European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT REPORT

FOR

RATIOGRASTIM

International Nonproprietary Name: filgrastim

Procedure No. EMEA/H/C/825

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

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 16
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

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1 BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant ratiopharm GmbH submitted on 29 January 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Ratiograstim, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The legal basis for this application refers to Article 10(4) of Directive 2001/83/EC, as amended – relating to applications for biosimilar medicinal products.

The application submitted is a complete dossier composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

Scientific Advice
The applicant received Scientific Advice from the CHMP on 3 June 2004, 15 December 2004 and 13 October 2005. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

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

Rapporteur: Dr Pirjo Laitinen-Parkkonen **Co-Rapporteur**: Dr Tomas P Salmonson

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 29 January 2007.
- The procedure started on 21 February 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 May 2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 May 2007. In accordance with Article 6(3) of Regulation (RC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 11-13 June 2007, the BWP agreed on the consolidated quality List of Questions to be sent to the CHMP for adoption.
- During the meeting on 18-21 June 2007, 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 21 June 2007.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 October 2007.
- The summary report of the inspection carried out at the following site: Lemery SA de CV, Planta Biotech, Av. Santa Ana No. 65, Parque Industrial Lerma Toluca, Mexico between 1 October 2008 and 4 October 2007 was issued on 17 January 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 23 November 2007.
- During the meeting on 3-5 December 2007, the BWP agreed on the consolidated quality List of outstanding issues to be sent to the CHMP for adoption.
- During the CHMP meeting on 10-13 December 2007, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 17 January 2008
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 4 February 2008.
- During the meeting on 18-21 February 2008, 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 Ratiograstim on 21 February 2008. The applicant

provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 7 February 2008.

- On 29 April 2008, the European Commission (EC) informed the EMEA that the preparation of a Commission decision on the basis of the CHMP opinion of 21 February 2008 had been suspended, and referred the Opinion back to the EMEA. The Commission requested that the relevance of data from a similar product containing filgrastim (Grasalva), authorised in Lithuania, should also be considered by the CHMP for the assessment of the benefit-risk ratio of the product Ratiograstim.
- The applicant provided written clarifications and new data on 16 May 2008.
- On 18 June 2008, the EC requested that the CHMP consider the need for a GCP inspection with regard to Ratiograstim.
- The Rapporteurs circulated the Joint Assessment Report to all CHMP members on 4 July 2008 and a revised Joint Assessment Report on 18 July 2008.
- The Applicant provided additional clarifications with regards to GCP in writing on 22 July 2008 and during an oral explanation on 23 July 2008.
- On 24 July 2008, the CHMP, in the light of the information submitted adopted a revised positive opinion for granting a Marketing Authorisation for Ratiograstim. The applicant provided an updated letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 10 July 2008.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

The current treatment of cancer with combination cytotoxic therapy targeting proliferating cells usually leads to bone marrow damage, anaemia, thrombocytopenia and, most importantly, neutropenia resulting in impaired host defence. Severe neutropenia will inevitably lead to serious infections. Life-threatening gastrointestinal and pulmonary infections as well as sepsis will occur as long as the severe neutropenia prevails. This leads to delays in subsequent chemotherapy cycles. The recovery of the bone marrow is stimulated by various growth factors. The most important growth factor for the recovery of neutrophils is granulocyte colony-stimulating factor, G-CSF.

G-CSF is a positive regulator of granulopoiesis, acting at different stages of myeloid cell development. It enhances the effector functions of normal mature neutrophils, including chemotaxis, phagocytosis and oxidative metabolism. It exerts its effects via a high-affinity G-CSF-specific receptor mechanism, which accounts for its selective action as compared with many other cytokines. The natural human G-CSF is a glycoprotein composed of a single polypeptide chain of 174 or 177 amino acids.

Filgrastim, the active substance of Ratiograstim (the applicant is using the name XM02, which is also being used in this document), is a non-glycosylated recombinant methionyl human granulocyte colony stimulating factor expressed in *E. coli* and consisting of 175 amino acids.

Ratiograstim, the medicinal product applied for, has been developed as a "*similar biological medicinal product*" according to Article 10 (4) and Annex 1, Part II, Chapter 4 of Directive 2001/83/EC as amended. The chosen reference medicinal product is Neupogen sourced from Amgen, Germany.

The medicinal product is indicated for reducing the duration of neutropenia and the incidence of febrile neutropenia in patients undergoing myelosuppressive chemotherapy for malignant diseases and for reducing the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation and who are at risk of prolonged severe neutropenia. It is also used to mobilise peripheral blood stem cells as monotherapy or after myelosuppressive chemotherapy as well as in long term treatment of severe congenital, cyclical or idiopathic neutropenia, or neutropenia associated with advanced human immunodeficiency virus infection.

Administration is by the subcutaneous or intravenous route, normally at a dose of 1 to 10 μg/kg/day depending on the indication. In congenital neutropenia, the starting subcutaneous dose is 12 μg/kg/day given as a single dose or in divided doses.

The medicinal product is supplied in pre-filled syringes containing 0.5 (for the lower strength) or 0.8 ml (for the higher strength) of sterile, preservative-free solution for injection consisting of 30 or 48 MIU (corresponding to 300 and 480 μg respectively) XM02 active substance together with acidic sodium acetate buffer, sorbitol, polysorbate and water for injections.

2.2 Quality aspects

Introduction

XM02 active substance is a recombinant human granulocyte-colony stimulating factor produced in *E. coli*, yielding a non-glycosylated protein with an N-terminal methionyl extension (INN filgrastim). The protein is expressed in inclusion bodies followed by renaturation of protein and chromatographic purification steps. The protein is a single chain of 175 amino acid polypeptide.

As required for a similar biological medicinal product, comparability to the reference medicinal product (Neupogen, sourced from Amgen, Germany) has been demonstrated.

The medicinal product is presented as solution for injection or infusion in 1 ml glass, single-use, pre-filled syringes. Two strengths are provided: 30 MIU/0.5 ml and 48 MIU/0.8 ml (corresponding to 300 and 480 µg respectively). The formulation is similar to Neupogen and only slight differences exist in the concentration of polysorbate and in the pH value. The concentration of medicinal product bulk solution is 0.6 mg/ml and the difference in the two strengths is achieved by the different fill volumes.

Active Substance

XM02 active substance is a recombinant form of human G-CSF, expressed in *E. coli*. The native human G-CSF is encoded by a gene on chromosome 17 that encodes two protein products due to differential splicing; isoform A of 177 amino acids and isoform B of 174 amino acids. Isoform A differs from isoform B in that it contains an additional three residues (Val-Ser-Gln) inserted after Leu35. The 174 amino-acid form is associated with greater biological activity and stability than the longer isoform and is the basis for commercial pharmaceutical G-CSF products, including Neupogen. XM02 active substance is a recombinant form of the 174 amino-acid isoform that contains an additional N-terminal methionine residue not found in the native human protein. The naturally occurring G-CSF is also glycosylated at threonine residue 133, a modification which is absent in XM02 active substance as an *E. coli* expression product.

Manufacture

The XM02 active substance is manufactured at SICOR Biotech UAB, Vilnius, Lithuania.

The active substance is produced by *E. coli* fermentation. After a predefined growth time, inductor is added to fermentation media. This induces the start the production phase, which continues for a predefined growth time. The cells are harvested and disrupted, and inclusion bodies are washed with buffer for removal of contaminants. The inclusion bodies are dissolved in a chaotropic agent and refolded by reducing-oxidising system. After refolding, a series of orthogonal chromatographic purification steps are applied. Following purification, the active substance is filtered, filled into bottles and stored at 2 to 8°C.

The manufacturing and purification processes were properly described and the process validation studies, as well as the in-process control system, were considered acceptable.

No major changes have been introduced into the manufacturing process during development. All batches of active substance manufactured at the developmental and commercial scales have been produced using the current WCB. The developmental scale batch was used only during phase I trials. Throughout process development, fermentation has been conducted at the same scale, but the site of fermentation and purification was changed when the manufacturing was transferred to a GMP production facility.

The *E. coli* host strain was transformed with the plasmid using standard techniques to generate the recombinant strain *E. coli* for production of G-CSF. The MCB and WCB for the commercial process were laid down according to cGMP. The cell banks were adequately addressed and stored.

- Specification

During the Marketing Authorisation Application procedure, the applicant has amended the active substance release- and end of shelf-life specifications according to the requirements of the CHMP. The current specifications, including the acceptance limits, are thereby considered as justified and acceptable.

- Stability

Data on three batches produced at commercial scale and stored in the current container closure system was provided. Therefore, the storage of the active substance for 12 months at 5 ± 3°C was considered acceptable.

- Comparability exercise for Active Substance

Extensive characterisation studies have been performed using a large number of batches of XM02 active substance, produced at the commercial scale process. Throughout the product development programme, the applicant has simultaneously with the characterisation of XM02 active substance conducted comparability studies with Neupogen.

The XM02 active substance has been characterised for molecular mass, primary amino acid sequence, spectral properties (fluorescence emission spectroscopy and circular dichroism), isoform distribution, hydrophobic properties, purity and potency. The characteristics of XM02 active substance were compared to the medicinal reference product, Neupogen and found to be similar. The analytical methods used were properly described and validation reports for the methods were provided and found acceptable.

Medicinal Product

Both the XM02 medicinal product and the reference medicinal product Neupogen are aqueous liquid formulations of similar composition. The two formulations differ only in pH and in the concentration of filgrastim and of polysorbate 80.

- Pharmaceutical development

A satisfactory presentation of the XM02 medicinal product pharmaceutical development was provided. The medicinal product is supplied in 1 ml glass, single-use, pre-filled syringes in two strengths:

- 30 MIU/0.5 ml dosage strength containing 300 μg of filgrastim active substance, to give a 0.5 ml extractable volume
- 48 MIU/0.8 ml dosage strength containing 480 μg of filgrastim active substance, to give a 0.8 ml extractable volume

The liquid formulation requires no reconstitution and, depending on the indication, it may be given subcutaneously or intravenously.

The concentration of medicinal product bulk solution is 0.6 mg/ml and the difference in the two strengths is achieved by the different fill volumes. The two strengths correspond to those marketed for the reference medicinal product, Neupogen. However, Neupogen syringes contain filgrastim at 0.6 mg/ml for the 30 MIU/0.5 ml strength and at 0.96 mg/ml for the 48 MIU/0.5 ml strength.

Each strength is to be supplied in packs of one, five, two x five, or ten pre-filled syringes. The liquid formulation is an acetate-buffered, sterile, isotonic solution for injection. The formulation of XM02 medicinal product has the same excipients as Neupogen, i.e acetic acid, polysorbate 80, sodium hydroxide, sorbitol and water for injections.

If necessary, the XM02 medicinal product may be used as a concentrate for solution for infusion, diluted in 5% glucose. For patients treated with XM02 medicinal product diluted to give filgrastim concentrations below 1.5 MIU (15 μg) per ml, human serum albumin (HSA) should be added to a final concentration of 2 mg/ml. Neither solution is supplied with the XM02 medicinal product.

During medicinal product formulation, the excipients are compounded as a buffer prior to mixing with the active substance. A portion of the final excipient content also derives from the active substance formulation. The product is sterilised by filtration and filled into 1 ml siliconised glass (Ph. Eur. Type I) syringes with fixed needle and needle shield, Flue Fluorotec-faced bromobutyl rubber plunger stopper (Ph. Eur 3.2.9) and a polypropylene plunger rod. The syringes are overfilled to ensure the correct expellable volume.

- Adventitious agents

The risk assessment on adventitious agents was adequately performed and described. The raw materials for the manufacture of XM02 active substance and medicinal product are subject to microbiological quality control. Three materials of biological origin are used in routine production;

bacterial host strain *E. coli*, casamino acids used as a fermentation medium component and polysorbate 80 used as a component of the formulation. The starting material of the casamino acids is bovine milk deemed fit for human consumption from healthy animals of New Zealand origin. As such, this material is compliant with the requirements to minimise TSE risks laid out in the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01). Furthermore, the hydrolysis process involves acid treatment at pH ≤1.0, 120°C for a minimum of six hours. It is expected that these conditions should be more than sufficient to inactivate any adventitious viruses. The polysorbate 80 used as an excipient is of vegetable origin, and therefore does not constitute a virus safety risk. Because the fermentation of *E. coli* does not support growth of viruses, no viral clearance studies have been performed.

- Manufacture of the product

Manufacture of XM02 medicinal product pre-filled syringes takes place at Lemery SA de CV, Mexico and employs a straightforward process, including compounding, sterile filtrations and aseptic filling.

The approvable range for control parameters such as mixing times, hold times, temperature, and filling rates have been defined and tests for in process control were described. The process validation studies were considered acceptable. Results from the validation of shipping of medicinal product to the sites used for packaging, labelling and release ensure that transportation is conducted under controlled conditions and that the quality of medicinal product is not affected.

- Product specification

The batch release specifications for the medicinal product are based on results from batch consistency testing and are considered acceptable. Appropriate tests (including tests for identity, purity, content, pharmaceutical tests and microbiological tests) and limits have been provided.

- Characterisation of impurities

The applicant has presented an overview of product related impurities detected by SE-HPLC, RP-HPLC, IE-HPLC, IEF and SDS-PAGE. The methods used for impurity control are essentially identical for both active substance and medicinal product. Validation of the methods has however been appropriately addressed separately for the active substance and the medicinal product.

- Stability of the product

Adequately designed stability studies have been reported, being in compliance with the requirements in the ICH Q5C guideline. In these studies, stability of the medicinal product is demonstrated over the proposed storage time of 24 months at 5±3°C.
The results from cool-chain interruption, freeze/thaw and transport deviation confirms the stability of the XM02 medicinal product under the conditions studied. Thus, the proposed storage time of 24 months at 5 ± 3°C is considered acceptable.

- Comparability exercise for Medicinal Product

The applicant performed extensive state-of-the-art characterisation studies to show biosimilarity between XM02 medicinal product and the chosen reference medicinal product. The composition, the physical properties, the primary and higher order structures and the biological activity of XM02 and Neupogen sourced from Amgen Germany have been assessed and found to be similar.

The applicant has characterised XM02 medicinal product related impurities in comparison with the reference medicinal product Neupogen to support the claim of biosimilarity of the two products. The product related impurity profiles between XM02 medicinal product and Neupogen were shown to be similar. The conclusion is based on impurity testing in stability studies as well as on the experimental evidences from comparability studies.

A major objection was raised regarding the source of the reference medicinal product, as the applicant appeared to have used Neupogen from three different sources: Amgen Germany; Amgen Lithuania and Roche Lithuania. The reference medicinal product must be a medicinal product authorised in the Community on the basis of a complete dossier and at the time of the study, Lithuania was not a member of the EU. It was unclear whether an EU authorised medicinal product was used as reference in the analyses for product-related impurities by RP-HPLC and IE-HPLC. In the responses, the

applicant provided both a summary of the data provided in the original dossier and new data regarding the product-related impurity profile as detected by RP-HPLC and IE-HPLC. The data confirmed that the XM02 medicinal product contains comparable or fewer product-related impurities compared to Neupogen sourced from Amgen, Germany. Together with the comparability exercise submitted in the original dossier, the comparability between XM02 medicinal product and Neupogen has been fully demonstrated using an EU authorised medicinal product as reference (i.e. Neupogen sourced from Amgen, Germany). All data produced with Neupogen from Lithuania can be regarded as supportive.

Discussion on chemical, pharmaceutical and biological aspects

The dossier was found to be of good quality, fulfilling the requirements for marketing authorisation of a similar biological medicinal product. Extensive comparability studies were performed using Neupogen, sourced from Germany, as the reference medicinal product. The characterisation of the active substance and the comparability studies are considered acceptable.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. 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.

2.3 Non-clinical aspects

Introduction

Table 1 displays synoptic information (which is not repeated within the subsections where the study results are presented) on the studies composing the non-clinical programme.

Table 1 Tabular listing of non-clinical studies

Study ID	Species	Primary objective	Secondary objectives	Number of animals	Dose level	Treatment duration	GLP compliance	Source* of the reference product
Primary pharmacodynamics								
XM02-PPD-0.01	*in vitro*	Comparison of binding of XM02 and Neupogen to human G-CSF receptor	-	-	-	-		Germany
XM02-PPD-0.02 XM02-PPD-0.03	*in vitro*	Relative potency determination of XM02 and Neupogen with the M-NFS-60 cell line		-	-	-		• 0.02 Lithuania • 0.03 Germany
XM02-PPD1-01 XM02-PPD1-02	Balb/C mice	Effects of XM02 and Neupogen following cyclophosphamide-induced neutropenia in mice		14 groups of 6 male	All groups s.c. injection of XM02 or Neupogen at 0.1, 0.2, 0.5, 1.0, 2.0 or 5.0 µg/kg) after having received one i.p. injection of CPA 100 mg/kg on Day 1 (except Group 1: control)	From Day 2 to Day 5		• 1.01 Germany • 1.02 Germany
XM02-PKPD-6.01	Cynomolgus monkeys	Effects of XM02 on haematology in the monkey upon single s.c. or i.v. administration	Pharmacokinetics of XM02 following s.c. and i.v. injection in the monkey	6 male	Single s.c. an i.v. of 800 µg/kg of XM02		Yes	NA
Secondary pharmacodynamics								
XM02-SPD-0.01	*in vitro*	Determination of the proliferation promoting effects of XM02 in comparison to Neupogen on human malignant cell lines	-	-	-	-		Lithuania
Safety pharmacology								
XM02-SPRS-2.01	Male albino rat	Effects of XM02 on the respiratory system in rats		6 male per group	Single s.c. injection of vehicle or 3,500 µg/kg of XM02	-		NA
XM02-SPCNS-2.01	Sprague Dawley rat	Effects of XM02 on the central nervous system in rats	Single-dose toxicity	16 male and 16 female	Single s.c. injection of vehicle or 3,500 µg/kg of XM02	Single injection with 14-day follow-up	Yes	NA
XM02-SPCV-5.01	Beagle dog	Effects of XM02 on the cardiovascular system in the dog		3 male per group	Single s.c. injection of vehicle or 3,500 µg/kg of XM02	-		NA
Pharmacokinetics								
XM02-PK4-2.01	Sprague Dawley rat	Pharmacokinetics of XM02 following s.c. injection in the rat		26 male	Daily s.c. injection of 500 µg/kg of XM02	4 weeks	Yes	NA
XM02-PKPD-6.01	Cynomolgus monkey	Pharmacokinetics of XM02 following s.c. and i.v. injection in the monkey	Effects of XM02 on haematology in the monkey upon single s.c. or i.v. administration	6 male	Single s.c. and i.v. injection of 800 µg/kg of XM02		Yes	NA

Study ID	Species	Primary objective	Secondary objectives	Number of animals	Dose level	Treatment duration	GLP compliance	Source* of the reference product
Toxicology								
XM02-SPCNS-2.01	Sprague Dawley rat	Single-dose toxicity	Effects of XM02 on the central nervous system in rats	16 male and 16 female	Single s.c. injection of 3,500 µg/kg of XM02	-	Yes	NA
XM02-RT26w-2.01	Sprague Dawley rat	26-week toxicity study with 4-week interim study in rats following s.c. injection of XM02		20 per sex per dose	Daily s.c. injection of 0*, 5, 50, 500* µg/kg of XM02 * 10 per sex for 4-week and recovery sacrifice	26 weeks	Yes	NA
XM02-RT26w-6.01	Cynomolgus monkey	26-week s.c. injection toxicity study (with a 4-week interim study) in the monkey		4 per sex per dose 4-week	Daily s.c. injection of 0*, 5, 25, 125* µg/kg of XM02 * 3 per sex for 4-week and recovery sacrifice	26 weeks	Yes	NA
XM02-LT-4.01	Rabbit/New Zealand White	Local tolerance of XM02 following a single administration in the rabbit		4 male per group	Single dose Group 1: 0.1 ml 0.9% saline Group 2: 0.1 ml XM02 diluent Group 3+4 : XM02 i.v., intra-arterial, s.c. and i.m. at 300 µg/0.5 ml or 600 µg/1.0 ml, for perivenous 60 µg/0.1 ml in both groups	-	Yes	NA
XM02-LT-4.02	Rabbit/New Zealand White	Local tolerance of XM02 and Neupogen following a single administration in the rabbit		4 male per group	Single dose Group 1: 0.1 ml 0.9% saline Group 2: 0.1ml XM02 diluent Group 3+4 : XM02 i.v., intra-arterial, s.c. and i.m. at 240 µg/0.4 ml or 480 µg/0.8 ml, for perivenous 60 µg/0.1 ml in both groups Group 5+6 : Neupogen i.v., intra-arterial, s.c. and i.m. at 240 µg/0.25 ml or 480 µg/0.5 ml, for perivenous 96 µg/0.1 ml in both groups	-	Yes	Germany
XM02-RT4w-2.01	CDrats	To compare immunogenicity between XM02 and Neupogen	To compare the primary pharmacological response i.e. increase in blood neutrophil count, between XM02 and Neupogen To compare the pharmacokinetic profiles of XM02 and Neupogen	20 per sex per dose of which 9 per sex per dose for PK	Daily s.c. injection of 5, 25 and 125 µg/kg of XM02 or Neupogen and control group	2 14-day periods of daily s.c. separated by a 14-day drug treatment free period in between	Yes	Germany

- Primary pharmacodynamics

Primary pharmacodynamic studies (key elements described in Table 1) comprised *in vitro* studies assessing comparability of receptor binding and biological activity between XM02 and Neupogen **(Studies XM02-PPD-0.01, XM02-PPD-0.02, XM02-PPD-0.03)** and *in vivo* studies in neutropenic mice **(Studies XM02-PPD1-01 and XM02-PPD1-02)** as well as in healthy rats **(Study XM02-RT4w-2.01)** and monkeys **(Study XM02-PKPD-6.01)** to support similar/equivalent pharmacological activity of XM02 compared to Neupogen.

