 of the SPC. In section 4.4 of the SPC recommendations concerning the detection and diagnosis of PRCA and information about the cross-reactivity of neutralising anti-erythropoietin antibodies are included. Hypersensitivity to the active substance is a contraindication (section 4.3 of the SPC) to the use of epoetin theta.
Increased cardiovascular risk in renal anaemia patients	**Routine** Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR. **Additional** Observational, non-interventional, post-authorization safety study with epoetin theta in patients with chronic kidney disease (XM01-30).	**Routine** In section 4.2 of the SPC it is mentioned that in patients with chronic renal failure the haemoglobin level should be increased to no greater than 12 g/dl and that patients should be monitored closely to ensure that the lowest approved dose of epoetin theta is used to provide adequate control of the symptoms of anaemia. In section 4.4 of the SPC it is mentioned that in patients with chronic renal failure, maintenance haemoglobin concentration should not exceed the upper limit of the target haemoglobin concentration mentioned in section 4.2. In clinical trials, an increased risk of death and serious cardiovascular events was observed when epoetins were administered to target a haemoglobin level in excess of 12 g/dl.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Tumour growth progression, Increased mortality in cancer patients	**Routine** Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR **Additional** Long-term follow-up (up to 5 years) for cancer patients treated in clinical studies XM01-21, -22 and -23 Feasibility study for a randomised controlled trial investigating the risk of a potentially increased mortality in cancer patients treated with epoetins.	**Routine** Routine risk minimisation including warning in section 4.4 of the SPC, mention that the upper limit of the recommended target haemoglobin concentration specified in section 4.2 should not be exceeded, and provision of information in section 5.1. In section 4.2 of the SPC it is mentioned that in cancer patients a sustained haemoglobin level of greater than 12 g/dl should be avoided and that patients should be monitored closely to ensure that the lowest approved dose of epoetin theta is used to provide adequate control of the symptoms of anaemia. In section 4.4 of the SPC it is mentioned that as with all growth factors, there is concern that epoetins could stimulate the growth of any type of malignancy. Special patient populations for whose use epoetins are not indicated are listed. The decision to administer recombinant erythropoietins should be based on a benefit-risk assessment for the individual patient. The effect of erythropoietin on tumour growth is described in detail in section 5.1 of the SPC. In this section it is also mentioned that data from three placebo-controlled clinical studies in anaemic cancer patients conducted with epoetin theta showed no negative effect of epoetin theta on survival. During the studies, mortality was lower in the epoetin theta group compared to placebo.
Hyporesponsiveness	**Routine** Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR	**Routine** Routine risk minimisation including warning in section 4.4 of the SPC (will be added as soon as finalised and provided by the CHMP) A warning will be added to section 4.4 of the SPC according to the demand of the PhVWP as soon as the wording is finalised and provided by the CHMP

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of Eporatio is considered to be acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

Non-clinical pharmacology and toxicology

The biological efficacy of epoetin theta has been demonstrated after intravenous and subcutaneous administration in various animal models *in vivo* (mice, rats, dogs). After administration of epoetin theta, the number of erythrocytes, the haematocrit values and reticulocyte counts increase.
Non-clinical data with epoetin theta reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated-dose toxicity.

Efficacy

Symptomatic anaemia associated chronic renal failure
Data from correction phase studies in 284 chronic renal failure patients show that the haemoglobin response rates (defined as haemoglobin levels above 11 g/dl at two consecutive measurements) in the epoetin theta group were high (88.4% and 89.4% in studies in patients on dialysis and not yet undergoing dialysis, respectively) and comparable to epoetin beta (86.2% and 81.0%, respectively). The median time to response was similar in the treatment groups with 56 days in haemodialysis patients and 49 days in patients not yet undergoing dialysis.
Two randomised controlled studies were conducted in 270 haemodialysis patients and 288 patients not yet undergoing dialysis, who were on stable treatment with epoetin beta. Patients were randomised to continue their current treatment or to be converted to epoetin theta (same dose as epoetin beta) in order to maintain their haemoglobin levels. During the evaluation period (weeks 15 to 26), the mean and median level of haemoglobin in patients treated with epoetin theta was virtually identical to their baseline haemoglobin level. In these two studies, 180 haemodialysis patients and 193 patients not undergoing dialysis were switched from maintenance phase treatment with epoetin beta to treatment with epoetin theta for a period of six months showing stable haemoglobin values and a similar safety profile as epoetin beta.
In two long-term studies, the efficacy of epoetin theta was evaluated in 124 haemodialysis patients and 289 patients not yet undergoing dialysis. The haemoglobin levels remained within the desired target range and epoetin theta was well tolerated over a period of up to 15 months.
In the clinical studies, pre-dialysis patients were treated once-weekly with epoetin theta, 174 patients in the maintenance phase study and 111 patients in the long-term study.

