Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Filgrastim

Proprietary Product Name: Tevagrastim

Sponsor: Aspen Pharmacare Australia Pty Ltd

October 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Similar Biological Medicinal Product
Decision:	Approved
Date of Decision:	16 August 2011
Active ingredient(s):	Filgrastim
Product Name(s):	Tevagrastim
Sponsor's Name and Address:	Aspen Pharmacare Australia Pty Ltd 34-36 Chandos St, St Leonards, NSW 2065
Dose form(s):	Solution for Injection or Infusion
Strength(s):	300 µg in 0.5 mL and 480 µg in 0.8 mL
Container(s):	Pre filled syringes
Pack size(s):	1, 5 and 10 syringes
Approved Therapeutic use:	· To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs in doses not usually requiring bone marrow transplantation. · To reduce the duration of neutropenia and clinical sequelae in patients undergoing induction and consolidation chemotherapy for acute myeloid leukaemia. · For the mobilisation of autologous peripheral blood progenitor cells alone, or following myelosuppressive chemotherapy, in order to accelerate neutrophil and platelet recovery by infusion of such cells after myeloablative or myelosuppressive therapy in patients with nonmyeloid malignancies. · For the mobilisation of peripheral blood progenitor cells, in normal volunteers, for use in allogeneic peripheral blood progenitor cell transplantation. · In patients receiving myeloablative chemotherapy, to reduce the duration of neutropenia and clinical sequelae following autologous or allogeneic bone marrow transplantation. · For chronic administration to increase neutrophil counts and to reduce the incidence and duration of infections in patients with severe chronic neutropenia. · In patients with HIV infection, for reversal of clinically significant neutropenia and subsequent maintenance of adequate neutrophil counts during treatment with antiviral and/or other myelosuppressive medications.
Route(s) of administration:	Subcutaneous (SC) injection or infusion, or Intravenous (IV) infusion
Dosage:	Doses of 5 µg/kg or 10 µg/kg administered as single daily subcutaneous injections, continuous subcutaneous infusion or intravenous infusions (15-30 minutes or 4-24 hours)
ARTG Number (s)	163657 and 163677

Product Background

Granulocyte colony-stimulating factor (G-CSF) is a haematopoietic cytokine released mainly by mononuclear cells and fibroblasts. The human form of G-CSF is a glycoprotein composed of a single polypeptide chain of 174 or 177 amino acids. After its purification and cloning, a bacterially synthesised (in *Escherichia coli* [E. coli]) non-glycosylated form of recombinant human G-CSF (r-metHuG-CSF) was expressed and introduced to clinical practice in 1991 under the trade name Neupogen (International Non-proprietary Name: filgrastim).

This AusPAR describes the evaluation of an application by Aspen Pharmacare Australia Pty Ltd to register their new product Tevagrastim, a "generic" version of the currently marketed in Australia biological product filgrastim (Neupogen). Tevagrastim (filgrastim) is a highly purified non-glycosylated form of r-metHuG-CSF.

In Australia there are currently three granulocyte colony stimulating factors (G-CSFs) registered. All are versions of endogenous G-CSF and are produced by recombinant DNA technology. The innovator products are:

·	Filgrastim	(Neupogen)	Amgen
·	Lenograstim	(Granulocyte)	Hospira
·	Pegfilgrastim	(Neulasta)	Amgen

"Generic" biological products are referred to as "similar biological medicinal products (SBMPs)" or "biosimilar" in recognition of the fact that due to the complexity of their molecular structure and manufacturing it is not possible to produce true generic versions.

The TGA has adopted several European Medicines Agency (EMA) guidelines as appropriate standards for data requirements for SBMPs and two of these are relevant to the current application; one is a general guideline outlining nonclinical and clinical data requirements for SBMPs[1] and the other is an annex to the first and outlines specific requirements to G-CSF SBMPs[2].

For small molecule drugs, a generic manufacturer is usually simply required to demonstrate bioequivalence between the generic and innovator products using pharmacokinetic criteria (area under the plasma concentration time curve (AUC) and maximal plasma concentration (C_{max})). For SBMPs, in addition to demonstrating pharmacokinetic bioequivalence, the manufacturer is required to provide data to demonstrate equivalent efficacy and safety, although the extent of the efficacy and safety data required is less than that required for registration of a new chemical entity.

The sponsor of Tevagrastim has conducted a series of studies designed in compliance with the EMA guidelines, to show equivalence of Tevagrastim with Neupogen. The comparator used was Neupogen as marketed in Europe by Amgen.

The sponsor is seeking approval for the same indications and dosage regimens currently registered for Neupogen in Australia.

The TGA has previously approved one other filgrastim SBMP (Nivestim; Hospira Pty Ltd). This product was considered and recommended for approval by Advisory Committee for

[1] Guideline on similar biological medicinal products containing Biotechnology-derived proteins as active substance: Non-clinical and clinical issues. EMEA/CHMP/BMWP/42832/2005. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003963.pdf

[2] Annex to 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. EMEA/CHMP/ BMWP/31329/05. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003955.pdf

Prescription Medicines (ACPM) at its August 2010 meeting. One other SBMP product (epoetin lambda, Novicrit; Novartis, an SBMP of epoetin alfa), has been registered in Australia, following consideration by Australian Drug Evaluation Committee (ADEC; now called ACPM) at its June 2009 meeting.

Regulatory Status

The current status of marketing authorisation of filgrastim is presented in Table 1. The Marketing authorisation holder (MAH) submitted a request for withdrawal of Filgrastim-Ratiopharm due to marketing considerations. The request was approved by the European Medicines Agency (EMA) in April 2011.

Table 1. International Regulatory Status.

Country	Approval date	Trade name(s)
European Union (EU) Centralised Procedure	September 2008	Ratiograstim Tevagrastim
Switzerland	December 2008 January 2010 December 2008	Tevagrastim Filgrastim-Teva Filgrastim-Mepha 30/Filgrastim-Mepha 48
Brazil	February 2010	Tevagrastim
Israel	April 2010	Tevagrastim
Russia	August 2010	Tevagrastim
Georgia	May 2011	Tevagrastim
Ukraine	June 2011	Tevagrastim

Amgen Pty Ltd has marketed Neupogen in the United States (US) since 1991 and Australia since 1995. Neupogen was authorised for marketing in the European Union (EU) in September 2008 and applications have been made to a number of other countries.

Product Information

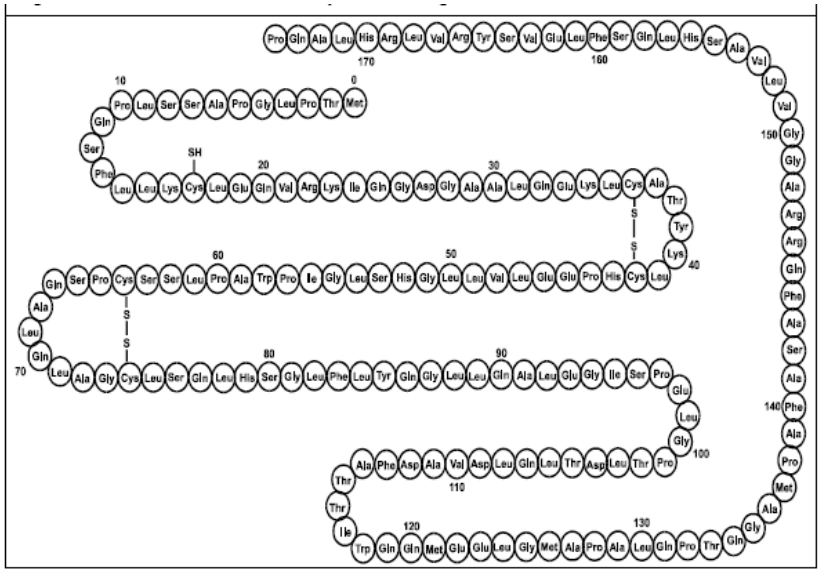
The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

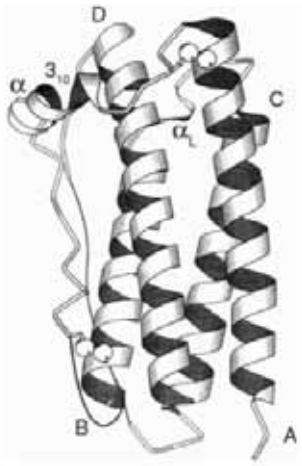
Drug Substance (active ingredient)

Filgrastim is a 175 amino acid single polypeptide ($C_{845}H_{1339}N_{223}O_{243}S_9$) produced by recombinant deoxyribonucleic acid (DNA) technology in *E. coli.* Filgrastim differs from endogenous G-CSF in that it is not glycosylated and contains an additional N-terminal methionine. It has two disulfide bonds located at cysteine (Cys) 37-Cys43 and Cys65-Cys75. Filgrastim has α-helical structure arranged in a four helical bundle motif.

Figure 1. A: Amino acid sequence showing disulfide bonds



B: Ribbon model showing helical structure



Drug Product

Manufacturing and quality control aspects for *Tevagrastim* have been considered separately, together with *in vitro* comparisons with *Neupogen.*

Tevagrastim is formulated as a clear colourless solution and supplied in 1 mL, ready to use pre-filled syringes:

- 300 µg/0.5 mL, containing 300 µg of filgrastim, supplied in packs of 1, 5 and 10 syringes
- 480 µg/0.8 mL, containing 480 µg of filgrastim, supplied in packs of 1, 5 and 10 syringes

The difference between the two strengths is achieved by fill volume alone.

The following excipients are included in the drug product: acetic acid, Polysorbate 80, sodium hydroxide, sorbitol and Water for Injection.

Depending on the indication, filgrastim is given by subcutaneous (SC) injection or by intravenous (IV) infusion after dilution in 5% glucose (with human serum albumin added if the final solution is very dilute).

Biopharmaceutics

The sponsor's application includes five clinical studies with the proposed 'XM02' formulation, of which two are bioequivalence studies in healthy volunteers. The bioequivalence studies used different clinical sites (in Lithuania and Germany).

Study XM02-01-LT made 5 µg/kg SC and 10 µg/kg SC single dose comparisons with *Neupogen* (product marketed in Lithuania by F. Hoffmann-La Roche).

Study XM02-05-DE made 5 µg/kg IV and SC and 10 µg/kg IV and SC single dose comparisons with *Neupogen* (product marketed in Germany made by Amgen Inc).

It is not certain that *Neupogen* from the different European sources is the same, although the sponsor argues that this is the case. It is also not certain whether either reference product matches filgrastim currently supplied in Australia.

The above studies used healthy volunteers. Pharmacokinetics were also measured in subsets of patients in clinical efficacy studies but these analyses were not designed to determine bioequivalence.

The equivalence studies also included pharmacodynamic comparisons [ANC and $CD34^+$].

Bioanalytical aspects of the two pharmacokinetic Studies XM02-01-LT and XM02-05-DE are considered suboptimal. In brief, there is a lack of information on the batches of injections used in these studies; some analytical run information has not been provided; only two quality control (QC) concentrations were used; and one study used multiple standard batches.

Quality Summary and Conclusions

Bioanalytical serum assays for filgrastim were considered suboptimal. The sponsor has also not addressed the issue of using different strengths of the test and reference products in Study XM02-05-DE.

The Pharmaceutical Subcommittee (PSC) was invited to comment.

The Subcommittee raised the issue of deficiencies in the bioavailability study. In particular, the PSC agreed that bioanalytical aspects of filgrastim serum assays were incomplete or suboptimal, making it difficult to draw appropriate conclusions from the submitted bioequivalence studies. The PSC noted that the application included pharmacodynamic comparisons and is also supported by clinical studies. The Committee therefore concluded that any approval should be based on the pharmacodynamic endpoints.

III. Nonclinical Findings

Introduction

The current nonclinical submission included several comparative studies, including *in vitro* and *in vivo* pharmacodynamics studies, a four-week repeat dose study in rats and a single dose local tolerance study in rabbits. The studies used Neupogen as a comparator, which is currently registered in Australia for the same indications as proposed for filgrastim. The choice of comparator was considered acceptable. Additional, non-comparative studies conducted with filgrastim included *in vivo* safety pharmacology studies in rats and dogs, a four-week pharmacokinetics study in rats, a single dose toxicity study in monkeys and 26-week repeat dose toxicity studies in rats and monkeys. Most nonclinical studies used only the SC route, although the proposed product is also indicated for IV administration (discussed further under '*General toxicity*' below).

Nonclinical studies submitted in support of the proposed product were Good Laboratory Compliant (GLP) and considered generally adequate, although limited analysis of the comparability of the toxicity profiles of filgrastim and Neupogen was conducted. The sponsor attributed this to the timing of the studies (the majority of non-comparative studies were conducted in 2003) in relation to the availability of relevant international guidelines for biosimilar products containing recombinant G-CSF. However, the importance of comparative studies for biosimilar products was emphasised in the guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance (EMEA/CPMP/3097/02/Final[3]), which was publicly available in draft form in 2002. Thus, the sponsor's explanation for the lack of an adequate comparative toxicity study is not fully justifiable. However, the repeat dose toxicity of the new product has been adequately studied in two animal species (rats and monkeys).

[3] Guideline on comparability of medicinal products containing biotechnology-derived proteins as active substances. Nonclinical and clinical issues. EMEA/CPMP/3097/02/Final. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003963.pdf

In the nonclinical sections of this AusPAR, the newly proposed product is referred to as filgrastim and the comparator product by its trade name (Neupogen).

Pharmacology

Primary Pharmacodynamics

The binding of filgrastim to the human G-CSF receptor (G-CSF-R) was compared with that of Neupogen in an *in vitro* study. Qualitatively and quantitatively similar binding was observed over the range of 8-500 nM (150-9500 ng/mL) filgrastim or Neupogen, with respective binding affinity constants (K_d) of 27 nM and 34 nM (508 ng/mL and 639 ng/mL). In a cell-based assay in three separate studies, proliferation of mouse G-CSF-responsive M-NFS-60 myeloid leukaemia cells was increased in response to filgrastim or Neupogen, with 50% effective concentrations (EC_{50}) and B_{max} values in the range 5.7-14.9 pM (0.11-0.28 ng/mL) and 10.4-24.5 pM (0.20-0.46 ng/mL), respectively; some variability between studies was noted, although values for the two products were comparable within experiments.

The *in vivo* pharmacology of filgrastim *compared to* Neupogen was compared in two studies using a rat model of cyclophosphamide (CP)-induced neutropenia. Daily SC doses of filgrastim or Neupogen (0.1-5 µg/kg; equivalent to ≤6 times the clinical exposure at 10 µg/kg/day IV, based on extrapolated AUC) for four days mitigated the CP-induced reduction in neutrophil counts on Days 3 and 5 (the only time points measured) in a dose-related manner. The neutrophil profile following administration of filgrastim or Neupogen varied slightly in each study, although no significant differences were observed when data from both studies were combined (filgrastim was slightly more potent than Neupogen in increasing neutrophil levels on Day 3 but not Day 5; 1 µg/kg filgrastim was considered equivalent to 2.43 µg/kg Neupogen).

The *in vivo* efficacy of filgrastim in normal (not neutropenic) animals was demonstrated in single and repeat dose toxicity studies in rats (SC route; including a Safety Pharmacology study) and monkeys (IV and SC routes); one four-week repeat dose study in rats was comparative with Neupogen. Absolute neutrophil counts were rapidly and markedly increased in filgrastim-treated rats at SC doses of 5-3500 µg/kg/day (equivalent to 0.04-174 times the clinical exposure at 10 µg/kg/day IV based on AUC) and in treated monkeys at SC doses of 5-800 µg/kg/day or single IV doses of 800 µg/kg/day. Increases were observed from 4 h onwards following a single dose to monkeys and neutrophil levels were similar to vehicle-treated rats within two weeks of cessation of treatment. The overall pattern of neutrophil levels throughout the treatment and observation periods was quantitatively similar for filgrastim and Neupogen in the comparative study in rats.

No investigation of the functionality of the neutrophils (such as superoxide production, phagocytic function and chemotaxis) produced in response to filgrastim or Neupogen was conducted, although it was not expected to be markedly different. Thus, these studies adequately compared the *in vitro* and *in vivo* pharmacodynamic properties of filgrastim and Neupogen.

Secondary Pharmacodynamics and Safety Pharmacology

The effect of filgrastim and Neupogen (10 pg/mL – 100 µg/mL) on the proliferation of human malignant cancer cell lines (U-937 histiocytic lymphoma, K-562 chronic myelogenous leukaemia, SK-OV-3 lung adenocarcinoma, T-24 bladder carcinoma and NIH:OVCAR-3 ovarian adenocarcinoma cells) was examined in an *in vitro* study. There was no evidence for increased proliferation of any cell line in response to either product for up to 6 days. A possible cytotoxic effect was observed at high concentrations. The concentration range tested in this study was markedly greater than B_{max} values for proliferation of known G-CSF-responsive cells in an *in vitro* primary pharmacodynamics study (refer to '*Primary Pharmacodynamics*' above) and was thus considered adequate.

Safety pharmacology studies investigated the effects of filgrastim on the central nervous system (CNS) and respiratory systems in rats and the cardiovascular system in dogs (single SC doses of 3500 µg/kg in rats equivalent to approximately 100 times the clinical C_{max} at 10 µg/kg/day IV). There were no treatment-related effects on the CNS (≤48 h post-dose, according to a modified Irwin screen), respiratory system (respiratory rate, tidal volume and minute volume; ≤4 h post-dose) in rats or cardiovascular system (electrocardiogram (ECG), blood pressure, heart rate and cardiac output; ≤48 h post-dose) in dogs. Effects on the renal system were not investigated in safety pharmacology studies, but no urinalysis findings were documented in repeat dose toxicity studies of up to 26 weeks duration in rats and monkeys (at approximately 6 and 4 times the clinical C_{max} at 10 µg/kg/day IV, respectively; data were extrapolated for rats). The safety pharmacology of filgrastim was considered to be adequately investigated, although safety pharmacology studies are generally not required for biosimilar products containing recombinant G-CSF.

Pharmacokinetics

Absorption

The pharmacokinetics of filgrastim were investigated following administration of repeated daily SC doses to rats for four weeks. Toxicokinetic data were obtained for filgrastim during a safety pharmacology study in rats, single and repeat dose toxicity studies in monkeys (up to four weeks duration; SC and IV routes for the single dose study) and for filgrastim and Neupogen in a comparative repeat dose study in rats.

The pharmacokinetics of filgrastim were generally similar in all tested species. Absorption of both products (where relevant) with SC dosing was rapid; plasma C_{max} values were reached in rats and monkeys after 1-2 h (which can be compared to 4-6 h in humans). AUC-based exposure in all species was slightly greater than dose-proportional and was generally greater in male rats and monkeys than females. There was generally no evidence for accumulation of filgrastim in rats, monkeys and humans, following repeated administration. In the comparative study in rats, the toxicokinetic profiles of filgrastim and Neupogen were generally similar.

Relative exposure

Exposure levels (AUC-based) of filgrastim (and Neupogen where relevant) in the submitted toxicity studies were compared with exposure data for both products from healthy human subjects in a comparative clinical trial and are presented in Table 2 below. The No Observable Adverse Effect Level (NOAEL) established in the comparative study is highlighted in bold (discussed further under '*Repeat dose toxicity*' below). The proposed dosage regimen for filgrastim is complicated and dependent on the specific indication; most recommended starting doses are within the range 5-10 µg/kg/day by SC injection or IV or SC infusion for most indications. Pharmacokinetic data were available for two single-dose clinical trials and animal: human exposure comparisons have been based on the human exposure following a single IV dose of 10 µg/kg in Study no. XM02-05-DE, as filgrastim exposure was greatest by this route.

According to the proposed Australian PI, the highest dose administered to a patient without toxic effects is 115 µg/kg/day. When compared to this maximum clinical dose, exposure ratios (based on µg/kg) ranging from 0.04 to 30 were obtained in toxicity studies (exposure ratios 0.04-1.1 in the comparative study). Thus, exposure margins (based on both AUC and µg/kg) were relatively low at some nonclinical doses associated with toxicity. The objective of this study was to compare the toxicities of the two products and AUC-based exposure margins were generally similar for both products.

Table 2. Exposure comparisons in pharmacokinetic/toxicokinetic studies.

Study no.	Species	Study duration	Route	Dose (µg/kg)	Sex	Filgrastim biosimilar		Neupogen	
						$AUC_{0-\infty}$ (ng.h/mL)[a]	Exposure margin (AUC)	$AUC_{0-\infty}$ (ng.h/mL)[a]	Exposure margin (AUC)
Pharmacokinetic studies									
XM02-PK-2.01	Rat	Four weeks	SC	500	M	18462	17.5	NA	NA
Toxicokinetic studies									
XM02- SPCNS-2.01	Rat	Single dose	SC	3500	M/F	171703	162	NA	NA
19332/05		2x2 weeks	SC	**5**, 25, 125	M	**43**, 296, 2229	**0.04**, 0.3, 2.1	**39**, 291, 2244	**0.04**, 0.3, 2.3
XM02-PK-6.01	Monkey	Single dose	IV	800	M	44815	42	NA	NA
			SC	800	M	35611	34	NA	NA
XM02-RT26-6.01		4 weeks	SC	125	M	3653	3.5	NA	NA
XM02-05-DE	Human	Single dose	IV	10	M/F	1057	NA	992	NA

[a]For repeat dose studies, AUC values at the final time point were used for calculations.

NA = not applicable

The NOAEL in the comparative study is highlighted in bold.

Toxicology

General toxicity

One acute toxicity study by the SC and IV routes was conducted for filgrastim in monkeys. However, in this study no control group was included and analysis was limited to clinical observations and haematology parameters for up to 3 days post dose. Toxicity data were also obtained following a single SC dose (3500 μg/kg) to rats in a Safety Pharmacology study. The primary finding in both species was increased neutrophil counts. Local toxicity (haematoma) was observed following IV dosing in monkeys; analysis in the study in monkeys was limited to clinical observations and measurement of body weight and haematology parameters.

Repeat dose studies of up to six months duration by the SC route were conducted in rats and monkeys; only one study in rats was comparative with Neupogen. The latter study was designed as an immunological comparison of the two products and involved treatment for four weeks, with a central two week treatment-free period and a two week recovery period. Pathology analysis was limited to macroscopic analysis of lymphoid tissue of toxicokinetic group rats. The sponsor stated that the other route of administration intended for human use (IV) was covered by the inclusion of IV dosing in local tolerance studies in rabbits, although these were single-dose studies. No repeat dose studies by the IV route were conducted and this was considered a deficiency when combined with the limited examination in the comparative toxicity study.

The sponsor provided the following reasons for the choice of study design in the comparative study, which was reportedly following advice from the EMEA: (i) treatment interruption of two weeks imitates the clinical situation of a chemotherapy patient treated in a chemotherapy cycle with a duration of four weeks, (ii) treatment interruption of two weeks is applied in standard immunisation protocols and could therefore possibly stimulate the immune response to the proteins and (iii) 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. This justification was not considered adequate, as (i) several proposed indications do not include treatment-free periods, particularly chronic neutropenia and (ii) whilst potentially useful for investigating the immunogenicity of filgrastim, an increased immune response may hinder the interpretation of other toxicity findings. Higher doses could also have been administered. As a consequence of limited toxicity findings resulting from the interposing treatment free period, limited pathology analysis and low doses, it was difficult to identify potential differences in the toxicity profiles of filgrastim *compared to* Neupogen in the comparative study.

The majority of findings in all studies occurred to some extent at all doses of filgrastim and Neupogen and were consistent with the primary pharmacology of filgrastim; namely increased neutrophil and other white blood cell parameters, extramedullary haematopoiesis in the spleen and liver and myeloid hyperplasia in the bone marrow. NOAELs were not established in the long-term studies due to the above findings being observed at all doses.

Hindlimb toxicity was observed at all doses (≥5 μg/kg; with dose-related incidence, onset and severity) in the six-month study in rats and was more pronounced in males, possibly consistent with increased exposure. Clinical signs (such as swelling of the ankle) were suggestive of similar findings at doses ≥25 μg/kg in the shorter comparative study, although further analysis was not conducted. In the six month study, this finding was described as swelling, with some degree of dysfunction. Histopathology of the hindlimbs identified changes such as hyperostosis, osteodystrophy, physeal dystrophy and joint inflammation and was accompanied by a dose-related increase in serum alkaline phosphatase. There was no evidence of hindlimb toxicity in the six-month study in monkeys, although alkaline phosphatase (ALP) levels were increased at the highest dose (125 μg/kg/day). The sponsor provided limited discussion of this finding; however it is a known adverse effect of filgrastim treatment in rats.

Reduced levels of serum cholesterol, glucose, triglycerides and total protein were observed after 26 weeks dosing in rats and cholesterol and glucose levels were slightly reduced in monkeys. The

sponsor stated that the changes in rats are consistent with failure to thrive; they may be related to liver toxicity.

To summarise, there was a lack of comparative repeat dose studies, however findings in 26-week studies in two species showed the same toxicity findings as in studies with Neupogen at doses 0.04 to 4 times the highest dose administered in a clinical trial for Neupogen (based on µg/kg).