***In vitro* studies**

Comparison of the binding of XM02 and Neupogen to the human G-CSF receptor (Study XM02-PPD-0.01)

The results demonstrate that the binding of human G-CSF receptor and XM02 or Neupogen was specific and dose dependent. In addition, the binding affinities for XM02 and Neupogen to the receptor were similar.

Relative potency determination of XM02 and Neupogen with M-NFS-60 cell line (Studies XM02-PPD-0.02 and XM02-PPD-0.03)

The data indicate that both, XM02 and Neupogen bind to the murine cellular G-CSF receptors with the same affinity and that both preparations are equally effective in inducing a cellular proliferation.

***In vivo* studies**

Effects of XM02 and Neupogen in a cyclophosphamide-induced neutropenic mouse model (Studies XM02-PPD1-01)

Blood sampling on Day 3 was suboptimal and only 1-4/6 samples per treatment group could be analysed, therefore Day 3 results cannot be regarded as appropriate.

On Day 5, neutrophil counts in cyclophosphamide (CPA) group were significantly lower than in the control group. XM02- and Neupogen–treatments increased neutrophil counts in CPA-deprived animals; in both XM02 and Neupogen groups the effect of the highest dose (5.0 µg/kg) was also statistically significant. The dose-response curves of XM02 and Neupogen were very similar. There were no deaths during the study and no abnormal clinical observations were noted.

Effects of XM02 and Neupogen in a cyclophosphamide-induced neutropenic mouse model (Study XM02-PPD1-02) including results of meta-analysis of Studies XM02-PPD1-01 and XM02-PPD1-02

The study had an identical protocol as the Study XM02-PPD1-01 which was repeated due to problems in blood sampling on Day 3.

On Days 3 and 5, neutrophil counts in CPA group were significantly lower than in the control group. XM02- and Neupogen–treatments increased neutrophil counts in CPA-deprived animals. On Day 3, there was a linear relationship between the neutrophil count and the $\log_{10}$ dose level, and that dose-response relationship was not significantly different between XM02 and Neupogen. On Day 5, there was a linear relationship between $\log_{10}$ neutrophil count and the $\log_{10}$ dose level and it was found that the dose-response relationship was significantly different between Neupogen and XM02 (XM02 having a smaller effect) but they were parallel. There were no deaths during the study and no abnormal clinical observations were noted.

Since the protocols in Studies XM02-PPD1-01 and XM02-PPD1-02 were similar, a meta-analysis of the results was carried out. According to relative potency estimation for Day 3, it can be estimated that the effect on neutrophil count of 1.0 µg/kg of XM02 is equivalent to the effect of 2.4 µg/kg of Neupogen. The value of 1.0 was included in the 95% CI (0.98, 7.42) of the relative potency. For Day 5, the dose-response relationships were not significantly different between Neupogen and XM02 but were parallel. Therefore, the relative potency between Neupogen and XM02 cannot be assessed for Day 5. The results of the meta-analysis were not unequivocal but XM02 and Neupogen induced neutrophilia to a similar extent in neutropenic mice and there was a tendency towards comparable potencies in terms of the *in vivo* biological activity of XM02 and Neupogen.

Comparison of pharmacological response between XM02 and Neupogen in healthy rats after s.c. administration (Study XM02-RT4w-2.01)

Although low- and high-dose XM02 treated male animals had a statistical significant lower mean ANC at the end of the first treatment period than males treated with a corresponding doses of Neupogen, there were no consistent differences in ANC between XM02 and Neupogen-treated animals. A clear difference was noted between male and female animals treated with either XM02 or Neupogen.

Regardless of the medicinal product and the dose level, the pharmacodynamic response was substantially lower in females than in males.

Effects of XM02 on haematology in monkeys upon single s.c. or i.v. administration (Study XM02-PKPD-6.01)

No treatment-related changes of behaviour, external appearance, faeces or body weight were recorded. None of the monkeys died prematurely. Two monkeys showed a haematoma of 0.5 cm diameter and one monkey showed a haematoma of 1.0 cm diameter after the 2nd and 3rd test days at the site of i.v. injection, respectively. Monkeys that received s.c. injections of XM02 showed no local tolerance reactions at the injection site.

Treatment with XM02 resulted in increases in leukocytes, neutrophilic granulocytes and monocytes. The number of lymphocytes was decreased. Maximum changes were evident 4 to 8 hours after administration and lasted for > 48 hours. No significant differences were observed between i.v. and s.c. administration. A significant increase in neutrophils was observed in both i.v. and s.c. groups. The response appeared to be somewhat stronger in the animals that had received the drug by the s.c. route. This difference was not, however, statistically significant. A decreasing trend in haemoglobin, RBC and haematocrit values could be seen but these changes were not statistically significant. The lobularity index fell close to zero at 8 hours in the s.c. treatment group but was normalised by 48 hours. No treatment-related effect was determined for the number of platelets, the thromboplastin time, the mean corpuscular volume and the mean corpuscular haemoglobin.

- Secondary pharmacodynamics

Determination of the proliferation promoting effects of XM02 in comparison to Neupogen on human malignant cell lines (Study XM02-SPD-0.01)

G-CSF stimulates the proliferation and differentiation of granulocytic progenitor cells and mature neutrophils. G-CSF can also affect non-haematopoietic tumour cells which express functional G-CSF receptors. In this study, the effects of XM02 and Neupogen as a control compound were investigated on cell proliferation in 5 human tumour cell lines.

All the cell lines originate from the ATCC. Using treatment times of 72 or 144 hours and G-CSF concentrations of 10 pg/ml–100 µg/ml and assaying cell proliferation with MTS/PMS viable cell dye, no effect on cell proliferation by the G-CSF products was found.

- Safety pharmacology programme

Despite the absence of a recommendation in the CHMP guidance on similar medicinal product containing rG-CSF (EMEA/CHMP/BWP/31329/2005), *in vivo* studies were conducted to assess the potential of XM02 to affect vital functions using classical safety pharmacology tests. The safety pharmacology studies (key elements described in Table 1) included evaluation of the effects of XM02 on the respiratory system in rats **(Study XM02-SPRS-2.01)**, on the central nervous system in rats **(Study XM02-SPCNS-2.01)** and on the cardiovascular system in dogs **(Study XM02-SPCV-5.01)**. These studies were conducted in compliance with GLP regulations.

Effect of XM02 on the respiratory system in rats (Study XM02-SPRS-2.01)

No overall treatment-related change in the measured respiratory parameters was found. Minor but statistically significant differences between treated and control animals were found in absolute values of tidal volume at pre-dose and 120 min post-dose and in baseline-adjusted (change from pre-dose) values and occasionally respiratory minute volume at 120, 150, 180, 210, 225, 240 and 360 minutes

post-dose. There were no unscheduled deaths or adverse clinical signs observed following administration of a high dose of XM02.

Effects of XM02 on the central nervous system in rats (Study XM02-SPCNS-2.01)
The modified Irwin screen test was performed once pre-treatment and at 1, 2, 4, 24 and 48 hours post-treatment and the following parameters were examined: body position; restlessness; writhing; stereotypic behaviour; convulsions; twitches and tremors; grooming; ease of removal; gait; palpebral closure; piloerection; respiratory rate/pattern; locomotor activity level; defecation/urination; escape response; lacrimation; pupil size; salivation; diarrhoea; body tone; staub tail; cutaneous blood flow; corneal reflex; pinna reflex; tail pinch; auricular startle; righting reflex; positional passivity; vocalisation; and geotropism. No pharmacologically significant differences between XM02-treated and control animals were detected.

Blood and urine samples were collected for analysis on days 3 and 14/15. No toxicologically significant changes were detected in the analysed parameters. However, significant increases in total white blood cell counts, neutrophils, lymphocytes and monocytes were found in males and females on day 3 but the changes were no longer apparent on day 15. Neither deaths, treatment-related clinical signs, nor treatment-related gross histopathological findings were detected.

Effects of XM02 on the cardiovascular system in the dog (Study XM02-SPCV-5.01)
Haemodynamic measures remained within normal ranges throughout the observation period in all animals. Electrocardiograms showed no treatment-related changes. No mortality or treatment-related clinical signs were noted.

- Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies are not required for biosimilar products.

Pharmacokinetics

According to the guideline EMEA/CHMP/BMWP/31329/2005, pharmacokinetic experiments are not required for the development of biosimilar products. However, pharmacokinetic studies with XM02 (key elements described in Table 1) were performed. A monkey study investigated the plasma disposition of XM02 after a single i.v. or s.c. administration **(Study XM02-PK-6.01)**. This was also documented in conjunction with a 26-week s.c. toxicity study **(Study XM02-RT26w-6.01)**. In rats, the plasma pharmacokinetics was documented after a single dose and after 28 daily s.c. doses **(Study XM02-PK-2.01)**. In conjunction with a comparative immunogenicity study in rats, the pharmacokinetics of XM02 was compared to that of Neupogen **(Study XM02-RT4w-2.01)**.

Toxicokinetic results are reported in the toxicology section.

Methods of analysis
An enzyme-linked immunosorbent assay (ELISA) was used to quantify XM02 in rat plasma in **Studies XM02-PK-2.01**, **XM02-SPCNS-2.01** and **XM02-RT26w-6.01**. A human G-CSF immunoassay was used to quantify XM02 in monkey plasma in the **Study XM02-PK-6.01**.

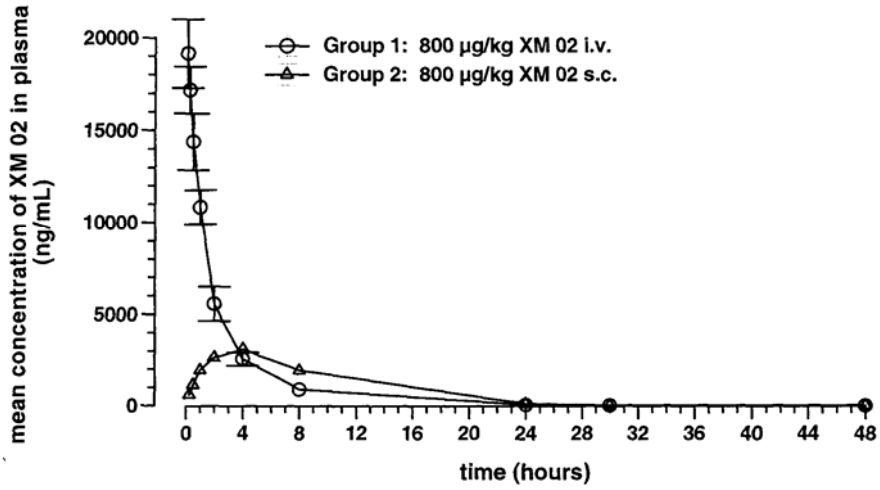
Absorption
Pharmacokinetics of XM02 following s.c. and i.v. injection in monkeys (Study XM02-PKPD-6.01)
Pharmacokinetic parameters following s.c. and i.v. administration are presented in Table 2.

Table 2 **Study XM02-PKPD-6.01 - Parameters of XM02 in monkeys following a single s.c. or i.v. administration**

Route	N	Dose (mg/kg)	C_{max} (ng/ml)	T_{max} (h)	$AUC_{0.08-48}$ (ng h/ml)	$AUC_{0.08-\infty}$ (ng h/ml)	$t_{1/2}$ elimination (h)
s.c.	M3	800 µg/kg	3083.33 ± 276.47	4	35609.01 ± 2312.43	35611.33 ± 2312.88	3.4 ± 0.2
i.v.	M3	800 µg/kg	19133.33 ± 1850.23	0.08	44815.05 ± 533.28	44815.32 ± 5330.63	2.6 ± 0.3

Plasma concentrations of XM02 over time after single i.v. and s.c. administrations are given in Figure 1.

Figure 1 **Study XM02-PKPD-6.01 - Plasma concentrations of XM02 in monkeys following a single s.c. or i.v. administration**



The AUC was slightly lower following s.c. administration (21%), however, the differences in the AUC values ($AUC_{0.08-48}$, $AUC_{0.08-\infty}$) of both application routes were not significant.

Pharmacokinetics of XM02 following repeated s.c. injection in rats (Study XM02-PK4-2.01)

Pharmacokinetic parameters of XM02 following daily s.c. injections to animals are presented in Table 3.

Table 3 **Study XM02-PK-2.01 - PK parameters of XM02 following daily s.c. injection in male rats on Days 1 and 28**

Day	Dose (µg/kg)	T_{max} (h)	C_{max} (ng/ml)	t_{last} (h)	$AUC_{0-tlast}$ (ng h/ml)	k (1/h)	AUC_{0-inf} (ng h/ml)	$t_{1/2}$ (h)
1	500	1	5216	24	18775	0.331	18779	2.1
28	500	1	5261	24	18448	0.226	18462	3.1

Since C_{max} and AUC parameters were virtually identical following repeated dosing and the half-lives were considered similar, it was considered that the kinetics of XM02 in rat plasma remained unchanged following repeated s.c. dosing.

Pharmacokinetics of XM02 following s.c. injection in rats (Study XM02-RT4w-2.01)

The pharmacokinetics of XM02 and Neupogen were also investigated in rats in association with a comparative immunogenicity study (key elements described in Table 1). The plasma concentration time profiles of XM02 over the three dose levels (single dose) are given in Figure 2 and pharmacokinetic parameters of XM02 and Neupogen in Tables 4 and 5.

Figure 2 **Study XM02-RT4w-2.01 - Plasma-concentration time profiles of XM02 after a single s.c. dose in rats**

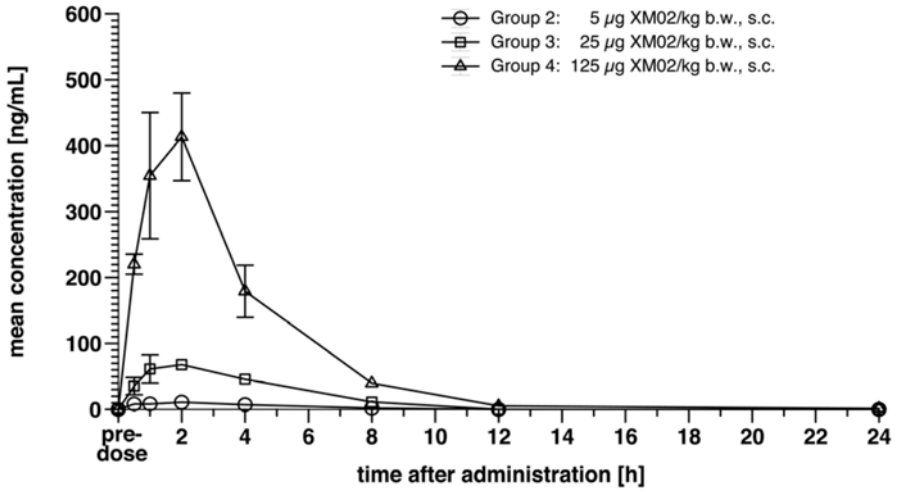


Table 4 **Study XM02-RT4w-2.01 - Non-compartmental PK analysis of XM02 in rats after single and repeated s.c. dosing**

Dose XM02 (µg/kg)	Sex	C_{max} ± SD (ng/ml)	T_{max} (h)	$t_{1/2elim}$ (h)	$AUC_{0\text{-}tlast}$ (ng h/ml)	AUC/dose (ng h kg/ml)	R	DPF
Day 1								
5	M	10.9±1.3	2.0	2.45	52.6	10.5	-	-
	F	13.3±4.4	1.0	2.29	39.8	8.0	-	-
25	M	68.0±8.4	2.0	2.26	326.1	13.0	-	1.2
	F	72.8±7.2	1.0	1.66	287.6	11.5	-	1.4
125	M	413.4±66.3	2.0	2.65	1743.6	13.9	-	1.3
	F	365.4±39.4	2.0	1.49	1488.8	11.9	-	1.5
Day 42								
5	M	11.0±0.4	2.0	1.06	43.5	8.7	0.8	-
	F	12.9±1.5	1.0	1.47	34.6	6.9	0.9	-
25	M	73.1±14.0	2.0	1.16	312.2	12.5	1.0	1.4
	F	69.2±25.5	1.0	1.29	277.0	11.1	1.0	1.6
125	M	452.6±138.5	2.0	1.28	2107.2	16.9	1.2	1.9
	F	584.7±23.1	1.0	1.26	2327.2	18.6	1.6	2.7

R accumulation factor (AUCTD42 0-t last/AUCTD1 0-t last)
DPF dose proportion factor [AUC0-t last (x µg/kg)/AUC0-t last (5 µg/kg)]/[(x µg/kg)/(5 µg/kg)] for the same day

The pharmacokinetics after a single s.c. injection of XM02 were linearly related to dose with an absorption T_{max} of 1 or 2 hours and a mean elimination half-life of approximately 2.5 hours in males and somewhat shorter half-life (1.6 hours) in females. At day 42, the elimination half-life became shorter and the relative exposure tended to increase with dose. In females, a slightly decreased clearance with time and, hence, a slight accumulation with time was noted.

Table 5 Study XM02-RT4w-2.01 - Non-compartmental PK analysis of Neupogen in rats after single and repeated s.c. dosing

Dose Neupogen (µg/kg)	Sex	C_{max} ± SD (ng/ml)	T_{max} (h)	$t_{1/2elim}$ (h)	$AUC_{0\text{-}tlast}$ (ng h/ml)	AUC/dose (ng h kg/ml)	R	DPF
Day 1								
5	M	11.8±1.1	2.0	1.89	52.9	10.6	-	-
	F	11.6±2.1	1.0	1.15	48.7	9.7	-	-
25	M	69.6±3.1	2.0	1.86	328.8	13.2	-	1.2
	F	75.5±15.6	1.0	1.63	284.4	11.4	-	1.2
125	M	409.7±20.3	1.0	1.89	1961.1	15.7	-	1.5
	F	463.7±110.2	1.0	1.43	1659.0	13.3	-	1.4
Day 42								
5	M	12.4±3.9	2.0	1.89	44.1	8.8	0.8	-
	F	6.9±4.6	1.0	1.34	30.8	6.2	0.6	-
25	M	77.0±41.9	2.0	1.68	264.3	10.6	0.8	1.2
	F	77.2±10.5	2.0	1.06	304.8	12.2	1.1	2.0
125	M	390.6±72.1	2.0	1.53	1565.1	12.5	0.8	1.4
	F	546.8±278.1	2.0	1.08	2199.0	17.6	1.3	2.9

R accumulation factor (AUCTD42 0-t last/AUCTD1 0-t last)
DPF dose proportion factor [AUC0-t last (x µg/kg)/AUC0-t last (5 µg/kg)]/[(x µg/kg)/(5 µg/kg)] for the same day

The pharmacokinetic parameters for Neupogen were very similar and no significant difference was observed.

Distribution
No studies on distribution of XM02 have been performed.

Metabolism
No studies on metabolism of XM02 have been performed.

Excretion
No studies on excretion of XM02 have been performed.

Pharmacokinetic drug interactions
No pharmacokinetic drug interaction studies on XM02 have been performed.

Other pharmacokinetic studies
Not applicable.

Toxicology

The toxicology programme included one single-dose toxicity study in rats **(Study XM02-SPCNS-2.01)**, a 26-week repeat-dose toxicity study in rats **(Study XM02-RT26w-2.01)** as well as in monkeys **(Study XM02-RT26w-6.01)**, two local tolerance studies in rabbits **(Studies XM02-LT-4.01** and **XM02-LT-4.02)** and a 28-day comparative immunogenicity study in rats **(Study XM02-RT4w-2.01)** (key elements of these studies are described in Table 1). One of the local tolerance studies, as well as the immunogenicity study, was comparative in nature. Contradictory to the requirements in the guideline EMEA/CHMP/BMWP/42832/2005, the repeat-dose toxicity studies were non-comparative. However, the applicant had sought scientific advice and CHMP was of the opinion (EMEA/CHMP/SAWP/317893/2005) that comparative repeat-dose studies were not required.