Symptomatic anaemia in cancer patients with non-myeloid malignancies receiving chemotherapy
409 cancer patients receiving chemotherapy were included in two prospective, randomised double-blind, placebo-controlled studies. The first study was conducted in 186 anaemic patients with non-myeloid malignancies (55% with haematological malignancies and 45% with solid tumours) receiving non-platinum chemotherapy. The second study was conducted in 223 patients with various solid tumours receiving platinum-containing chemotherapy. In both studies, treatment with epoetin theta resulted in a significant haemoglobin response ($p < 0.001$), defined as an increase in haemoglobin of ≥ 2 g/dl without transfusion, and a significant reduction in transfusion requirements ($p < 0.05$) in comparison to placebo.

Safety

The safety of epoetin theta has been evaluated based on results from clinical studies including 972 patients. From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.
Approximately 9% of patients can be expected to experience an adverse reaction. The most frequent undesirable effects are hypertension, influenza-like illness and headache.
Shunt thrombosis may occur, especially in patients who have a tendency to hypotension or whose arterio-venous fistulae exhibit complications (e.g. stenoses, aneurisms) (see SPC section 4.4).
One of the most frequent adverse reactions during treatment with epoetin theta is an increase in blood pressure or aggravation of existing hypertension. Hypertension occurs more often during the correction phase than during the maintenance phase. Hypertension can be treated with appropriate medicinal products (see SPC section 4.4).
Skin reactions such as rash, pruritus or injection site reactions may occur.
Symptoms of influenza-like illness such as fever, chills and asthenic conditions have been reported.
Certain adverse reactions have not yet been observed with epoetin theta, but are generally accepted as being attributable to other epoetins: In isolated cases in patients with chronic renal failure, neutralising anti-erythropoietin antibody-mediated PRCA associated with therapy with other epoetins has been reported. If PRCA is diagnosed, therapy with epoetin theta must be discontinued and patients should not be switched to another recombinant epoetin (see SPC section 4.4).
Erythropoietin is a growth factor that primarily stimulates red cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells. Survival and tumour progression have been examined in several large controlled studies. These studies have shown a consistent unexplained statistically significant excess mortality in patients who have anaemia associated with various common cancers who received recombinant human erythropoietin compared to controls. Overall survival outcome in the trials could not be satisfactorily explained by differences in the incidence of thrombosis and related complications between those given recombinant human erythropoietin and those in the control group.
Data from three placebo-controlled clinical studies in 586 anaemic cancer patients conducted with epoetin theta, showed no negative effect of epoetin theta on survival. During the studies, mortality was lower in the epoetin theta group compared to placebo.
Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The Applicant performed a readability testing (“user consultation”) and a satisfactory report has been provided.

Risk-benefit assessment

The preclinical pharmacodynamical effects of Epoetin theta were in full agreement with the expected profile of an epoetin. The provided clinical data globally demonstrated the efficacy of epoetin theta in the treatment of symptomatic anaemia associated with chronic renal failure and in the treatment of symptomatic anaemia in cancer patients with non-myeloid malignancies.
No special risks of Epoetin theta were detected in the safety pharmacology or general toxicology studies that would be beyond the risks of other epoetins. In clinical studies, Epoetin theta seems to be as well tolerated as Epoetin beta by both I.V. and S.C. routes. Overall the safety profile of Epoetin theta is consistent with the known safety profile of epoetins and as expected for the investigated (patient) populations. There were no new or unexpected findings.
A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns and no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Eporatio in the treatment of 'symptomatic anaemia associated with renal failure and symptomatic anaemia in cancer patients with non-myeloid malignancies receiving chemotherapy' was favourable and therefore recommended the granting of the marketing authorisation.