Immunogenicity

Serum obtained from rats and monkeys in the repeat dose toxicity studies was analysed for anti-G-CSF antibodies and the neutralising ability of these antibodies was investigated in all but the six-month study in rats. As expected for a protein product, rats and monkeys with detectable antibodies were identified at all doses and the incidence was generally dose-related (5-39% in rats and 7-75% in monkeys). Most of the rats and monkeys with anti-G-CSF antibodies had neutralising activity and in some cases this was associated with smaller increases in neutrophil counts and was possibly related to one case of severe neutropenia in a female rat as a result of cross-reactivity with endogenous G-CSF. In the comparative study, the incidence of rats with anti-G-CSF antibodies was lower at the highest dose (HD) tested (but not at the two lower doses tested) with filgrastim *compared to* Neupogen.

Genotoxicity, carcinogenicity and reproductive toxicity

No data were submitted and this was considered acceptable for a biosimilar product.

Pregnancy classification

The sponsor proposes a Pregnancy Category B3 for filgrastim, which is the same as that for Neupogen. This was considered acceptable.

Local tolerance

The local toxicity of filgrastim was investigated following administration of single IV, intra arterial (IA), SC, intramuscular (IM) and perivenous (PV) doses to rabbits in two studies; one study was comparative with Neupogen. In the comparative study, local doses of 240 µg and 480 µg were administered per IV, IA, SC and IM injection site, with 96 µg for the PV route (80, 160 and 32 µg/kg, respectively, for a 3 kg rabbit) resulting in total doses of 1020 and 1980 µg per rabbit. The respective local doses were 0.7, 1.4 (lowest dose (LD) and HD) and 0.3 times (PV) the highest documented clinical dose of filgrastim in clinical trials, based on µg/kg.

Very slight to well-defined erythema (without oedema) was frequently documented for up to 4 days post-dose in this study, particularly at PV or IV injection sites, with no clear relationship to treatment. Gross pathology on Day 5 identified frequent cases of dark areas and/or scabs at injection sites, irrespective of route or treatment. Similarly, a low incidence of dermal/epidermal inflammation, ulceration, haemorrhage, degeneration/necrosis and fibrosis were identified by histopathology analysis at injection sites, irrespective of route or treatment. There was no apparent difference in findings for filgrastim or Neupogen. There was no treatment-related local toxicity noted in the six-month SC repeat dose studies in rats and monkeys.

Thus, filgrastim treatment by the SC or IV route resulted in a similar local toxicity profile in rabbits to that of Neupogen.

Nonclinical Summary and Conclusions

- The pharmacodynamic properties of Tevagrastim and Neupogen were similar *in vitro* and *in vivo* in normal and neutropenic rats, with efficacy observed at doses markedly less than exposures (AUC) at a recommended starting dose (10 µg/kg IV) in a clinical trial.

- Tevagrastim (10 pg/mL – 100 µg/mL) did not increase proliferation of five human malignant cancer cell lines *in vitro*.

- There were no CNS or respiratory findings in safety pharmacology studies with Tevagrastim in rats or cardiovascular findings in dogs, at SC doses of 3500 µg/kg (in rats, equivalent to >100 times the clinical C_{max}). There were also no effects on the renal system in 26-week studies in rats and monkeys at doses 4-6 times the clinical C_{max}.

- It was difficult to identify potential differences in the toxicity profile of Tevagrastim compared to Neupogen in a comparative repeat dose study in rats due to limited pathology analysis, an interposing 2-week treatment free period and the low doses administered. However, findings in 26-week studies in rats and monkeys showed the same toxicity findings as in studies with Neupogen at doses 0.04 to 4 times the highest dose administered in a clinical trial for Neupogen (based on µg/kg).

- The toxicity profiles of Tevagrastim in 6-month SC studies in rats and monkeys were generally consistent with exaggerated primary pharmacology (increased neutrophil and other white blood cell parameters, extramedullary haematopoiesis in the spleen and liver and myeloid hyperplasia in bone marrow). Hindlimb toxicity occurred in rats and it was considered a species-specific effect. No nonclinical studies using the clinically indicated IV route were conducted.

- The toxicokinetic profiles of Tevagrastim and Neupogen were generally similar in rats following SC administration in the comparative study.

- Genotoxicity, carcinogenicity and reproductive toxicity studies were not conducted and this was considered acceptable for a biosimilar product.

- Tevagrastim treatment by the IV, IA, IM, SC or perivenous routes resulted in a similar local toxicity profile (that is, no treatment related effects) in rabbits, compared to Neupogen.

- Tevagrastim was antigenic in rats and monkeys; the development of neutralising antibodies was dose-related (5-75%). The incidence of anti-G-CSF antibodies appeared to be lower with Tevagrastim compared to Neupogen treatment in the comparative study in rats.

Conclusions and Recommendations

The comparability of Tevagrastim to Neupogen, in terms of primary pharmacodynamics, toxicokinetics, immunogenicity and local tolerance, has been adequately demonstrated in nonclinical studies.

Limited data were available comparing the toxicity of Tevagrastim with Neupogen. However, the safety profile of Tevagrastim following SC dosing has been adequately established in rats and monkeys.

There are no nonclinical objections to the registration of Tevagrastim.

IV. Clinical Findings

Introduction

During the clinical trial development programme Tevagrastim was referred to as XM02 in the clinical trials and this terminology will be used in the clinical sections of this AusPAR. XM02 has been developed as a similar biological medicinal product with Neupogen being the reference product. The formulation of XM02 has the same excipients as Neupogen and is quantitatively very similar. The aim of the clinical trial programme was to demonstrate the clinical equivalence of XM02 and Neupogen in all respects, that is, clinical pharmacology, efficacy and safety, thereby supporting the approval of XM02 with the same product label as Neupogen.

Within the drug development programme for XM02, the sponsor conducted five clinical studies comparing XM02 with Neupogen (filgrastim) to support their claim of XMO2's biosimilarity with Neupogen. There were two Phase I studies, comparing pharmacodynamic and pharmacokinetic (PK) properties of XM02 and filgrastim in healthy volunteers (Study XM02-01-LT and Study XM02-05-DE) and three Phase III studies which were conducted in patients with breast cancer (Study XM02-02-INT), lung cancer (Study XM02-03-INT), or Non-Hodgkin's Lymphoma (NHL) (Study XM02-04-INT) who received G-CSF prophylaxis in addition to chemotherapy (CTX).

According to the guideline on similar biological medicinal products[4], Neupogen was chosen as reference product since it is a medicinal product which contains filgrastim as drug substance and is authorised for use in the European Union.

In this clinical evaluation, Neupogen was used as comparator in all five clinical studies it will be referred to as Filgrastim or Neupogen throughout the document. The study medication used in the pivotal clinical trials to demonstrate comparability is representative to the commercial medicinal drug product.

All five clinical studies were performed in compliance with Good Clinical Practice guidelines. The clinical development programme was designed to address the relevant European Medicines Agency (EMA) guideline[4]. The design of the Phase I studies and the design and conduct of the Phase III studies[1] were based on recommendations outlined relevant EMA guidelines[5,1] and the latter also took into account the guideline for conducting clinical trials with haematopoietic growth factors for the prophylaxis of infection following myelosuppressive or myeloablative therapy [6]. In addition, therapeutic guidelines and recommendations as proposed by the American Society of Clinical Oncology (ASCO in the year 2000) and the European Society of Medical Oncology (ESMO) were considered. The design of the Phase I Study XM02-05-DE followed the product-specific (EMA) guidance on biosimilar medicinal products containing recombinant G-CSF[2].

Pharmacokinetics

STUDY XM02-01-LT

Study Design, Objectives and Methods

This was a Phase I, single centre, single blind, single dose, randomised, two-period crossover, two-arm study in 56 healthy male subjects compared PK and pharmacodynamic profiles of XM02 and Filgrastim. All subjects were Caucasian. The median age was 21.5 years (19 to 40 years). Each subject was randomly assigned to receive either SC 5 µg/kg (Group A) or SC 10 µg/kg (Group B) of study drug. Every subject received single SC doses of both the test (XM02) and the reference treatment (Filgrastim) in two treatment periods, separated by a 2 week washout period. The study duration for each subject was approximately 7 weeks including screening. Four subjects in Group A and 2 subjects in Group B withdrew prematurely.

The primary objective was comparison of the pharmacodynamic parameters (absolute neutrophil count maximum (ANC_{max}), ANC AUC, time of maximum ANC, ANC t_{max}) of XM02 and Filgrastim formulations after SC administration of 5 µg/kg or 10 µg/kg of product in healthy male subjects.

Secondary objectives were to compare the PK parameters (C_{max}, AUC, t_{max}, half life ($t_{1/2}$) and the elimination rate constant, λz) of XM02 and Filgrastim formulations after SC administration of 5 µg/kg or 10 µg/kg of product in healthy male subjects, to collect tolerability and safety data, calculate the relative bioavailability (F) of XM02 preparation versus Filgrastim and also to compare

[4] Guideline on Similar Biological Medicinal Products. CHMP/437/04, 30 October 2005. http://www.biolawgics.com/files/CHMP-437-04.pdf

[5] Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/1401/98). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003519.pdf

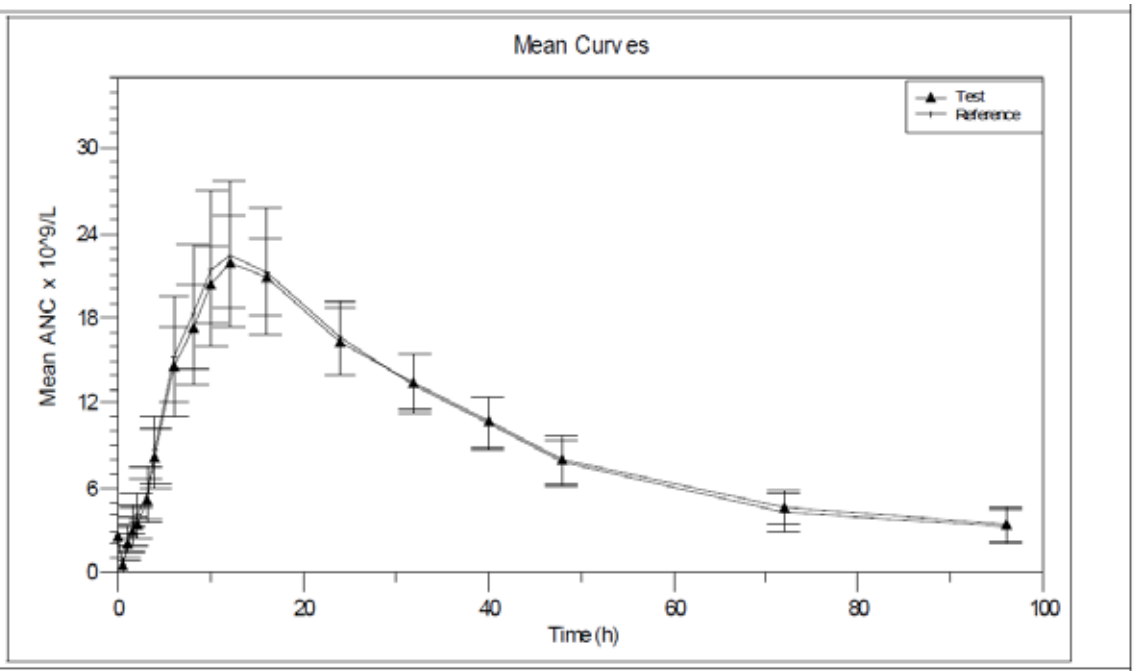
[6] Note for guidance on clinical trials with haematopoietic growth factors for the prophylaxis of infection following myelosuppressive or myeloablative therapy. CPMP/Efficacy Working Party [EWP]/555/95http://www.tga.gov.au/pdf/euguide/ewp055595enrev1.pdf

the pharmacodynamic and pharmacokinetic parameters following doses of 5 µg/kg and 10 µg/kg XM02.

Pharmacodynamic Results

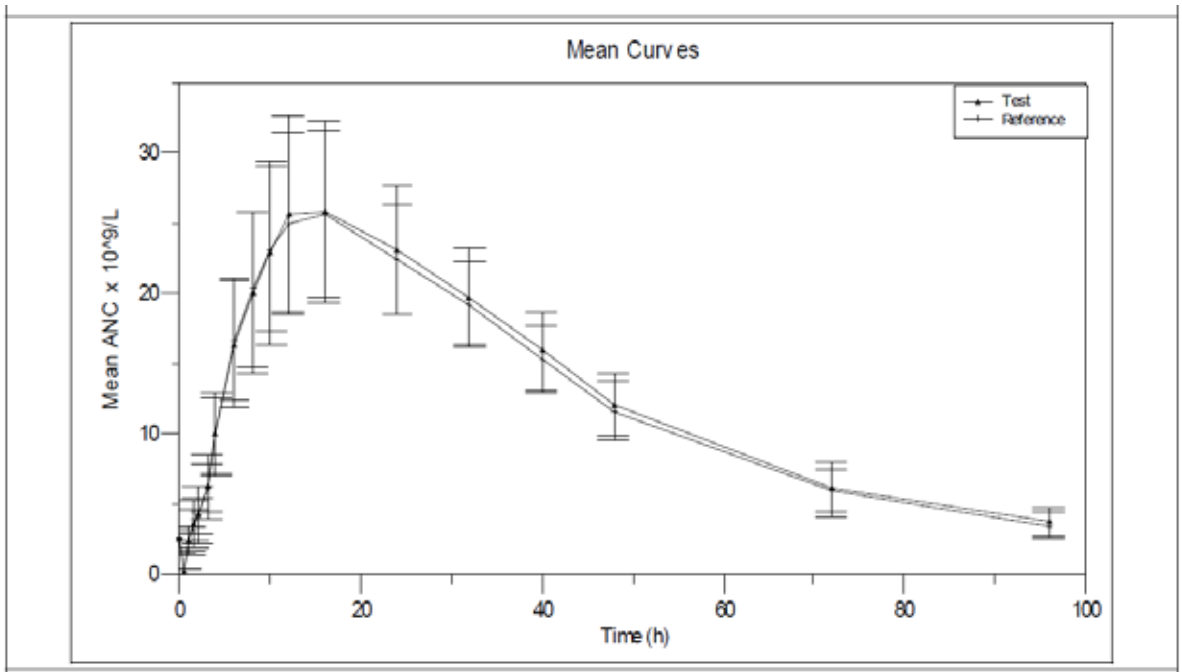
Mean ANC time profiles following a single SC injection of XM02 or Filgrastim are presented for the 5 µg/kg dose and the 10 µg dose in Figures 2 and 3 below. In both treatment groups there was an initial fall at 0.5 to 1 hours. Peak ANC values were observed about 12 and 16 hours after injection of 5 and 10 µg/kg, respectively. ANC values had returned to baseline values after 96 hours.

Figure 2: Study XM02-01-LT: Mean ANC Over Time Following a Single Subcutaneous Injection of 5 µg/kg of XM02 or Filgrastim to Healthy Male Subjects



Abbreviations: h = hours; Test = XM02; Reference = Filgrastim; ANC = absolute neutrophil count

Figure 3: Study XM02-01-LT: Mean ANC Over Time Following a Single Subcutaneous Injection of 10 µg/kg of XM02 or Filgrastim to Healthy Male Subjects



Abbreviations: h = hours; Test = XM02; Reference = Filgrastim; ANC = absolute neutrophil count

Analysis of Variance (ANOVA) demonstrated equivalence of XM02 and Filgrastim with regard to the pharmacodynamic variables in both the 5 µg/kg and 10 µg/kg dose group after single SC injection. Confidence intervals (CIs) for all log transformed and non log-transformed variables (ANC AUC from time zero to time t (ANC AUC_{0-t}), ANC AUC from time zero to infinity (ANC $AUC_{0-\infty}$), ANC_{max}) were enclosed in the 80%-125% acceptance intervals for both dose regimens. The variable ANC t_{max} was enclosed in 80%-125% acceptance interval for the 5 µg/kg, but not for the 10 µg/kg dose (see Tables 3-6). Administration of 10 µg/kg compared to 5 µg/kg of G-CSF did not yield a proportional increase of ANC.

Table 3: Study XM02-01-LT: ANC AUC_{0-t}, ANC $AUC_{0-\alpha}$ and ANCmax Following a Single Subcutaneous Injection of 5 µg/kg of XM02 or Filgrastim to Healthy Male Subjects

Variable		XM02	Filgrastim	90% CI [%]	Point estimate [%]
ANC AUC_{0-t} [h*10^9/L]	LSmean	899.69	898.52	97.8–102.5	100.1
	Geometric Mean	901.68	901.57		
	CV% intra-subject	4.66			
ANC $AUC_{0-\infty}$ [h*10^9/L]	LSmean	1042.00	1015.61	99.7–105.6	102.6
	Geometric Mean	1046.22	1016.30		
	CV% intra-subject	5.85			
ANC_{max} [10^9/L]	LSmean	22.30	22.64	93.6–103.6	98.5
	Geometric Mean	22.23	22.91		
	CV% intra-subject	10.22			

Abbreviations: LSmean = least squares mean; CI = confidence interval; CV% = coefficient of variation
ANC = absolute neutrophil count

Table 4: Study XM02-01-LT: ANC tmax Following a Single Subcutaneous Injection of 5 µg/kg of XM02 or Filgrastim to Healthy Male Subjects

Variable		XM02	Filgrastim	Non-parametric point estimator of difference	Non-parametric 90% CI of difference	Bio-equivalence interval
ANC t_{max} [hours]	Minimum	10	10	0	[-1; 0]	[-2.4; 2.4]
	Maximum	16	16			
	Median	12	12			
Abbreviations: CI = confidence interval; ANC = absolute neutrophil count						

Table 5: Study XM02-01-LT: ANC AUC_{0-t} , ANC $AUC_{0-\alpha}$ and ANCmax Following a Single Subcutaneous Injection of 10 µg/kg of XM02 or Filgrastim to Healthy Male Subjects

Variable		XM02	Filgrastim	90% CI [%]	Point estimate [%]
ANC AUC_{0-t} [h*10^9/L]	LSmean	1199.67	1187.85	97.2–104.9	101.0
	Geometric Mean	1199.66	1187.85		
	CV% intra-subject	8.05			
ANC $AUC_{0-\infty}$ [h*10^9/L]	LSmean	1345.54	1325.57	97.9–105.2	101.5
	Geometric Mean	1345.54	1325.57		
	CV% intra-subject	7.54			
ANC_{max} [10^9/L]	LSmean	25.79	25.96	94.5–104.5	99.4
	Geometric Mean	25.79	25.96		
	CV% intra-subject	10.64			
Abbreviations: LSmean = least squares mean; CI = confidence interval; CV% = coefficient of variation ANC = absolute neutrophil count					

Table 6: Study XM02-01-LT: ANC tmax Following a Single Subcutaneous Injection of 10 µg/kg of XM02 or Filgrastim to Healthy Male Subjects

Variable		XM02	Filgrastim	Non-parametric point estimator of difference	Non-parametric 90% CI of difference	Bio-equivalence interval
ANC t_{max} [hours]	Minimum	10	12	2	[0; 4]	[-3.2; 3.2]
	Maximum	24	24			
	Median	14	16			
Abbreviations: CI = confidence interval; ANC = absolute neutrophil count						

Evaluator Comment

XM02 was shown to be bioequivalent to the reference formulation Filgrastim (Neupogen) with respect to the ANC time profile.

STUDY XM02-05-DE

Study Design, Objectives and Methods

This was a Phase I, multicentre, single dose, single-blind, randomised, two period crossover study to compare PK and pharmacodynamic characteristics of IV or SC XM02 and Neupogen (Filgrastim) in healthy male and female Caucasian volunteers. The study was performed in four subgroups:

- Subgroup 1: 5 µg/kg of XM02 and Filgrastim as IV infusion (n=36)
- Subgroup 2: 10 µg/kg of XM02 and Filgrastim as IV infusion (n=35)
- Subgroup 3: 5 µg/kg of XM02 and Filgrastim as SC injection (n=35)
- Subgroup 4: 10 µg/kg of XM02 and Filgrastim as SC injection (n=34)

A total of 144 healthy female and male subjects (36 in each subgroup and at least 12 of each gender in each subgroup) were planned to be examined. A three week washout period followed the first treatment period before crossover to the second period. Seventeen subjects withdrew prematurely from the study; 124 completed both study periods without major protocol deviations and were included in PK and pharmacodynamic analyses, that is, 31, 30, 33 and 30 in subgroups 1, 2, 3 and 4, respectively. 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.

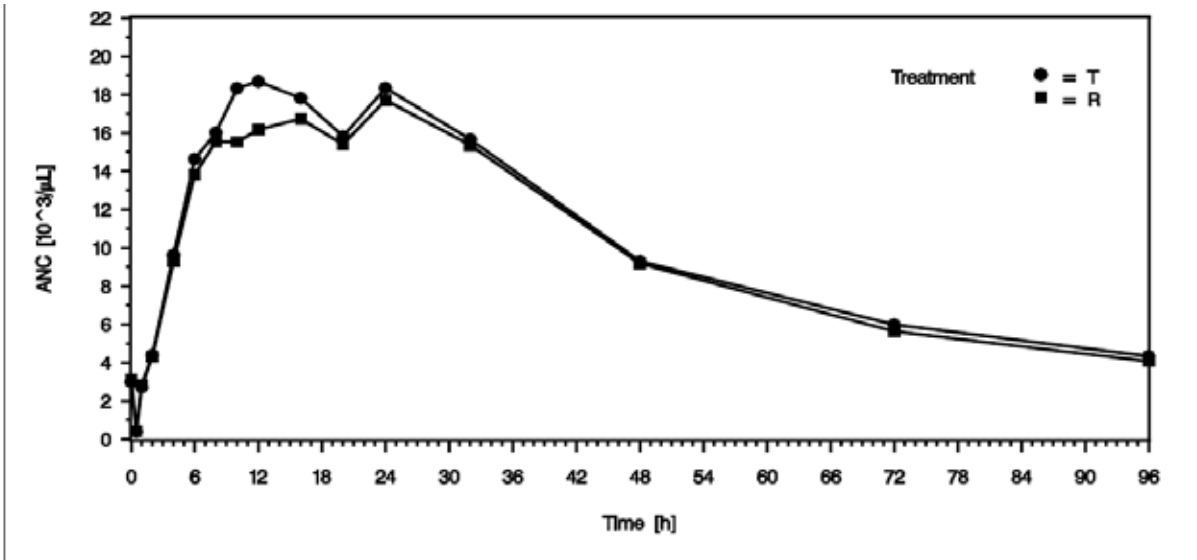
The reference product was Neupogen (Amgen) as marketed in Germany. This is in line with the regulations laid down in the EMA guideline on Similar Biological Medicinal Products[4] and therefore data generated in this study can be regarded as pivotal.

Pharmacodynamic Results

Absolute Neutrophil Count (ANC)

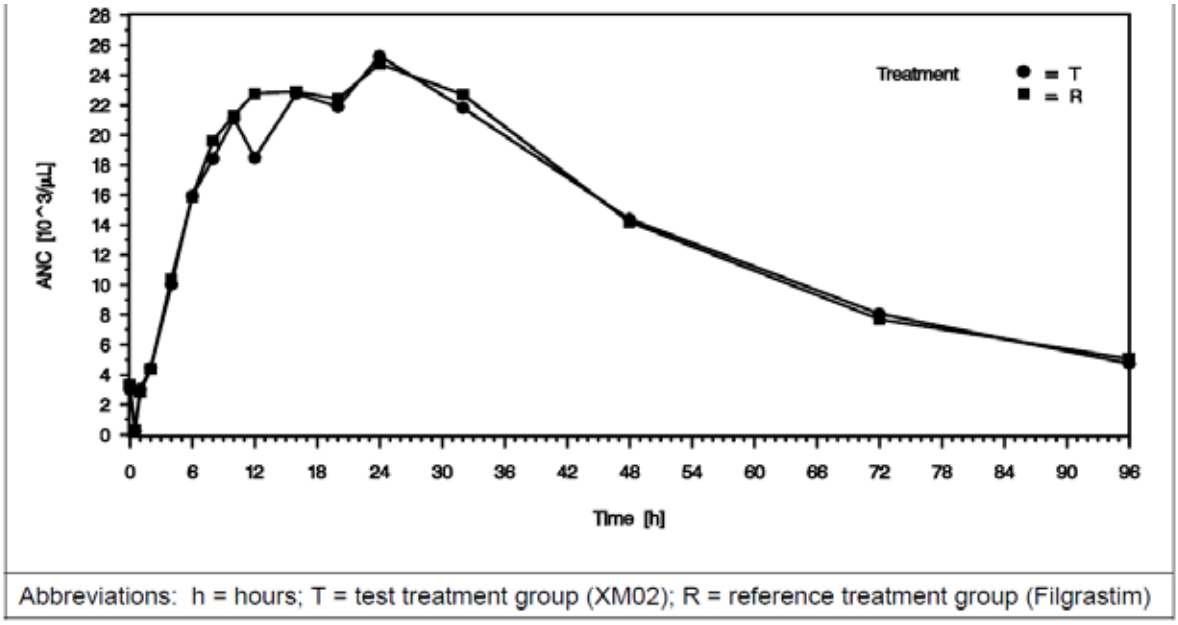
Mean ANC time profiles following a single SC injection of XM02 or Filgrastim are presented for the 5 µg/kg and 10 µg/kg doses in Figures 4 and 5, respectively. In both treatment and dose groups, a first peak was observed at around 12 hours and a second peak at 24 hours. ANC values had returned to baseline values after 96 hours.