- Single-dose toxicity

Single-dose toxicity study on XM02 in the rat following s.c. injection in rats (Study XM02-SPCNS-2.01)
In a single-dose toxicity study evaluation was performed in conjunction with the modified Irwin screen test assessing central nervous system effects in rats with 14-day observation period, XM02 at

3500 µg/kg showed an increase in white blood cell parameters in males and females on day 3 and no other important findings.

- Repeat-dose toxicity

Repeat-dose toxicity study (with a 4-week interim study) in rats (Study XM02-RT26w-2.01) and repeat-dose toxicity study (with a 4-week interim study) in monkeys (Study XM02-RT26w-6.01)

In rats, the main toxicological finding was swelling of hindlimbs/hindpaws and/or forepaws, necessitating premature sacrifice in mid- and high-dose animals. Macroscopically, all dose groups showed enlargement of the tarsal joint with histological findings of osteopathy primarily in mid- and high-dose males but also occasionally in females. An increased incidence of hyperostosis, osteodystrophy and/or physeal dystrophy was observed also in the femoro-tibial joint of mid- and high-dose animals. Dose-related increases in serum alkaline phosphatase were consistent with the increased bone turnover.

Bone changes following G-CSF treatment have been observed in rodents and humans, as a result of increased bone resorption mediated by osteoclast activation. The effect is regarded as an extension of the pharmacological effect of G-CSF.

Findings more clearly related to the primary pharmacological effect consisted of a dose-related increase in neutrophil count and increases in other white blood cells in mid-and high-dose animals. These groups also showed reductions in red blood cell count, haemoglobin concentration and increases in reticulocyte count consistent with observations made in other rat studies with rG-CSF.

In monkeys, a drug-related but not strongly dose-related local irritant effect was observed at the injection sites. Effects on bone were less marked than in the rat study with no clinical symptoms linked to the observed hyperostosis that affected the periosteum and/or endosteum of high-dose animals. Dose-related increases in the primary pharmacodynamic parameter, neutrophil count, were generally similar at the 4-, 12- and 26-week readings with increases in other white blood cells and smaller decreases in red blood cell count and haemoglobin as also observed in the rat study.

Table 6 summarises the comparative findings in toxicology studies with XM02 and those from a review of existing data for Neupogen.

Table 6 Study XM02-RT26w-2.01 and XM02-RT26w-6.01 - Comparison of toxicological findings in rat and monkeys between XM02 and rhG-CSF (filgrastim) data obtained from US FDA pharmacology reviews on pegfilgrastim

Finding	Rat		Monkey	
	XM02	Filgrastim	XM02	Filgrastim
Clinical observations				
Articular and hind limb swelling	√	√		
Cerebral haemorrhage				√
Haematology				
Increased neutrophil count	√	√	√	√
Morphological changes in neutrophils		√	√	√
Increased monocytes (modest)	√	√	√	√
Increased lymphocytes (modest)	√	√	√	√
Decreased erythrocyte count, haematocrit, haemoglobin	√	√	√	√
Decreased platelet counts		√		
Clinical Chemistry				
Increased serum alkaline phosphatase	√	√	√	√
Decreased serum cholesterol	√	√	√	√
Increased total protein			√	
Decreased serum potassium	√	√		
Decreased serum glucose	√	√	√	√
LDH elevations	√	√	√	√
ALT, AST elevations	√	√		
Gross Pathology				
Splenomegaly; increased weight	√	√	√	√
Liver weight increases (modest)	√	√	√	
Thyroid weight decrease (females)			√	
Histopathology				
Increased granulopoiesis in bone marrow	√	√	√	√
Extramedullary haematopoiesis in spleen, liver and lymph nodes	√*	√		√
Leucocytosis in e.g. liver and/or lymph nodes	√	√	√	√
Injection site inflammation, mononuclear cell infiltration			√	√
Increased osteoblast, osteoclast activity	√	√	√**	

* only seen in spleen with XM02
** observed in 1 of 4 high-dose males and females

- Genotoxicity

Not applicable.

- Carcinogenicity

No carcinogenicity studies have been conducted on any marketed G-CSF product.

- Reproduction toxicity

No studies on reproductive and developmental toxicity were performed since it is not requirement for a biosimilar product.

- Toxicokinetic data

Repeat-dose toxicity study (with a 4-week interim study) in monkeys (Study XM02-RT26w-6.01)

Toxicokinetics was determined in monkeys following a 4-week daily s.c. administration of XM02. The results are summarised in Table 7.

Table 7 Study XM02-RT26w-6.01 - Toxicokinetic analysis in monkey following daily s.c. administration of XM02

Sex	Dose XM02 (µg/kg)	T_{max} (h)	C_{max} (ng/ml)	$AUC_{0\text{-tlast}}$ (ng h/ml)	K_{el} (1/h)	$t_{1/2elim}$ (h)	$AUC_{0\text{-inf}}$ (ng h/ml)	% extrapolation $AUC_{0\text{-inf}}$	RV_z (ml/kg	CL (ml/h/kg)
Day 1										
M	0	-	-	-	-	-	-	-	-	-
	125	2	1024	3169	0.180	3.85	3186	0.56	218	39.2
F	0	-	-	-	-	-	-	-	-	-
	125	1	908	2597	0.201	3.46	2604	0.29	239	48.0
Day 28										
M	0	-	-	-	-	-	-	-	-	-
	125	2	905	3724	0.0603	10.5	3772	1.28	500	33.1
F	0	-	-	-	-	-	-	-	-	-
	125	2	812	3510	0.0890	7.79	3553	0.64	398	35.4

Exposure was slightly higher in males. Elimination half-time was clearly increased from Days 1 to 28 in both males and females. Concomitant increase in exposure indicates accumulation of XM02. Although C_{max} from Days 1 to 28 decreased slightly, exposure as assessed by AUC increased. This, together with changes in $t_{1/2}$ and clearance measurements from Days 1 to 28 suggested a slight decrease in XM02 elimination from plasma over time. In general, the C_{max} and AUC in high-dose were approximately 19 and 5-fold higher than the corresponding exposures in humans given a s.c. dose of 10 µg/kg.

- Interspecies comparison

Comparison of toxicokinetic parameters in rats and monkeys is presented in the Table 8.

Table 8 Study XM02- XM02-RT4w-2.01 and XM02-RT26w-6.01 - Mean exposure to XM02 in rats and monkeys following s.c. repeated dosing

Study	Daily Dose (µg/kg)	$AUC_{0\text{-tlast}}$ (ng.h/ml)				C_{max} (ng/ml)			
		Day 1		Day 42		Day 1		Day 42	
		M	F	M	F	M	F	M	F
Rat XM02-RT4w-2.01	5	52.6	39.8	43.5	34.6	10.9	13.3	11.0	12.9
	25	326.1	287.6	312.2	277.0	68.0	72.8	73.1	69.2
	125	1743.6	1488.8	2107.2	2327.2	413.4	365.4	452.6	584.7
Monkey XM02-RT26w-6.01	5	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	25	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	125	3169	2597	3724	3510	1024	908	905	812

Generally, the exposure (AUC) was 3- to 5-fold higher in humans than in rats at the corresponding dose level 5 µg/kg (Table 9). Toxicokinetics in monkeys were measured only in high-dose (125 µg/kg) animals. In both rats and monkeys, a slightly increased exposure was observed in males. Many of the toxicological findings in rats were clearly more profound in males than in females. Also, the pharmacological response appeared to be different in male and female rats, females being less responsive. In monkeys this effect was not evident.

Table 9 Geometric means of AUC and C_{max} of G-CSF following a s.c. injection of 5 µg/kg of XM02 or Neupogen to healthy volunteers and cancer patients

Geometric mean	AUC* (ng.h/ml)		C_{max} (ng/ml)	
	XM02	Neupogen	XM02	Neupogen
Phase I study XM02-01-LT	158.4	143.1	23.5	21.2
Phase I study XM02-05-DE	157.6	159.4	18.0	18.4
Phase III study XM02-02-INT	305.3	258.5	36.1	29.0
Phase III study XM02-03-INT	272.5	240.1	25.2	23.7
Phase III study XM02-04-INT	183.5	188.1	20.1	18.8

$AUC_{0\text{-t}}$ $_{in}$ Phase I studies t was 48 hours, in Phase III studies t was 24 hours

Note in Phase III studies, results are from the first injection during the first chemotherapy cycle

- Local tolerance

Local tolerance of XM02 following a single administration to rabbits (Study XM02-LT-4.01)

Evaluation of the injection sites according to the Draize criteria up to 4 days post-dose revealed no test article-related irritant potential after intravenous, intramuscular, intra-arterial, subcutaneous or peri-venous administration, either through macroscopic or microscopic evaluation.

Local tolerance of XM02 and Neupogen following a single administration in rabbits (Study XM02-LT-4.02)

Similarly to the first study, no irritant potential of XM02 after intravenous, intramuscular, intra-arterial, subcutaneous and peri-venous administration either through macroscopic or microscopic evaluation was observed.

- Other toxicity studies

Antigenicity

Repeat-dose toxicity study on XM02 vs. Neupogen daily s.c. injection in rats (Study XM02-RT4w-2.01)

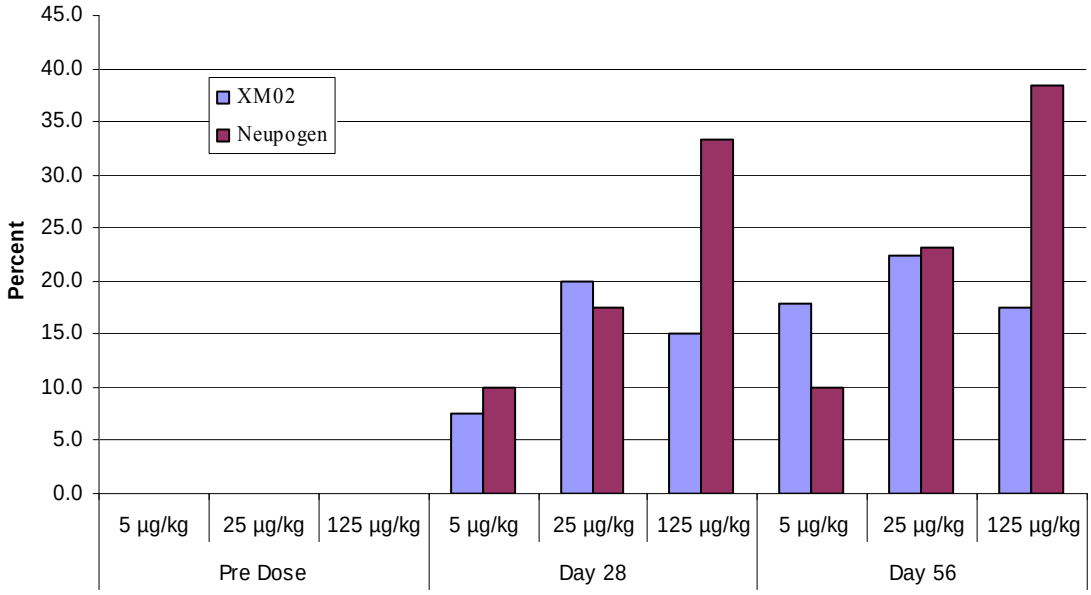
The administration scheme (2 weeks of treatment followed by a 2-week treatment-free period and then followed by another 2 weeks of treatment) was chosen following Scientific Advice from the EMEA in order to fulfil several requirements:

- overall treatment duration of 28 days
- daily administrations
- treatment interruption of 2 weeks:
  - imitates the clinical situation of a chemotherapy patient treated in a chemotherapy cycle with a duration of 4 weeks
  - is applied in standard immunisation protocols and could therefore possibly stimulate the immune response to the proteins
- antibody determination after a treatment-free interval avoids interference of the test serum antigen, minimises immune complexes and therefore the antibody results are more reliable.

The s.c. route was chosen because this is the predominant route for administration of XM02 to humans. Main study animals were left for a treatment-free period of 2 weeks after the final drug administration.

The assessment of antibody formation was done sequentially where initially all samples were screened for anti-XM02 and anti-Neupogen IgG and IgM antibodies. The qualitative assessment of the antibody response showed a higher antibody response to XM02 compared to Neupogen in the lowest dose at Day 56 but a lower antibody response in the highest dose at both time points (Figure 3).

Figure 3 **Study XM02-RT4w-2.01 – Distribution of positive antibody samples as percentage of total samples in the various dose groups**



In the quantitative xMAP assay, 76 out of the 92 samples that tested positive in the screening test could be quantified for their IgG anti-XM02 and anti-Neupogen antibodies. This would suggest that the non-quantifiable antibodies (approximately 17%) were IgM antibodies. The median concentration of IgG antibodies in the Day 28 samples was similar for the two compounds but somewhat higher in samples from Neupogen treated animals collected on Day 56. The maximum IgG antibody concentration was also higher in Neupogen-treated animals at the last sampling time (Table 10).

Table 10 **Study XM02-RT4w-2.01 - Median and maximum IgG antibody concentration (ng/ml) in XM02- and Neupogen-treated animals**

	Median antibody concentration			Maximum antibody concentration		
	5 µg/kg	**25 µg/kg**	**125 µg/kg**	**5 µg/kg**	**25 µg/kg**	**125 µg/kg**
XM02						
Day 28	NA	18.2	33.1	20.3	31.3	248.7
Day 56	67.7	58.5	80.6	141.2	280.1	698.9
Neupogen						
Day 28	8.0	19.0	26.4	29.9	437.4	304.0
Day 56	92.7	187.0	148.3	456.7	4127.7	2419.3

Ecotoxicity/environmental risk assessment

The lack of an environmental risk assessment for XM02 is justified by three reasons:

4 According to EMEA guideline CHMP/SWP/4447/00 proteins in general are unlikely to result in significant risk to the environment.

5 XM02 active substance is a recombinant protein, which is very similar to naturally occurring human G-CSF. Therefore no potentially harmful effects to the environment are expected.

6 XM02 is a biosimilar product of existing G-CSF. It is intended to substitute for other identical products on the market. The approval of XM02 should not result in an increase of the total quantity released into the environment.

2.4 Clinical aspects

Introduction

Filgrastim (recombinant human granulocyte colony stimulating factor, rG-CSF) is a haematopoietic growth factor that regulates the production and function of neutrophils. Filgrastim controls the proliferation of committed progenitor cells and influences their maturation into mature neutrophils. Filgrastim also stimulates the release of neutrophils from bone marrow storage pools and reduces their maturation time. Filgrastim acts to increase the phagocytic activity of mature neutrophils. The first filgrastim product was introduced in 1991 under the trade name Neupogen.

Of note, throughout the report, XM02 will be used to identify the filgrastim under evaluation and Neupogen (manufactured by Roche or Amgen) for the reference product.

The formulation of XM02 has the same excipients as Neupogen and is quantitatively very similar. In order to show the biosimilarity between XM02 and Neupogen, the clinical programme is composed of 5 clinical studies, summarised in Table 11 and focuses on showing the clinical equivalence of XM02 and Neupogen in all respects, i.e. clinical pharmacology in 2 phase I studies, efficacy and safety in 3 phase III studies.

Table 11 Tabular listing of clinical studies

Type of Study	Study Code; Status; Type of Report	Objective(s) of the Study	Healthy Subjects or Diagnosis of Patients	Study design	Test Product(s); Dosage Regimen; Route of Admin.	Number of Subjects	Duration of Treatment
PK (PK/PD)	XM02-01-LT complete full	Comparison of PK-and PD parameters	Healthy male	Cross over, 2 arms with 2 periods	T: XM02 vs. R: Neupogen, Single dose A: 5 µg/kg s.c. B: 10 µg/kg s.c.	56 (2x28 random.) completed: A: 24 B: 26	single dose 96-hour periods 2-week wash-out
BE (PK/PD)	XM02-05-DE complete full	Demonstration of equivalence of PK and PD parameters	Healthy female or male	Cross over, 4 groups with 2 periods	T: XM02 vs. R: Neupogen; Single dose of 1: 5 µg/kg i.v. 2: 10 µg/kg i.v. 3: 5 µg/kg s.c. 4: 10 µg/kg s.c	144 (4x36 random.) completed: (PK) 1: 36 2: 35 3: 35 4: 34	single dose 16-day periods 3-week wash-out
Efficacy	XM02-02- INT complete full	Demonstration of equivalence in efficacy (DSN) - Safety - PK (subgroup)	Breast cancer with chemotherapy (CTX)	Randomised, placebo- and active-controlled	T: XM02 vs. R: Neupogen P: Placebo (CTX Cycle 1) then switch to XM02 5 µg/kg s.c.	ITT/PP T:140/133 R:136/129 P: 72/58	per CTX-cycle: 5-14 days (until ANC $\geq 10x10^9$/l) up to 4 CTX cycles
Safety	XM02-03-INT complete full	Safety - Efficacy (DSN) - PK (subgroup)	Lung cancer with CTX (platinum-based)	Randomised, active controlled (first cycle)	T: XM02 vs. R: Neupogen (CTX Cycle 1) then switch to XM02 5 µg/kg s.c.	Safety/PP T:158/148 R: 79/ 77	per CTX-cycle: 5-14 days (until ANC $\geq 10x10^9$/l) up to 6 CTX cycles
Safety	XM02-04-INT complete full	Safety - Efficacy (DSN) - PK (subgroup)	Non-Hodgkin lymphoma with CTX (CHOP)	Randomised, active controlled (first cycle)	T: XM02 vs. R: Neupogen (CTX Cycle 1) then switch to XM02 5 µg/kg s.c.	Safety/PP T: 63/55 R: 29/29	per CTX-cycle: 5-14 days (until ANC $\geq 10x10^9$/l) up to 6 CTX cycles

According to the guideline on similar biological medicinal products (CHMP/437/04), Neupogen Amgen (German trade ware) was chosen as reference product. Neupogen is a medicinal product authorised in the European Union and therefore fulfils the criteria laid down in this guideline.

Design and conduct of all 3 clinical efficacy studies were based on recommendations as outlined in the CHMP "Note for guidance on the comparability of medicinal products containing biotechnology-derived proteins as active substance non-clinical and clinical issues" (CPMP/3097/02/Final) and took into account the "Note for guidance on clinical trials with haematopoietic growth factors for the prophylaxis of infection following myelosuppressive or myeloablative therapy" (CPMP/EWP/555/95).

Study XM02-02-INT followed advice given by the SAWG of the EMEA, as well as therapeutic guidelines and recommendations as proposed by the American Society of Clinical Oncology (ASCO) in 2000 and the European Society of Medical Oncology (ESMO). **Studies XM02-03-INT** and **XM02-04-INT** followed the recommendations of the SAWG regarding the study design.

GCP

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

According to the Annex to the Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues - Guidance on Biosimilar Medicinal Products containing Recombinant Granulocyte-Colony Stimulating Factor (CHMP/31329/05), the pharmacokinetic properties of the similar biological medicinal product and the reference medicinal product should be compared in single-dose cross-over studies using subcutaneous and intravenous administration. The primary pharmacokinetic parameter should be AUC and the secondary PK parameters C_{max} and $t_{½}$.

Comparative pharmacokinetic studies were designed to demonstrate clinical comparability between the similar biological medicinal product and the reference medicinal product with regard to key pharmacokinetic parameters. Two Phase I studies compared the pharmacokinetic and pharmacodynamic properties of XM02 and Neupogen in healthy volunteers (**Studies XM02-05-DE** and **XM02-01-LT**). Both Phase I studies were single-blind, randomised, single-dose, two-period crossover studies, in healthy volunteers. Doses of 5 and 10 µg/kg were administered since they are recommended in Neupogen Summary of Product Characteristics (SPC) as usually employed for most indications.

In Study XM02-01-LT, the reference product was Neupogen (Roche) sourced from Lithuanian trade ware before accession to the European Union on request from the Lithuanian Ministry of Health during the approval process of the study. Therefore, according to the Guideline on Similar Biological Medicinal Products (Committee for Medicinal Products for Human Use [CHMP]/437/04), the data generated in this study are regarded as supportive.

In Study XM02-05-DE, the reference product was Neupogen (Amgen) sourced from German trade ware. The data generated in this study are considered as pivotal as the study design followed the product-specific guidance on biosimilar medicinal products containing recombinant granulocyte-colony stimulating factor (CHMP/Biosimilar Medicinal Products Working Party/31329/2005).

In addition, pharmacokinetics of XM02 and Neupogen after s.c. dosing were evaluated in subset of patients receiving chemotherapy (**Studies XM02-02-INT, XM02-03-INT** and **XM02-04-INT**). The dose of 5 µg/kg/day XM02 or Neupogen was chosen based on the recommended dose for Neupogen.