Figure 4: Study XM02-05-DE: Geometric Mean Concentration-Time Profile of Absolute Neutrophil Count Following a Single Subcutaneous Injection of 5 µg/kg of XM02 or Filgrastim to Healthy Male and Female Subjects



Abbreviations: h = hours; T = test treatment group (XM02); R = reference treatment group (Filgrastim)

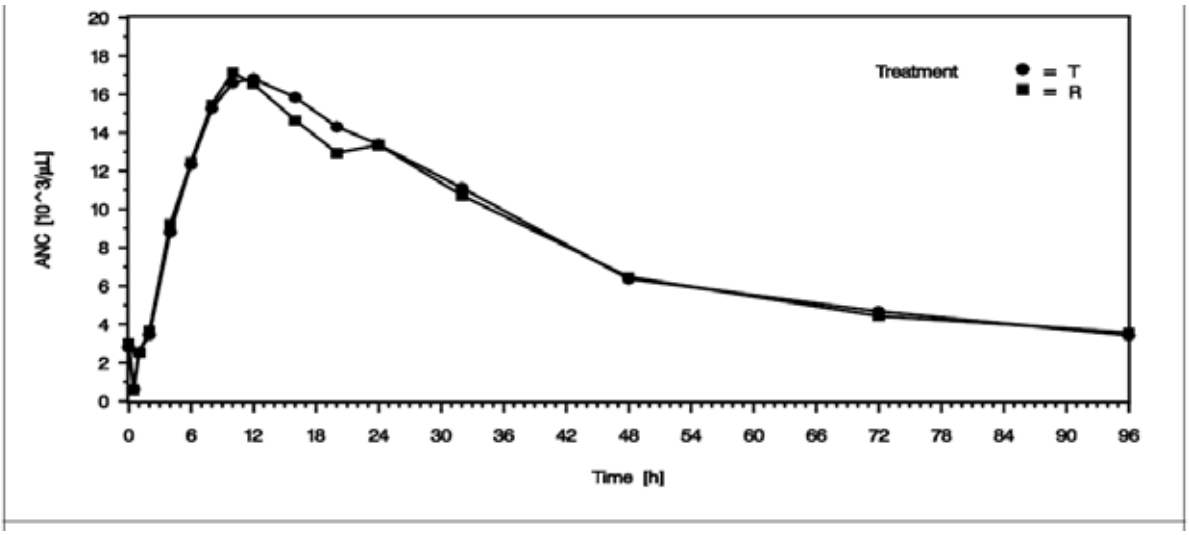
Figure 5: Study XM02-05-DE: Geometric Mean Concentration-Time Profile of Absolute Neutrophil Count Following a Single Subcutaneous Injection of 10 µg/kg of XM02 or Filgrastim to Healthy Male and Female Subjects



Abbreviations: h = hours; T = test treatment group (XM02); R = reference treatment group (Filgrastim)

Mean ANC time profiles following a single IV infusion of XM02 or Filgrastim are presented for the 5 µg/kg and 10 µg/kg doses in Figures 6 and 7 below. Peak ANC concentrations were observed after 12 and 16 hours in the 5 µg/kg and 10 µg/kg dose groups, respectively. ANC values had returned to baseline values after 96 hours.

Figure 6: Study XM02-05-DE: Geometric Mean Concentration-Time Profile of Absolute Neutrophil Count Following a Single Intravenous Infusion of 5 µg/kg of XM02 or Filgrastim to Healthy Male and Female Subjects



ANOVA demonstrated equivalence of XM02 and Filgrastim with regard to the pharmacodynamic variable ANC in both the 5 µg/kg and 10 µg/kg dose groups after both a single SC injection and following an IV infusion. CIs for the target variables ANC $AUC_{0\text{-}t}$ and ANC_{max} were enclosed in the 80%-125% acceptance intervals for both dose regimens and administrations. Geometric means of ANC $AUC_{0\text{-}t}$ and ANC_{max} and median of ANC t_{max} are shown in Tables 7 and 8 below.

Table 7: Study XM02-05-DE: Geometric Mean of ANC AUC_{0-t} and ANC_{max} and Median of ANC t_{max} Following a Single Subcutaneous Injection of 5 and 10 µg/kg XM02 or Filgrastim to Healthy Male and Female Subjects

Variable	5 µg/kg s.c.		10 µg/kg s.c.	
	XM02	Filgrastim	XM02	Filgrastim
ANC AUC_{0-t} [$h*10^9/L$]	956.93	983.14	1305.93	1245.18
ANC_{max} [$10^9/L$]	22.58	21.14	26.94	26.98
ANC t_{max} [h]	12.03	12.00	18.03	20.00
Abbreviations: s.c. = subcutaneous				

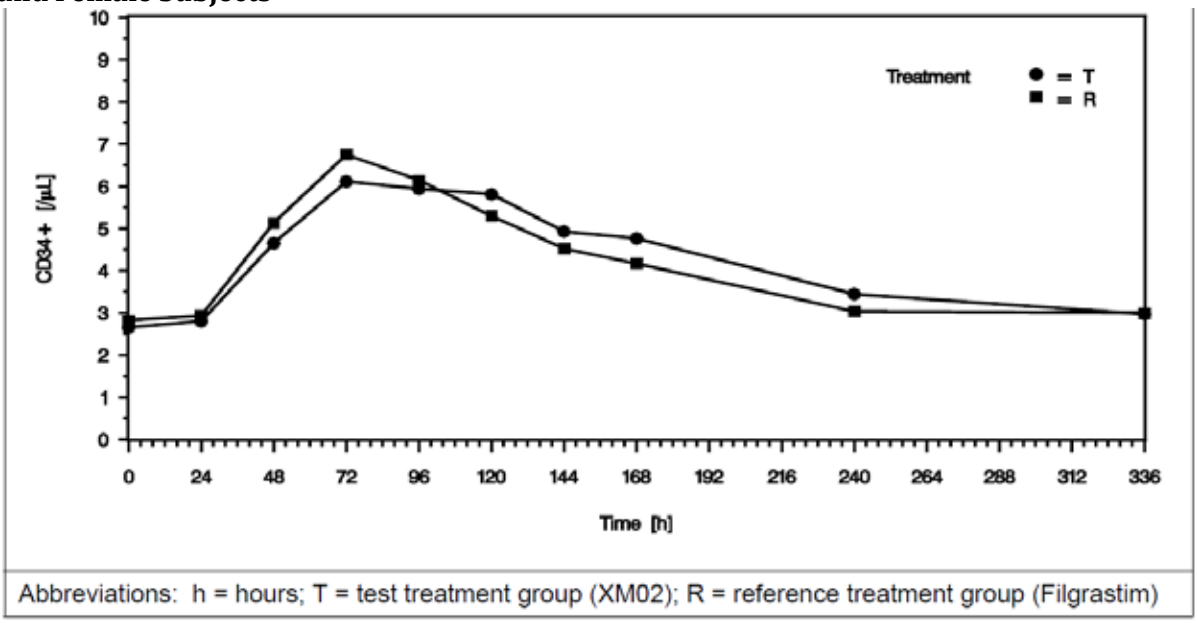
Table 8: Study XM02-05-DE: Geometric Mean of ANC AUC_{0-t} and ANC_{max} and Median of ANC t_{max} Following a Single Intravenous Injection of 5 and 10 µg/kg XM02 or Filgrastim to Healthy Male and Female Subjects

Variable	5 µg/kg i.v.		10 µg/kg i.v.	
	XM02	Filgrastim	XM02	Filgrastim
ANC AUC_{0-t} [$h*10^9/L$]	738.37	776.67	916.96	958.90
ANC_{max} [$10^9/L$]	18.73	19.46	21.71	22.21
ANC t_{max} [h]	12.00	12.00	16.00	16.00
Abbreviations: i.v. = intravenous				

CD34+ Count

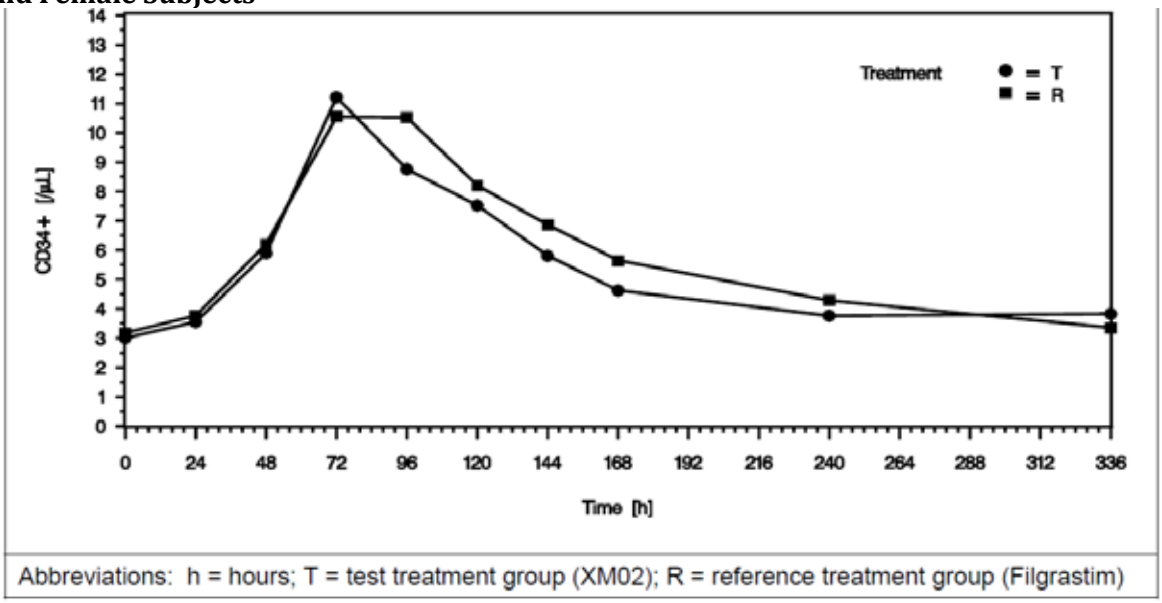
Mean CD34+ count time profiles following a single SC injection of XM02 or Filgrastim are presented for the 5 µg/kg and 10 µg/kg doses in Figures 7 and 8, respectively. In both treatment and dose groups, a peak was observed around 72 hours after dosing. Values had returned to baseline values after 336 hours.

Figure 7: Study XM02-05-DE: Geometric Mean Concentration-Time Profile of CD34+ Count Following a Single Subcutaneous Injection of 5 µg/kg of XM02 or Filgrastim to Healthy Male and Female Subjects



Abbreviations: h = hours; T = test treatment group (XM02); R = reference treatment group (Filgrastim)

Figure 8: Study XM02-05-DE: Geometric Mean Concentration-Time Profile of CD34+ Count Following a Single Subcutaneous Injection of 10 µg/kg of XM02 or Filgrastim to Healthy Male and Female Subjects



Abbreviations: h = hours; T = test treatment group (XM02); R = reference treatment group (Filgrastim)

Mean CD34+ count time profiles following a single IV infusion of XM02 or Filgrastim are presented for the 5 µg/kg and 10 µg/kg doses in Figures 9 and 10, respectively. In both dose groups, a peak was observed around 72 hours after dosing. Values had returned to baseline values after 336 hours.

Figure 9: Study XM02-05-DE: Geometric Mean Concentration-Time Profile of CD34+ Count Following a Single Intravenous Infusion of 5 µg/kg of XM02 or Filgrastim to Healthy Male and Female Subjects

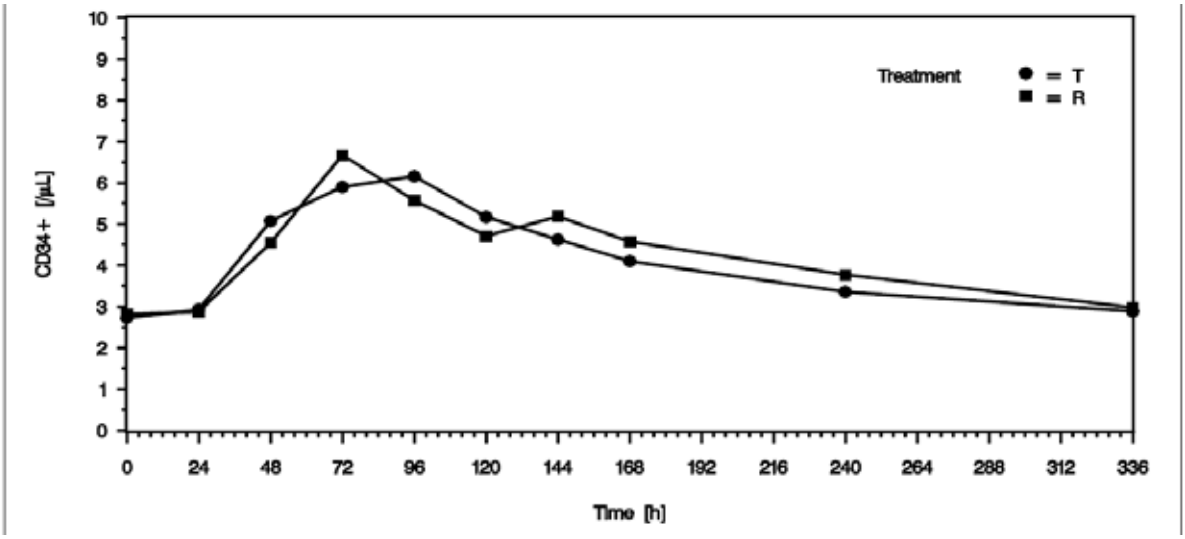
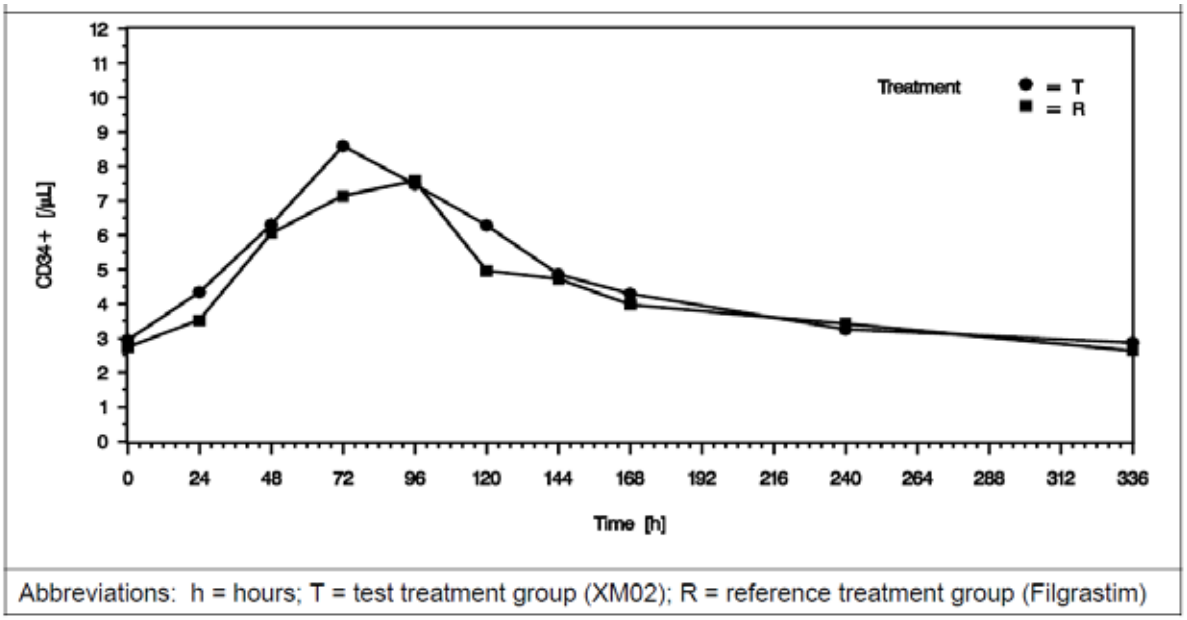


Figure 10: Study XM02-05-DE: Geometric Mean Concentration-Time Profile of CD34+ Count Following a Single Intravenous Infusion of 10 µg/kg of XM02 or Filgrastim to Healthy Male and Female Subjects



ANOVA demonstrated equivalence of XM02 and Filgrastim with regard to the pharmacodynamic variable CD34+ count in both the 5 µg/kg and 10 µg/kg dose groups after both a single SC injection and an IV infusion. Results of the geometric means of CD34+ $AUC_{0\text{-}t}$ and CD34+ C_{max} and median of CD34+ t_{max} are shown in Tables 9 and 10 below.

Table 9: Study XM02-05-DE: Geometric Mean of CD34+ AUC_{0-t} and CD34+ C_{max} and Median of CD34+ t_{max} Following a Single Subcutaneous Injection of 5 and 10 µg/kg XM02 or Filgrastim to Healthy Male and Female Subjects

Variable	5 µg/kg s.c.		10 µg/kg s.c.	
	XM02	Filgrastim	XM02	Filgrastim
CD34+ AUC_{0-t} [h*/µL]	1462.63	1448.61	1860.82	2063.90
CD34+C_{max} [/µL]	8.42	8.78	12.23	13.29
CD34+ t_{max} [h]	72.05	72.30	72.09	74.94
Abbreviations: s.c. = subcutaneous				

Table 10: Study XM02-05-DE: Geometric Mean of CD34+ AUC_{0-t} and CD34+ C_{max} and Median of CD34+ t_{max} Following a Single Intravenous Injection of 5 and 10 µg/kg XM02 or Filgrastim to Healthy Male and Female Subjects

Variable	5 µg/kg i.v.		10 µg/kg i.v.	
	XM02	Filgrastim	XM02	Filgrastim
CD34+ AUC_{0-t} [h*/µL]	1451.35	1545.21	1644.85	1525.62
CD34+ C_{max} [/µL]	8.56	8.79	10.43	9.68
CD34+ t_{max} [h]	72.97	72.38	72.06	71.83
Abbreviations: i.v. = intravenous				

Evaluator Comment

The pharmacodynamic response (on ANC and CD34+) for XM02 was equivalent (for AUC_{0-t} and C_{max}) to that of Filgrastim (Neupogen™ Amgen) in doses of 5 µg/kg or 10 µg/kg after a single IV infusion or a single SC injection.

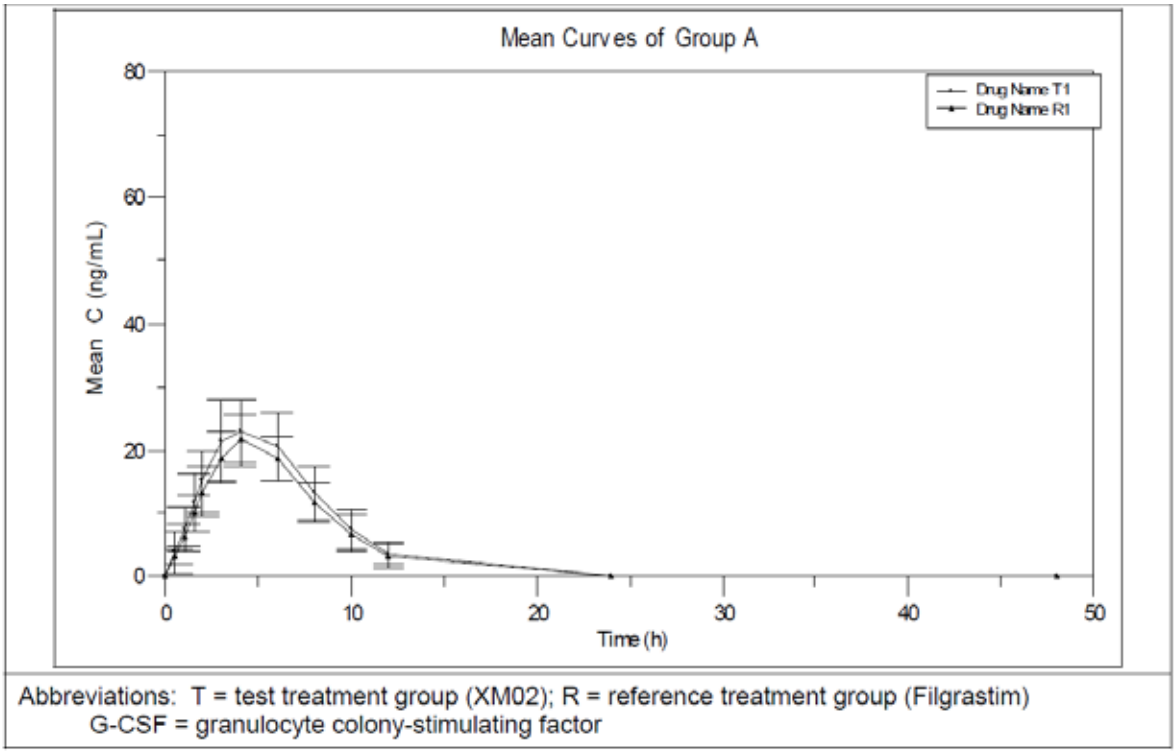
Pharmacokinetics

STUDY XM02-01-LT

Pharmacokinetic Results

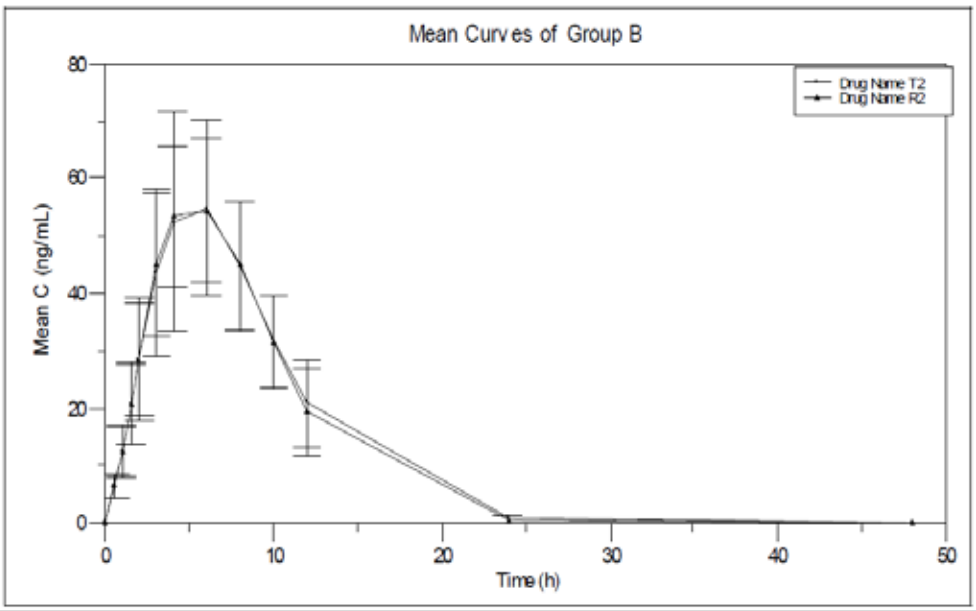
Mean G-CSF concentration-time profiles following a single SC injection of XM02 or Filgrastim are presented for the 5 µg/kg and 10 µg/kg doses in Figures 11 and 12. In both dose and treatment groups, mean G-CSF serum concentrations rapidly increased, reaching a maximum around 5 hours, and decreasing to pre-dose values at 24 hours.

Figure 11: Study XM02-01-LT: Mean Serum Concentration-Time Profile of G-CSF Following a Single Subcutaneous Injection of 5 µg/kg of XM02 or Filgrastim to Healthy Male Subjects



Abbreviations: T = test treatment group (XM02); R = reference treatment group (Filgrastim)
G-CSF = granulocyte colony-stimulating factor

Figure 12: Study XM02-01-LT: Mean Serum Concentration-Time Profile of G-CSF Following a Single Subcutaneous Injection of 10 µg/kg of XM02 or Filgrastim to Healthy Male Subjects



Abbreviations: T = test treatment group (XM02); R = reference treatment group (Filgrastim)
G-CSF = recombinant N-methionyl granulocyte colony-stimulating factor

ANOVA demonstrated equivalence of XM02 and Filgrastim with regard to PK variables in both the 5 µg/kg and 10 µg/kg dose group after a single SC injection. CIs for all log transformed and non log-transformed variables (AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max} and λ_z respectively) were enclosed in the 80%-

125% acceptance intervals for both dose regimens. The variable $t_{1/2}$ was enclosed in the 80%-125% acceptance interval for the 5 µg/kg but not for the 10 µg/kg dose (see Tables 11 and 12). Relative bioavailability of XM02 versus Filgrastim 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.

Table 11: Study XM02-01-LT: AUC_{0-t}, $AUC_{0-\alpha}$, C_{max} t_{max}, $t_{1/2}$ and λz Following a Single Subcutaneous Injection of 5 µg/kg of XM02 or Filgrastim to Healthy Male Subjects

Variable		XM02	Filgrastim	90% CI [%]	Point estimate [%]
AUC_{0-t} [ng/mL*h]	LSmean	158.25	143.17	102.7-119.0	110.5
	Geometric Mean	158.45	143.10		
	CV% intra-subject	14.92			
$AUC_{0-\infty}$ [ng/mL*h]	LSmean	168.18	153.00	101.9-118.6	109.9
	Geometric Mean	168.39	152.77		
	CV% intra-subject	15.34			
C_{max} [ng/mL]	LSmean	23.56	21.26	102.2-120.1	110.8
	Geometric Mean	23.54	21.23		
	CV% intra-subject	16.33			

		XM02	Filgrastim	Point estimator of difference*	90% CI of difference*	Bio-equivalence interval
t_{max} [hours]	Minimum	1.50	3	0	[-0.5; 0.5]	[-0.8; 0.8]
	Maximum	6	6			
	Median	4	4			
$t_{1/2}$ [hours]	Minimum	1.52	1.28	-0.0225	[-0.26; 0,275]	[-0.4; 0.4]
	Maximum	3.31	3.97			
	Median	2.10	2			
λ_z [1/hours]	Minimum	0.21	0.17	0.0125	[-0.03; 0.055]	[-0.07; 0.07]
	Maximum	0.45	0.54			
	Median	0.33	0.35			

Abbreviations: LSmean = least squares mean; CI = confidence interval; CV% = coefficient of variation
* nonparametric estimator or confidence interval

Table 12: Study XM02-01-LT: AUC_{0-t}, $AUC_{0-\alpha}$, C_{max} t_{max}, $t_{1/2}$ and λz Following a Single Subcutaneous Injection of 10 µg/kg of XM02 or Filgrastim to Healthy Male Subjects

Variable		XM02	Filgrastim	90% CI [%]	Point estimate [%]
AUC_{0-t} [ng/mL*h]	LSmean	473.90	475.18	93.9-105.9	99.7
	Geometric Mean	473.91	475.20		
	CV% intra-subject	12.64			
$AUC_{0-\infty}$ [ng/mL*h]	LSmean	530.68	511.14	97.9-110.1	103.8
	Geometric Mean	530.67	511.17		
	CV% intra-subject	12.34			
C_{max} [ng/mL]	LSmean	55.74	56.28	92.1-106.5	99.0
	Geometric Mean	55.74	56.28		
	CV% intra-subject	15.42			
		XM02	**Filgrastim**	**Point estimator of difference***	**90% CI of difference***	**Bio-equivalence interval**
t_{max} [hours]	Minimum	3	3	0.5	[0; 1]	[-1.2; 1.2]
	Maximum	6	8			
	Median	6	6			
$t_{1/2}$ [hours]	Minimum	1.66	1.57	-0.07	[-0.985; 0.195]	[-0.532; 0.532]
	Maximum	5.91	4.43			
	Median	2.75	2.66			
λ_z [1/hours]	Minimum	0.12	0.16	0	[-0.02; 0.035]	[-0.052; 0.052]
	Maximum	0.42	0.44			
	Median	0.25	0.26			

Abbreviations: LSmean = least squares mean; CI = confidence interval; CV% = coefficient of variation
* nonparametric estimator or confidence interval

STUDY XM02-05-DE

Pharmacokinetic Results

Mean G-CSF concentration-time profiles following a single SC injection of XM02 or Filgrastim are presented for the 5 µg/kg and 10 µg/kg doses in Figures 13 and 14 below. In both dose and treatment groups, mean G-CSF serum concentrations rapidly increased, reaching a maximum around 5 hours, and then decreased to pre-dose values at 24 hours.

Figure 13: Study XM02-05-DE: Mean Serum Concentration-Time Profile of G-CSF Following a Single Subcutaneous Injection of 5 µg/kg of XM02 or Filgrastim to Healthy Male and Female Subjects

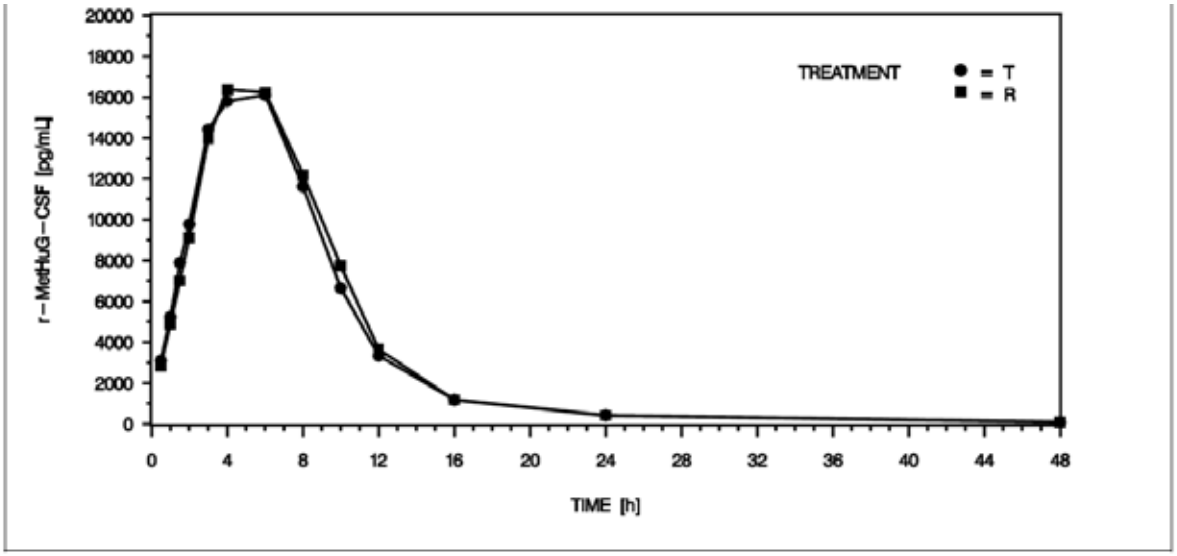
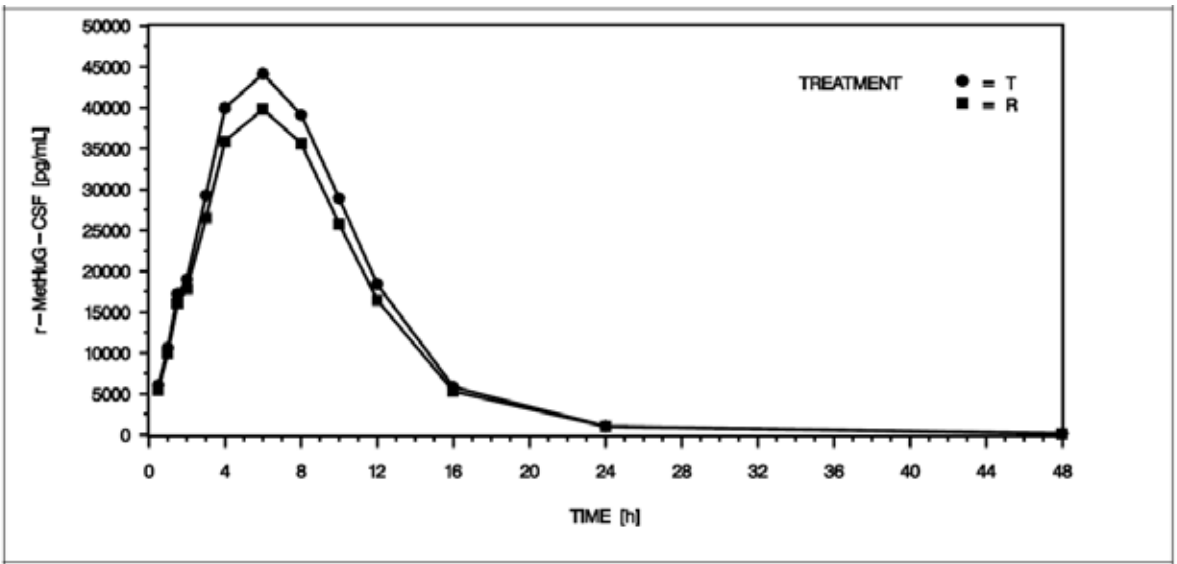


Figure 14: Study XM02-05-DE: Mean Serum Concentration-Time Profile of G-CSF Following a Single Subcutaneous Injection of 10 µg/kg of XM02 or Filgrastim to Healthy Male and Female Subjects



Abbreviations: h = hours; T = test treatment group (XM02); R = reference treatment group (Filgrastim)
G-CSF = granulocyte colony-stimulating factor

Mean G-CSF concentration-time profiles following a single IV infusion of XM02 or Filgrastim are presented for the 5 µg/kg and 10 µg/kg doses in Figures 15 and 16, respectively. In both dose and treatment groups, mean G-CSF serum concentrations rapidly increased, reaching a maximum around 0.75 hours, and then decreased to pre-dose values at 24 hours.

Figure 15: Study XM02-05-DE: Mean Serum Concentration-Time Profile of G-CSF Following a Single Intravenous Infusion of 5 µg/kg of XM02 or Filgrastim to Healthy Male and Female Subjects

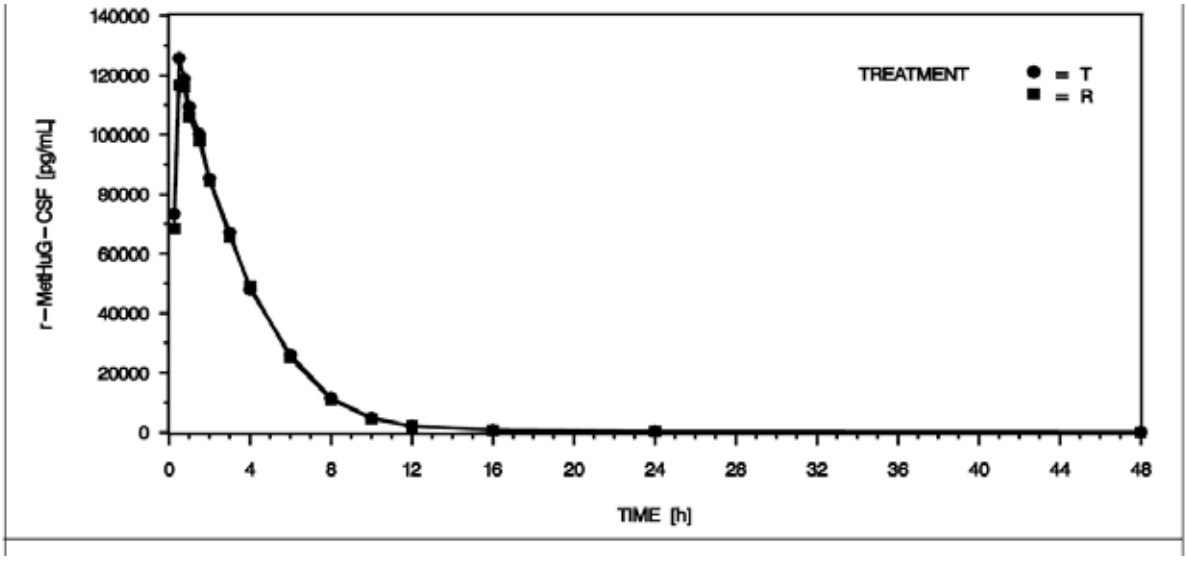
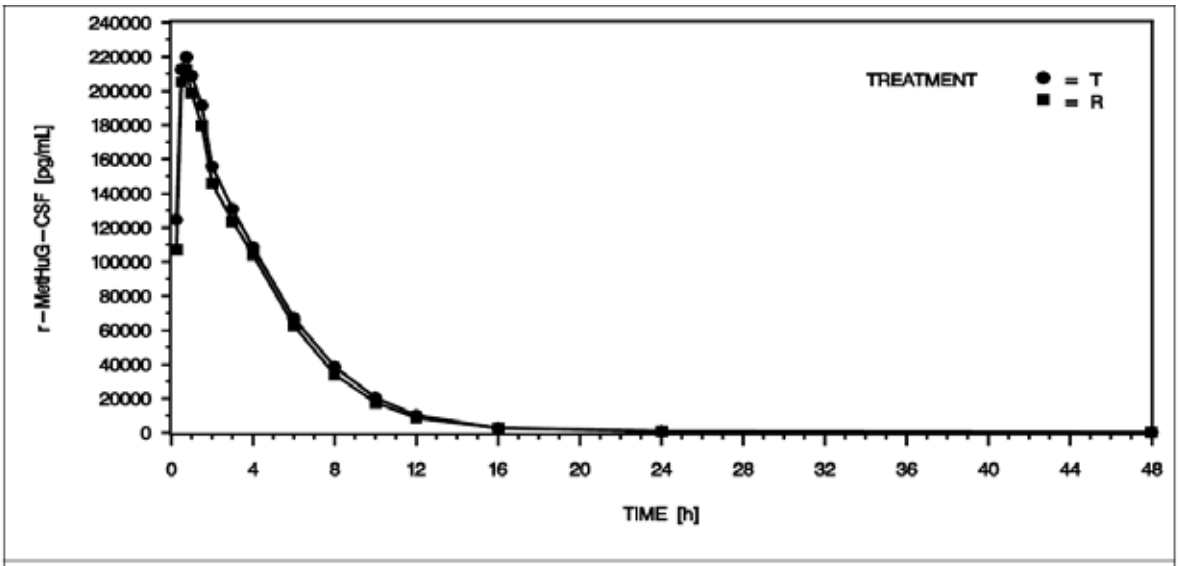


Figure 16: Study XM02-05-DE: Mean Serum Concentration-Time Profile of G-CSF Following a Single Intravenous Infusion of 10 µg/kg of XM02 or Filgrastim to Healthy Male and Female Subjects



Abbreviations: h = hours; T = test treatment group (XM02); R = reference treatment group (Filgrastim)
G-CSF = granulocyte colony-stimulating factor

ANOVA demonstrated equivalence of XM02 and Filgrastim with regard to PK variables in both the 5 µg/kg and 10 µg/kg dose group after single SC and IV administrations. CIs for all log transformed PK variables were enclosed in the 80%-125% acceptance intervals for both dose regimens. There were no statistically significant period or sequence effects ($p>0.05$) for AUC_{0-t}, $AUC_{0-\infty}$, C_{max} and $t_{1/2}$.

After IV administration there was a dose-proportional increase in AUC_{0-t} and C_{max} from the 5 µg/kg to the 10 µg/kg dose. After SC administration there was a 3-fold increase in AUC_{0-t} and C_{max} from the 5 µg/kg to the 10 µg/kg dose (see Tables 13 and 14). The absolute bioavailability of SC XM02 was 33% and 45% for the 5 µg/kg and 10 µg/kg doses, respectively.

Table 13: Study XM02-05-DE: Geometric Mean of AUC_{0-t}, $AUC_{0-\alpha}$ and C_{max} and Median of t_{max} and $t_{1/2}$ of G-CSF Following a Single Subcutaneous Injection of 5 and 10 µg/kg XM02 of Filgrastim to Healthy Male and Female Subjects

Variable	5 µg/kg s.c.		10 µg/kg s.c.	
	XM02	Filgrastim	XM02	Filgrastim
AUC_{0-t} [ng/mL*h]	157.585	159.426	471.148	430.717
$AUC_{0-\infty}$ [ng/mL*h]	158.975	160.783	472.239	431.860
C_{max} [ng/mL]	17.976	18.416	46.239	43.145
t_{max} [h]	6.00	4.12	6.00	6.00
$t_{1/2}$ [h]	8.93	9.36	5.15	5.21
Abbreviations: s.c. = subcutaneous; G-CSF = granulocyte colony-stimulating factor				

Table 14: Study XM02-05-DE: Geometric Mean of AUC_{0-t} , $AUC_{0-\alpha}$ and C_{max} and Median of t_{max} and $t_{1/2}$ of G-CSF Following a Single Intravenous Infusion of 5 and 10 µg/kg XM02 or Filgrastim to Healthy Male and Female Subjects

Variable	5 µg/kg i.v.		10 µg/kg i.v.	
	XM02	Filgrastim	XM02	Filgrastim
AUC_{0-t} [ng/mL*h]	480.201	470.373	1056.472	990.996
$AUC_{0-\infty}$ [ng/mL*h]	481.103	471.431	1057.420	991.892
C_{max} [ng/mL]	129.786	126.124	231.142	221.562
t_{max} [h]	0.50	0.75	0.75	0.75
$t_{1/2}$ [h]	9.38	9.35	7.15	7.30
Abbreviations: i.v. = intravenous; G-CSF = granulocyte colony-stimulating factor				

STUDY XM02-02-INT (BREAST CANCER)

Study Design, Objectives and Methods

This was a multinational, multicentre, randomised, controlled Phase III study performed in patients with breast cancer. A total of 348 patients were randomised. PK properties of XM02, Filgrastim, or endogenous G-CSF were examined in up to 12 patients per treatment group (XM02, Filgrastim, and placebo) in a parallel-group design. Study drug was administered daily starting 1 day after chemotherapy (CTX) as SC 5 µg/kg injection for at least 5 days and a maximum of 14 days in each cycle. Blood samples for the determination of serum concentrations were taken in CTX Cycle 1 and Cycle 4 on Day 2 of a cycle (first profile) and on the day the ANC had reached at least 2 x 10^9/L after nadir (lowest level) (second profile). On the four PK days, samples were taken pre-dose and 1, 2, 3, 4, 6, 12 and 24 hours after SC injection of the study drug. Note that patients of the placebo/XM02 group received XM02 in Cycle 4. Reference product was Neupogen Amgen as marketed in Germany.

CTX-naïve patients with high-risk Stage II or with Stage III or IV breast cancer needing CTX were enrolled. Patients were randomised to treatment with either XM02 (n=140), Filgrastim (n=136) or placebo (n=72). Patients of the placebo group switched to XM02 after completion of Cycle 1. The CTX regimen in this study consisted of doxorubicin (60 mg/m^2, IV bolus) and docetaxel (75 mg/m^2, at least 1 hour IV infusion) on Day 1 of each cycle (3 weeks per cycle).

The patients underwent a maximum of 4 CTX cycles (3 weeks per cycle), each cycle beginning with a day of CTX with doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2. One day after CTX, daily

subcutaneous (SC) injections of either XM02 or Filgrastim (5 □g/kg/day based on actual body weight) or SC placebo (in the first cycle only) were given for at least 5 days but with a maximum of 14 days. The Study drug had to be stopped earlier when an ANC of ≥10 x 10^9/L after the nadir was reached.

In Cycle 1, blood samples for the determination of ANC were taken within 24 hours before CTX and then daily from Day 2 until Day 15 or longer (until ANC reached ≥2.0 x 10^9/L). In Cycles 2, 3 and 4, ANC were measured within 24 hours before CTX and then daily starting on Day 5 until Day 15 or longer (until ANC reached ≥2.0 x 10^9/L). In every cycle, body temperature (axillary) was measured daily until Day 15 or longer (until ANC reached ≥2.0 x 10^9/L).

Safety assessments (laboratory parameters, antibody sampling, physical examination and vital signs) were performed at screening, within 24 hours before CTX in each cycle (Day 1) and at the end of study visit. Patients were monitored for adverse events (AEs) and concomitant medication throughout the study. Three weeks after the last CTX infusion (Day 85 □1) end of study assessments were performed. On Day 180 □5, there was an additional assessment for determination of antibodies against XM02 or Filgrastim.

Primary objectives were:

- Confirmation of assay sensitivity with respect to duration of severe neutropaenia (DSN) by comparing XM02 versus placebo in Cycle 1.
- Demonstration of equivalence of XM02 and Filgrastim (Neupogen - Amgen) in patients with breast cancer during the first cycle of CTX with respect to the primary endpoint, DSN in Cycle 1, defined as Grade 4 neutropaenia with an ANC <0.5 x 10^9/L.

Secondary objectives were:

- Demonstration of efficacy and safety of XM02 in comparison to Filgrastim in patients with breast cancer under CTX, based on the secondary endpoints.
- Evaluation of PK properties of XM02 in comparison to Filgrastim.

Main Criteria for Inclusion

The main criteria for inclusion in the study were female and male patients of any ethnic origin with a diagnosis of breast cancer meeting all criteria listed below:

- Signed and dated written informed consent.
- Age ≥18 years.
- Breast cancer high risk Stage II, or Stage III or IV (classification according to American Joint Committee on Cancer [AJCC]).
- Patients planned/eligible to receive treatment with docetaxel/doxorubicin as routine CTX for their breast cancer disease.
- CTX-naïve.
- ANC ≥1.5 x 10^9/L.
- Platelet count ≥100 x 10^9/L.
- Adequate cardiac function (including left ventricular ejection fraction ≥50% as assessed by echocardiography within 4 weeks prior to randomisation).
- Adequate hepatic function; alanine and aspartate aminotransferases (ALT/AST) at <2.5 x upper limit of normal (ULN), alkaline phosphatase (AP) <5 x ULN and bilirubin <ULN.
- Adequate renal function; creatinine <1.5 x ULN.

• Eastern Cooperative Oncology Group (ECOG) performance status ≤2.[7]

Study Endpoints

Primary efficacy endpoint

• DSN in Cycle 1, defined as the number of days with Grade 4 neutropaenia with an ANC <0.5 x 10^9/L.

Secondary efficacy endpoints

• Incidence of observed febrile neutropaenia (FN) (observed FN defined as body temperature of >38.5°C for more than 1 hour, measured axillary with a calibrated standard device and ANC <0.5 x 10^9/L, both measured on the same day) and of protocol defined FN (intake of systemic antibiotics) by cycle and across all cycles.

• DSN in Cycles 2 to 4.

• Depth of ANC nadir in Cycles 1 to 4.

• Times to ANC recovery in Cycles 1 to 4.

• Mortality.

Statistical Methods

First, assay sensitivity with respect to DSN in Cycle 1 was confirmed by comparing XM02 versus placebo. If this difference was significant (analysis of covariance [ANCOVA], two-sided p≤0.05 with shorter DSN for XM02), equivalence between XM02 and Filgrastim was assessed. To show equivalence between XM02 and Filgrastim, the two sided 95% CI for the difference in DSN in Cycle 1 had to lie entirely within the equivalence range of [-1 day, +1 day]. A difference of 1 day was considered to be the maximum clinically acceptable difference. The per protocol (PP) set was the primary analysis set for the efficacy comparison of XM02 versus Filgrastim, but consistent results should be found in the full analysis (FA) set to support equivalence. The comparison of XM02 versus placebo was based primarily on the FA Set.

All analyses of secondary endpoints were done without alpha adjustment and were interpreted as descriptive/exploratory analyses. All safety endpoints were summarised using descriptive statistics. In addition, the incidence of treatment emergent adverse events (TEAEs) was compared for XM02 versus Filgrastim using Fisher's exact test (two-sided p-values).

Study Population

Of the 348 patients, 346 were female and two were male. The majority of patients were Caucasian (86.2%), 7.5% were Hispanics, 2.3% Blacks and 4.0% of another race. The median age of the

[7] ECOG Performance Status. The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient and determine appropriate treatment and prognosis. The following are used:

0 - Fully active, able to carry on all pre-disease performance without restriction

1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work

2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours

3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours

4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

5 – Dead

patients was 50 years (range: 25 to 75 years). The mean body height was 161.3 cm (range: 141 to 186 cm) and mean body weight was 72.5 kg (range: 39 to 153 kg).

In the FA and PP Sets, demographic characteristics were generally similar across countries and for those who received adjuvant or metastatic therapy.

In the FA Set, 48.8% of the women were post-menopausal and 43.1% were potentially able to bear children. Results were similar for the PP Set. In both analysis sets, in the placebo/XM02 group, the proportion of women with childbearing potential was higher (52.8% FA Set, 51.7% PP Set) than in the XM02 (39.6% FA Set, 39.4% PP Set) and Filgrastim group (41.5% FA Set, 40.6% PP Set). The proportion of post-menopausal women was slightly higher in patients who received metastatic therapy (62.0% FA Set, 62.0% PP Set) than in those who received adjuvant therapy (42.9% FA Set, 44.5% PP Set).

The majority of patients (53.4%) had breast cancer Stage III disease whereas 25.3% had Stage IV and 21.3% high risk Stage II disease. The median time since first diagnosis was 24 days (range: 0 to 9879 days; 25% had a duration of >56 days between first diagnosis and study start). Ten (10) patients had a duration of >5 years, 6 of these of >10 years between first diagnosis and study start.

A prior medical condition was reported by 85.3% of the patients. Most common past diseases and medical conditions were hypertension (in 27.0% of patients), mastectomy (17.5%) and uterine leiomyoma (11.2%). The treatment groups were similar with regard to the patients' medical history.