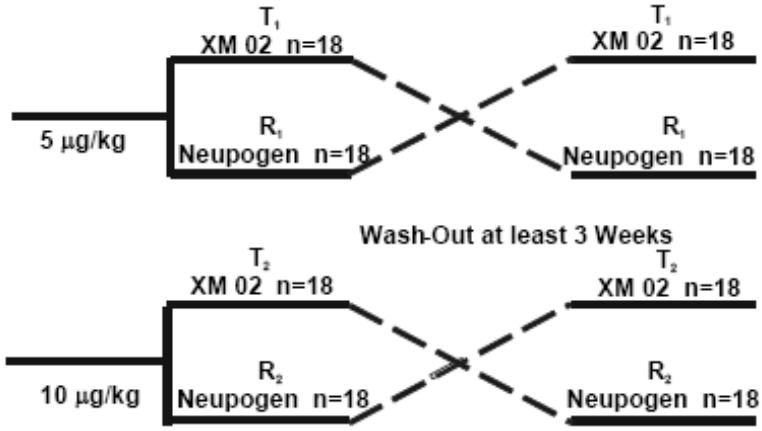
- Pharmacokinetics in healthy volunteers

Study XM02-05-DE
This was a phase I, multicentre, single-dose, single-blind, randomised, 2-period crossover study to compare pharmacokinetic and pharmacodynamic characteristics of i.v. or s.c. XM02 and Neupogen in 144 healthy male and female Caucasian volunteers. Each subject was randomly assigned to receive:

- Either Group 1: 5 µg/kg of XM02 and Neupogen (or vice versa) as an i.v. infusion;
- Or Group 2: 10 µg/kg of XM02 and Neupogen (or vice versa) as an i.v. infusion;
- Or Group 3: 5 µg/kg of XM02 and Neupogen (or vice versa) as an s.c. injection;
- Or Group 4: 10 µg/kg of XM02 and Neupogen (or vice versa) as an s.c. injection.

Figure 4 displays the treatment allocation and in schematic manner the study design.

Figure 4 Study XM02-05-DE: Schematic presentation of study design



T = test treatment group (XM02); R = reference treatment group (Neupogen)

Blood samples for determination of pharmacodynamic data were collected at 0, 30, 60 minutes and 2, 4, 6, 8, 10, 12, 16, 20, 24, 32, 48, 72 and 96 hours for ANC determination and at 0, 24, 48, 72, 96, 120, 144, 168 (Day 8), 240 (Day 11) and 336 hours (Day 15) for CD34+ cell count determination.

Study objectives
The primary study objective was the comparison of r-MetHuG-CSF pharmacokinetic concentration-time parameter AUC_{0-t} to demonstrate equivalence of XM02 and Neupogen after a single 5 or 10 µg/kg dose i.v. infusion or s.c. injection in healthy subjects.

The secondary study objectives were to demonstrate equivalence of XM02 and Neupogen after a single 5 or 10 µg/kg dose i.v. infusion or s.c. injection in healthy subjects in comparing:

- r-MetHuG-CSF pharmacokinetic parameters;
- r-MetHuG-CSF pharmacodynamic parameters for absolute neutrophil count and CD34+;
- collection of the tolerability and safety data.

Data analysis
The pharmacokinetic parameters were calculated from serum concentrations of r-MetHuG-CSF (test and reference product) using non-compartmental procedures. The primary pharmacokinetic objective was AUC_{0-t} and secondary objectives were C_{max}, AUC_{0-inf}, t_{max}, $T_{1/2}$, and λ_z.

The equivalence between the test and reference products was tested by parametric and non-parametric approaches. Parametric (normal-theory) methods (analyses of variance [ANOVA]) were applied for the analysis of log-transformed parameters (AUC_{0-t}, AUC_{0-inf}, C_{max}, $t_{1/2}$). Non log-transformed parameters (t_{max}) were evaluated by nonparametric tests. ANOVA point estimates with coefficients of variation (CV) and 90% confidence intervals (CI) are given in for the test/reference ratios of the

primary and secondary (except for t_{max}) pharmacokinetic parameters. The applicant defined that the primary endpoint AUC_{0-t} of r-MetHuG-CSF serum concentration needs to be within 80-125% of the reference product.

Non-parametric point estimates and 90% CI for the "test-reference" difference of non log-transformed parameters (t_{max}) were calculated. The non-parametric point estimators and the non-parametric 90% confidence intervals for the difference "test-reference" were calculated according to the Mann/Whitney/Wilcoxon statistics using the non log-transformed parameters.

Only those subjects who completed both study periods were included in comparative pharmacodynamic/pharmacokinetic analysis.

Results
Seventeen (17) subjects withdrew prematurely from the study; 124 completed both study periods without major protocol deviations and were included in pharmacokinetic and pharmacodynamic analyses: Group 1 n = 31, Group 2 n = 30, Group 3 n = 33, Group 4 n = 30.

Pharmacokinetic parameters and summary of the bioequivalence evaluation of r-MetHuG-CSF are presented in Table 12.

Table 12 Study XM02-05-DE: ANOVA and 90% confidence intervals for (log-transformed) pharmacokinetic characteristics of r-MetHuG-CSF

Pharmacokinetic characteristics r-MetHuG-CSF	ANOVA CV [%]	Point estimate Test/Ref. Ratio	90% Confidence interval
	Group 1 (i.v. 5 µg/kg)		
AUC_{0-t}	11.90	101.65	96.55 - 107.01
$AUC_{0-\infty}$	11.84	101.61	96.54 - 106.95
C_{max}	11.42	102.37	97.44 - 107.55
$t_{1/2}$	42.02	97.71	82.03 - 116.37
	Group 2 (i.v. 10 µg/kg)		
AUC_{0-t}	9.78	106.62	102.14 - 111.30
$AUC_{0-\infty}$	9.75	106.62	102.15 - 111.29
C_{max}	8.19	104.58	100.88 - 108.41
$t_{1/2}$	35.00	102.87	88.58 - 119.48
	Group 3 (s.c. 5 µg/kg)		
AUC_{0-t}	16.62	98.63	92.05 - 105.66
$AUC_{0-\infty}$	16.47	98.66	92.15 - 105.64
C_{max}	27.28	97.55	87.22 - 109.10
$t_{1/2}$	31.83	87.84	77.15 - 100.01
	Group 4 (s.c. 10 µg/kg)		
AUC_{0-t}	11.49	109.39	104.02 - 115.03
$AUC_{0-\infty}$	11.43	109.35	104.01 - 114.96
C_{max}	17.50	107.17	99.30 - 115.66
$t_{1/2}$	18.53	94.34	87.02 - 102.27

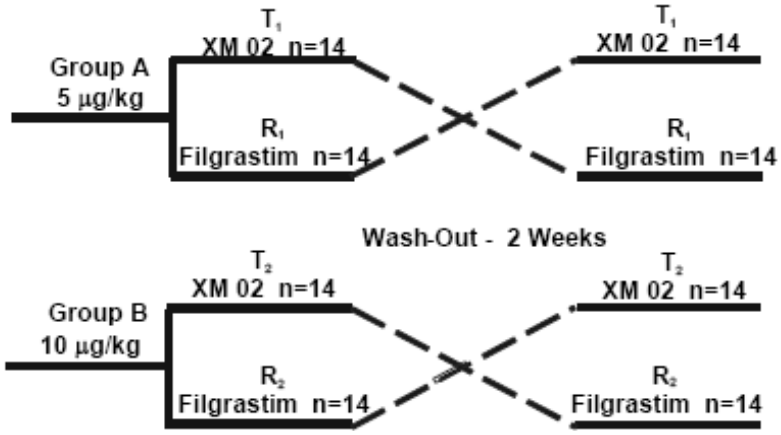
On the basis of the primary target parameter AUC_{0-t}, the equivalence between XM02 and Neupogen in both dose groups after either s.c. or i.v. administration was demonstrated.

After i.v. administration, there was a dose-proportional increase of AUC_{0-t} and C_{max} from the 5 to the 10 µg/kg dose. After s.c. administration, there was a 3-fold increase of AUC_{0-t} and C_{max} from the 5 to the 10 µg/kg dose. The absolute bioavailability of s.c. XM02 was 33 and 45% for the 5 and 10 µg/kg doses, respectively.

Study XM02-01-LT
This was a phase I, single-centre, single-blind, single-dose, randomised, 2-period cross-over, 2-arm study in 56 healthy male Caucasian subjects to compare pharmacokinetic and pharmacodynamic profiles of XM02 and Neupogen. Each subject was randomly assigned to receive either s.c. 5 µg/kg

(Group A) or s.c. 10 µg/kg (Group B) of the study drugs. Figure 5 gives a synoptic view of the overall study design.

Figure 5 Study XM02-01-LT - Schematic presentation of study design



T = test treatment group (XM02); R = reference treatment group (Neupogen)

Blood samples for determination of pharmacodynamic data (i.e., ANC_{max}, ANC_{AUC}, ANC_{tmax}) were collected at 0, 30, 60 and 90 minutes, and 2, 3, 4, 6, 8, 10, 12, 16, 24, 32, 40, 48, 72 and 96 hours after study drug injection.

Study objectives

The primary study objective was the comparison of the pharmacodynamic parameters (ANC_{max}, ANC_{AUC}, ANC_{tmax}) of XM02 and Neupogen after s.c. administration of 5 µg/kg or 10 µg/kg , in healthy male subjects.

The secondary study objectives were:

- comparison of the pharmacokinetic parameters (C_{max}, AUC, T_{max}, $T_{1/2}$, λz) of XM02 and Neupogen after s.c. administration of 5 µg/kg in healthy male subjects;
- comparison of the pharmacokinetic parameters (C_{max}, AUC, T_{max}, $T_{1/2}$, λz) of XM02 and Neupogen after s.c. administration of 10 µg/kg in healthy male subjects;
- collection of tolerability and safety data;
- calculation of the relative bioavailability (F) of XM02 formulation versus Neupogen;
- comparison of the pharmacodynamic and pharmacokinetic parameters of 5 and 10 µg/kg doses of XM02.

Results

All 56 subjects were healthy male Caucasians. Median age was 21.5 years (range 19 to 40 years). BMI range was 18.5-29.9 kg/m^2. Of the 56 subjects, 50 completed the study.

Mean G-CSF serum concentrations over time following a single s.c. injection of XM02 or Neupogen are presented in Figures 6 and 7 for the 5 and 10 µg/kg doses, respectively.

Figure 6 **Study XM02-01-LT - Mean serum concentration-time profile of G-CSF following a single s.c. injection of 5 µg/kg of XM02 or Neupogen**

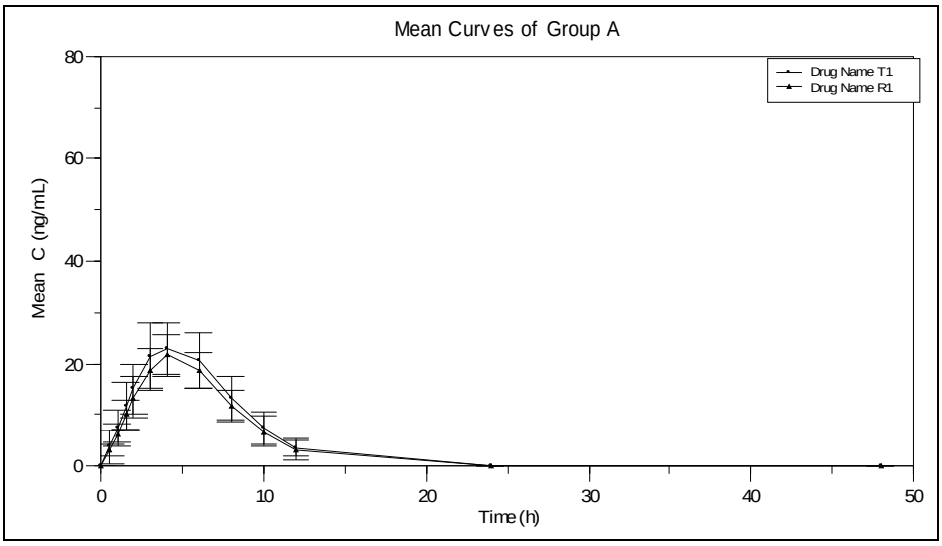
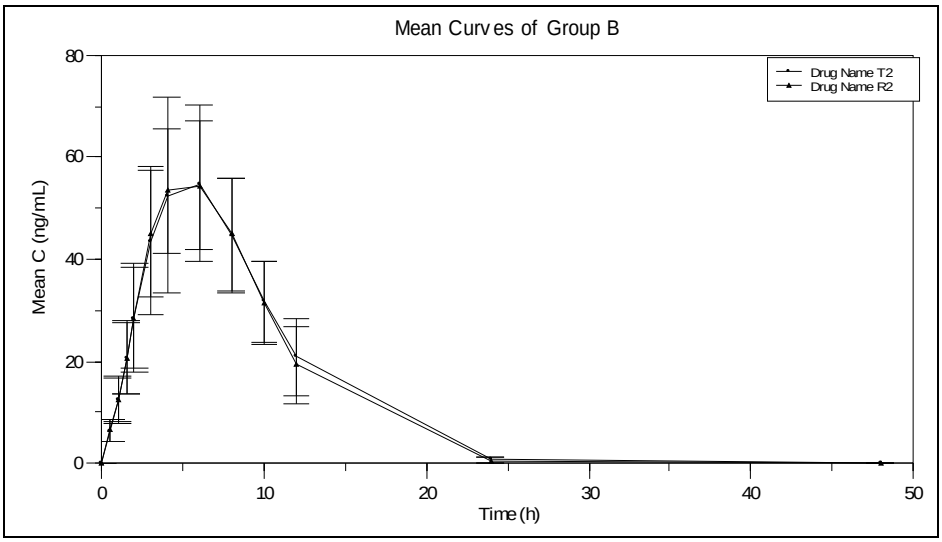


Figure 7 **Study XM02-01-LT - Mean serum concentration-time profile of G-CSF following a single s.c. injection of 10 µg/kg of XM02 or Neupogen**



In both dose and treatment groups, mean G-CSF serum concentrations rapidly increased, reached a maximum around 5 hours, and decreased to pre-dose values at 24 hours.

ANOVA demonstrated equivalence of XM02 and Neupogen with regard to pharmacokinetic variables in both 5 and 10 µg/kg dose groups after a single s.c. injection. CIs for all log-transformed and non log-transformed variables (AUC_{0-t}, $AUC_{0-\infty}$, C_{max} and t_{max}, λ_z, respectively) were enclosed within the 80-125% acceptance intervals for both dose regimens. The variable $t_{1/2}$ was enclosed within the 80-125% acceptance interval for the 5 µg/kg but not for the 10 µg/kg dose.

The relative bioavailability of XM02 versus Neupogen was estimated to be 1.12 for the 5 µg/kg dose and 1.04 for the 10 µg/kg dose. Serum concentrations and AUC of G-CSF increased over-proportionally after a 10 µg/kg dose compared to a 5 µg/kg dose.

- Pharmacokinetic in target population

The PK profiles of XM02 and Neupogen were investigated in a subset of patients in 3 phase III studies: breast cancer (**Study XM02-02-INT**), lung cancer (**Study XM02-03-INT**) and Non-Hodgkin-Lymphoma (**Study XM02-04-INT**), who received G-CSF support in addition to CTX. The studies did not employ cross-over designs and it was not planned to demonstrate bioequivalence.

In all 3 phase III studies, patients received 5 µg/kg XM02 or Neupogen daily for between 1 and 6 cycles, and pharmacokinetic profiles were determined during cycles 1 and 4 (after initial dosing and after ANC nadir). The s.c. administration site was chosen by the drug administrator in order to reflect the situation in clinical practice.

Table 13 displays the main study results.

Table 13 Studies XM02-02-INT, XM02-03-INT and XM02-04-INT - Geometric means of AUC and C_{max} of G-CSF following a s.c. injection of 5 µg/kg of XM02 or Neupogen cancer patients

	Treatment		AUC_{0-24} (ng/ml/h)	C_{max} (ng/ml)	t_{max} (h)	$t_{½}$ (h)
XM02-02-INT	Test	n = 14	305.3	36.1	4	3.0
	Reference	n = 13	258.5	29.0	4	3.2
	Ratio		1.18	1.24		
XM02-03-INT	Test	n = 13	272.5	25.2	6	3.5
	Reference	n = 12	240.1	23.7	6	3.3
	Ratio		1.13	1.06		
XM02-04-INT	Test	n = 11	183.5	20.1	6	3.2
	Reference	n = 4	188.1	18.8	5	3.8
	Ratio		0.98	1.07		

Note results are from the first injection in the first chemotherapy cycle

In all cycles and profiles, mean G-CSF serum concentrations reached a maximum around 4 to 6 hours and decreased to pre-dose values at 24 hours (as in healthy volunteers). Mean AUC and C_{max} values of G-CSF in cycle 1 were slightly higher in the cancer patients compared to healthy volunteers, as might be expected for patients with poor clinical condition. There were no signs of accumulation after repeated dosing in cancer patients (in all 3 studies, mean serum concentrations of G-CSF were lower in cycle 4 than in cycle 1).

- Special populations

According to the guidance, PK investigations in special populations (e.g., hepatic or renal impairment, elderly, etc.) are not required for products claimed to be biosimilar.

Pharmacodynamics

- Mechanism of action

Endogenous G-CSF is a haematopoietic cytokine and is a lineage-specific colony-stimulating factor that is produced by monocytes, fibroblasts and endothelial cells. G-CSF regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected cell-functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody-dependent killing, and the increased expression of some functions associated with cell-surface antigens). G-CSF is not species-specific and has been shown to have minimal direct *in vivo* or *in vitro* effects on the production of haematopoietic cell types other than the neutrophil lineage.

The human form of G-CSF is a glycoprotein composed of a single polypeptide chain of 174 or 177 amino acids. XM02 is a recombinant human granulocyte-colony stimulating factor produced in *E. coli*, yielding a protein without glycosylation and with an N-terminal methionyl extension (rmetHuG-CSF, INN filgrastim). It stimulates the proliferation, differentiation and activation of late progenitor cells of the granulocyte lineage, as well as enhances the activity of mature neutrophils.

- Primary and secondary pharmacology

Primary and secondary pharmacology is based on the two phase I studies that compared the pharmacokinetic and pharmacodynamic properties of XM02 and Neupogen in healthy volunteers (**Studies XM02-05-DE and XM02-01-LT**).

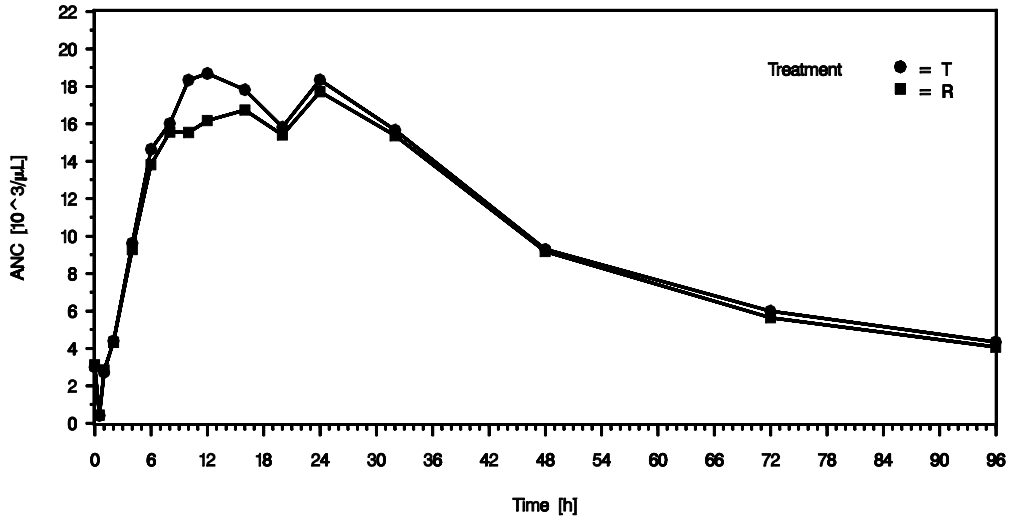
Study XM02-05-DE
The study objectives and design are described in the pharmacokinetics section.

Results
A total of 124 subjects completed both study periods without major protocol deviations and were included in the pharmacokinetic and pharmacodynamic analyses.

The mean age of the subjects was 32.5 years (range 18 to 45). The study duration for each subject was up to 11 weeks including screening.