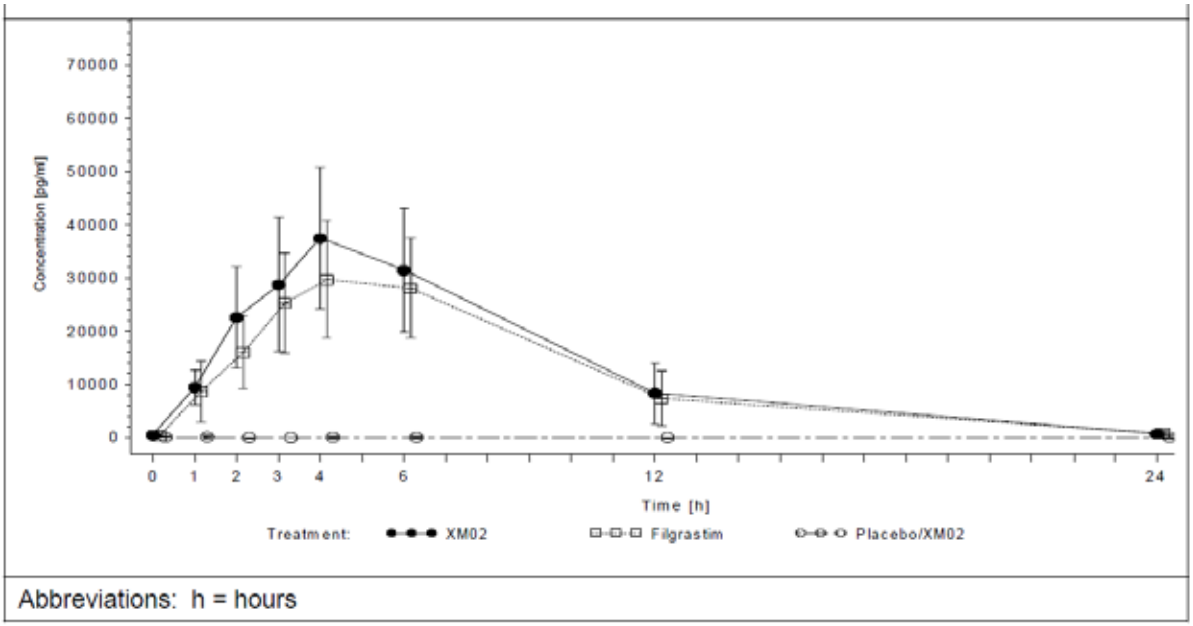
Intake of prior medication was reported for 92.0% of the patients. Most common prior medications were ondansetron (in 71.6% of patients), dexamethasone (54.3%) and diphenhydramine (10.1%). The treatment groups were similar with regard to the patients' prior medication.

Pharmacokinetic Results

PK analyses were conducted on a subset of 37 female patients. The majority were Caucasian (86.5%), 8.1% were Hispanics and 5.4% were Black. The median age of the patients was 57 years (range: 35 to 74 years). The treatment groups were similar with regard to the demographic characteristics.

Results are presented only for those patients providing all four profiles with active drug application. In Cycle 1 and Cycle 4 in both profiles, mean serum concentrations of XM02 and Filgrastim increased, reaching a maximum at 4 to 6 hours after dosing. Plasma XMO2 levels had returned to pre-dose values by 24 hours. No accumulation after repeated dosing was observed. Overall, mean serum concentrations were lower in Cycle 4 than in Cycle 1. In the placebo group in Cycle 1, mean serum concentrations of endogenous G-CSF remained at a low level at all measurement points (see Figure 17).

Figure 17: Study XM02-02-INT: Mean (± SD) Serum Concentrations of XM02, Filgrastim or Endogenous G-CSF in Cycle 1, First Profile



Abbreviations: h = hours

ANOVA of XM02 versus Filgrastim showed no significant differences with regard to the relative bioavailability of the two drugs, considering C_{max}, AUC over the 0 to 12 h dosing interval (AUC_{0-12}) and the 0 to 24 h dosing interval (AUC_{0-24}) (see Table15).

Table 15: Study XM02-02-INT: Geometric means of AUC_{0-12}, AUC_{0-24} and C_{max} Following Subcutaneous Injection of 5 µg/kg of XM02 or Filgrastim to Patients with Breast Cancer in Chemotherapy Cycle 1

Variable	First Profile		Second Profile	
	XM02	Filgrastim	XM02	Filgrastim
AUC_{0-12} [ng/mL*h]	254.923	212.089	219.941	201.341
AUC_{0-24} [ng/mL*h]	305.299	258.499	276.030	229.534
C_{max} [ng/mL]	36.148	28.985	29.631	28.358

Note: First profile was on Day 2 of cycle 1, second profile was on the day the absolute neutrophil count had reached at least 2 x 10^9/L after nadir in cycle 1.

The median t_{max} value was 4.0 hours in the XM02 and Filgrastim groups in both profiles in Cycle 1. The median $t_{1/2}$ value was similar in the XM02 and Filgrastim groups in Cycle 1 first profile (3.040 and 3.225 hours, respectively) and second profile (3.390 and 3.085 hours, respectively). For Cycle 4, similar results were observed to those described above for Cycle 1.

Evaluator Comment

The study showed there were no statistically significant differences between XM02 and Filgrastim (Neupogen™ Amgen) with regard to PK profiles or the relative bioavailability of the two drugs. In this study no crossover design was used and it was not planned to demonstrate bioequivalence.

STUDY XM02-03-INT (LUNG CANCER)

Study Design, Objectives and Methods

This was a multinational, multicentre, randomised, controlled Phase III study. A total of 240 patients with small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC) requiring CTX participated. Patients were randomised to treatment with either XM02 (n=160) or Filgrastim (n=80) in the first CTX cycle. In the subsequent cycles, all patients received XM02.

The patients underwent a maximum of six CTX cycles (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 (for example, on Day 2 with 1 CTX infusion day, on Day 4 with 3 CTX infusion days), the patients received daily SC injections of 5 µg/kg/day (based on actual body weight) XM02 or Filgrastim (Filgrastim in the 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.

Main Criteria for Inclusion

Female and male patients of any ethnic origin with a diagnosis of lung cancer meeting all criteria listed below could be included in the study.

- Signed and dated written informed consent
- Age ≥18 years
- Patients with SCLC, histologically or cytologically documented or patients with advanced NSCLC disease
- Patients who were 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 previous CTX more than 4 weeks before randomisation
- Eastern Cooperative Oncology Group (ECOG) performance status ≤2
- ANC ≥1.5 x 10^9/L
- Platelet count ≥100 x 10^9/L
- Adequate hepatic, cardiac and renal function for the chosen CTX regimen.

Study Endpoints

Safety endpoints

- AEs
- Safety laboratory assessment
- Physical examination
- Injection site reactions
- Vital signs
- ECOG performance
- Immunogenicity (development of antibodies against study drug)

Efficacy endpoints

- Duration of severe neutropaenia (DSN) in Cycles 1 and 4.
- Incidence of observed febrile neutropaenia (FN) (observed FN defined as body temperature of >38.5°C for more than 1 hour, measured axillary with a calibrated standard device and ANC <0.5 x 10^9/L, both measured on the same day) and of protocol defined FN (intake of systemic antibiotics) by cycle and across all cycles.
- Depth of ANC nadir in Cycles 1 and 4.
- Time to ANC recovery in Cycles 1 and 4.
- Mortality.

Other

- PK in a subset of patients.

Primary objective

- Demonstration of safety of XM02 when administered for up to a maximum of six cycles of chemotherapy in patients with lung cancer.

Secondary objectives

- Demonstration of efficacy of XM02 (in the first cycle compared to Filgrastim) in patients with lung cancer.
- Evaluation of pharmacokinetic properties of XM02 in comparison to Filgrastim.

Statistical Methods

All safety analyses were done for the safety set and were summarised using descriptive statistics. In addition, the incidence of treatment emergent adverse events (TEAEs) was compared for XM02 versus Filgrastim using Fisher's exact test (two-sided p-values). The Wilcoxon test was used to compare changes of safety laboratory parameters from baseline between the two active groups.

The Per Protocol (PP) set was the primary analysis set for the efficacy comparison of XM02 versus Filgrastim but consistent results should be found for the FA set. Analysis of covariance (ANCOVA) was applied for DSN, ANC nadir and time to ANC recovery. All analyses of efficacy endpoints were done without alpha-adjustment and were interpreted as descriptive/exploratory analyses. Analyses were repeated stratified by country, previous CTX, cancer type and myelotoxic potency category. Incidences of FN were compared between XM02 and Filgrastim by means of the Cochran-Mantel-Haenszel test.

Study Population

In total, 240 patients were randomised (XM02 = 160, Filgrastim/XM02 = 80) and 237 patients (XM02 = 158, Filgrastim/XM02 = 79) received CTX and study drug in Cycle 1.

Of the 237 patients in the safety set, 188 were male (79.3%) and 49 were female (20.7%). The majority of patients were Caucasian (94.9%); 4.6% were Hispanics and 0.4% were of another race. The median age of the patients was 59 years (range: 34 to 78 years). The mean body height was 170.4 cm (range: 141 to 187 cm) and mean body weight was 70.1 kg (range: 40 to 126 kg). The patients had a mean body mass index (BMI) of 24.13 kg/m^2 (range: 16.0 to 39.6 kg/m^2). The treatment groups were similar with regard to the demographic characteristics.

The majority of patients (198 or 83.5%) had non-small-cell lung cancer (NSCLC). Of these, 122 patients (51.5%) had Stage IV disease and 76 patients (32.1%) had Stage III disease. Thirty nine patients (16.5%) had small cell lung cancer (SCLC) and of these, 31 patients (13.1%) had extensive and 8 patients (3.4%) had limited disease stage. The median time since first diagnosis was 20 days (range: 0 to 1181 days).

A prior medical condition was reported by 97.9% of the patients. Most common past diseases and medical conditions were cough (in 28.7% of patients), hypertension (27.0%), dyspnoea (23.2%) and chest pain (17.7%). The treatment groups were similar with regard to the patients' medical history.

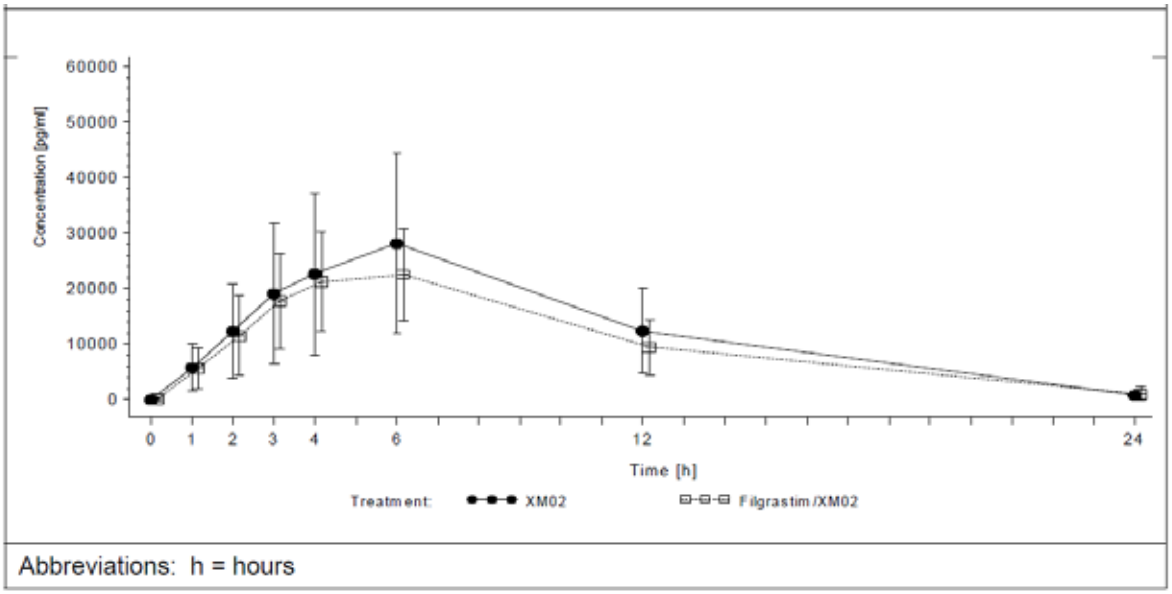
Intake of prior medication was reported for 92.8% of the patients. Most common prior medications were ondansetron (in 60.8% of patients), dexamethasone (31.6%) and furosemide (23.6%). The treatment groups were similar with regard to the patients' prior medication.

Pharmacokinetic Results

Results are presented for the PK set excluding implausible profiles. Four profiles were considered implausible (all in Cycle 1, second profile), three because apparently no study drug was administered and one due to an implausibly high concentration at pre-dose.

In Cycle 1 and Cycle 4 in both profiles, mean serum concentrations of XM02 and Filgrastim increased, reaching a maximum at 4 to 6 hours after dosing, and returned to pre-dose values by 24 hours (see Figure 18). Overall, mean serum concentrations were lower in Cycle 4 than in Cycle 1 and in the second profile compared to the first profile. There were no signs for accumulation after repeated dosing.

Figure 18: Study XM02-03-INT: Mean (± SD) Serum Concentrations of XM02 and Filgrastim in Cycle 1, First Profile



Abbreviations: h = hours

ANOVA of XM02 versus Filgrastim showed no significant differences with regard to the relative bioavailability of the two drugs in the first and second profile of Cycle 1, that is, geometric means of AUC_{0-12}, AUC_{0-24} and C_{max} were very similar in the XM02 and Filgrastim groups (Table 16).

Table 16: Study XM02-03-INT: Geometric means of AUC_{0-12}, AUC_{0-24} and C_{max} Following Subcutaneous Injection of 5 µg/kg of XM02 or Filgrastim to Patients with Lung Cancer in Chemotherapy Cycle 1

Variable	First Profile		Second Profile	
	XM02	Filgrastim	XM02	Filgrastim
AUC_{0-12} [ng/mL*h]	193.371	176.901	128.763	117.456
AUC_{0-24} [ng/mL*h]	272.481	240.127	200.852	148.173
C_{max} [ng/mL]	25.223	23.664	14.807	15.638
Note: First profile was on Day 2 of cycle 1, second profile was on the day the absolute neutrophil count had reached at least 2 x 10^9/L after nadir in cycle 1.				

In Cycle 1, the median t_{max} value was 6.0 hours in the XM02 and Filgrastim/XM02 groups in the first profile. In the second profile, median t_{max} were 6.0 and 3.0 hours in the XM02 and Filgrastim/XM02 groups, respectively. In Cycle 1, the median $t_{1/2}$ values were 3.530 and 3.340 hours in the XM02 and Filgrastim/XM02 groups, respectively, in the first profile and 4.230 and 3.380 hours, respectively, in the second profile. For Cycle 4, similar results were observed to those described above for Cycle 1.

Evaluator Comment

In Study XM02-03-INT there were no statistically significant differences between XM02 and Filgrastim (Neupogen™ Amgen) with regard to PK profiles or the relative bioavailability of the two drugs. Once again, there was no cross-over design and the study was not designed to demonstrate bioequivalence.

STUDY XM02-04-INT (NON-HODGKIN'S LYMPHOMA)

Study Design, Objectives and Methods

This was a multinational, multicentre, randomised, controlled Phase III study conducted in patients with Non-Hodgkin's Lymphoma receiving CTX. Patients were randomised to treatment with either XM02 or Filgrastim in the first cycle. From Cycle 2 onwards, all patients received XM02. The patients underwent a maximum of 6 CTX cycles (3 weeks per cycle), each cycle beginning on Day 1 with CTX according to the cyclophosphamidehydroxydaunomycin-oncovin-prednisolon (CHOP) regimen. Beginning on Day 2 of each cycle, approximately 24 hours after end of CTX, the patients received daily SC injections (5 µg/kg/day, based on actual body weight) with XM02 or Filgrastim (Filgrastim in the first cycle only) for at least 5 days and a maximum of 14 days (until Day 15). Study drug was stopped when an absolute neutrophil count (ANC) ≥10 x 10^9/L after nadir was reached. In Cycle 1, blood samples for the determination of ANC were taken daily from Day 1 until Day 15 (in Cycle 4: on Day 1 and daily from Day 5 until Day 15), or until ANC reached ≥2.0 x 10^9/L. In Cycles 2, 3, 5 and 6, ANC was only assessed on Days 1, 5, 7, 10 and 15 of each cycle and additionally on days when body temperature was >38.5°C. In every cycle, body temperature (axillary) was measured daily until Day 15 or longer (until ANC reached ≥2.0 x 10^9/L).

Safety assessments (laboratory parameters, antibody sampling, physical examination, vital signs) were performed at screening, within 24 hours before CTX in each cycle (Day 1) and at the end of study (EOS) visit (Day 127). Patients were monitored for adverse events (AEs) and concomitant medication taken throughout the study. On Day 180, there was an additional assessment for determination of antibodies against XM02 or Filgrastim.

Primary objective

- Demonstration of safety of XM02 when administered for up to a maximum of 6 cycles in patients with Non-Hodgkin's-Lymphoma (NHL) receiving chemotherapy (CTX) according to the CHOP regimen.

Secondary objectives

- Demonstration of efficacy of XM02 (in the first cycle compared to Filgrastim) in patients with NHL.
- Evaluation of pharmacokinetic (PK) properties of XM02 in comparison to Filgrastim.

Main Criteria for Inclusion

Patients of any ethnic origin with aggressive NHL who met all criteria listed below were eligible for participation in the study:

- Signed and dated written informed consent.
- Men and women aged ≥18 years.
- Aggressive NHL, defined as diffuse large B-cell lymphoma, mediastinal large B-cell lymphoma, follicular lymphoma Grade 3 or anaplastic large cell lymphoma.
- Patients planned/eligible to receive CHOP regimen as routine CTX for their NHL requiring granulocyte colony-stimulating factor (G-CSF) support in the investigator's opinion.
- Life-expectancy of at least 6 months as judged by the investigator.
- CTX-naïve
- International Prognostic Index (IPI) score ≤3
- ANC ≥1.5 x 10^9/L
- Platelets ≥100 x 10^9/L
- Adequate cardiac function as assessed by the investigator
- Alanine and aspartate aminotransferases (ALT/AST) <3 x upper limit of normal (ULN), bilirubin <2 x ULN
- Creatinine <2 x ULN

Study Endpoints

Safety endpoints

- AEs
- Safety laboratory assessment
- Physical examination
- Injection site reactions
- Vital signs
- Immunogenicity (development of antibodies against study drug).

Efficacy endpoints

- Duration of severe neutropaenia (DSN) in Cycles 1 and 4.
- Incidence of observed febrile neutropaenia (FN) (observed FN defined as body temperature of >38.5°C for more than 1 hour, measured axillary with a calibrated standard device and ANC <0.5 x 10^9/L, both measured on the same day) and of protocol defined FN (intake of systemic antibiotics) by cycle and across all cycles.

- Depth of ANC nadir in Cycles 1 and 4.
- Times to ANC recovery in Cycles 1 and 4.
- Mortality.

Other

- PK in a subset of patients

Statistical Methods

All safety analyses were done for the safety set and were summarised using descriptive statistics. In addition, the incidence of TEAEs was compared between the XM02 and Filgrastim/XM02 group using Fisher's exact test (two-sided p-values). The Wilcoxon test was used to compare changes of safety laboratory parameters from baseline between the two active groups.

The PP set was the primary analysis set for the efficacy comparison of XM02 versus Filgrastim, but consistent results should be found for the full analysis (FA) set. Analysis of covariance (ANCOVA) was applied for DSN, ANC nadir and time to ANC recovery. All analyses of efficacy endpoints were performed without alpha-adjustment and were interpreted as descriptive/exploratory analyses. Analyses were repeated stratified by country and concomitant treatment with rituximab. Incidences of FN were compared between the XM02 and Filgrastim/XM02 group by means of the Cochran-Mantel-Haenszel test.

Study Population

A total of 92 patients with CTX-naïve aggressive NHL (allowed subtypes: diffuse large B-cell lymphoma, mediastinal large B-cell lymphoma, follicular lymphoma Grade 3, anaplastic large cell lymphoma) needing CTX participated. Patients were randomised to treatment with either XM02 (n=63) or Filgrastim (n=29) in the first CTX cycle. In the subsequent cycles, all patients received XM02.

Of the 92 patients in the safety set, 48 were male (52.2%) and 44 were female (47.8%), 15 of the 44 female (34.1%) were potentially able to bear children. The majority of patients were Caucasian (88.0%); 8.7% were Hispanics, 1.1% Black and 2.2% were of another race. The median age of the patients was 55 years (range: 18 to 83 years). The mean body height was 166.6 cm (range: 143 to 187 cm) and mean body weight was 70.6 kg (range: 38 to 106 kg). The patients had a mean body mass index (BMI) of 25.47 kg/m^2 (range: 16.1 to 40.1 kg/m^2). The treatment groups were similar with regard to the demographic characteristics.

The majority of patients, (68 or 73.9%) had diffuse large B-cell lymphoma. Ten (10.9%) patients presented with Grade 3 follicular lymphoma, 9 (9.8%) with anaplastic large cell lymphoma and 5 (5.4%) with mediastinal B-cell lymphoma. Presence of B-symptoms was reported for 29 (31.5%) patients and bone marrow infiltration for 8 (8.7%) patients. The median time since first diagnosis of NHL was 17 days (range: 0 to 261 days). No patient had a prior bone marrow or stem cell transplantation. One patient had received radiation therapy 2159 days prior to enrolment. In general, the treatment groups were similar with regard to NHL history.

A prior medical condition was reported by 94.6% of the patients. Most common were lymphadenopathy (in 26.1% of patients), hypertension (18.5%), essential hypertension (10.9%) and coronary artery disease (10.9%). The treatment groups were similar with regard to the patients' medical history.

Intake of prior medication was reported for 70.7% of the patients. Most common prior medication was ondansetron (in 42.4% of patients). The treatment groups were similar with regard to the patients' prior medication.

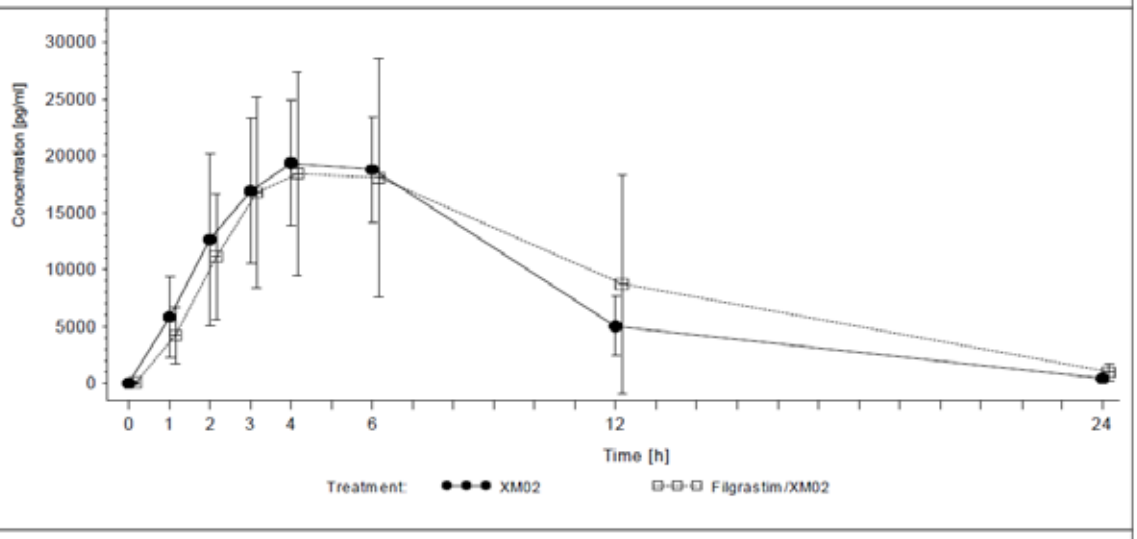
Pharmacokinetic Results

There were 15 patients in the PK set, the majority of which were male (60%). All patients were Caucasian. The median age of the patients was 53 years (range: 22 to 76 years). The treatment

groups were similar with regard to the demographic characteristics. There were only four patients in the Filgrastim/XM02 group, leading to a large variability of PK results in this group.

In Cycle 1 in both profiles, mean serum concentrations of XM02 and Filgrastim increased, reaching a maximum at 4 to 6 hours after dosing, and returned to pre-dose values by 24 hours (see Figure 19). There were no signs of accumulation after repeated dosing.

Figure 19: Study XM02-04-INT: Mean (± SD) Serum Concentrations of XM02 and Filgrastim in Cycle 1, First Profile



Abbreviations: h = hours

ANOVA of XM02 versus Filgrastim showed no significant differences with regard to the relative bioavailability of the two drugs for both the first and second profile of Cycle 1, i.e., geometric means of AUC_{0-12}, AUC_{0-24} and C_{max} were very similar in the XM02 and Filgrastim/XM02 groups (see Table 17).