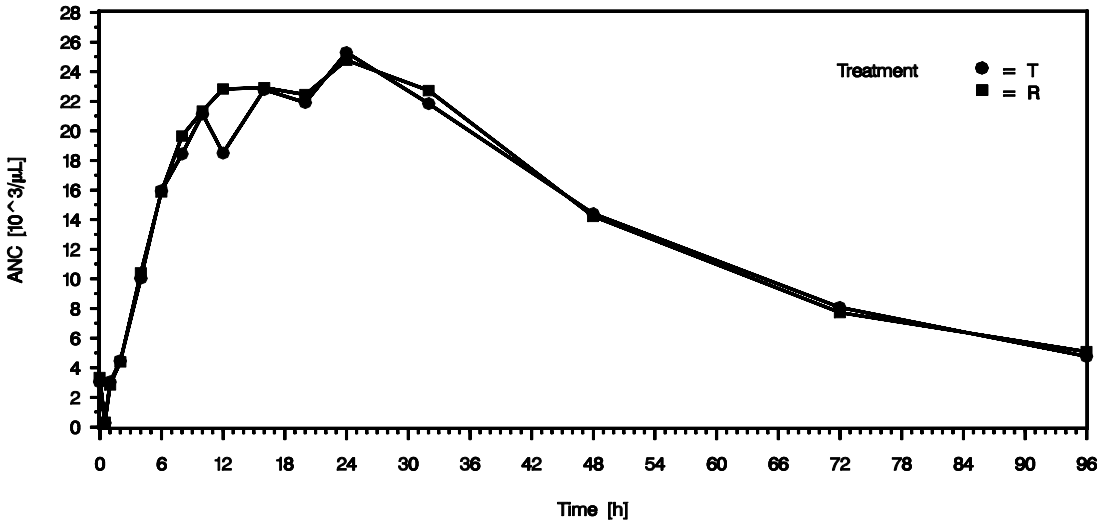
Absolute neutrophil count
Mean ANC time profiles following a single s.c. injection of XM02 or Neupogen are presented in Figures 8 and 9 for the 5 and 10 µg/kg doses, respectively. In both treatment and dose groups, a first peak was observed around 12 hours and a second peak at 24 hours. ANC values returned to baseline values after 96 hours.

Figure 8 **Study XM02-05-DE – Mean of absolute neutrophil counts following a single s.c. injection of 5 µg/kg of XM02 or Neupogen**



T = test treatment group (XM02); R = reference treatment group (Neupogen)

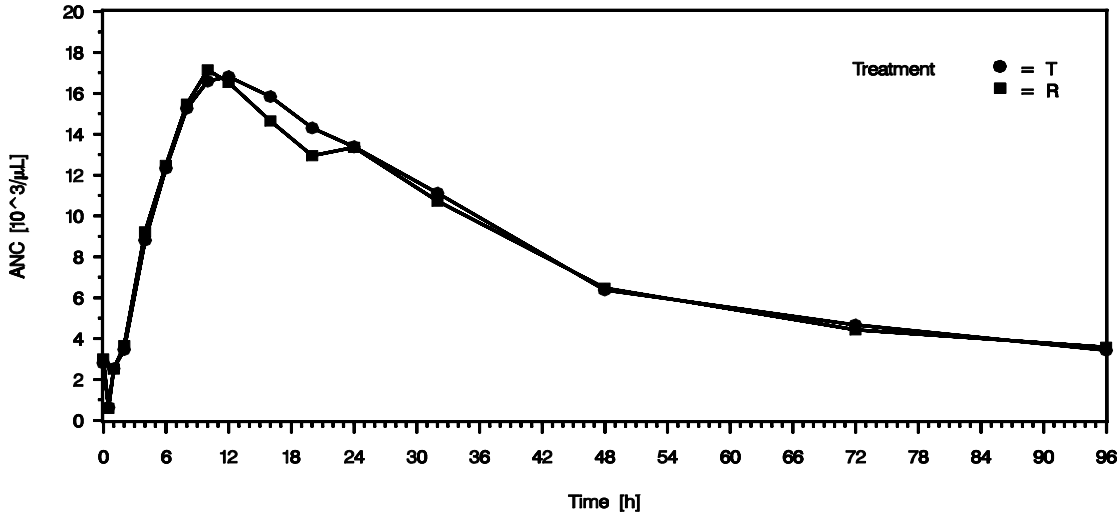
Figure 9 **Study XM02-05-DE - Mean of absolute neutrophil counts following a single s.c. injection of 10 µg/kg of XM02 or Neupogen**



T = test treatment group (XM02); R = reference treatment group (Neupogen)

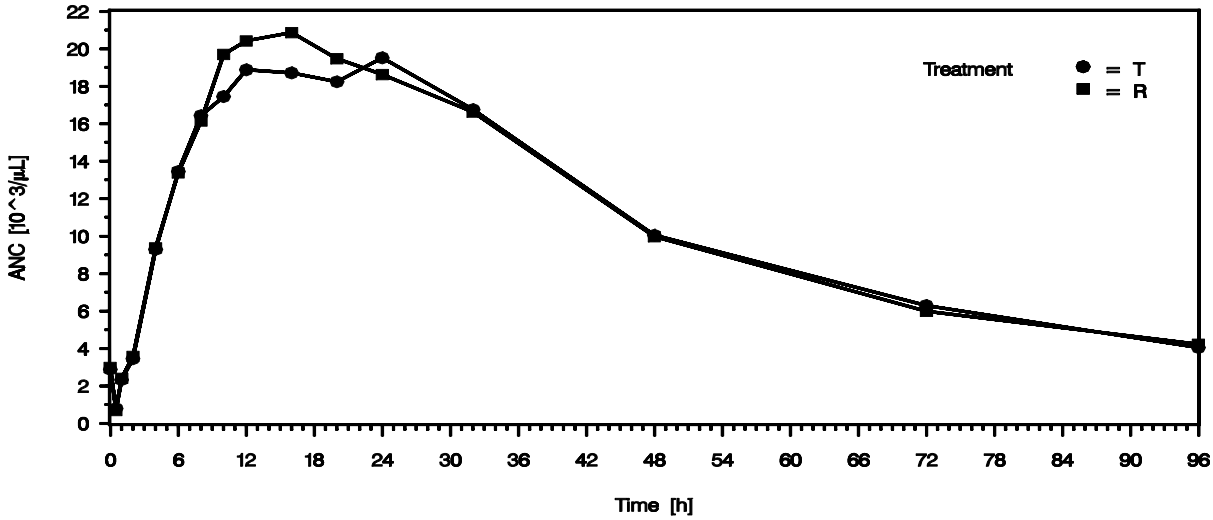
Mean ANC time profiles following a single i.v. infusion of XM02 or Neupogen are presented in Figures 10 and 11 for the 5 and 10 µg/kg doses, respectively. Peak ANC concentrations were observed in both treatment groups after 12 and 16 hours in the 5 and 10 µg/kg dose groups, respectively. ANC values returned to baseline values after 96 hours.

Figure 10 Study XM02-05-DE - Mean of absolute neutrophil counts following a single i.v. injection of 5 µg/kg of XM02 or Neupogen



T= test treatment group (XM02); R = reference treatment group (Neupogen)

Figure 11 Study XM02-05-DE - Mean of absolute neutrophil counts following a single i.v. injection of 10 µg/kg of XM02 or Neupogen



T = test treatment group (XM02); R = reference treatment group (Neupogen)

ANOVA demonstrated equivalence of XM02 and Neupogen with regard to the pharmacodynamic variable ANC in both the 5 and 10 µg/kg dose groups after both single s.c. injection and i.v. infusion. CI for the target variables ANC $AUC_{0\text{-}t}$, and ANC_{max} were enclosed within the 80-125% acceptance intervals for both dose regimens and administration routes.

CD34+ count

In both treatment (XM02 an Neupogen) and dose groups (5 and 10 µg/kg) following a single s.c. injection, a peak of mean CD34+ count was observed around 72 hours after dosing. Values returned to baseline after 336 hours.

As for the i.v. administration, in both treatment and dose groups a peak was observed around 72 hours after dosing following a single i.v. infusion. Values returned to baseline after 336 hours.

ANOVA demonstrated equivalence of XM02 and Neupogen with regard to the pharmacodynamic variable CD34+ count in both the 5 and 10 µg/kg dose groups after both single s.c. injection and i.v. infusion. CI for the target variables CD34+ AUC_{0-t}, and CD34+ C_{max} were enclosed within the predefined 70-143% acceptance intervals for both dose regimens and administrations.

Study XM02-01-LT
The study objectives and design are described in the pharmacokinetics section.

Results
Median age was 21.5 years (range 19 to 40 years). Four subjects in Group A, and two in Group B withdrew prematurely.

In both treatment groups, there was an initial decrease at 0.5–1 hour, then peak ANC values were observed about 12 and 16 hours after a single s.c. injection of 5 or 10 µg/kg, respectively. ANC values returned to baseline values after 96 hours.

ANOVA demonstrated equivalence of XM02 and Neupogen with regard to the pharmacodynamic variables in both the 5 and 10 µg/kg dose groups after single s.c. injection. CIs for all log transformed variables (ANC AUC_{0-t}, ANC AUC_{0-inf}, ANC_{max}) were enclosed within the 80-125% acceptance intervals for both dose regimens. The non-log-transformed variable ANC_{tmax} was enclosed within the 80-125% acceptance interval for the 5 µg/kg, but not for the 10 µg/kg dose. Administration of 10 µg/kg compared to 5 µg/kg of G-CSF did not yield a proportional increase in ANC.

Clinical efficacy

Clinical efficacy was investigated in one pivotal study (**Study XM02-02-INT**) concerning efficacy, which was performed in patients with breast cancer. Two other studies in patients with lung cancer and non-Hodgkin lymphoma focused on safety.

In all 3 studies, blinding of the investigator and patient was ensured. Only the "drug administrator" and the pharmacist were unblinded, due to the different volumes of formulated XM02 and Neupogen and body weight-dependent dosing.

- Dose response study(ies)

As this application concerns a biosimilar product and the bioequivalence with Neupogen has been demonstrated, no dose-response studies are needed.

- Main study(ies)

There is one pivotal study (Study XM02-02-INT) performed in patients with breast cancer with the following title: Efficacy and Safety of XM02 compared to filgrastim in patients with breast cancer receiving chemotherapy. A multinational, multicentre, randomised, controlled study

METHODS
Study participants
This was a multicentre study conducted at 52 centres in 10 countries.

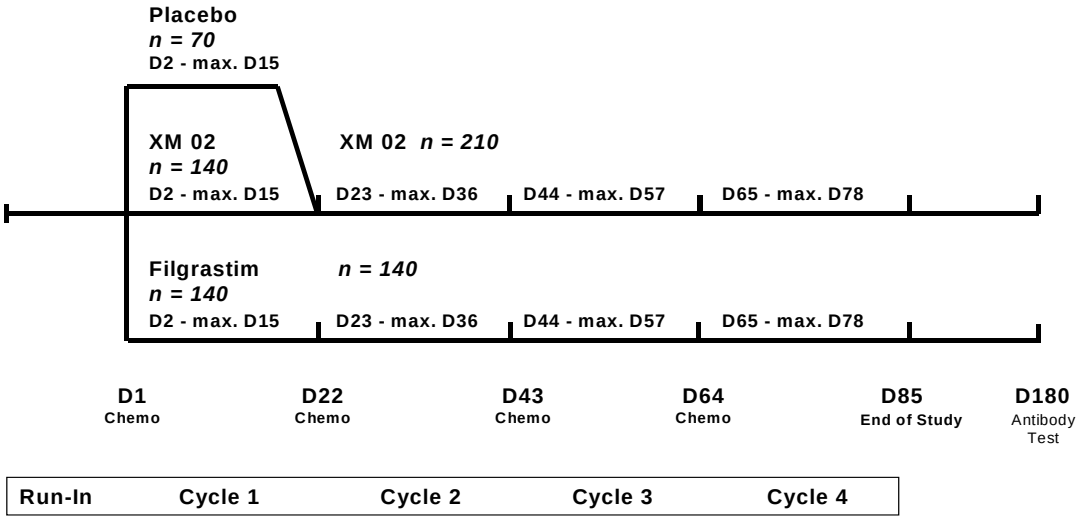
Main inclusion criteria were: Adult female or male patients of any ethnic origin with a diagnosis of breast cancer meeting all of the criteria listed below, could be included in the study:
- breast cancer high risk stage II, III or IV (classification according to American Joint Committee on Cancer [AJCC]);
- eligible to receive treatment with docetaxel/doxorubicin as routine CTX;
- CTX naïve;
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2;
- ANC ≥ 1.5 x 10^9/l and platelet count ≥ 100 x 10^9/l;

- adequate cardiac, hepatic and renal functions.

Main non-inclusion criteria were:
- previous exposure to filgrastim, pegfilgrastim or lenograstim;
- underlying neuropathy of Grade 2 or higher;
- treatment with systemically active antibiotics within 72 hours before CTX;
- treatment with lithium;
- chronic use of oral corticosteroids;
- prior radiation therapy within 4 weeks before randomisation;
- prior bone marrow or stem cell transplantation.

Treatments
Patients were randomised to treatment with either XM02, Neupogen or placebo. Patients in the placebo group switched to XM02 after completion of CTX cycle 1 (Figure 12). The CTX regimen in this study consisted of doxorubicin (60 mg/m^2) i.v. bolus and docetaxel (75 mg/m^2) at least 1 hour i.v. infusion on day 1 of each cycle (3 weeks per cycle). Up to 4 CTX cycles were given. Both drugs are known to cause neutropenia frequently. The study drug was administered daily starting 1 day after CTX was completed as an s.c. 5 µg/kg injection for at least 5 days and a maximum of 14 days in each cycle. The study drug was stopped, if an ANC of ≥ 10 x 10^9/l was reached after nadir.

Figure 12 Study XM02-02-INT – Study flow chart



Objectives
The main study objective was to demonstrate the equivalence of XM02 and Neupogen in patients with breast cancer during the first cycle of CTX on DSN confirmed by assay sensitivity in comparing XM02 versus placebo.

Outcomes/endpoints
The primary efficacy endpoint was duration of severe neutropenia (DSN) during cycle 1.

The secondary efficacy endpoints were:

- DSN, defined as the number of days with Grade 4 neutropenia (ANC < 0.5 x 10^9/l), for cycles 2, 3 and 4;
- depth of ANC nadir, defined as the patient's lowest ANC for each cycle, for cycles 1, 2, 3 and 4;
- time to ANC recovery, defined as the time in days from CTX administration until the patient's ANC increased to ≥ 2.0 x 10^9/l after the expected nadir, for cycles 1, 2, 3 and 4;

- incidence of febrile neutropenia (FN) by cycle and across all cycles. FN was defined* as "observed" FN when body temperature was > 38.5°C for > 1 hour (axillary measurement with a calibrated standard device) and ANC < 0.5 x 10^9/l, both measured on the same day or "protocol-defined FN" for patients receiving systemic antibiotics in a cycle (since intake of antibiotics could have masked an otherwise occurring high body temperature);
- mortality.

Sample size
In order to show equivalence between XM02 and Neupogen, the two-sided 95% CI for the difference in DSN had to lie within the equivalence range [-1 day, +1 day]. A sample size of 109 patients per active treatment group was necessary to have 90% power for rejecting the null hypothesis of a difference in mean DSN is larger than 1 day) that XM02 is different to Neupogen in favour of the alternative hypothesis assuming an expected difference in mean DSN of < 0.25 days and a standard deviation of 1.7 days.

Therefore, it was planned to randomise 140 patients into each active treatment group, taking into account the fact that there would be an attrition rate of about 20% for the PP analysis with respect to the primary endpoint. An additional 70 patients were randomised into the placebo arm to allow demonstration of sensitivity, assuming a difference of 2 days between XM02 and placebo, a larger standard deviation of 5 days in the placebo arm, and 90% power.

Randomisation
Patients were randomly assigned in a 2:2:1 ratio to receive XM02, Neupogen or placebo using an Interactive Voice Response System (IVRS).

Blinding (masking)
Due to different fill volumes of XM02 and Neupogen and body-weight-dependent dosing, full double-masking was not possible, but the following steps were undertaken to reduce possible bias:

- The study drug was administered after blood sampling (for determination of the ANC) and body temperature measurement had taken place.
- The unmasked drug administrator injected the exact volume of the study drug that had been calculated with respect to the patient's body weight and had been made known to the drug administrator via the IVRS.
- The drug administrator documented in the drug dispensation log the type of study drug administered (XM02, Neupogen or placebo), the volume prepared and administered and the batch number, and attached the tear-off label in the log. The investigator did not have access to the drug dispensation log.
- In a separate source document ("drug administrator's diary"), the drug administrator documented all measured body temperature values, blood samples and study drug administrations. The diary did not contain information about the administered volume or the type of study drug (XM02, Neupogen, or placebo). The diary was provided to the investigator on a daily basis, and the investigator documented his or her review of this information.

Statistical methods
ANCOVA was applied using "DSN in Cycle 1" as dependent variable, including the factors "treatment", "country" and "adjuvant vs. metastatic therapy", and with the baseline ANC value as covariates (last non-missing ANC value before chemotherapy, either at day 1 or at screening).

Assay sensitivity was evaluated by comparing XM02 versus placebo for the full analysis set with the ANCOVA. At the next step, equivalence of XM02 and Neupogen was assessed based on the PP set, using the ANCOVA model to calculate a two-sided 95% confidence interval for "XM02 minus

* These criteria were derived from the recommendations of the ESMO concerning primary G-CSF prophylaxis and were introduced into the XM02 clinical Phase III programme following scientific advice from the EMEA in June 2004, and discussed within a follow-up SAWG procedure in December 2004

Neupogen". Equivalence was to be concluded if this confidence interval lay entirely within the equivalence rage [−1 day, +1 day], provided that assay sensitivity was confirmed in step 1.

A sequential testing procedure was used to assess assay sensitivity and equivalence. First, assay sensitivity was evaluated by comparing XM02 versus placebo for the FA Set with the ANCOVA. If the upper bound of the two-sided 95% CI for "XM02 minus placebo" was ≤ 0, assay sensitivity could be confirmed. Note that this was equivalent to the p-value for treatment comparison being ≤ 0.05 and mean DSN being smaller in the XM02 group. This sequential procedure guaranteed an overall type I error level of 5% at most. All other analyses of the primary or secondary endpoints were considered to be exploratory.

Analysis Populations
The statistical analysis was based on the following populations:

- Full Analysis (FA) Set: All randomised patients.
- Safety Set (SF): All patients who received at least one dose of study treatment (XM02, Neupogen or placebo).
- Per Protocol (PP) Set: All patients included the FA Set, who received at least one cycle of CTX, who received their study treatment (XM02, Neupogen or placebo) and who did not have any major protocol violations including violations of eligibility criteria.
- Pharmacokinetic (PK) Set: All patients selected for PK analyses.

In the FA and PP Set, data from cycle 2 onwards of patients randomised to placebo, i.e., data of these patients after having switched to XM02, were only summarised descriptively as a separate study arm (i.e., they were not pooled with the original XM02 treatment arm) and were not used for formal efficacy comparisons of XM02 versus Neupogen.

RESULTS
Participant flow
Table 14 summarises the patient disposition for this study.

Table 14 Study XM02-02-INT - Patient disposition, n (%)

	XM02	Neupogen	Placebo/XM02	Overall
Enrolled into the study				378
Not eligible to continue to baseline	-	-	-	30
Non-fulfilment of inclusion criteria	-	-	-	13
Fulfilment of exclusion criteria	-	-	-	6
Other	-	-	-	13
Eligible to continue to baseline	-	-	-	348
Randomised*	140	136	72	348
Received CTX and study drug in cycle 1	140 (100)	136 (100)	72 (100)	348 (100)
Received CTX and study drug in cycle 2	137 (97.9)	131 (96.3)	70 (97.2)	338 (97.1)
Received CTX and study drug in cycle 3	136 (97.1)	131 (96.3)	69 (95.8)	336 (96.6)
Received CTX and study drug in cycle 4	135 (96.4)	130 (95.6)	68 (94.4)	333 (95.7)
Completed entire course of study	135 (96.4)	130 (95.6)	68 (94.4)	333 (95.7)
Terminated prematurely	5 (3.6)	6 (4.4)	4 (5.6)	15 (4.3)
Primary reason for premature termination				
Adverse event				
AE related to study drug	-		1 (1.4)	1 (0.3)
AE related to chemotherapy	1 (0.7)	1 (0.7)	1 (1.4)	3 (0.9)
Other AE	-	2 (1.5)	-	2 (0.6)
Consent withdrawn	2 (1.4)	3 (2.2)	-	5(1.4)
Death				
unrelated to underlying disease	-	-	2 (2.8)	2 (0.6)
relationship to underlying disease not known	1 (0.7)	-	-	1 (0.3)
Other	1 (0.7)	-	-	1 (0.3)

CTX = chemotherapy
Percentages are based on the number of randomised patients
* Excluding 2 screening failures who received random numbers erroneously, but who received no chemotherapy and no study treatment

No patient terminated the study prematurely for lack of efficacy.

Recruitment
The enrolment period started on 30 December 2004 (first patient enrolled) to 16 June 2005 and the study was completed on 26 September 2005 (last patient's final visit).

Most patients were enrolled at study centres in Russia. One investigational centre was the highest-enrolling centre (7.2%). The other study centres enrolled between 0.3 and 6.0% of patients overall.

Conduct of the study
The protocol for this study, originally dated 26 April 2004, was amended 3 times. The first amendment was dated 31 August 2004, i.e. prior to the initiation of the trial, and was based on CHMP Scientific Advice. Amendments 2 and 3 were dated January 2005, were based on CHMP follow-up advice and did not affect the integrity of the study, even though the study had been ongoing since December 2004. The final statistical analysis plan was dated December 2005.

The major protocol deviations are summarised in Table 15.