Table 17: Study XM02-04-INT: Geometric means of AUC_{0-12}, AUC_{0-24} and C_{max} Following Subcutaneous Injection of 5 µg/kg of XM02 or Filgrastim to Patients with Non-Hodgkin-Lymphoma in Chemotherapy Cycle 1

Variable	First Profile		Second Profile	
	XM02	Filgrastim	XM02	Filgrastim
AUC_{0-12} [ng/mL*h]	150.832	140.921	130.101	168.274
AUC_{0-24} [ng/mL*h]	183.495	188.119	144.209	210.294
C_{max} [ng/mL]	20.116	18.833	19.897	22.684

Note: First profile was on Day 2 of cycle 1, second profile was on the day the absolute neutrophil count had reached at least 2 x 10^9/L after nadir in cycle 1.

In Cycle 1 in the first profile, the median t_{max} values were 6.0 and 5.0 hours in the XM02 and Filgrastim/XM02 groups, respectively. In the second profile, the median t_{max} values were 4.0 and 6.0 hours, respectively. The median $t_{1/2}$ values were 3.160 and 3.840 hours in the XM02 and Filgrastim/XM02 groups, respectively, in the first profile and 3.110 and 2.890 hours, respectively, in the second profile. For Cycle 4, similar results were observed to those described above for Cycle 1.

Evaluator Comment

There were no statistically significant differences between XM02 and Filgrastim (Neupogen™ Amgen) with regard to the PK profile or relative bioavailability of the two drugs. The study was not designed to demonstrate bioequivalence.

Efficacy

All three Phase III efficacy studies were multinational, multicentre, randomised and controlled studies assessing the efficacy and safety of XM02 compared to Filgrastim in different oncological indications under different CTX regimens. The sponsor stated that the pivotal study was XM02-02-INT (breast cancer), a three-arm study of XM02, Filgrastim or placebo in the first cycle of CTX. This study confirmed assay sensitivity with respect to duration of severe neutropaenia (DSN) by comparing XM02 versus placebo and assessed the equivalence of XM02 and Filgrastim with respect to the primary endpoint, duration of severe neutropaenia (DSN) in Cycle 1. Supportive studies, with main focus on safety, were Studies XM02-03-INT (lung cancer) and XM02-04-INT (NHL).

In all three studies, blinding of the investigator and patient was ensured. Only the "drug administrator" and the pharmacist were unblinded and had knowledge of the treatment (due to the different volumes of formulated XM02 and Filgrastim and body weight-dependent dosing).

In all studies, patients were randomly allocated to treatment with XM02 or Filgrastim in a 2:1 ratio (XM02-02 breast cancer study in a 2:2:1 ratio for XM02 and Filgrastim and placebo) in the first CTX cycle. There were slight differences between the three studies with regard to stratification during randomisation. Patients in the breast cancer study were stratified by country and adjuvant versus metastatic therapy. In the lung cancer study, patients were stratified by country, previous CTX and kind of lung cancer. Patients in the NHL study were stratified by country and concomitant treatment with rituximab. In Study XM02-02-INT, placebo patients switched to XM02 after completion of Cycle 1. In Studies XM02-03-INT and XM02-04-INT, Filgrastim patients switched to XM02 after completion of Cycle 1.

All three studies used the same definitions for the following:

- **Duration of Severe Neutropaenia (DSN)**

  DSN was defined as the number of days with Grade 4 neutropaenia (ANC $<0.5 \times 10^9$/L).

- **Depth of Absolute Neutrophil Count (ANC) Nadir**

  The patient's lowest ANC in each cycle was determined.

- **Timed to Absolute Neutrophil Count (ANC) Recovery**

  Time to ANC recovery was defined as the time in days from CTX administration until the patient's ANC increased to $\geq 2.0 \times 10^9$/L after the expected nadir.

- **Febrile Neutropaenia (FN)**

  FN was defined as body temperature of >38.5°C for >1 hour (axillary measurement with a calibrated standard device) and ANC $<0.5 \times 10^9$/L, both measured on the same day.

STUDY XM02-02-INT (BREAST CANCER)

Table 18 summarises the data sets analysed in this study. No patient terminated the study prematurely due to lack of efficacy.

Table 18: XM02-02-INT: Data Sets Analysed

	XM02	Filgrastim	Placebo/XM02*	Total
Enrolled	140	136	72	348
Completed	135	130	68	333
Full analysis set	140	136	72	348
Per protocol set	133	129	58	320
* Patients in this group received placebo in cycle 1 and switched to XM02 in the subsequent cycles.				

Primary Efficacy Endpoint

The primary endpoint was the DSN in Cycle 1. In the PP set, mean DSN in Cycle 1 were 1.1, 1.1 and 3.9 days in the XM02, Filgrastim and placebo groups, respectively. DSN ranged from 0 to 5 days in the XM02 and Filgrastim group and from 0 to 9 days in the placebo group. Results were similar in the full analysis (FA) set, with mean DSN of 1.1, 1.1 and 3.8 days, respectively.

Assay sensitivity was evaluated by comparing XM02 versus placebo for the FA set using analysis of covariance (ANCOVA). The least square mean of DSN was shorter in the XM02 group (1.141 days) than in the placebo group (3.823 days). The upper bound of the two-sided 95% confidence interval (CI) for "XM02 minus placebo" was $\leq$0 days (-2.151 days). This corresponded to a p-value for treatment comparison of <0.0001. Thus, assay sensitivity was concluded. Results for the PP set were similar and confirmed assay sensitivity.

Equivalence of XM02 and Filgrastim was assessed based on the PP set using the ANCOVA model to calculate a two-sided 95% CI for "XM02 minus Filgrastim". Least square means of DSN in Cycle 1 were 1.119 and 1.087 days in the XM02 and Filgrastim groups, respectively. The 95% CI [-0.262 days, 0.325 days] lay entirely within the pre-specified equivalence range of [-1, 1] days. Thus, equivalence was concluded. Results for the FA set were similar and confirmed equivalence of XM02 and Filgrastim.

Secondary Efficacy Endpoints

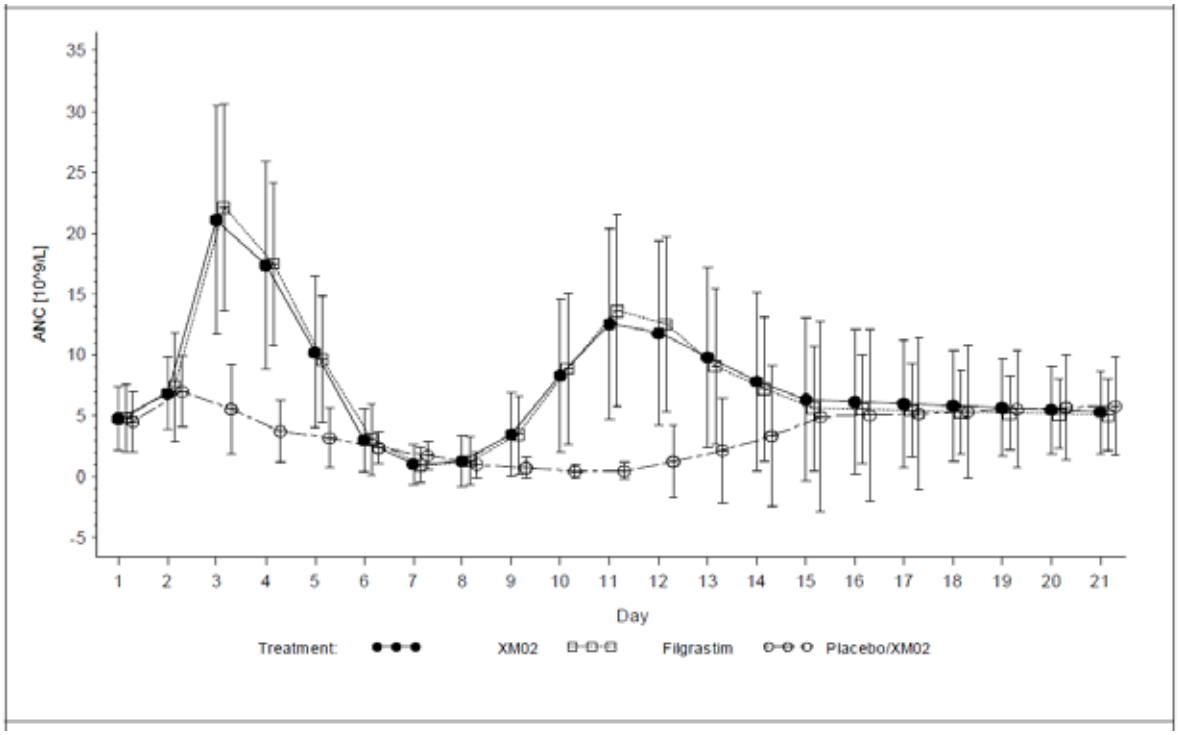
Data of secondary efficacy endpoints are presented for the FA set.

DSN: 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. The mean DSN ranged from 0.5 to 0.7 days in Cycles 2 to 4 in all treatment groups.

The mean DSN were 0.7, 0.7 and 0.5 days in Cycle 2, 0.6, 0.7 and 0.6 days in Cycle 3 and 0.7, 0.7 and 0.6 days in Cycle 4 in the XM02, Filgrastim 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. In contrast, in the XM02 and Filgrastim 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, the mean values had returned to Day 1 values in all treatment groups (see Figure 20). In subsequent cycles, all treatment groups demonstrated the same trends as for XM02 and Filgrastim in Cycle 1.

Figure 20: XM02-02-INT: Mean (± SD) Absolute Neutrophil Count Over Time in Cycle 1. FA set



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 that of the XM02 and Filgrastim 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, the mean ANC nadirs were 1.0, 1.0 and 1.1 x 10^9/L in the XM02, Filgrastim and placebo/XM02 groups, respectively.

A tabular summary of ANC nadir in Cycles 1 to 4 is provided in Table 19.

Table 19: Study XM02-02 –INT - Summary of ANC Nadir [10^9/L] in Cycles 1 to 4. FA Set

		XM02 [N= 140]	Filgrastim [N= 136]	Placebo/XM02 [N= 72] 1)
Cycle 1	N	140	136	72
	N imputed	1	1	0
	MEAN	0.655	0.651	0.163
	SD	0.813	0.778	0.222
	MIN	0.00	0.00	0.00
	MEDIAN	0.300	0.300	0.100
	MAX	4.50	3.60	1.10
Cycle 2	N	140	136	72
	N imputed	3	5	2
	MEAN	1.010	1.112	1.236
	SD	0.957	1.111	1.228
	MIN	0.00	0.00	0.00
	MEDIAN	0.700	0.750	0.800
	MAX	4.00	5.90	5.05
Cycle 3	N	140	136	72
	N imputed	4	5	4
	MEAN	1.023	1.090	1.252
	SD	0.951	1.101	1.078
	MIN	0.00	0.00	0.00
	MEDIAN	0.695	0.700	1.000
	MAX	4.20	5.10	4.20
Cycle 4	N	140	136	72
	N imputed	5	6	4
	MEAN	0.975	1.042	1.087
	SD	0.976	1.026	0.993
	MIN	0.00	0.00	0.00
	MEDIAN	0.700	0.750	0.750
	MAX	5.91	5.90	4.30

1) For patients with placebo receiving therapeutic G-CSF treatment, the ANC nadir values in cycle 1 were replaced with the median ANC nadir value of patients with placebo who received no G-CSF treatment, provided the ANC nadir was larger than this median

Placebo/XM02: patients of this group were randomised to placebo in cycle 1 and switched to XM02 afterwards

Time to ANC recovery: In Cycle 1, the mean time to ANC recovery was shorter in the XM02 and Filgrastim groups (8.0 and 7.8 days) than in the placebo group (14.0 days). In Cycles 2, 3 and 4, mean times to ANC recovery were similar in all treatment groups with a median of 8.0 days. In Cycle 4, mean times to ANC recovery were 7.6, 7.1 and 7.2 days in the XM02, Filgrastim and placebo/XM02 groups, respectively. A tabular summary of time to ANC recovery in Cycles 1 to 4 (FA Set) is provided in Table 20.

Table 20: Study XM02-02-INT - Summary of Time [days] to ANC Recovery in Cycles 1 to 4. FA Set

		XM02 [N= 140]	Filgrastim [N= 136]	Placebo/XM02 [N= 72] 1)
Cycle 1	N	140	136	72
	N imputed	1	1	0
	MEAN	8.0	7.8	14.0
	SD	2.6	2.8	3.8
	MIN	0	0	3
	MEDIAN	8.0	8.0	15.0
	MAX	20	17	20
Cycle 2	N	140	136	72
	N imputed	3	5	2
	MEAN	7.2	6.9	7.5
	SD	3.5	3.7	4.9
	MIN	0	0	0
	MEDIAN	8.0	8.0	8.0
	MAX	20	17	28
Cycle 3	N	140	136	72
	N imputed	4	5	4
	MEAN	7.3	7.5	6.5
	SD	3.5	4.1	4.6
	MIN	0	0	0
	MEDIAN	8.0	8.0	8.0
	MAX	20	20	20
Cycle 4	N	140	136	72
	N imputed	5	6	4
	MEAN	7.6	7.1	7.2
	SD	3.7	3.8	4.5
	MIN	0	0	0
	MEDIAN	8.0	8.0	8.0
	MAX	20	20	20

1) For patients with placebo receiving therapeutic G-CSF treatment, the times to ANC recovery in cycle 1 were replaced with the median of patients with placebo who received no G-CSF treatment, provided the individual time was shorter than this median.
Placebo/XM02: patients of this group were randomised to placebo in cycle 1 and switched to XM02 afterwards

Incidence of FN: The incidence of observed or protocol defined FN across all cycles was lower in the XM02 and Filgrastim groups (20.7% and 22.1%, respectively) compared to the placebo/XM02 group (41.7%). Observed FN was seen in only one patient in the XM02 group and four patients in the placebo/XM02 group, all in Cycle 1. There were no statistically significant differences with regard to FN incidence between the XM02 and Filgrastim groups.

In Cycle 1, where patients of the placebo/XM02 group received placebo, the incidence of observed or protocol defined FN was lower in the XM02 and Filgrastim groups (12.1% and 12.5%, respectively) compared to the placebo/XM02 group (36.1%). In Cycles 2, 3 and 4, the incidence of observed or protocol defined FN was similar in all treatment groups. Between the three 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 three deaths in CTX Cycle 1 (2 in the placebo/XM02 group and 1 in the XM02 group) and one death after the end of the study (XM02 group). All deaths were considered not related to the study drug. There were no statistically significant differences between patients treated with XM02 or Filgrastim with respect to the mortality rate.

Evaluator Comment

In Study XM02-02-INT, XM02 and Filgrastim were shown to be significantly more effective than placebo in reducing DSN in Cycle 1 of CTX in patients with breast cancer. XM02 was as effective as Filgrastim in reducing the DSN in Cycle 1 of CTX in patients with breast cancer. XM02 and Filgrastim had a similar effect on the incidence of FN and the time to ANC recovery.

STUDY XM02-03-INT (LUNG CANCER)

Table 21 summarises the data sets analysed in this study. No patient terminated the study prematurely due to a lack of efficacy. All data are presented for the FA set.

Table 21: XM02-03-INT: Data Sets Analysed

	XM02	Filgrastim/XM02*	Total
Enrolled	160	80	240
Completed	83	42	125
Full analysis set	160	80	240
Per protocol set	148	77	225
* Patients in this group received Filgrastim in cycle 1 and switched to XM02 in the subsequent cycles.			

DSN: The mean DSN in Cycles 1 and 4 was similar in both treatment groups. The majority of patients had a DSN of 0 days. Overall, DSN ranged from 0 to 6 days. The mean DSN was 0.5 and 0.3 days in Cycle 1 and 0.4 and 0.3 days in Cycle 4 (after the switch from Filgrastim to XM02 in the reference group) in the XM02 and Filgrastim/XM02 groups, respectively.

ANC over time: In Cycle 1 in both treatment groups, mean ANC values increased, reaching a maximum on Day 5, and then decreased to a nadir on Day 11 (Day 12 Filgrastim/XM02 group). Thereafter, mean values in the active treatment groups increased again, reaching a maximum on Day 14. On Day 21, mean values approached those observed on Day 1 in both treatment groups. The ANC profile was similar in subsequent cycles.

Depth of Absolute Neutrophil Count Nadir in Cycles 1 and 4 ANC nadir in a given cycle was defined as the lowest (possibly imputed) ANC value after start of CTX in the given cycle. In Cycle 1, the mean ANC nadir in the XM02 group (2.1 x 10^9/L) was lower than in the Filgrastim/XM02 group (2.9 x 10^9/L). In Cycle 4, after switch from Filgrastim to XM02 in the reference group, the mean ANC nadir was also lower in the XM02 group (2.3 x 10^9/L) than in the Filgrastim/XM02 group (3.2 x 10^9/L).

Times to ANC recovery: In Cycle 1, the mean time to ANC recovery was shorter in the Filgrastim/XM02 group (4.5 days) compared to the XM02 group (6.3 days). In Cycle 4, after switch from Filgrastim to XM02 in the reference group, mean time to ANC recovery was also shorter in the Filgrastim/XM02 group (4.5 days) than in the XM02 group (6.4 days).

Incidence of FN: Across all cycles, there were no incidences of observed FN in either the XM02 or Filgrastim/XM02 treatment groups. The incidence of protocol defined FN (corresponding to the administration of systemic antibiotics) was lower in the Filgrastim/XM02 group than in the XM02 group (23.8% and 33.1%, respectively) but this difference was not statistically significant (p=0.318). In Cycle 1, the incidences of protocol defined FN were 15.0% for XM02 and 8.8% for Filgrastim (p=0.235) and in Cycle 4, after switch from Filgrastim to XM02 in the reference group, the incidences of FN were 4.3% and 3.3%, respectively (p=0.904).

Mortality: In the observation period until Day 127/169, 31 patients died (19 in the XM02 group and 12 in the Filgrastim/XM02 group). There was no statistically significant difference between patients treated with XM02 or Filgrastim/XM02 with respect to the mortality rate.

Evaluator Comment

In Study XM02-03-INT, XM02 and Filgrastim were shown to have similar effects with regard to DSN and the incidence of FN in Cycle 1 during CTX in patients with lung cancer.

STUDY XM02-04-INT (NON-HODGKIN's-LYMPHOMA)

Table 22 summarises the data sets analysed in this study. No patient terminated the study prematurely due to a lack of efficacy. All data are presented for the FA set.

Table 22: XM02-04-INT: Data Sets Analysed

	XM02	Filgrastim/XM02*	Total
Enrolled	63	29	90
Completed	55	21	100
Full analysis set	63	29	92
Per protocol set	55	29	84
* Patients in this group received Filgrastim in cycle 1 and switched to XM02 in the subsequent cycles.			

DSN: The mean DSN in Cycles 1 and 4 was similar in both treatment groups. The majority of patients had a DSN of 0 days. Overall, DSN ranged from 0 to 5 days. The mean DSN was 0.5 and 0.9 days in Cycle 1 and 0.2 and 0.7 days in Cycle 4 (after the switch from Filgrastim to XM02 in the reference group) in the XM02 and Filgrastim/XM02 groups, respectively.

ANC over time: In Cycle 1 in both treatment groups, mean ANC values increased after Day 2, reaching a maximum on Day 4, and then decreased to a nadir on Day 9. Thereafter, mean values increased again, reaching a maximum on Day 11. On Day 21, the mean values approached those observed on Day 1 in both treatment groups. The ANC profile was similar in subsequent cycles.

Depth of ANC nadir: In Cycle 1, the mean ANC nadir in the XM02 group (1.7 x 10^9/L) was higher than in the Filgrastim/XM02 group (1.1 x 10^9/L, p=0.1531). A similar difference (2.1 versus 1.8 x 10^9/L) between the treatment groups was observed in Cycle 4, after the switch from Filgrastim to XM02 in the reference group.

Times to ANC recovery: In Cycle 1, the mean time to ANC recovery was similar in the XM02 group (6.0 days) and the Filgrastim/XM02 group (6.7 days, p=0.4939). Similar data were observed in Cycle 4 (4.9 and 6.1 days) after the switch from Filgrastim to XM02 in the reference group.

Incidence of FN: Across all cycles, there were no incidences of observed FN in either the XM02 or the Filgrastim/XM02 treatment groups. In Cycle 1, the incidences of protocol defined FN were 11.1% for XM02 and 20.7% for Filgrastim (p=0.1232). Across all cycles, incidences of protocol defined FN in the XM02 group and Filgrastim/XM02 group, respectively, were 31.7% and 41.4%, respectively (p=0.2094).

Mortality: In the period until Day 127, one patient (Filgrastim/XM02 group) died due to disease progression one month after the last study drug administration in Cycle 2.

Evaluator Comment

In Study XM02-04-INT, XM02 and Filgrastim were shown to have similar effects with regard to DSN, the incidence of FN, ANC nadir and the time to ANC recovery in Cycle 1 during CTX in patients with NHL.

Results in Subpopulations

In the three efficacy studies, there was no evaluation of a population of special interest. Efficacy variables stratified by age, gender, or race were not examined. However, the effect intrinsic and extrinsic factors on the efficacy variables were examined:

- Disease severity

  adjuvant versus metastatic therapy (breast cancer study)

  SCLC versus NSCLC (lung cancer study)

- Previous CTX

  CTX versus CTX-naïve (lung cancer study)

- Concomitant therapy

  rituximab yes or no (NHL study).

The analyses showed that XM02 and Filgrastim had similar effects on the efficacy variables across these subpopulations.

A meta-analysis of the three studies examined the influence of the myelotoxic potency of the different CTX regimens on the incidence of FN in Cycle 1. Three categories of myelotoxic potency (high, medium and low) were identified. The three categories were similar with regard to incidence of FN in Cycle 1 and there were no statistically significant differences between XM02 and Filgrastim.

Analysis of Clinical Information Relevant to Dosing Recommendations

The recommended dose of Filgrastim after conventional cytotoxic CTX is 5 µg/kg body weight per day, administered as single daily SC injections or IV infusions. Treatment should start not earlier than 24 hours after completion of CTX. It is applied until the number of neutrophil granulocytes has reached normal values after having passed the nadir (minimum of neutrophil granulocytes). This same dosing regimen (using SC application) was applied in the three clinical studies using XM02 and proved to be as effective as Filgrastim, supporting the current dosing recommendations.

Evaluator Comments

The pivotal Phase III study in patients with breast cancer and the supportive Phase III studies in patients with lung cancer and NHL demonstrated the equivalence of XM02 and Neupogen™ in terms of their effects on DSN, incidence of FN and measures of ANC change over time. These efficacy data support the approval of XM02 in the proposed indications.

The clinical trials conducted have also demonstrated bioequivalence of XM02 and Neupogen™ in all respects investigated in the clinical development programme and it is considered that the current Australian submission provides adequate support for the approval of XM02 for the proposed indications, under the same labelling as Neupogen™.

Safety

Extent of Exposure

Cancer Patients

In the three submitted studies, 677 patients received at least one dose of study drug. Overall, 535 (78.7%) patients received study drug in all planned cycles. More patients in the Filgrastim only and placebo/XM02 groups received study drug in all cycles compared to the other groups. The majority of patients were from Study XM02-02-INT (n=348). Studies XM02-03-INT and XM02-04-INT contributed 237 and 92 patients, respectively. 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.

All patients were to be exposed for 5-14 days in each cycle for up to 4 or 6 cycles. Overall, median duration of exposure to study drug for a patient was 40 days (1 to 84 days). The median duration of exposure was longer in the Filgrastim/XM02 group (49 days) compared to the other groups since this group included patients of the two studies with 6 CTX-cycles (lung cancer and NHL). In each cycle, patients were exposed to approximately 9 to 11 days of study drug. This was consistent across studies and cycles.

All patients received XM02 or Filgrastim at a dose of 5 µg/kg/day. In the three studies, the mean ±standard deviation (SD) total dose of XM02 was 11526.2 ± 8475.5 µg. Mean ±SD exposure to Filgrastim was 3200.6±5309.9 µg. For a patient who received XM02 only or Filgrastim only, the mean ±SD exposure was 15599.6 ± 6958.0 µg or 12736.8 ± 3843.6 µg, respectively. Within each

cycle, mean doses were approximately 3200 to 3600 µg. No patients were exposed to Filgrastim alone in Cycles 5 or 6. The differences between the treatment groups in drug exposure were due to the differences in the number of cycles and the duration of treatment within the cycles.