Table 15 Study XM02-02-INT – Major protocol deviations

	XM02 N=140	Neupogen N=136	Placebo/XM02 N=72	Overall N=348
Any major protocol violation	7 (5.0)	7 (5.1)	14 (19.4)	28 (8.0)
Baseline ANC < 1.5 x 10^9/l during cycle 1	-	-	1 (1.4)	1 (0.3)
CTX dose during cycle 1 ≤ 90 % of required dose	3 (2.1)	1 (0.7)	1 (1.4)	5 (1.4)
G-CSF medication received	-	-	11 (15.3)*	11 (3.2)
Insufficient ANC data during cycle 1	1 (0.7)	1 (0.7)	-	2 (0.6)
No study drug on > 2 consecutive days during cycle 1	4 (2.9)	4 (2.9)	2 (2.8)	10 (2.9)
No study drug on > 30 % of days during cycle 1	4 (2.9)	4 (2.9)	1 (1.4)	9 (2.6)
Previous chemotherapy	1 (0.7)	2 (1.5)	-	3 (0.9)
Wrong medication on all days during cycle 1	1 (0.7)	1 (0.7)	-	2 (0.6)

* Patients in the placebo group treated with therapeutic G-CSF according to the study protocol were excluded from the PP population as pre-defined in the study protocol and are therefore listed as major protocol deviation

Baseline data
Of the 348 patients, 346 were female and 2 were male. The majority of patients were Caucasian (86.2%), 7.5% were Hispanic, 2.3% black and 4.0% of another race. The median age of the patients was 50 years (range: 25 to 75 years). Mean body height was 161.3 cm, mean body weight was 72.5 kg and 48.8% of the women were post-menopausal.

Disease characteristics are summarised in Table 16.

Table 16 Study XM02-02-INT – Disease characteristics

	XM02 N=140	Neupogen N=136	Placebo/XM02 N=72	Total N=348
Cancer stage				
High risk stage	23 (16.4)	36 (26.5)	15 (20.8)	74 (21.3)
Stage III	79 (56.4)	69 (50.7)	38 (52.8)	186 (53.4)
Stage IV	38 (27.1)	31 (22.8)	19 (26.4)	88 (25.3)
Time since first diagnosis [days]				
n	140	136	72	348
Mean	124.7	232.8	378.3	219.4
SD	436.6	1056.6	1337.6	941.1
Min	0	0	0	0
Median	21.0	25.0	30.0	24.0
Max	3759	7661	9879	9879
Therapy				
Adjuvant	96 (68.6)	96 (70.6)	47 (65.3)	239 (68.7)
Metastatic	44 (31.4)	40 (29.4)	25 (34.7)	109 (31.3)
Prior radiation therapy				
No	125 (89.3)	127 (93.4)	63 (87.5)	315 (90.5)
Yes	15 (10.7)	9 (6.6)	9 (12.5)	33 (9.5)
Time since most recent radiation therapy [days]				
n	15	9	9	33
Mean	1808.6	473.2	2404.4	1606.9
SD	2548.2	925.0	3163.0	2472.9
Min	26	26	32	26
Median	90.0	182.0	1553.0	194.0
Max	7230	2900	9719	9719

In the FA and PP sets, demographic and disease characteristics were generally similar across countries.

Numbers analysed
Table 17 displays the datasets analysed and sample size.

Table 17 Study XM02-02-INT – Analysed datasets

	XM02 N=140	Neupogen N=136	Placebo/XM02 N=72	Total N=348
Full dataset	140 (100.0)	136 (100.0)	72 (100.0)	348 (100.0)
Safety dataset	140 (100.0)	136 (100.0)	72 (100.0)	348 (100.0)
Per protocol dataset	133 (95.0)	129 (94.9)	58 (80.6)	320 (92.0)
Pharmacokinetic dataset	14 (10.0)	13 (9.6)	10 (13.9)	37 (10.6)

Outcomes and estimation
Primary endpoint
The primary endpoint was the DSN in cycle 1. Table 18 presents these results.

Table 18 Study XM02-02-INT – Duration of severe neutropenia in Cycle 1, Full Analysis Set

		XM02 N=140			Neupogen N=136			Placebo/XM02 N=72		
Descriptive statistics for DSN [days]										
Cycle 1	N		140			136			72	
	N imputed 1)		1			1			0	
	Mean		1.1			1.1			3.8	
	SD		1.2			1.3			2.1	
	Min		0			0			0	
	Median		1.0			1.0			4.0	
	Max		5			5			9	
Frequencies for DSN [days]		N	(%)	Cum.%	N	(%)	Cum.%	N	(%)	Cum.%
	0	61	(43.6)	43.6	59	(43.4)	43.4	8	(11.1)	11.1
	1 day	24	(17.1)	60.7	28	(20.6)	64.0	5	(6.9)	18.1
	2 days	39	(27.9)	88.6	30	(22.1)	86.0	4	(5.6)	23.6
	3 days	10	(7.1)	95.7	13	(9.6)	95.6	8	(11.1)	34.7
	4 days	3	(2.1)	97.9	3	(2.2)	97.8	19	(26.4)	61.1
	5 days	3	(2.1)	100.0	3	(2.2)	100.0	14	(19.4)	80.6
	6 days			100.0			100.0	7	(9.7)	90.3
	7 days			100.0			100.0	6	(8.3)	98.6
	8 days			100.0			100.0			98.6
	9 days			100.0			100.0	1	(1.4)	100.0

1 Imputed DSN values in case of insufficient ANC data. Other (non-imputed) DSN values are based on the individual ANC values, some of which may also be imputed

2 For patients with placebo receiving therapeutic G-CSF treatment, the DSN values in Cycle 1 were replaced with the median DSN value of patients with placebo who received no G-CSF treatment

Assay sensitivity was evaluated by comparing XM02 versus placebo for the FA set using an ANCOVA, is presented in Table 19.

Table 19 Study XM02-02-INT – Assay Sensitivity: DSN in Cycle 1 – ANCOVA for XM02 vs. Placebo, Full Analysis Set

				Least square means		Estimate and 2-sided 95% CI for difference XM02 - placebo		
Source of variation	**DF**	**F**	**2-sided p-value**	**XM02**	**Placebo**	**Estimate**	**Lower bound**	**Upper bound**
FA Set								
Baseline ANC	1	0.27	0.6039	-	-	-	-	-
Country	8	2.47	0.0145	-	-	-	-	-
Therapy	1	0.03	0.8642	-	-	-	-	-
Treatment	1	100.43	< 0.0001	1.141	3.823	-2.682	-3.214	-2.151

Note 1: Assay sensitivity can be concluded, if the upper bound of the 2-sided 95% CI for XM02 minus placebo is ≤ 0. The FA Set is the primary analysis set for this comparison

Note 2: DSN for patients of the placebo group receiving therapeutic G-CSF treatment were used as calculated

Results for the PP set were similar and confirmed assay sensitivity.

Equivalence of XM02 and Neupogen was assessed based on the PP set, using also the ANCOVA model. Table 20 provides the results of these analyses for both datasets.

Table 20 Study XM02-02-INT –Duration of severe neutropenia in cycle 1 ANCOVA XM02 versus Neupogen, Per Protocol and Full Analysis Sets

Source of variation	DF	F	2-sided p-value	Least square means		Estimate and 2-sided 95% CI for difference XM02 - placebo		
				XM02	Neupogen	Estimate	Lower bound	Upper bound
PP Set								
Baseline ANC	1	0.24	0.6245	-	-	-	-	-
Country	9	2.77	0.0042	-	-	-	-	-
Therapy	1	0.09	0.7583	-	-	-	-	-
Treatment	1	0.05	0.8305	1.119	1.087	0.032	-0.262	-0.325
FA Set								
Baseline ANC	1	0.60	0.4400	-	-	-	-	-
Country	9	2.83	0.0034	-	-	-	-	-
Therapy	1	0.66	0.4183	-	-	-	-	-
Treatment	1	0.04	0.8508	1.148	1.120	0.028	-0.261	-0.316

Note: Equivalence can be concluded, if the 2-sided 95% CI for XM02 minus Neupogen lies entirely in the equivalence range [-1, 1]. The comparison is based primarily on the PP Set

Secondary endpoints

Data of the secondary efficacy endpoints are presented for the FA set.

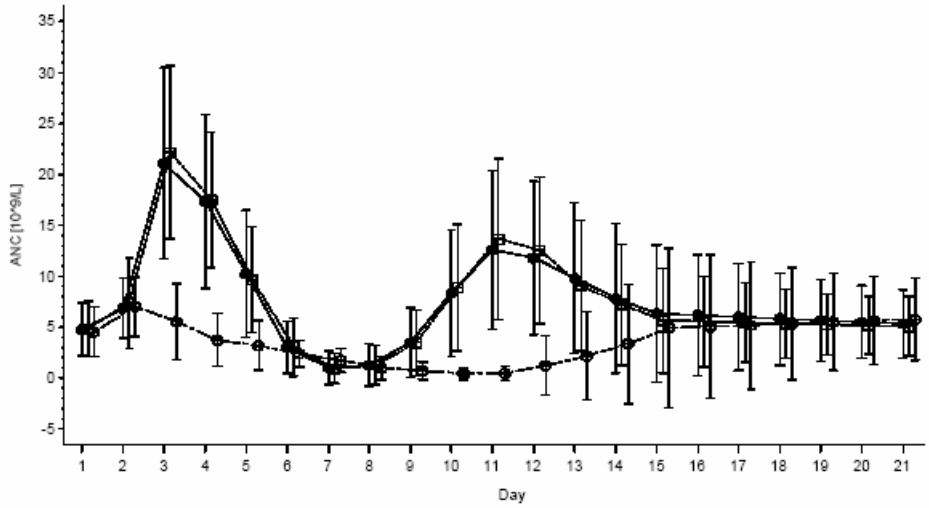
Duration of severe neutropenia in cycles 2 to 4

The mean DSN in cycles 2 to 4 was similar in all treatment groups. The majority of patients had a DSN of 0 days. Overall, DSN ranged from 0 to 6 days. Mean DSN ranged from 0.5 to 0.7 days in cycles 2 to 4 in all treatment groups. In cycle 4, the mean DSN was 0.7, 0.7, and 0.6 days in the XM02, Neupogen and placebo/XM02 groups, respectively.

ANC over time

In cycle 1 in the placebo group, mean ANC values decreased after day 2 and reached a nadir on day 11, whereas in the XM02 and Neupogen groups, mean values distinctly increased, reaching a maximum on day 3 and then decreased to a nadir on day 7. Thereafter, mean values in the active treatment groups increased again, reaching a maximum on day 11. On day 21, mean values returned to values as observed on day 1 in all treatment groups (Figure 13).

Figure 13 Study XM02-02-INT –Mean of absolute neutrophil count over time in cycle 1, full analysis set



In the subsequent cycles, all treatment groups demonstrated the same trends as for XM02 and Neupogen in cycle 1.

Depth of ANC nadir
In cycle 1, the mean ANC nadir was deeper in the placebo group (0.163 x 10^9/l) compared to the XM02 and Neupogen groups (0.655 x 10^9/l and 0.651 x 10^9/l, respectively). In cycles 2, 3 and 4, the mean ANC nadir was not as deep as in cycle 1 and was similar across treatment groups with a mean value of approximately 1.0 x 10^9/l. In cycle 4, mean ANC nadir was 1.0, 1.0, and 1.1 x 10^9/l in the XM02, Neupogen and placebo/XM02 groups, respectively.

Time to ANC recovery
In cycle 1, the mean time to ANC recovery was shorter in the XM02 and Neupogen groups (8.0 and 7.8 days) compared to the placebo group (14.0 days). In cycles 2, 3 and 4, mean time to ANC recovery were similar in all treatment groups with a median of 8.0 days. In cycle 4, mean time to ANC recovery was 7.6, 7.1, and 7.2 days in the XM02, Neupogen and placebo/XM02 groups, respectively.

Incidence of FN
The overall incidence of observed or protocol defined FN across all cycles was lower in the XM02 and Neupogen groups (20.7 and 22.1%, respectively) compared to the placebo/XM02 group (41.7%).

Table 21 gives the detailed results for cycle 1.

Table 21 Study XM02-02-INT – Febrile neutropenia in cycle 1, full analysis set

Cycle 1	XM02 [N = 140]			Neupogen [N = 136]			Placebo/XM02 [N = 72]		
	n	(%)	95% CI	n	(%)	95% CI	n	(%)	95% CI
Observed FN p = 0.3173	1	(0.7)	[0.1-3.9]	0	(0.0)	[0.0-2.7]	4	(5.6)	[2.2-13.4]
Systemic antibiotics without observed FN p = 0.8285	16	(11.4)	[7.2-17.8]	17	(12.5)	[8.0-19.1]	22	(30.6)	[21.1-42.0]
Observed or protocol defined FN p = 0.9810	17	(12.1)	[7.7-18.6]	17	(12.5)	[8.0-19.1]	26	(36.1)	[26.0-47.6]

n = number of patients with febrile neutropenia; CI = confidence interval; FN = febrile neutropenia
p-value: Cochran-Mantel-Haenszel test, adjusted for country and adjuvant vs. metastatic therapy, comparing XM02 and Neupogen group

In cycles 2, 3, and 4, the incidence of observed or protocol defined FN was similar in all treatment groups. Between the 3 treatment groups, the incidence ranged from 6.9 to 8.0% in cycle 2, from 1.4 to 9.9% in cycle 3, and from 5.9 to 8.5% in cycle 4.

Mortality
There were 3 deaths during cycle 1 (2 in the placebo group, 1 in the XM02 group) and 1 death after the end of study visit (XM02 group). None of the deaths were considered to be related to the study drug. There were no statistically significant differences between patients treated with XM02 or Neupogen with respect to the mortality rate.

Ancillary analyses
No ancillary analyses were performed.

- Clinical studies in special populations

No studies have been conducted in special populations (the elderly, children or patients with impaired renal or hepatic function).

All subjects in the Phase I studies and 86-95% of patients in the Phase III studies were Caucasian.

- Supportive study(ies)

There were 2 supportive studies: Study XM02-03-INT and Study XM02-04-INT.

Study XM02-03-INT
This was a phase II, multinational, multicentre, randomised, controlled study to enrol 240 lung cancer (either small cell or non-small cell lung cancer) patients. Patients were randomly allocated to treatment with XM02 or Neupogen in a 2:1 ratio in the first CTX cycle. In the subsequent cycles all patients

received XM02. Patients were stratified by country, previous CTX and lung cancer type. The reference product was the same as in study XM02-02-INT, i.e. Neupogen, German trade ware.

The main inclusion criteria were adult female and male patients of any ethnic origin with a diagnosis of lung cancer meeting following criteria:

- SCLC, histologically or cytologically documented or patients with advanced NSCLC disease;
- planned/eligible to receive a platinum-based, myelosuppressive CTX requiring, in the investigator's opinion, G-CSF support;
- life-expectancy of at least 6 months;
- CTX-naïve or had received no more than 1 previous regimen of CTX completed more than 4 weeks before randomisation;
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2;
- ANC ≥ 1.5 x 10^9/l and platelet count ≥ 100 x 10^9/l;
- adequate hepatic, cardiac and renal functions for the chosen CTX regimen.

The main non-inclusion criteria were:

- previous exposure to filgrastim, pegfilgrastim or lenograstim;
- treatment with systemically active antibiotics within 72 hours before CTX;
- treatment with lithium;
- candidate for combined CTX/radiotherapy or prior radiation therapy within 4 weeks before randomisation;
- chronic use of oral corticosteroids (except low dose chronic treatment with ≤ 20 mg/day prednisolone or equivalent dose for chronic obstructive pulmonary disease);
- prior bone marrow or stem cell transplantation.

The patients had to undergo a maximum of 6 CTX cycles of 3 or 4 weeks per cycle, depending on the CTX protocol), each cycle beginning with a CTX infusion on day 1. Starting 1 day after the last CTX infusion day, the patients received daily s.c. injections of 5 µg/kg/day (based on actual body weight) XM02 or Neupogen (first cycle only) for at least 5 days and a maximum of 14 days. Study drug was stopped earlier, when an absolute neutrophil count (ANC) ≥ 10 x 10^9/l after nadir was reached.

The primary study objective was to demonstrate of safety of XM02 when administered for up to a maximum of six cycles of CTX in patients with lung cancer.

The secondary study objectives were to:

- demonstrate the efficacy of XM02 during cycle 1 compared to Neupogen in patients with lung cancer;
- evaluate the pharmacokinetic properties of XM02 in comparison to Neupogen in a subset of patients.

Table 22 summarises the datasets analysed in this study. No patient terminated the study prematurely for lack of efficacy.

Table 22 Study XM02-03-INT – Patient disposition and datasets analysed

	XM02 N = 160	**Neupogen N = 80**	**Total N = 240**
Full analysis dataset	160	80	240
Per protocol dataset	148	77	225
Safety dataset	160	80	240

Efficacy results

Study results are presented for the FA set and are provided further in this section, which compares the results of the 3 phase III studies.

Study XM02-04-INT
This was a multinational, multicentre, randomised, controlled phase III study in CTX-naïve patients with aggressive NHL (allowed subtypes: diffuse large B-cell lymphoma, mediastinal large B-cell lymphoma, follicular lymphoma grade 3, and anaplastic large cell lymphoma) undergoing CTX.

Patients were randomised to treatment with either XM02 or Neupogen in a 2:1 ratio in the first CTX cycle. In the subsequent cycles, all patients received XM02. Patients were stratified by country and concomitant treatment with rituximab. The reference product was the same as in study XM02-02-INT, i.e. Neupogen, German trade ware.

The main inclusion criteria were adult female and male patients of any ethnic origin with a diagnosis of aggressive NHL defined as diffuse large B-cell lymphoma, mediastinal large B-cell lymphoma, follicular lymphoma grade 3, or anaplastic large cell lymphoma meeting the additional following criteria:

- CTX-naïve;
- planned/eligible to receive a CHOP regimen as routine CTX for their NHL requiring G-CSF support in the investigator's opinion;
- life-expectancy of at least 6 months as judged by the investigator;
- International Prognostic Index (IPI) score ≤ 3;
- ANC $\geq 1.5 \times 10^9$/l and platelets $\geq 100 \times 10^9$/l;
- adequate hepatic, cardiac and renal function.

The main non-inclusion criteria were:

- lymphoblastic lymphoma, Burkitt's lymphoma, transformed lymphoma, central nervous system lymphoma;
- previous exposure to filgrastim, pegfilgrastim or lenograstim;
- underlying neuropathy of Grade 2 or higher;
- treatment with systemically active antibiotics within 72 hours before CTX;
- treatment with lithium;
- chronic use of oral corticosteroids;
- prior bone marrow or stem cell transplantation;
- HIV infection, positivity for hepatitis B surface antigen and/or hepatitis C virus.

The study drug was administered daily starting 1 day after CTX as an s.c. 5 µg/kg injection for at least 5 days and for a maximum of 14 days in each cycle. The s.c. administration site was chosen by the drug administrator reflecting daily clinical practice. The CTX regimen in this study was according to the CHOP protocol: cyclophosphamide i.v. 750 mg/m^2, doxorubicin i.v. 50 mg/m^2, vincristine i.v. 1.4 mg/m^2 (maximum 2 mg) on day 1 of each cycle and prednisolone 100 mg/day orally from day 1 to day 5. Patients on CHOP could receive rituximab (stratification criterion). Up to 6 CTX cycles were given.

The primary study objective was to demonstrate the safety of XM02 when administered for up to a maximum of 6 cycles in patients with non-Hodgkin's lymphoma (NHL) receiving CTX (CHOP regimen).

The secondary study objectives were to:

- demonstrate the efficacy of XM02 during cycle 1 compared to Neupogen in patients with NHL;
- evaluate pharmacokinetic properties of XM02 in comparison to Neupogen a subset of patients.

Table 23 summarises the datasets analysed in this study. No patient terminated the study prematurely due to lack of efficacy.

Table 23 Study XM02-04-INT – Patient disposition and datasets analysed

	XM02 N = 63	Neupogen N = 29	Total N = 92
Full analysis dataset	63	29	92
Per protocol dataset	55	29	84
Safety dataset	63	29	92

Efficacy results
Study results are presented for the FA set and are provided further in this section, which compares the results of the 3 phase III studies.

Study populations
This section summarises the study results of the 3 phase III studies.

Table 24 displays the demographic patient characteristics.

Table 24 Study XM02-02-INT, XM02-03-INT and XM02-04-INT – Patient demography

	XM02-02-INT Breast cancer N = 348	XM02-03-INT Lung cancer N = 240	XM02-04-INT NHL N = 92
Gender			
Male	2 (0.6)	191 (79.6)	48 (52.2)
Female	346 (99.4)	49 (20.4)	44 (47.8)
Race			
Caucasian	300 (86.2)	228 (95.0)	81 (88.0)
Black	8 (2.3)	-	1 (1.1)
Hispanic	26 (7.5)	11 (4.6)	8 (8.7)
Other	14 (4.0)	1 (0.4)	2 (2.2)
Age (years)			
Median (range)	50 (25-75)	58.5 (34-78)	55 (18-83)

Within each study, the treatment groups were similar with regard to demographic characteristics. It is considered that these patients are representative of the population for whom the drug is to be marketed.