Healthy Subjects

Overall, 200 healthy subjects were randomised in the two Phase I studies and 196 (56 in Study XM02-01-LT and 140 in Study XM02-05-DE) received at least one dose of study drug and constituted the safety population. Overall, 19 subjects did not complete the study. The majority of these were due to entry violations or withdrawn consent. Two subjects discontinued due to adverse events (AEs). The subjects were planned to receive two single doses (interrupted by a washout period) of study drug (5 or 10µg/kg SC or IV). The mean overall exposure was 1054.8 µg and 1018.6 µg in Study XM02-01-LT and XM02-05-DE, respectively. The subjects were exposed to a similar amount of XM02 and Filgrastim

Adverse Events

Overall, the safety profiles of XM02 and Neupogen were equivalent. In the pooled analysis of the Phase III studies in Cycle 1, 80.2% of patients overall experienced a treatment-emergent adverse event (TEAE) (see Table 23). Generally, most TEAEs were sequelae of the underlying malignancy or CTX and only 16.7% of patients overall had drug-related TEAEs. Although the incidence of TEAEs overall and drug-related TEAEs was higher in the Neupogen only group than in the XM02 only group this is unlikely to be clinically significant since the incidences were not higher in the Neupogen/XM02 group (patients who switched to XM02 after Cycle 1). In addition there were also no clinically relevant differences between XM02 and Neupogen in the overall incidences of deaths, serious TEAEs, severe TEAEs or discontinuations due to TEAEs in Cycle 1. It should be noted that the incidences of deaths and discontinuations due to TEAEs were higher in Study XM02-03-INT, probably due to the poor clinical condition of these lung cancer patients.

Table 23: Overview of Adverse Events (Cycle 1) - Cancer Patients Set

	XM02 only (N=356)	Neupogen™ only (N=134)	Neupogen™ /XM02 (N=115)	Placebo/ XM02 (N=72)	Any XM02 (N=541)	Overall (N=677)	
Percentage of patients with TEAEs							
	%	%	%	%	%	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	3.1	3.0	0.0	0.0	2.0	15	2.2
Died due to TEAE	2.0	1.5	0.0	2.8	1.3	11	1.6

Abbreviations: TEAE = treatment emergent adverse event; CTX = chemotherapy, n = number of patients

\# $p<0.05$ (Fishers exact test comparing the first 3 groups).

In the pooled analysis, 93.5% of patients overall experienced at least one TEAE and 27.3% experienced a drug-related TEAE. Across the three Phase III studies in Cycle 1, the most commonly reported TEAEs were nausea, alopecia, neutropaenia, diarrhoea, asthenia and vomiting (see Table 24). A similar profile was seen for all cycles. These correlate well with the most commonly reported events in patients receiving CTX in the Neupogen labelling (nausea and vomiting, alopecia, diarrhoea, fatigue, anorexia, mucositis, headache, cough, skin rash, chest pain, generalised weakness, sore throat, constipation and unspecified pain). There were statistically significant differences between the XM02 and Neupogen groups in the incidences of several TEAEs (in Cycle 1: alopecia, neutropaenia, diarrhoea, asthenia, bone pain, abdominal pain), all of which demonstrated

a higher incidence in the Neupogen only group than in the XM02 only group. However, these differences are unlikely to be of clinical relevance since the incidences in Cycle 1 and across all cycles were not higher in the Neupogen/XM02 group (patients who switched to XM02 after Cycle 1) compared to the XM02 only group.

Table 24: Treatment Emergent Adverse Events (≥5% of Patients in Any Group) (Cycle 1). Cancer Patients Set

Preferred Term	XM02 only (N=356)	Filgrastim only (N=134)	Filgrastim 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
LEUKOPENIA	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
DYSPEPSIA	1.4	1.5	0.9	5.6	1.7	12	1.8
PHARYNGOLARYNGEAL 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

Table shows percentage and number (n) of patients with treatment emergent adverse events
# p<0.05 Fisher's exact test comparing first 3 groups

The incidences of neutropaenia and FN were higher in the placebo group than in the XM02 or Neupogen groups, as were the incidences of pharyngolaryngeal pain and pharyngitis (which are sequelae of neutropaenia). The incidence of injection site reactions was low in all three studies (1.5% of patients overall across all cycles).

Most TEAEs were the consequence of concomitant CTX. When only drug-related TEAEs are considered, the most commonly reported drug-related TEAEs across all three studies in Cycle 1 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 from the known pharmacological profile of G-CSF. A similar profile was seen for all cycles. The drug-related TEAEs observed in the three studies correlate with those described in the Neupogen Product Information, where most frequent undesirable effects attributable to Neupogen at the recommended dose were mild or moderate musculoskeletal pain (in 10% of patients) and severe musculoskeletal pain (in 3% of patients).

Severe and Serious Adverse Events

The equivalence of XM02 and Neupogen was also supported by the incidences and types of severe and serious TEAEs. Only five patients had serious TEAEs that were considered drug-related across all three studies: these were an allergic reaction (bronchospasm) in Cycle 1 (XM02 group) and syncope in Cycle 3 (placebo/XM02 group) in the breast cancer study and myocardial infarction in Cycle 2 (Neupogen/XM02 group), thrombocytopenia in Cycle 5 (Neupogen/XM02 group), 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 CTX-related.

No deaths in any of the three studies were considered drug-related (all were the result of the underlying condition or the CTX).

Laboratory Variables

Analysis of laboratory safety variables revealed no distinct changes in the three Phase III studies. Although there were decreases in mean haemoglobin, haematocrit, eosinophils and lymphocytes levels and a proportion of patients experienced reversible Common Terminology Criteria[8] for Adverse Events (CTCAE) toxicity of Grade ≥3 for alkaline phosphatase, uric acid and leukocytes, there were no clinically relevant treatment group differences. This further supported the equivalence of XM02 and Neupogen.

Safety in Healthy Subjects

Pooled safety data analyses of the two Phase I studies showed a similar safety profile of XM02 and Neupogen. Most common TEAEs were headache (36.7% overall, 33.7% drug-related), myalgia (19.9% overall, 19.4% drug-related) and back pain (17.3% overall, 16.8% drug-related). Other drug-related TEAEs were bone pain (2.7%), nausea (2.4%) and fatigue (2.1%). Number and percentage of periods with these drug-related TEAEs were similar between the treatment groups with exception of myalgia (14.7% versus. 7.7% in the XM02 and Neupogen groups, respectively). There were no incidences of splenomegaly, deterioration of adult respiratory distress syndrome (ARDS) or anaemia in the two Phase I studies. The median haemoglobin values slightly decreased between screening and follow-up.

Specific Safety Issues

Specific pharmacological class effects of G-CSF include spleen enlargement/rupture, ARDS and bone pain. Allergic reactions (sometimes severe) are also observed as a result of the biological nature of the product. These issues are discussed below. In addition, anaemia is also discussed due to the relatively high incidence seen in the lung cancer study.

Bone Pain

Bone pain is presumed to result from bone marrow expansion during increased haematopoiesis under G-CSF therapy. In the Neupogen PI, medullary bone pain was reported in 24% of patients receiving CTX and was most often associated with IV administration and with higher doses (20-100 µg/kg/day). In the pooled analysis of the Phase III studies, bone pain was experienced by 13.7% of patients overall in Cycle 1 (drug-related in 6.9%). Across all cycles, the incidence of bone pain was 24.8% (drug-related in 11.7%). The analysis of localisation of bone pain by preferred term in Cycle 1 showed incidences of bone pain (overall incidence of 5.6%), back pain (3.1%), arthralgia (2.2%), musculoskeletal pain (2.1%), pain in extremity (0.7%), pelvic pain (0.1%), pain in jaw (0.1%) and sacral pain (0.1%).

Although the incidence of bone pain was higher in the Neupogen only group than in the XM02 only group, it was not higher in the Neupogen/XM02 group which indicates a lack of clinical relevance.

[8] Common Terminology Criteria (CTC) is a standardised classification of side effects used in assessing drugs for cancer therapy, in particular. Specific conditions and symptoms may have values or descriptive comment for each level, but the general guideline is 1 – Mild, 2 – Moderate, 3 – Severe, 4 - Life threatening, 5 - Death.

There were very few instances of bone pain that were considered severe. Overall, the incidence and severity of bone pain was consistent with those reported in the Neupogen PI.

Spleen Enlargement/Rupture

Rare cases of splenic rupture (sometimes fatal) have been reported following administration of Neupogen. In the three Phase III studies, symptomatic splenomegaly did not occur in any of the 677 patients studied, indicating an incidence in these studies of <0.15%. This does not account for asymptomatic splenic enlargement.

Patients who report left upper abdominal and/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Deterioration of Acute Respiratory Distress Syndrome

ARDS is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Lung cancer patients represent a specific population at risk of worsening of ARDS under treatment with G-CSF. ARDS has been reported in neutropaenic patients with sepsis receiving Neupogen. Rare pulmonary adverse effects including interstitial pneumonia, pulmonary oedema and pulmonary infiltrates have been reported in some cases with an outcome of respiratory failure or ARDS which may be fatal. In the three Phase III studies, three (0.4%) patients (1 in Cycle 1), reported symptoms which could have potentially represented cases of ARDS. All cases were in Study XM02-03-INT, that is, in patients with lung cancer. No pulmonary infiltrations were reported for these cases. There was no temporal relationship to study medication administration that would indicate a causal relationship to study drug. None of these cases were reported as study drug related.

Allergic Reactions

Well recognised class related side effects of protein products include hypersensitivity reactions and other allergic type reactions. Allergic reactions have been reported in <1 in 4000 patients treated with Neupogen, tending to occur within 30 minutes of administration and requiring supportive measures. Allergic-type reactions, including anaphylaxis, skin rash, urticaria, angioedema, dyspnoea and hypotension occurring on initial or subsequent treatment have been reported.

In the pooled analysis of XM02 in the Phase III studies, “potential allergic reactions” (including angioneurotic oedema, dermatitis allergic, drug hypersensitivity, hypersensitivity, rash, pruritic rash and urticaria) occurred in 12 (1.8%) patients overall in Cycle 1 and in 25 (3.7%) patients across all cycles. This incidence of “potential allergic reactions” includes all events which could have been caused by a real allergic reaction but potentially also by other pathophysiological mechanisms. Of the reactions across all cycles, 8 (1.2%) patients had reactions that were considered drug related. Only one allergic reaction was serious; bronchospasm in Cycle 1 requiring temporary interruption of study drug (XM02 group in Study XM02-02-INT). However, the study drug was well tolerated in the same patient in subsequent cycles. The re-challenge, which did not provoke the same bronchospastic reaction, indicates that the cause for the event was probably different from a real allergic reaction. In terms of allergic reactions, there were no differences between treatment groups in either the pooled analyses or in the individual studies.

In the two Phase I studies across the treatment periods, 8 (4.1%) subjects reported allergic reactions at least once. In 7 (3.6%) subjects, allergic reactions were considered study drug related. None of the events were serious. The incidence of allergic reactions was similar between the treatment groups and between the studies.

Anaemia

It was noticed during the Phase III studies that anaemia was reported in a relatively high proportion of patients, in particular in the lung cancer study. In the pooled analysis, anaemia was reported as a TEAE in 5.0% of patients overall in Cycle 1 (0.1% study drug-related) and in 20.4% of patients across all cycles (1.0% study drug-related). The incidence was similar across treatment groups in Cycle 1. However, across all cycles, the incidence was statistically significantly lower in the Neupogen only group (6.7%) compared to the XM02 only group (22.8%) and the Neupogen/XM02 group (33.9%). The generally higher incidence of anaemia TEAEs in the XM02

group compared with the Filgrastim group from Cycle 2 onwards may be due to the platinum component introduced in the lung cancer study (XM02-03-INT).

Platinum-based chemotherapy has a higher potency to induce anaemia than the chemotherapies applied in the breast cancer (XM02-02-INT) and NHL (XM02-04-INT) studies. As there was no reference group in the lung cancer study, a bias in regard to the incidence of anaemia in cycles subsequent to Cycle 1 was introduced into the integrated safety analysis. The incidence of anaemia in the fully controlled breast cancer study was comparable over all four cycles of chemotherapy.

It is notable that the incidence of anaemia was much higher in the lung cancer Study XM02-03-INT (40%) than in the other two Phase III studies (10-11%) and that almost all incidences (25/27 patients) of severe anaemia occurred in this study and during the later cycles (after Cycle 1). It is likely that the platinum-based CTX has contributed to this effect as decrease in haemoglobin levels is a very common adverse effect of this treatment. It should be noted that patients in Study XM02-03-INT were generally in a poor clinical condition. Therefore, the development of anaemia most likely represents sequelae of CTX or general deterioration in the clinical condition of the patients due to their underlying disease rather than an effect of filgrastim treatment.

Immunogenicity

As with all therapeutic proteins there is a potential for immunogenicity. Development of antibodies to XM02 and Neupogen was investigated in the Phase III studies.

Immunogenicity was assessed by a predefined characterisation cascade of antibody assays using XM02 as test antigen (anti-XM02 immunoglobulin G [IgG] Enzyme-Linked Immuno Sorbent Assay [ELISA] and anti-XM02 [IgG-IgM] Luminex assay followed by Western Blot confirmation assays on positive or questionable results, followed by three further assays in parallel for any positive or questionable results from Western blot).

Excluding implausible test results, one (0.1%) patient each tested positive in the assay for neutralising antibodies (NAB) before Cycles 2, 4, 5 and at the end of study visit, respectively. Overall 6 (0.9%) patients tested positive in the NAB assay at follow-up (~6 months after study start); two in the XM02 only group, two in the Neupogen only group and two in the placebo/XM02 group (under treatment with XM02 from Cycle 2 onwards). No clinical signs indicating neutralising properties of antibodies were observed.

Following redetermination of the cut off of the NAB by using pre-dose (screening and baseline) cancer patient samples which were randomly selected from all three XM02 Phase III studies, one patient (0.1%) remained with one borderline positive NAB result at the antibody follow up visit (XM02 only group). This finding was found not conclusive, as the observed neutralising activity does not correlate with antibody binding activity.

Overdose, Withdrawal and Rebound

Overdose, withdrawal and rebound effects are not applicable for this submission.

Evaluator Comments

s: The methods used for capturing safety data were appropriate. Overall, safety analyses demonstrated the equivalence of XM02 and Neupogen with respect to their safety profiles. In comparison to the known toxicity profile of Neupogen, no new or major safety issues emerged in the three Phase III trials of Tevagrastim.

Post-Marketing Experience

No post-marketing data have been submitted for evaluation.

Clinical Summary and Conclusions

In this application the sponsor is seeking registration of Tevagrastim (filgrastim) 300 µg/0.5mL, 480 µg/0.8mL injections. In the drug development program for filgrastim the aim was to demonstrate biosimilarity with Neupogen.

The sponsor conducted five clinical studies comparing filgrastim (XM02) with Neupogen (filgrastim). There were two Phase I studies, comparing pharmacodynamic and PK properties of XM02 and filgrastim in healthy volunteers (Study XM02-01-LT and Study XM02-05-DE) and three Phase III studies, which were conducted in patients with breast cancer (Study XM02-02-INT), lung cancer (Study XM02-03-INT), or Non-Hodgkin's Lymphoma (NHL) (Study XM02-04-INT) who received G-CSF prophylaxis in addition to chemotherapy (CTX).

According to the EMA guideline on similar biological medicinal products[4], Neupogen was chosen as reference product, since it is a medicinal product which contains filgrastim as drug substance and is authorised in the European Union.

In Study XM02-01-LT, XM02 was shown to be bioequivalent to the reference formulation Filgrastim (Neupogen) with respect to the ANC time profile. In Study XM-02-05-DE, the pharmacodynamic response (ANC and CD34+) for XM02 was equivalent for AUC_{0-t} and C_{max} to Filgrastim (Neupogen Amgen) at doses of 5 µg/kg or 10 µg/kg after IV single dose infusion or SC single dose injection.

The studies submitted for evaluation supported that there were no statistically significant differences between XM02 and Filgrastim (Neupogen Amgen) with regard to the PK profile and relative bioavailability of the two drugs.

The pivotal Phase III study in patients with breast cancer and the supportive Phase III studies in patients with lung cancer and NHL demonstrated the equivalence of XM02 and Neupogen in terms of their effects on DSN, incidence of FN and measures of ANC change over time. These efficacy data support the approval of XM02 in the indications proposed.

Safety analyses demonstrated the equivalence of XM02 and Neupogen with respect to their safety profiles. In comparison to the known toxicity profile of Neupogen, no new or major safety issues emerged in the three Phase III trials of XM02.

Overall, the clinical trials conducted have demonstrated bioequivalence and similar efficacy and safety between XM02 and Neupogen in all respects investigated in the clinical development program. It is considered that the Australian submission provides adequate support for the approval of XM02 for the proposed indications under the same labelling as Neupogen.

Recommendation: At present and on the basis of the data evaluated, it is recommended that the application for registration of filgrastim (Tevagrastim) ***should be approved.***

V. Pharmacovigilance Findings

Risk Management Plan

Aspen Pharmacare Australia Pty Ltd submitted a Risk Management Plan (RMP) dated 19 February 2008, which was reviewed by the TGA's Office of Medicines Safety Monitoring (OMSM). It was considered to be well presented and clearly indicated attention to the relevant EMA guidelines. The reference medication to demonstrate comparability is Neupogen.

The following risks were addressed:

- Identified risk: Allergic type reactions.
  Adult Respiratory Distress Syndrome (ARDS).
  Interstitial pneumonia.

		Pulmonary oedema.
		Pulmonary infiltrates.
		Respiratory failure.
		Sweet's syndrome.
		Sickle cell crisis in patients with sickle cell disease.
		Exacerbation of rheumatoid arthritis.
		Cutaneous vasculitis.
		Splenic rupture.
		Splenomegaly.
		Increased risk of graft versus host disease (GVHD).
		Osteoporosis.
		Identified risk.
		Transformation to leukaemia or myelodysplastic syndrome (MDS).
		Myalgia.
·	Potential risk:	Immunogenicity. Haematological malignancy.
		Off label use.

With the exception of myalgia (identified risk) and haematological malignancy (potential risk), these are derived from the Summary of Medicine Product Characteristics (SmPC) for Neupogen. It is noted that there is no important missing information.

Data is presented on toxicity (including immunogenicity) studies and, from Phase I and II trials undertaken in healthy subjects and patients with cancer. Information provided on the non clinical safety concerns, limitations of the human database and additional EU requirements is satisfactory and in accordance with EMA guidelines.

It is indicated that pregnant and lactating women were excluded from trials as use of Filgrastim in this population is not recommended. No studies were conducted in children and it is considered that, based on the available data from the reference product and the identical mechanism of action of Tevagrastim, its efficacy and safety in paediatric patients can be assumed. A number of patients with renal and hepatic impairment participated in the trials with no impact on the safety of Tevagrastim observed. The Phase III studies included 131 (19.4 %) patients aged 65 years or above with 111 treated with Tevagrastim and no differences in the safety profile detected.

For the identified risks, approaches to assess and prevent Tevagrastim immunogenicity and, concerns regarding the risk of haematological malignancy and splenomegaly in patients with severe chronic neutropaenia (SCN) and haematological malignancy in normal donors are presented.

Comparisons between Tevagrastim and Neupogen for ARDS, splenomegaly, bone pain, alkaline phosphatase and lactate dehydrogenase are presented in pharmacological class effects. These data do not indicate any significant difference between patients treated with either medication.

Detailed information on the assessment of the immunogenic potential of Tevagrastim in animal and human studies is provided. The sponsor states that results on the immunogenic potential for Tevagrastim from all studies did not exceed the expected pattern and denote a higher risk compared to Neupogen.

The sponsor considers that there is no reason to believe that Tevagrastim would be less safe in other tumour types than Neupogen based on the safety profile observed in the Phase III studies. It is stated that:

- The safety profile of Tevagrastim in studies conducted in healthy volunteers and cancer patients is very similar to that Neupogen.
- No special Adverse Events (AEs) have been observed with Tevagrastim treatment to indicate a significant deviation from the expected safety profile.

The validity of this statement cannot be assessed as no data on the total or common AEs observed in the Phase III studies were presented. It is recognised that the EU RMP template does not include the need to provide data on these AEs. However, a recommendation is made for this to be provided given concerns about the safety profile of biosimilars.

Information on the occurrence of leukaemia, myelodysplastic syndrome (MDS) and increased splenomegaly in patients with neutropaenia following filgrastim administration is presented.

References are cited indicating that, in patients with SCN treated with filgrastim, MDS and myeloid leukaemia have become significant complications in about 10 %. However, it is noted that prior to filgrastim, 42 % of all published SCN cases died within the first 2 years of their life from infections, the inference being that the benefit of using filgrastim outweighs this risk.

It is also stated that prior to filgrastim treatment, the incidence of splenomegaly is 21 % in congenital neutropenia patients and, that during filgrastim therapy initiation, spleen size may further increase and may be associated with the occurrence of infections or transformation to MDS or myeloid leukaemia.

The occurrence of haematological malignancy after filgrastim treatment has raised the question of its safety in healthy donors when used for the mobilisation of peripheral blood stem cells to be harvested for allogeneic transplantation. It is noted that the long-term safety of filgrastim use for stem cell mobilisation in related and unrelated donors is under close review due to concerns about the potential for promotion of a malignant myeloid clone. It is considered that currently, there is insufficient evidence to suggest that normal donors given filgrastim have an increased risk of haematological malignancies.

Monitoring of this risk is attended to in the proposed Tevagrastim Product Information (PI). This is addressed in evaluation of the PI and a recommendation is made to strengthen this process.

It is stated that, due to the sensitivity of rapidly dividing myeloid cells to chemotherapy (CTX), the use of Neupogen is not recommended from 24 hours before to 24 hours after its administration as the severity of neutropaenia may be exacerbated. Preliminary evidence from a small number of patients treated concomitantly with Neupogen and 5-Fluorouracil confirming this effect is cited. It is noted that lithium promotes the release of neutrophils and is likely to potentiate the effect of Neupogen. It is indicated that, although this interaction has not been formally investigated, there is no evidence that such an interaction is harmful.

For each of the safety concerns, the sponsor proposes routine PhV activities. It is concluded there is no need for additional risk minimisation activities for the identified and potential risks as these are adequately addressed in the proposed Australian Tevagrastim PI.

Detailed information for the monitoring of immunogenicity and haematological malignancy through ascertainment and follow-up of AE reports where these are suspected and through signal detection, were presented.

Of note, the sponsor does not propose to conduct a post-marketing study on immunogenicity in patients treated with Tevagrastim. However, it is acknowledged that such effects cannot be prevented or fully excluded. Thus, the sponsor proposes establishment of system to investigate Tevagrastim immunogenicity within the framework of routine PhV. This is to include signal detection, obtaining standardised patient documentation and undertaking antibody testing.

The sponsor also indicates that they plan to work cooperatively with the SCN International Registry (SCNIR) to obtain data on immunogenicity for integration into the Periodic Safety Update Report. It would appear that SCNIR cooperation has been confirmed but there is no information on how this will proceed.

It was concluded that this approach to antibody detection, testing and evaluation was appropriate to prevent the patients treated with Tevagrastim from harm.

There are concerns with this approach. Pharmacovigilance (PhV) will only provide retrospective unsolicited reports that cannot be related to total Tevagrastim use. Also, the numbers of patients with SCN are small and the majority of filgrastim users are patients who have cancer.

Taking this and the EMEA guidelines into account, it is considered that post-marketing immunogenicity studies are required to enable collection and analysis of robust data.

Also, there are concerns with the proposed approach to monitoring the risk of haematological malignancy in normal donors. Routine PhV[9] and 10 years follow up by clinicians in apheresis centres are recommended. These do not engender a standardised approach to follow up, or, enable quantification of the risk and outcome of the development of cytogenetic abnormalities, or, the risk of developing a malignancy. A recommendation is made for the sponsor and clinicians to collaboratively monitor this risk through a patient registry.

The proposed Australian Tevagrastim PI was compared with the current Australian Neupogen PI (November 2008), the EU Tevagrastim SmPC (February 2010) and, the US Neupogen Label (October 2006). This review revealed some inconsistencies and recommendations have been made to ensure consistency with the EU SmPC.

Of note, even though US Neupogen Label includes a section on immunogenicity, it was considered that reference to development of antibodies in the proposed Australian Tevagrastim PI was sufficient at this stage.

The recommendations made by the OMSM evaluator, sponsor's responses and OMSM evaluator's commentary on the sponsor's responses are given below.

1. Comparative data on total and common Adverse Events (AEs) for Tevagrastim and Neupogen® from the Phase III trials should be provided.

- The sponsor indicates that these data are presented in the European Public Assessment Report.
- These were reviewed and it was considered that there are no major differences in the AEs of Tevagrastim and its comparator, Neupogen.

2. A post-marketing study sufficiently powered to detect an immunogenic safety concern should be undertaken.

- The sponsor reiterated that they are proposing to undertake immunogenicity tests whenever an AE related to lack of efficacy or an allergic reaction is reported and notes that tests done to date in the European Union have not demonstrated any concerns. They indicated that the

[9] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

clinical relevance of immunogenicity and its incidence are unclear as there were no studies done with the comparator.

- It wa considered that the lack of studies the incidence and clinical relevance of, and the concerns around, potential immunogenicity emphasise and reinforce the need for a post-marketing study sufficiently powered to detect an immunogenic safety concern.