Patient disposition across studies is summarised in Table 25.

Table 25 Study XM02-02-INT, XM02-03-INT and XM02-04-INT – Patient disposition

	XM02-02-INT Breast cancer	XM02-03-INT Lung cancer	XM02-04-INT NHL
Number of patients randomised	348	240	92
Who completed the study	333 (95.7)	125 (52.1)	76 (82.6)
Who terminated prematurely	15 (4.3)	115 (47.9)	16 (17.4)
Primary reason for premature termination			
AE related to study drug	1 (0.3)	1 (0.4)	-
AE related to study drug	3 (0.9)	13 (5.4)	4 (4.3)
AE related to study drug	2 (0.6)	6 (2.5)	1 (1.1)
Death	3 (0.9)	12 (5.0)	-
Progression of underlying disease	-	41 (17.1)	6 (6.5)
Consent withdrawn	5 (1.4)	21 (8.8)	2 (2.2)
Non compliance		6 (2.5)	1 (1.1)
Other	1 (0.3)	15 (6.3)	2 (2.2)

In Study XM02-03-INT, more patients discontinued the study prematurely compared to the other studies. This was probably due to the poor health status of the patients in the lung cancer study since the most frequent reason for discontinuation was underlying disease progression and death. No patients discontinued the study prematurely due to lack of efficacy.

Table 26 summarises results of the efficacy endpoints across the 3 studies for the FA set.

Table 26 Study XM02-02-INT, XM02-03-INT and XM02-04-INT – Results of efficacy endpoint across studies

	XM02-02-INT			XM02-03-INT		XM02-04-INT	
	XM02	Neupogen*	Plac*	XM02	Neupogen*	XM02	Neupogen*
	140	136	72	160	80	63	29
Mean DSN [days]							
Cycle 1	1.1	1.1	3.8	0.5	0.3	0.5	0.9
ANCOVA [CI]#	0.028 [-0.261, 0.316]		-	0.157 [-0.114, 0.428]		-0.378 [-0.837, 0.081]	
Cycle 4	0.7	0.7	0.6	0.4	0.3	0.2	0.7
ANC over time (Cycle 1)							
First maximum (Day)	3	3	N/A	5	5	4	4
ANC nadir (Day)	7	7	11	11	12	9	9
Second maximum (Day)	11	11	N/A	14	14	11	11
Mean ANC nadir [10^9/l]							
Cycle 1	0.7	0.7	0.2	2.1	2.9	1.7	1.1
ANCOVA [CI]#	-0.001 [-0.190, 0.189]			-0.660 [-1.146, -0.173]+		0.504 [-0.191, 1.199]	
Cycle 4	1.0	1.0	1.1	2.3	3.2	2.1	1.8
Mean time to ANC recovery [days]							
Cycle 1	8.0	7.8	14.0	6.3	4.5	6.0	6.7
ANCOVA [CI]#	0.207 [-0.425, 0.838]			1.686 [0.092, 3.280]+		-0.765 [-2.980, 1.450]	
Cycle 4	7.6	7.1	7.2	6.4	4.5	4.9	6.1
Incidence of FN [%]							
Cycle 1	12.1	12.5	36.1	15.0	8.8	11.1	20.7
Across all cycles	20.7	22.1	41.7	33.1	23.8	31.7	41.4
Mortality (%)	1 (0.7)	-	2 (2.8)	19 (11.9)	12 (15.0)	-	1 (3.4)

* Patients in these groups received either placebo or Neupogen in Cycle 1 and XM02 afterwards

\# ANCOVA estimate and 2-sided 95% CI for difference XM02 – Neupogen in Cycle 1

\+ Estimated difference "XM02 – Neupogen" $p < 0.05$

Duration of severe neutropenia

During cycles 1 and 4, the mean DSN was slightly longer in the pivotal study XM02-02-INT compared to the 2 supportive studies XM02-03-INT and XM02-04-INT. The longer DSN observed in the pivotal study can be explained by the CTX regimen used in this study (docetaxel/doxorubicin), which is considered to have a higher myelotoxic potency in comparison with the CTX regimens used in the other 2 studies. There were no statistically significant differences between XM02 and Neupogen with regard to the mean DSN in any study.

Absolute neutrophil count over time

In all three studies, in the XM02 and Neupogen groups, mean ANC values had a similar profile, increasing after day 1, reaching a first maximum on days 3 to 5 and then decreasing to a nadir on day 7 to day 12. Thereafter, mean values increased again, reaching a second maximum on days 11 to 14. On day 21, mean values returned to those observed on day 1.

Depth of absolute neutrophil count nadir

In both cycles 1 and 4, the mean ANC nadir was deeper in the pivotal study compared to the 2 supportive studies. There were no statistically significant differences between XM02 and Neupogen with regard to the mean ANC nadir in the studies, except for the difference of 2.1 versus 2.9 x 10^9/l in cycle 1 of Study XM02-03-INT. This is not considered clinically significant due to the high absolute ANC values in both groups.

Time to absolute neutrophil count recovery

In both cycles 1 and 4, the mean time to ANC recovery was longer in the pivotal study compared to the 2 supportive studies. There were no statistically significant differences between XM02 and Neupogen with regard to time to ANC recovery in the studies, except for the difference of 6.3 versus 4.5 days in cycle 1 of Study XM02-03-INT.

Incidence of febrile neutropenia
The incidence of observed or protocol defined FN across all cycles ranged from 20.7 to 41.7% across the treatment groups of the studies. There were no statistically significant differences between XM02 and Neupogen with regard to incidence of FN in any study. The estimated common risk difference (XM02 minus Neupogen) of observed or protocol-defined FN, adjusted by study, was 1.7% [-3.8, 7.1] across studies, a difference, which was not statistically significant.

Mortality
Mortality rates were distinctly higher in Study XM02-03-INT (lung cancer) compared to the other studies (possibly reflecting the clinical course of patients with advanced NSCLC and an overall poor prognosis) but the mortality observed in this study was within the expected range. There were no statistically significant differences counted between XM02 and Neupogen with regard to mortality in any study.

Clinical safety

Safety evaluations of XM02 have included analyses of five clinical studies: two phase I studies with healthy volunteers and three studies in cancer patients (i.e. in patients with breast cancer [**Study XM02-02-INT**], lung cancer [**Study XM02-03-INT**] or non-Hodgkin's lymphoma [**Study XM02-04-INT**]). Studies XM02-03-INT and XM02-04-INT were designed primarily to investigate the safety of XM02. In the pivotal efficacy breast cancer study, patients were treated with the reference product Neupogen for up to 4 cycles of chemotherapy. In the primary safety studies (Studies XM02-03-INT and XM02-04-INT) patients initially randomised to the Neupogen group for cycle 1 (to allow for a comparative determination of efficacy) received XM02 in all subsequent CTX cycles to ensure maximal patient exposure to XM02 for the determination of safety. Therefore, there was no Neupogen (reference) group over the enitre duration of these studies.

A pooled analysis of safety was performed for the 3 cancer patient studies and separately for the two phase I studies. Due to the study design, the most relevant comparison concerns the first cycle of CTX.

Safety assessments included treatment-emergent adverse events (TEAEs), laboratory tests, physical examinations, vital signs assessments, injection site reactions and immunogenicity. All safety variables were analysed using descriptive statistics. In addition, the incidence of TEAEs was compared between treatment groups using Fisher's exact test (2-sided p-values) and changes in laboratory parameters from baseline were compared between treatment groups using the Wilcoxon test.

- Patient exposure

In the 3 cancer patient studies all patients received XM02 or Neupogen at a dose of 5 μg/kg/day. Overall, the median duration of exposure to the study drug for a patient was 40 days (1 to 84 days). In each cycle, patients were exposed to the study drug for approximately 9 to 11 days. Table 27 provides details on patient exposure.

Table 27 Cancer patient dataset - Demographic characteristics by treatment group

	XM02 only N=356	Neupogen only N=134	Neupogen/ XM02 N=115	Placebo/ XM02 N=72	Any XM02 N=541	Overall N=677
XM02 exposure						
Mean	15599.6	0.0	13689.1	9382.1	14423.7	11526.2
SD	6958.0	0.0	7341.4	3026.4	6932.2	8475.5
Min	270	0	210	0	210	0
Median	15030	0	14490	9585	13740	11880
Max	36960	0	32400	17820	36960	36960
Neupogen exposure						
Mean	0.0	12736.8	3822.1	285.3	850.4	3200.6
SD	0.0	3843.6	2230.7	736.7	1875.9	5309.9
Min	0	1152	0	0	0	0
Median	0	12768	3456	0	0	0
Max	0	22704	12288	4032	12288	22704

Within each cycle, mean doses were approximately 3200 to 3600 µg. Differences between the treatment groups in exposure were due to differences in number of cycles, and duration of treatment within cycles.

The demographics of the patients of three clinical studies are presented in Table 28.

Table 28 Cancer patient dataset - Demographic characteristics by treatment group

	XM02 only N=356	Neupogen only N=134	Neupogen/ XM02 N=115	Placebo/ XM02 N=72	Any XM02 N=541	Overall N=677
Gender						
Female	199 (55.9)	129 (96.3)	39 (33.9)	72 (100)	308 (56.9)	439 (64.8)
Male	157 (44.1)	5 (3.7)	76 (66.1)	0 (0.0)	233 (43.1)	238 (35.2)
Age [years]						
Mean	54.3	52.0	56.7	49.5	54.2	53.7
SD	11.44	11.28	11.38	10.29	11.43	11.44
Min	18	28	33	28	18	18
Median	55.0	51.0	57.0	48.0	55.0	54.0
Max	83	75	83	74	83	83
Age categories						
< 65 years	285 (80.1)	115 (85.8)	83 (72.2)	63 (87.5)	430 (79.5)	546 (80.6)
≥ 65 years	71 (19.9)	19 (14.2)	32 (27.8)	9 (12.5)	111 (20.5)	131 (19.4)
Race, n ()						
Caucasian	319 (89.6)	116 (86.6)	109 (94.8)	62 (86.1)	488 (90.2)	606 (89.5)
Other	37 (10.4)	18 (13.4)	6 (5.2)	10 (13.9)	53 (9.8)	71 (10.5)
Renal or Hepatic Impairment						
Renal	–	–	1 (0.9)	–	1 (0.2)	1 (0.1)
Hepatic	6 (1.7)	1 (0.7)	4 (3.5)	2 (2.8)	11 (2.0)	13 (1.9)

Studies XM02-02-INT and XM02-04-INT included a homogeneous patient population with regard to the severity of malignant disease and CTX, whereas XM02-03-INT was performed with a heterogeneous patient population – including CTX pre-treated patients.

The completion rate was distinctly lower in Study XM02-03-INT (52.5%) compared to the other two studies (95.7 and 82.6%), due to the poor health status and high rate drop-out rate of patients in the lung cancer study.

In the cancer patient studies, median time from the first diagnosis of cancer disease to the study start was 22 days (range 0 to 9879 days). A prior radiation therapy was performed in 61 (9.0%) patients. Median time between radiation therapy and study start in these patients was 194 days (range 26 to 10809 days). No patient had a prior bone marrow or stem cell transplantation. The treatment groups

were different with regard to cancer history due to different inclusion criteria in the studies, e.g. in the breast cancer study, a homogeneous patient population with stage II to IV disease without prior CTX was included, and in the lung cancer study, one previous CTX-regimen was allowed.

- Adverse events

In the pooled analysis of the 3 studies in cancer patients, 543 (80.2%) of the patients experienced at least one TEAE in the Cycle 1. TEAEs were considered study drug-related in 16.7% (113 patients) and CTX-related in 70.5% (477 patients).

An overview of adverse events in the cancer patient set (Cycle 1) is presented in Table 29.

Table 29 Cancer patient dataset - Overview of adverse events (cycle 1)

	XM02 only N=356	**Neupogen only N=134**	**Neupogen/ XM02 N=115**	**Placebo/ XM02 N=72**	**Any XM02 N=541**	**Overall N=677**	
	%	%	%	%	%	n	%
At least one TEAE[#]	75.3	91.0	73.0	95.8	77.4	543	80.2
Study drug-related[#]	14.9	28.4	11.3	12.5	13.9	113	16.7
CTX-related[#]	64.9	83.6	57.4	94.4	67.1	477	70.5
Severe	17.7	17.9	12.2	44.4	19.8	133	19.6
Serious	11.0	9.7	5.2	22.2	10.9	74	10.9
Stopped study drug due to a TEAE	3.1	3.0	0.0	0.0	2.0	15	2.2
Died due to a TEAE	2.0	1.5	0.0	2.8	1.3	11	1.6

# $p < 0.001$ Fisher's exact test comparing first 3 groups

In the pooled analysis across all cycles, 93.5% (633 patients) experienced at least one TEAE, of which 27.3% (185 patients) were considered to be study drug-related and 86.1% (583 patients) CTX-related.

The 3 studies in cancer patients were similar with regard to the most common TEAEs (Table 30), which were nausea (27.3% of patients in cycle 1 and 46.2% across all cycles), alopecia (25.0% in cycle 1 and 33.8% across all cycles), neutropenia (16.1% in cycle 1 and 22.6% across all cycles), diarrhoea (13.0% in cycle 1 and 20.4% across all cycles), asthenia (12.9% in cycle 1 and 28.7% across all cycles) and vomiting (12.6% in cycle 1 and 25.6% across all cycles).

Table 30 Cancer patient dataset - Treatment-emergent adverse events (≥ 5% of patients in any group) (cycle 1)

	XM02 only N=356	Neupogen only N=134	Neupogen/ XM02 N=115	Placebo/ XM02 N=72	Any XM02 N=541	Overall N=677	
	%	%	%	%	%	n	%
Nausea	26.4	29.9	23.5	33.3	26.8	185	27.3
Alopecia[#]	21.3	39.6	12.2	36.1	21.4	169	25.0
Neutropenia[#]	13.8	21.6	6.1	33.3	14.6	109	16.1
Diarrhoea[#]	10.4	23.1	5.2	19.4	10.2	88	13.0
Asthenia[#]	8.7	18.7	11.3	25.0	11.3	87	12.9
Vomiting	15.2	10.4	10.4	6.9	13.1	85	12.6
Pyrexia	6.2	5.2	6.1	9.7	6.5	43	6.4
Headache	6.5	6.0	4.3	8.3	6.3	42	6.2
Bone pain[#]	5.9	9.7	1.7	2.8	4.6	38	5.6
Abdominal pain[#]	3.7	11.2	2.6	5.6	3.7	35	5.2
Stomatitis	3.7	6.0	2.6	15.3	4.8	35	5.2
Anorexia	5.1	6.0	4.3	2.8	4.4	33	4.9
Anaemia	5.1	3.7	5.2	4.2	5.0	32	4.7
Febrile neutropenia	2.5	3.0	1.7	23.6	5.2	32	4.7
Leucopenia	3.7	3.0	3.5	9.7	4.4	28	4.1
Thrombocytopenia	4.5	2.2	5.2	4.2	4.6	28	4.1
Back pain	3.1	1.5	6.1	1.4	3.5	21	3.1
Alopecia totalis[#]	2.8	5.2	0.0	5.6	2.6	21	3.1
Insomnia	3.1	0.7	3.5	5.6	3.5	20	3.0
Myalgia	2.0	6.0	0.9	2.8	1.8	18	2.7
Chest pain	2.2	0.7	5.2	0.0	2.6	15	2.2
Dyspnoea	1.4	1.5	0.9	5.6	1.7	12	1.8
Pharyngo-laryngeal pain	0.3	1.5	0.0	5.6	0.7	7	1.0
Pharyngitis	0.0	0.0	0.0	5.6	0.6	4	0.6

# $p < 0.001$ Fisher's exact test comparing first 3 groups

The incidence of several TEAEs (in cycle 1: alopecia, neutropenia, diarrhoea, asthenia, bone pain and abdominal pain) were statistically significantly higher in the Neupogen-only group than in the XM02-only group. However, these differences are unlikely to be of clinical relevance.

The incidence of febrile neutropenia was much higher in the placebo/XM02 group, as expected due to an higher incidence during cycle 1. In the placebo/XM02 group, the incidence of stomatitis, pharyngitis, and pharyngolaryngeal pain was also higher compared to the other groups.

The most commonly reported drug-related TEAEs across all studies in cancer patients during cycle 1 (Table 31) were bone pain (3.4%), diarrhoea (2.2%), asthenia (2.2%), myalgia (1.9%), arthralgia (1.5%), headache (1.2%) and pyrexia (1.0%). These are expected adverse events from the known pharmacological profile of G-CSF. A similar profile was seen for all cycles. The overall incidence of possibly drug-related TEAEs across all cycles was higher in the breast cancer study.

Table 31 Cancer patient dataset - Drug–related treatment-emergent adverse events (≥ 1% of patients in any group) (Cycle 1)

	XM02 only N=356	Neupogen only N=134	Neupogen/ XM02 N=115	Placebo/ XM02 N=72	Any XM02 N=541	Overall N=677	
	%	%	%	%	%	n	%
Bone pain[#]	3.4	7.5	0.0	1.4	2.4	23	3.4
Diarrhoea[#]	1.1	6.0	0.0	4.2	1.3	15	2.2
Asthenia[#]	1.4	4.5	0.0	5.6	1.7	15	2.2
Myalgia	1.4	3.7	0.9	2.8	1.5	13	1.9
Arthralgia	1.4	3.0	0.9	0.0	1.1	10	1.5
Headache	1.4	0.7	0.9	1.4	1.3	8	1.2
Pyrexia	1.4	0.7	0.9	0.0	1.1	7	1.0
Musculoskeletal pain	0.8	2.2	0.9	0.0	0.7	7	1.0
Back pain	0.6	0.7	2.6	0.0	0.9	6	0.9
Fatigue	0.6	0.7	1.7	0.0	0.7	5	0.7
Thromcythaemia	0.6	0.7	0.0	0.0	0.4	3	0.4
Abdominal pain	0.3	0.7	0.0	1.4	0.4	3	0.4
Abdominal pain upper	0.0	1.5	0.0	1.4	0.2	3	0.4
Constipation	0.0	0.0	0.0	1.4	0.2	1	0.1
Haemorrhoids	0.0	0.0	0.0	1.4	0.2	1	0.1
Alopecia	0.0	0.0	0.0	1.4	0.2	1	0.1

# $p < 0.001$ Fisher's exact test comparing first 3 groups

When analysed by system organ class (SOC), the data were consistent with the above-mentioned analyses of TEAEs by preferred term. The most commonly reported SOCs in cycle 1 were gastrointestinal disorders, skin and subcutaneous tissue disorders, and blood and lymphatic system disorders. Looking at drug-related events, the most commonly reported SOCs in cycle 1 were musculoskeletal and connective tissue disorders, general disorders, administration site conditions, and gastrointestinal disorders.

Bone pain: Within individual studies, the treatment groups were similar with regard to incidence of bone pain when all the cycles were counted (20% of patients in XM02 group vs. 28% of patients in Neupogen group). In cycle 1, the overall incidence of bone pain was 13.7%, with a higher incidence in the Neupogen-only group (20.9%) compared to the XM02-only and Neupogen/XM02 groups (12.6% and 11.3%, respectively; $p = 0.049$). The overall incidence of study drug-related bone pain was 6.9%, with a higher incidence in the Neupogen-only group (14.2%) compared to the XM02-only and Neupogen/XM02 groups (6.2% and 4.3%, respectively; $p = 0.007$). There was a lower incidence of bone pain in the placebo/XM02 group.

Allergic reactions: In the pooled analysis of XM02 studies in cancer patients, "potential allergic reactions" (including angioneurotic oedema, dermatitis allergic, drug hypersensitivity, hypersensitivity, rash, pruritic rash and urticaria) occurred in 12 (1.8%) of the patients in cycle 1 (1.4% in the XM02-only and 2.2% in the Neupogen-only groups, respectively) and in 25 (3.7%) of the patients across all cycles (4.5% in the XM02-only and 3.7% in the Neupogen-only groups, respectively). Of the reactions across all cycles, 8 (1.2%) of the patients had reactions that were considered drug-related. Only 1 allergic reaction was serious, i.e. bronchospasm in cycle 1 requiring temporary interruption of the study drug (XM02 group in Study XM02-02-INT).

Anaemia: In cycle 1, the overall incidence of anaemia was 5.0% and comparable across the treatment groups (5.2, 4.7 and 4.2% in the XM02, Neupogen and placebo groups, respectively). Most of these anaemia TEAEs were considered to be CTX-related (4.1, 3.9 and 4.2% in the XM02, Neupogen and placebo groups, respectively). One patient (0.4%) experienced a study drug-related anaemia TEAE, in the Neupogen group. There were no severe or serious anaemia TEAEs, and no patients stopped study drug due to a TEAE.

Across all cycles, the overall incidence of anaemia was 20.4% with a lower incidence in the Neupogen only group (6.7%) compared to the XM02 only and Neupogen/XM02 groups (22.8 and 33.9%,

respectively; $p < 0.001$). Most of the anaemia was CTX-related (6.0, 21.3 and 31.3% in the XM02, Neupogen and placebo groups, respectively). The higher incidence of anaemia in the XM02 group was driven by TEAEs reported in the lung cancer study (**Study XM02-03-INT**), which had no reference group. There were 7 patients whose anaemia was considered to be drug-related (1 each in the breast cancer and NHL studies and 5 in the lung cancer study).

Injection site reactions: The injection site was assessed for signs of redness, swelling, bruising and tenderness. The incidence of injection site reactions was low in all cancer patient studies (1.5% of patients overall across all cycles). There were no differences between the treatment groups or within individual studies.

Immunogenicity: The development of antibodies against XM02 and Neupogen was investigated in the 3 cancer patient studies. Immunogenicity was assessed by a predefined characterisation cascade of antibody assays using XM02 as test antigen:

1. Screening with Anti-XM02 (IgG) ELISA and Anti-XM02 (IgG-IgM) Luminex assay.

If positive or questionable:

2. IgG- and IgM-specific Western Blot Confirmation Assays.

Western-Blot positive or questionable - three assays in parallel:

3. Quantitative Anti-XM02 (IgG) Luminex assay using polyclonal calibrator sera and relative assay units (RU-MFI IgG);
4. Neutralising antibodies (NAB) using a G-CSF-depended NFS-60 cell-based assay;
5. Binding antibodies using a BIAcore total antibody assay.

Table 32 displays these results.

Table 32 Cancer patient dataset - Immunogenicity: antibodies and neutralising antibodies results

	XM02 only N=356		**Filgrastim only N=134**		**Filgrastim/ XM02 N=115**		**Placebo/ XM02 N=72**		**Overall N=677**	
	n	%	n	%	n	%	n	%	n	%
Positive antibody test results										
Screening	12	3.4	2	1.5	2	1.7	2	2.8	18	2.7
Before cycle 1	4	1.1	1	0.7	1	0.9	0	0.0	6	0.9
Any subsequent visits	7	2.0	2	1.5	0	0.0	2	2.8	13	1.9
End of study	2	0.6	0	0.0	0	0.0	1	1.4	3	0.4
Antibody follow-up	2	0.6	2	1.5	2	1.7	2	2.8	8	1.2
Positive antibody test results excluding test with implausible results										
Excluded	33	9.3	11	8.2	7	6.1	6	8.3	57	8.4
Screening	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Before cycle 1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Any subsequent visits	3	0.8	0	0.0	0	0.0	0	0.0	3	0.4
End of study	1	0.3	0	0.0	0	0.0	1	1.4	2	0.3
Antibody follow-up	1	0.3	1	0.7	2	1.7	2	2.8	6	0.9
Positive neutralising antibody test results										
Screening	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Before cycle 1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Any subsequent visits	1	0.3	0	0.0	0	0.0	0	0.0	1	0.1
End of study	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Antibody follow-up	1*	0.3	0	0.0	0	0.0	0	0.0	1	0.1
Positive neutralising antibody test results excluding tests with implausible results										
Excluded	7	2.0	3	2.2	1	0.9	2	2.8	13	1.9
Screening	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Before cycle 1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Any subsequent visits	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
End of study	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Antibody follow-up	1*	0.3	0	0.0	0	0.0	0	0.0	1	0.1

* borderline positive sample with 23.0% inhibition (cut-off 23.0%)

The incidence of binding and neutralising antibodies was low. As expected for G-CSF and as described in the EMEA guidance CHMP/BMWP/31329/2005[*12*], there were no immunogenicity findings of clinical relevance which had "major consequences for efficacy and safety".

- Serious adverse event/deaths/other significant events

In cycle 1, 74 (10.9%) patients reported a serious adverse event (SAE) with more patients in the placebo/XM02 group (22.2%) than in the other groups. Across all cycles, 135 (19.9%) of the patients reported an SAE. There was an overall higher incidence of SAEs in the lung cancer study (30%) than in the breast cancer study (14%) and the NHL study (15%).

Five patients had SAEs that were considered to be drug-related across all 3 studies. These were:

- an allergic reaction (bronchospasm) in cycle 1 (XM02 group) in the breast cancer study;
- syncope in cycle 3 (placebo/XM02 group) in the breast cancer study;
- myocardial infarction in cycle 2 (Neupogen/XM02 group) in the lung cancer study;
- thrombocytopenia in cycle 5 (Neupogen/XM02 group) in the lung cancer study;
- thrombocytopenia in cycle 1 and hyperuricaemia in Cycle 2 (XM02 group) in the lung cancer study.

With exception of syncope, these events were also considered to be CTX-related.

Deaths

In the 3 studies in cancer patients, 26 (3.8%) of the patients died, 11 (1.6%) of whom during cycle 1. No differences in the incidence of death were observed between the treatment groups. Of the 26 deaths, 22 occurred in the study involving patients with lung cancer and 4 in the study conducted in patients with breast cancer. About 25% of these TEAEs were CTX-related. None were judged to be related to the study drug.

- Laboratory findings

The laboratory safety parameters alkaline phosphatase (AP), lactate dehydrogenase (LDH), uric acid, leukocytes, haemoglobin and platelets were of special interest. There were no clinically relevant differences between the treatment groups.

- Safety in special populations

No differences in safety profile with regard to age, gender, race or body weight were observed. Only a few patients with renal (n = 1) and hepatic impairment (n = 13) were included in the studies. Thus, assessment of influence of these co-morbidities on G-CSF use is limited.

- Safety related to drug-drug interactions and other interactions

No studies on drug interactions were performed.

Recommendations from the Neupogen SPC: 1) Neupogen should not be administered from 24 hours before up to 24 hours after chemotherapy as neutropenia may be increased with concomitant treatment, 2) potential interactions with other haematopoietic growth factors and cytokines have not been investigated as part of clinical studies and 3) lithium may potentiate the effects of Neupogen.

- Discontinuation due to adverse events

Overall in cycle 1, 15 (2.2%) of the patients discontinued the study drug due to a TEAE (11 cases in the XM02 group and 4 in the Neupogen group). Across all cycles, 40 (5.9%) of the patients withdrew from the study drug due to a TEAE (27, 5, 6 and 2 in XM02, Neupogen, Neupogen/XM02 and placebo/XM02 groups, respectively). The majority of TEAEs leading to study drug discontinuation were classified as CTX-related. Overall, 6 (0.9%) of the patients had a study drug-related TEAE that led to study drug discontinuation. There was a higher incidence of withdrawal due to TEAEs in the lung cancer study than in the other studies.

- Post-marketing experience

Not applicable.

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.

Table 33 Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important identified risks known from the originator product		
Allergic type reactions (PT: Hypersensitivity)	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR	Routine risk minimisation (labelling) - Allergic reactions (allergic-type reactions, including anaphylaxis, skin rash, urticaria, angioedema, dyspnoea and hypotension) are mentioned in section 4.8 of the SPC - Hypersensitivity is mentioned in section 4.3 (Contraindications) of the SPC
Adult respiratory distress syndrome (ARDS) (PT: acute respiratory distress syndrome) Interstitial pneumonia (PT: interstitial lung disease) Pulmonary oedema (PT) Pulmonary infiltrates (PT: lung infiltrates) Respiratory failure (PT)	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR	Routine risk minimisation (labelling) - Pulmonary undesirable effects including interstitial pneumonia, pulmonary oedema and pulmonary infiltrates in some cases with an outcome of respiratory failure or adult respiratory distress syndrome (ARDS) which may be fatal are mentioned in section 4.8 of the SPC - Mention in section 4.4 of the SPC that patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk. The onset of pulmonary signs such as cough, fever and dyspnoea in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function may be preliminary signs of Adult Respiratory Distress Syndrome (ARDS)
Sweet's syndrome (PT: acute febrile neutrophilic dermatosis)	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR	Routine risk minimisation (labelling) - Sweet's syndrome (acute febrile dermatosis) is mentioned in section 4.8 of the SPC.

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important identified risks known from the originator product		
Sickle cell crisis in patients with sickle cell disease (PT: sickle cell anaemia with crisis)	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR	Routine risk minimisation (labelling) - Sickle cell crisis in patients with sickle cell disease is mentioned in section 4.8 of the SPC - Mention in section 4.4 of the SPC that physicians should exercise caution when considering the use of filgrastim in patients with sickle cell disease and only after careful evaluation of the potential risks and benefits
Exacerbation of rheumatoid arthritis (PT: rheumatoid arthritis)	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR	Routine risk minimisation (labelling) - Exacerbation of rheumatoid arthritis is mentioned in section 4.8 of the SPC
Cutaneous vasculitis (PT)	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR	Routine risk minimisation (labelling) - Cutaneous vasculitis is mentioned in section 4.8 of the SPC
Splenic rupture (PT) Splenomegaly (PT)	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR	Routine risk minimisation (labelling) - Splenomegaly and splenic rupture are mentioned in section 4.8 of the SPC. - Mention in section 4.4 of the SPC that splenic enlargement is a direct effect of treatment with filgrastim Therefore, spleen size should be carefully monitored. A diagnosis of splenic rupture should be considered in donors and/or patients reporting left upper abdominal pain or shoulder tip pain
Increased risk of GVHD (PTs: chronic graft-versus-host disease, acute graft-versus-host disease, graft-versus-host disease)	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR	Routine risk minimisation (labelling) - In section 4.4 of the SPC it is mentioned that current data indicate that immunological interactions between the allogeneic PBPC graft and the recipient may be associated with an increased risk of acute and chronic graft versus host disease when compared with bone marrow transplantation
Osteoporosis (PT)	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR	Routine risk minimisation (labelling) - Osteoporosis is mentioned in section 4.8 of the SPC
Transformation to leukaemia (PT) or myelodysplastic syndrome (PT)	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR	Routine risk minimisation (labelling) - Transformation to leukaemia or myelodysplastic syndrome is mentioned in section 4.4 of the SPC under special precautions in severe chronic neutropenia patients
Important identified risks known from clinical trials		
Myalgia (PT)	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR	Routine risk minimisation (labelling) - Musculoskeletal pain is mentioned in section 4.8 of the SPC. This term is considered to cover also the term myalgia

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important potential risks		
Immunogenicity in individual patients treated	Routine pharmacovigilance Signal detection procedure for all incoming ADR reports from whatever sources (including the SCNIR) and indications, and scheduled antibody assessment in case of suspected immunogenicity. Co-operation with SCNIR (Severe Chronic Neutropenia International Registry) and analysis of corresponding Ratiograstim-SCNIR data The results will be presented and analysed in each PSUR	
Risk of haematological malignancies with granulocyte colony stimulating factor (G-CSF) use in normal donors (PT: haematological malignancy)	Signal detection procedure for all incoming ADR reports from whatever sources; bi-annually literature search for publications on haematological malignancies related to G-CSF use	Routine risk minimisation - In section 4.4 of the SPC it is mentioned that transient cytogenetic modifications have been observed in normal donors following G-CSF use. The significance of these changes in terms of the development of haematological malignancy is unknown. Long-term safety follow-up of donors is ongoing. A risk of promotion of a malignant myeloid clone cannot be excluded. It is recommended that the aphaeresis centre perform a systematic record and tracking of the stem cell donors for at least 10 years to ensure monitoring of long-term safety
Off-label use (PT)	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR	Routine risk minimisation - Approved indications are described in section 4.1 of the SPC

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.

Further considerations following positive opinion in February 2008

Following the positive opinion in February 2008 for Ratiograstim, the European Commission referred the opinion back to the CHMP on 29 April 2008. This was due to concerns over available safety information for the filgrastim-containing medicinal product Grasalva authorised in Lithuania in 2003 (by Sicor Biotech UAB, part of the Teva group) and a relevance for Ratiograstim. The CHMP was requested to consider whether any data provided for the authorisation of Grasalva, or collected post-authorisation, are relevant for the assessment of the marketing authorisation application for Ratiograstim.

Upon request from the EMEA/CHMP, the Applicant provided the full Grasalva dossier, including data on quality, safety and efficacy. The Applicant confirmed that the active substances for Grasalva and Ratiograstim are the same and manufactured using to the same process. However, there are some differences on the level of the drug product, which, according to the Applicant, provide evidence that the two products are not the same. Nevertheless, the differences between the drug products were considered by the CHMP to be minor and therefore the assessment of the Grasalva data focused on clinical aspects in order to address the request from the European Commission.

The clinical data provided for Grasalva included one phase I study in healthy male volunteers (GCSF-BQL-02) and one pivotal study (GCSF-IV-03) in patients with metastatic breast cancer. The evaluation of safety included analyses of adverse events, serious adverse events and deaths, discontinuation due to adverse events, laboratory findings, safety in special populations, immunogenicity, post-marketing experience, identified and potential risks, and missing information.

Among the limited data included in the Grasalva dossier, a single death and a number of other serious adverse events were reported. As details in the Grasalva dossier were limited in some areas, a thorough assessment of these adverse events was difficult. However, a satisfactory review of the safety data for Grasalva has been provided by the Applicant. The CHMP concluded that the events reported were not unexpected in the patient population (oncology) being studied.

The CHMP concluded that the data provided in the Grasalva dossier do not affect the opinion for Ratiograstim. As a result, the benefit-risk profile for Ratiograstim and the Risk Management Plan at the time of opinion remain unchanged following consideration of the data submitted on Grasalva.

In a letter dated 18 June 2008, the European Commission requested that the CHMP consider the need for GCP inspections of the clinical studies carried out for Ratiograstim. The Applicant provided further clarifications in writing 22 July 2008 as to why a GCP inspection of the Ratiograstim clinical trial sites would not be needed. In particular, the Applicant provided reassurance regarding the quality control of the clinical trials conducted for Ratiograstim, which were performed in adherence with GCP standards. In addition, the Applicant presented its position to the CHMP at an oral explanation on 23 July 2008.

The CHMP considered that the documentation presented for Ratiograstim does not indicate a need for a GCP inspection. The CHMP concluded that the Applicant had demonstrated satisfactorily that the clinical development for Ratiograstim was clearly separate from the clinical development of Grasalva and conducted by two separate companies, i.e. Biogenerix for Ratiograstim and Sicor Biotech for Grasalva. The CHMP concluded that information provided for Grasalva did not raise any concerns regarding the GCP compliance of clinical trials conducted for the Ratiograstim application.

In conclusion, the CHMP concluded that data generated for the medicinal product Grasalva did not affect the benefit-risk balance of Ratiograstim. In addition, the CHMP concluded that the documentation submitted for the Ratiograstim application does not indicate a need for a GCP inspection.

3 OVERALL CONCLUSIONS, RISK/BENEFIT ASSESSMENT AND RECOMMENDATION

Quality

The dossier was found to be of good quality, fulfilling the requirements for marketing authorisation of a similar biological medicinal product. Extensive comparability studies were performed using Neupogen, sourced from Germany, as the reference medicinal product. The characterisation of the active substance and the comparability studies are considered acceptable.

During the evaluation, two major objections were raised. The first concerned the lack of real-time stability results to support the proposed shelf life of the active substance and medicinal product. Appropriate data were however provided by the applicant in their responses and the major objection was considered resolved. The second major objection related to the sourcing of the reference medicinal product as it was unclear whether an EU-authorised medicinal product was used as reference throughout the comparability exercise. It was clarified as part of the responses to the List of Questions that comparability had been fully demonstrated using an EU-authorised medicinal product as the reference (i.e. Neupogen sourced from Amgen, Germany). Thus, the major objection regarding the origin of the medicinal product used for impurity profiling by RP-HPLC and IE-HPLC was adequately addressed.

Other concerns have also been adequately addressed. However, four commitments have been made by the applicant to provide further information post-approval.

Non-clinical pharmacology and toxicology

Non-clinical studies have not demonstrated any differences between XM02 and Neupogen with respect to the primary or secondary pharmacodynamic activities.

Non-clinical data revealed no special hazards for humans based on conventional studies of safety pharmacology, genotoxicity or local tolerance.

Non-clinical data from conventional repeat-dose toxicity studies revealed the expected pharmacological effects, including increases in leukocyte counts, myeloid hyperplasia in bone marrow, extramedullary haematopoiesis and splenic enlargement.

No effects on the fertility of male and female rats or gestation in rats were observed. There is no evidence from studies in rats and rabbits that XM02 is teratogenic. An increased incidence of embryo loss was observed in rabbits but no malformations have been seen.

Efficacy and safety

Randomised, single-blind, single dose, crossover studies in 196 healthy volunteers showed that the pharmacokinetic profile of XM02 was comparable to that of the reference product, Neupogen (filgrastim), after subcutaneous and intravenous administration.

Clearance of XM02 has been shown to follow first-order pharmacokinetics after both subcutaneous and intravenous administration. The serum elimination half life of XM02 is approximately 3.5 hours, with a clearance rate of approximately 0.6 ml/min/kg. Continuous infusion with filgrastim over a period of up to 28 days in patients recovering from autologous bone-marrow transplantation resulted in no evidence of drug accumulation and comparable elimination half-lives. There is a positive linear correlation between the dose and the serum concentration of XM02, whether administered intravenously or subcutaneously. Following subcutaneous administration of recommended doses, serum concentrations were maintained above 10 ng/ml for 8 to 16 hours. The volume of distribution in blood is approximately 150 ml/kg.

In cancer patients, the pharmacokinetic profiles of XM02 and the reference product were comparable after single and repeated subcutaneous administration.

The efficacy and safety of XM02 have been assessed in randomised, controlled phase III studies in breast cancer, lung cancer and non-Hodgkin's lymphoma. There were no relevant differences between XM02 and the reference product with regard to duration of severe neutropenia or the incidence of febrile neutropenia.

From the safety database, all the adverse reactions reported in clinical trials have been taken into account in the Summary of Product Characteristics.

User consultation

The Patient Information Leaflet (PIL) for Ratiograstim (filgrastim) has been tested in English in accordance with Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended by Directive 2004/27/EC. The PIL for Ratiograstim (filgrastim) was found to contain all the necessary information in a form that is accessible and understandable to those who participated in this test.

It is considered that the tested PIL meets the requirements set for User Testing.

Risk-benefit assessment

Since Ratiograstim as biosimilar product has shown a comparable quality, safety and efficacy compared with the reference product, it is expected that Ratiograstim provides the same benefits as Neupogen in the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy and in patients undergoing myeloablative therapy followed by bone marrow transplantation both in adults and children, as well as in mobilisation of peripheral blood progenitor cells. Finally, the long-term benefits in children or adults with severe congenital, cyclic or idiopathic neutropenia and in neutropenic HIV-positive individuals are expected to be the same as with Neupogen.

The only area of uncertainty is the mobilisation of peripheral blood progenitor cells because it is not known whether the efficacy in oncology can be fully extrapolated to this area of use. The uncertainty is due to the lack of complete understanding of the mechanism of peripheral blood progenitor cell mobilisation from the bone marrow. This issue has now been satisfactorily addressed by the RMP.

The development programme has not revealed unexpected safety issues. The adverse event profiles of the test and the reference products appeared to be comparable and this has been fully taken into account in the SPC and RMP.

In principle, the potential additional risks of a biosimilar product must be related to differences in the quality of the test and the reference products. The observed major deficiencies in the quality documentation pertained to insufficient demonstration of the stability of the active substance and the medicinal product. The applicant was asked for more information according to these questions and the responses were adequate.

Immune-related problems have been rare for the reference product Neupogen. Immune-mediated neutropenia has been demonstrated in animal experiments. The immunological studies conducted did not provide any signals for enhanced immunogenicity. Unfortunately, the documentation of the immunoassays and assay strategy was incomplete during the first assessment. The Applicant provided further information which supported the application and the final decision is now positive.

Screening for rare immunological adverse effects in the post-marketing setting is difficult. In principle, it must be driven by reported adverse events that have a potential immunological origin. These events should be investigated for immunogenicity as agreed in the Risk Management Plan.

The present Marketing Authorisation Application is based on appropriate studies and the test product is comparable to the reference product. The observed major deficiencies have been resolved and the granting of a marketing authorisation is recommended. In conclusion, the overall B/R is positive.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product. No additional risk minimisation activities were required beyond those included in the product information.

Following a positive opinion in February 2008 the CHMP, upon request from the European Commission, assessed data generated for the medicinal product Grasalva and concluded that these data did not affect the benefit-risk balance of Ratiograstim. In addition, the CHMP concluded that the scientific data collected in the clinical trials conducted for the Ratiograstim application does not indicate a need for a GCP inspection.

Recommendation

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

> Ratiograstim is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy

(with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and for the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia. The safety and efficacy of filgrastim are similar in adults and children receiving cytotoxic chemotherapy.

Ratiograstim is indicated for the mobilisation of peripheral blood progenitor cells (PBPC).

In patients, children or adults, with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of 0.5 x 10^9/l, and a history of severe or recurrent infections, long term administration of Ratiograstim is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

Ratiograstim is indicated for the treatment of persistent neutropenia (ANC less than or equal to 1.0 x 10^9/l) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.

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