3. Information about any ongoing trials or post marketing studies that are being undertaken should be provided.

- The sponsor has forwarded a Periodic Safety Update Report (PSUR) covering April – September 2009. This indicated that no nonclinical, clinical or epidemiological studies were finalised or analysed during this time frame. There is reference to a study being done in Germany in around 2,000 patients with chemotherapy induced neutropaenia to ascertain the duration of afebrile and febrile neutropaenia, prescribing habits, tolerability and AEs. Three published studies were also described. It was indicated that there is no new evidence that would warrant a change to the reference safety information and, for some, that the issue is covered in the RMP. The studies comprise:
    - A review on the benefit of filgrastim use in allogeneic hematopoietic stem cell transplantation and concerns around its impact on immune reconstitution and the risk of leukaemic transformation in patients with chromosome 7 abnormalities;
    - AEs among 2,408 unrelated donors of peripheral blood stem cell from results of a prospective trial from a national marrow donor program; and
    - Bioequivalence of 2 recombinant granulocyte colony-stimulating factors (G-CSF) products after subcutaneous use in healthy volunteers.
- This response was considered satisfactory.

4. Information on the status of arrangements with the Severe Chronic Neutropaenia International Registry (SCNIR) should be provided and include the agreed or proposed specifications for the frequency and type of data to be exchanged.

5. Data already obtained from the SCNIR, if available, should be provided as an addendum to this RMP.

- The arrangements and data exchange between the sponsor and SCNIR have not been finalised. It was indicated that this information will be provided to the TGA when available.
- This response was considered satisfactory.

6. Information on the activities to be undertaken by the sponsor to focus on the risk of haematological malignancy should be provided.

- It was indicated that haematological malignancies are a serious AE which will be followed up and reported according to relevant timelines.
- It was considered that this is a description of usual practice and does not answer the question of what constitutes a “focus” on this risk.

7. The sponsor should collaborate with clinicians in apheresis centres using Tevagrastim in normal donors to monitor the risk of haematological malignancy. This should include, but not be limited to:

- Establishing and maintaining a register of normal donors who receive Tevagrastim.
- Establishing a protocol specifying the type and frequency of follow up.
- Detailing the management of patient information including frequency and method of reporting to the sponsor, and publication in the literature, and,
- Consideration of sponsor funding for this follow up.
- The sponsor states that this is a class effect for G-CSF and not related to Tevagrastim

only. It is indicated that monitoring should apply to normal donors treated with all G-CSF products.

- It was considered that the sponsor comment about having a consistent approach across all G-CSF products was reasonable and this clearly would be optimal. The difficulties with implementing this given the longevity of Neupogen marketing are acknowledged. Also, it would appear that there is little scientific basis for an increased risk of this with biosimilars. Notwithstanding this, it was considered that sponsor should develop a recommended protocol specifying the type and frequency of follow up and that this should be included in the Product Information (PI).

8. It is considered that the Australian Tevagrastim PI should:

- Refer to the use of filgrastim in patients who are elderly or have hepatic or renal impairment.
- Indicate the likelihood that lithium may potentiate the action of filgrastim.
- Specify that use of Tevagrastim is contraindicated in patients with severe congenital neutropenia (Kostman's syndrome) with abnormal cytogenetics.
- Be modified to reflect changes in the monitoring of normal donors.
- The sponsor notes that these are addressed in various sections of the PI.
- This response was considered satisfactory.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The product was considered at the July 2010 meeting of the PSC. There were no objections raised to registration on chemistry, quality control and manufacturing grounds.

Bioavailability/Bioequivalence

The submission included two bioequivalence studies comparing Tevagrastim to Neupogen (Studies XM02-01-LT and XM02-05-DE). Tevagrastim was found to be bioequivalent to Neupogen according to conventional PK parameters (AUC and C_{max}), using either the 5 or 10 mcg/kg dose and via IV or SC administration.

At its July 2010 meeting the PSC raised two issues regarding these bioequivalence studies:

- detailed information on the bioanalytical method used for the study samples was absent;
- it was not clear that the Neupogen product used in the studies was identical to the Neupogen product marketed in Australia.

The PSC was unable to recommend approval until these issues were resolved.

The application was considered again by the PSC at its July 2011meeting where the Committee agreed that the issues of concern in relation to the bioavailability data raised at its previous meeting have not been addressed. In particular, bioanalytical aspects of filgrastim serum assays were incomplete or suboptimal, making it difficult to draw appropriate conclusions from the submitted bioequivalence studies. The PSC noted that the application included pharmacodynamic comparisons and is also supported by clinical studies. The Committee therefore concluded that any approval should be based on the pharmacodynamic endpoints.

Nonclinical

There are no nonclinical objections to registration. The submission included several *in vitro* and *in vivo* pharmacodynamic studies which compared Tevagrastim with Neupogen. The pharmacodynamic properties of the two products were not significantly different. Repeat dose toxicity studies were conducted in rats and monkeys. Toxicities observed were consistent with the

known pharmacology of filgrastim (such as neutrophilia). A local tolerance study in rabbits demonstrated comparable effects with Tevagrastim and Neupogen.

Clinical

The clinical evaluator has recommended approval of the application. In the evaluation report Tevagrastim is referred to as'XM02'.

Pharmacodynamics (PD)

The submission included two studies conducted in healthy volunteers comparing the effects of single doses of Tevagrastim and Neupogen on absolute neutrophil count (ANC). Equivalence was concluded if the 90% confidence intervals for the ratio of Tevagrastim to Neupogen for the area under the ANC versus time curve (AUC) and maximum ANC fell entirely within the interval of 80 to 125 %.

Study **XM02-01** compared the effect of single subcutaneous doses of the two products on ANC. Two dose levels were studied (5 and 10 µg/kg). For the AUC and maximum ANC, the two products were found to be equivalent at both dose levels. With respect to the time of maximum ANC, the two products were equivalent at the 5 µg/kg dose, but not at the 10 µg/kg dose.

Study **XM02-05** compared the effect of single doses of the two products on ANC and CD34+ve cell counts. Two dose levels were studied (5 and 10 µg/kg) via two routes of administration (IV and SC). For the AUC and maximum count, the two products were found to be equivalent for both ANC and CD34+ve count, at both dose levels and via both routes of administration (see Tables 25 and 26).

Study XM02-05-DE: Absolute Neutrophil count (ANC) – C_{max} and AUC analyses

Table 25. ANOVA and 90% CI for (log transformed) pharmacodynamic parameter of ANC.

Pharmacodynamic parameter ANC	ANOVA CV [%]	Point estimate Test/Ref. ratio	90% Confidence interval
Subgroup 1 (i.v. 5 µg/kg)			
$AUC_{(0-t)}$	24.83	97.25	87.47 - 108.13
C_{max}	12.40	98.21	93.08 - 103.61
Subgroup 2 (i.v. 10 µg/kg)			
$AUC_{(0-t)}$	44.55	96.56	80.07 - 116.45
C_{max}	15.74	98.97	92.39 - 106.03
Subgroup 3 (s.c. 5 µg/kg)			
$AUC_{(0-t)}$	24.47	97.58	88.23 - 107.92
C_{max}	10.70	107.27	102.60 - 112.16
Subgroup 4 (s.c. 10 µg/kg)			
$AUC_{(0-t)}$	32.58	104.88	91.22 - 120.58
C_{max}	8.70	99.84	96.10 - 103.72

Study XM02-05-DE: CD34+ve cell count. C_{max} and AUC analyses

Table 26. ANOVA and 90% CI for (log transformed) pharmacodynamic parameter of ANC.

Pharmacodynamic parameter CD34+	ANOVA CV [%]	Point estimate Test/Ref. ratio	90% Confidence interval
Subgroup 1 (i.v. 5 µg/kg)			
$AUC_{(0-t)}$	17.37	93.77	87.02 - 101.05
C_{max}	26.04	96.78	86.61 - 108.15
Subgroup 2 (i.v. 10 µg/kg)			
$AUC_{(0-t)}$	13.84	107.71	101.37 - 114.44
C_{max}	21.67	107.09	97.46 - 117.68
Subgroup 3 (s.c. 5 µg/kg)			
$AUC_{(0-t)}$	19.09	100.96	93.29 - 109.26
C_{max}	27.11	95.67	85.60 - 106.92
Subgroup 4 (s.c. 10 µg/kg)			
$AUC_{(0-t)}$	14.04	90.16	84.79 - 95.87
C_{max}	25.58	92.05	82.42 - 102.81

Pharmacokinetics (PK)

The clinical evaluator has reviewed the PK bioequivalence data from Studies XM02-01 and XM02-05. As indicated above, these studies were reconsidered by the PSC at its July 2011 meeting.

The submission also included PK data from three efficacy and safety studies.

- Study **XM02-02** compared Tevagrastim with Neupogen in subjects receiving chemotherapy for breast cancer. AUC and Cmax were determined for a subset of 37 subjects in the trial. The PK of the two products were comparable.
- Study **XM02-03** compared Tevagrastim with Neupogen in subjects receiving chemotherapy for lung cancer. AUC and Cmax were determined for a subset of 25 subjects in the trial. The PK of the two products were again comparable.
- Study **XM02-04** compared Tevagrastim with Neupogen in subjects receiving chemotherapy for Non-Hodgkin's lymphoma (NHL). AUC and Cmax were determined for a subset of 15 subjects in the trial. The PK of the two products were again comparable.

Efficacy

Evidence for efficacy comes primarily from one pivotal randomised controlled trial (Study **XM02-02**). The study compared the efficacy of Tevagrastim with that of Neupogen in the setting of prevention of severe neutropaenia in patients receiving chemotherapy for breast cancer, either as adjuvant therapy or for the treatment metastatic disease.

All subjects received the same chemotherapy regimen – doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2 on Day 1 of a 21-day cycle, for a total of 4 cycles.

A total of 348 subjects were randomised (2:2:1) to receive Tevagrastim, Neupogen or placebo for the first cycle of chemotherapy. The Neupogen was sourced from Germany. Subjects randomised to the active treatment groups received 5 µg/kg/day subcutaneously, commencing on Day 2 of chemotherapy and continued for a minimum of 5 days and a maximum of 14 days or until ANC > 10.0 x 10^9 was reached. This regimen is consistent with the currently approved regimen for Neupogen. Patients randomised to placebo in the first cycle were treated with Tevagrastim in subsequent cycles.

The primary endpoint was the duration of severe neutropaenia (that is, ANC < 0.5 x 10^9). The study was designed as an equivalence trial, with equivalence concluded if the 95% CI for the difference between Tevagrastim and Neupogen in duration of severe neutropaenia (DSN) after the first cycle of chemotherapy lay entirely within the interval of -1.0 to +1.0 days.

Results are summarised in the following table (Table 27). Tevagrastim was demonstrated to be superior to placebo. Equivalence with Neupogen was concluded as the 95% CI for the difference in DSN lay entirely within the pre-specified interval of -1.0 to +1.0 days.

Table 27. DSN results.

	Tevagrastim	**Placebo**
DSN in days (least square means)*	1.141	3.823
Difference (95% CI)	-2.682 (-3.214 to -2.151)	
p value	< 0.0001	

*full analysis population

	Tevagrastim	**Neupogen**
DSN in days (least square means)*	1.119	1.087
Difference (95% CI)	0.032 **(-0.262 to +0.325)**	
p value	0.8305	

*per protocol population

Several secondary endpoints were also assessed, including:

- DSN in Cycles 2, 3 and 4;
- ANC over time;
- depth of ANC nadir;
- time to ANC recovery;
- incidence of febrile neutropaenia.

These endpoints supported superior efficacy of Tevagrastim over placebo in Cycle 1 and comparable efficacy to Neupogen in Cycles 1 to 4.

Two supportive studies were included in the submission.

- Study **XM02-03** compared Tevagrastim with Neupogen in subjects receiving chemotherapy for lung cancer.
- Study **XM02-04** compared Tevagrastim with Neupogen in subjects receiving chemotherapy for NHL.

In these studies, assessment of efficacy was a secondary objective and formal equivalence testing was not conducted. Results for DSN in Cycle 1 are shown in Table 28 below.

Table 28. Results for DSN in Cycle 1.

	DSN in days (LS means)		
Study	**Tevagrastim**	**Neupogen**	Difference (95% CI)
XM02-03	0.507	0.325	0.182 (-0.104 to +0.467)
XM02-04	0.569	0.782	- 0.213 (-0.685 to + 0.259

These results suggest comparable efficacy of the two products. Secondary endpoints also suggested comparable efficacy.

Safety

A total of approximately 540 oncology patients received at least one dose of Tevagrastim in the three efficacy studies. In these studies the planned treatment duration was 5 – 14 days per chemotherapy cycle for up to 6 cycles. The median number of total days of Tevagrastim exposure was 41 days.

The pivotal Study XM02-02 provides a direct comparison of the safety profiles of Tevagrastim versus Neupogen in a population of patients receiving the same chemotherapy regimen over 4 cycles. An overview of adverse events and a tabulation of individual adverse events seen in this trial are shown in Tables 29-30 below. The adverse event profiles of Tevagrastim and Neupogen appeared broadly comparable.

The other two efficacy studies (XM02-03 and XM02-04) compared Tevagrastim and Neupogen in the first cycle only (all patients were treated with Tevagrastim in subsequent cycles). The comparison of adverse events in the first cycle for these two studies is shown in Tables 31-34 below. The adverse event profiles appeared broadly comparable.

A total of 200 healthy volunteers were treated with Tevagrastim and Neupogen in the PK/PD studies. Adverse events were similar with the two treatments.

Study XM-02. Breast cancer

Table 29. Table X. Overview of AEs (Cycle 1). Safety set.

	XM02 (N=140)			Filgrastim (N=136)			Placebo/XM02 (N=72)			Overall (N=348)		
	N	%	E	N	%	E	N	%	E	N	%	E
All TEAEs												
At least one TEAE	129	92.1	1249	128	94.1	1233	72	100.0	786	329	94.5	3268
At least one severe TEAE	38	27.1	63	30	22.1	49	36	50.0	65	104	29.9	177
At least one serious TEAE	17	12.1	25	14	10.3	25	18	25.0	22	49	14.1	72
Discontinued drug due to TEAE	2	1.4	4	3	2.2	4	2	2.8	2	7	2.0	10
Discontinued study due to TEAE	2	1.4		3	2.2		4	5.6		9	2.6	
Deaths	2	1.4	2	0	0.0	0	2	2.8	2	4	1.1	4
Possibly study drug related TEAEs												
At least one TEAE (*)	36	25.7	97	54	39.7	137	22	30.6	60	112	32.2	294
At least one severe TEAE	2	1.4	2	3	2.2	3	1	1.4	1	6	1.7	6
At least one serious TEAE	1	0.7	1	0	0.0	0	1	1.4	1	2	0.6	2
Discontinued drug due to TEAE	0	0.0	0	1	0.7	1	1	1.4	1	2	0.6	2
Discontinued study due to TEAE	0	0.0		1	0.7		2	2.8		3	0.9	
Deaths	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Possibly CTX related TEAEs												
At least one TEAE	122	87.1	966	123	90.4	985	72	100.0	630	317	91.1	2581
At least one severe TEAE	30	21.4	49	25	18.4	41	35	48.6	61	90	25.9	151
At least one serious TEAE	15	10.7	20	10	7.4	19	16	22.2	20	41	11.8	59
Discontinued drug due to TEAE	0	0.0	0	2	1.5	3	1	1.4	1	3	0.9	4
Discontinued study due to TEAE	1	0.7		3	2.2		4	5.6		8	2.3	
Deaths	0	0.0	0	0	0.0	0	1	1.4	1	1	0.3	1

CTX = chemotherapy, TEAE = treatment emergent adverse event
N = number of patients exposed to study drug or number of patients affected by TEAEs
% = 100 * (N affected / N exposed)
E = number of events for the N patients. Adverse events were coded using MedDRA 7.1.
(*) p<0.05,XM02 vs. Filgrastim group
Placebo/XM02: patients of this group were randomised to placebo in cycle 1 and switched to XM02 afterwards

Study XM-02. Breast cancer.

Table 30. Frequently reported TEAEs by Preferred Term (All cycles). Safety set.

Preferred Term	XM02 (N=140)			Filgrastim N=136)			Placebo/XM02 (N=72)			Overall (N=348)		
	N	%	E	N	%	E	N	%	E	N	%	E
Nausea	74	52.9	165	65	47.8	145	33	45.8	83	172	49.4	393
Alopecia	62	44.3	65	72	52.9	73	33	45.8	36	167	48.0	174
Asthenia	43	30.7	89	51	37.5	104	33	45.8	78	127	36.5	271
Neutropenia	43	30.7	108	39	28.7	88	28	38.9	82	110	31.6	278
Diarrhoea	36	25.7	73	47	34.6	94	25	34.7	34	108	31.0	201
Vomiting	33	23.6	57	27	19.9	52	13	18.1	25	73	21.0	134
Stomatitis	20	14.3	41	25	18.4	39	11	15.3	20	56	16.1	100
Bone pain	17	12.1	43	27	19.9	38	11	15.3	19	55	15.8	100
Anorexia	16	11.4	26	22	16.2	34	7	9.7	11	45	12.9	71
Myalgia	13	9.3	24	19	14.0	30	10	13.9	13	42	12.1	67
Headache	19	13.6	33	11	8.1	16	11	15.3	19	41	11.8	68
Abdominal pain	13	9.3	25	20	14.7	33	7	9.7	9	40	11.5	67
Abdominal pain upper	15	10.7	22	14	10.3	17	8	11.1	11	37	10.6	50
Pyrexia	13	9.3	17	14	10.3	20	10	13.9	12	37	10.6	49
Anaemia	14	10.0	20	10	7.4	17	9	12.5	15	33	9.5	52
Fatigue	13	9.3	19	13	9.6	20	6	8.3	7	32	9.2	46
Febrile neutropenia	4	2.9	6	8	5.9	13	19	26.4	19	31	8.9	38
Leukopenia	13	9.3	26	9	6.6	16	8	11.1	34	30	8.6	76
Insomnia	9	6.4	14	7	5.1	9	8	11.1	11	24	6.9	34
Constipation	7	5.0	9	9	6.6	17	5	6.9	9	21	6.0	35
Cough	9	6.4	11	7	5.1	9	5	6.9	7	21	6.0	27
Arthralgia	5	3.6	7	11	8.1	13	3	4.2	4	19	5.5	24
Oedema peripheral	6	4.3	8	6	4.4	7	5	6.9	6	17	4.9	21
Back pain	10	7.1	10	5	3.7	5	2	2.8	2	17	4.9	17
Dyspepsia	4	2.9	4	5	3.7	7	5	6.9	5	14	4.0	16
Mucosal inflammation	6	4.3	11	3	2.2	5	5	6.9	6	14	4.0	22
Weight decreased	2	1.4	4	5	3.7	5	5	6.9	5	12	3.4	14
Pharyngolaryngeal pain	1	0.7	1	2	1.5	2	6	8.3	6	9	2.6	9

Study XM-03. Lung cancer. Overview of adverse events in Cycle 1

Table 31. Overview of AEs (Cycle 1). Safety set.

	XM02 (N=158)			Filgrastim (N=79)			Overall (N=237)			XM02 vs. Filgrastim
	N	%	E	N	%	E	N	%	E	
Exposed to study drug	158			79			237			
All TEAEs										
At least one TEAE	124	78.5	478	58	73.4	172	182	76.8	650	p= 0.4162
At least one severe TEAE	30	19.0	49	12	15.2	17	42	17.7	66	p= 0.5888
At least one serious TEAE	19	12.0	24	5	6.3	5	24	10.1	29	p= 0.2527
Discontinued drug due to TEAE	8	5.1	16	2	2.5	4	10	4.2	20	p= 0.5028
Deaths *	6	3.8	7	2	2.5	2	8	3.4	9	p= 0.7222
Possibly study drug related TEAEs										
At least one TEAE	18	11.4	28	8	10.1	12	26	11.0	40	p= 0.8293
At least one severe TEAE	4	2.5	4	1	1.3	1	5	2.1	5	p= 0.6673
At least one serious TEAE	1	0.6	1	0	0.0	0	1	0.4	1	p= 1.0000
Discontinued drug due to TEAE	0	0.0	0	1	1.3	1	1	0.4	1	p= 0.3333
Deaths *	0	0.0	0	0	0.0	0	0	0.0	0	p= -
Possibly CTX related TEAEs										
At least one TEAE	101	63.9	292	46	58.2	112	147	62.0	404	p= 0.3986
At least one severe TEAE	24	15.2	31	8	10.1	10	32	13.5	41	p= 0.3198
At least one serious TEAE	14	8.9	16	1	1.3	1	15	6.3	17	p= 0.0234
Discontinued drug due to TEAE	7	4.4	10	1	1.3	2	8	3.4	12	p= 0.2747
Deaths *	2	1.3	2	1	1.3	1	3	1.3	3	p= 1.0000

* TEAEs starting in cycle 1 with outcome death after cycle 1
N = number of patients exposed to study drug or number of patients affected by TEAEs
% = 100 * (N affected / N exposed)
E = number of events for the N patients.
p: 2-sided p-value of Fisher's exact test

Study XM-03. Lung cancer. Individual adverse events in Cycle 1

Table 32. Commonly reported TEAEs by Preferred Term (Cycle 1). Safety set.

	XM02 (N=158)			Filgrastim (N=79)			Overall (N=237)		
	N	%	E	N	%	E	N	%	E
NAUSEA	46	29.1	53	23	29.1	30	69	29.1	83
VOMITING	31	19.6	31	11	13.9	12	42	17.7	43
ALOPECIA	17	10.8	17	8	10.1	8	25	10.5	25
ASTHENIA	14	8.9	18	9	11.4	11	23	9.7	29
THROMBOCYTOPENIA	16	10.1	32	5	6.3	8	21	8.9	40
ANAEMIA	13	8.2	17	4	5.1	4	17	7.2	21
NEUTROPENIA	10	6.3	16	4	5.1	4	14	5.9	20
CHEST PAIN	8	5.1	9	6	7.6	6	14	5.9	15
PYREXIA	9	5.7	9	5	6.3	6	14	5.9	15
DIARRHOEA	10	6.3	13	3	3.8	3	13	5.5	16
ANOREXIA	8	5.1	9	5	6.3	5	13	5.5	14
HEADACHE	9	5.7	10	3	3.8	3	12	5.1	13
FATIGUE	8	5.1	9	2	2.5	2	10	4.2	11
BACK PAIN	5	3.2	5	5	6.3	5	10	4.2	10
DYSPNOEA	7	4.4	10	2	2.5	2	9	3.8	12
BONE PAIN	7	4.4	7	2	2.5	2	9	3.8	9
LEUKOPENIA	6	3.8	11	2	2.5	2	8	3.4	13
CONSTIPATION	5	3.2	6	3	3.8	3	8	3.4	9
INSOMNIA	6	3.8	7	1	1.3	1	7	3.0	8
HAEMOPTYSIS	6	3.8	7	1	1.3	1	7	3.0	8
ABDOMINAL PAIN	5	3.2	5	2	2.5	2	7	3.0	7
WEIGHT DECREASED	5	3.2	5	2	2.5	2	7	3.0	7
PNEUMONIA	4	2.5	4	1	1.3	1	5	2.1	5
COUGH	4	2.5	4	1	1.3	1	5	2.1	5
FEBRILE NEUTROPENIA	4	2.5	4	0	0.0	0	4	1.7	4
EPISTAXIS	3	1.9	3	1	1.3	1	4	1.7	4
BLOOD CREATININE INCREASED	3	1.9	5	0	0.0	0	3	1.3	5
HYPERKALAEMIA	3	1.9	4	0	0.0	0	3	1.3	4
GRANULOCYTOPENIA	2	1.3	2	1	1.3	1	3	1.3	3
THROMBOCYTHAEMIA	3	1.9	3	0	0.0	0	3	1.3	3
ABDOMINAL PAIN UPPER	3	1.9	3	0	0.0	0	3	1.3	3
URINARY TRACT INFECTION	2	1.3	2	1	1.3	1	3	1.3	3
BODY TEMPERATURE INCREASED	1	0.6	1	2	2.5	2	3	1.3	3
PLATELET COUNT DECREASED	2	1.3	2	1	1.3	1	3	1.3	3
MYALGIA	2	1.3	2	1	1.3	1	3	1.3	3
ANXIETY	1	0.6	1	2	2.5	2	3	1.3	3
DYSPNOEA EXACERBATED	2	1.3	2	1	1.3	1	3	1.3	3
PRODUCTIVE COUGH	2	1.3	2	1	1.3	1	3	1.3	3
HYPERTENSION	2	1.3	2	1	1.3	1	3	1.3	3

Cut-off at incidence >1% overall
N = number of patients exposed to study drug or number of patients affected by TEAEs
% = 100 * (N affected / N exposed)
E = number of events for the N patients. Adverse events were coded using MedDRA 7.1

Study XM-04. NHL Overview of adverse events in Cycle 1

Table 33. Overview of AEs (Cycle 1). Safety set.

	XM02 [N=63]			Filgrastim [N=29]			Overall [N=92]			XM02 vs. Filgrastim
	N	%	E	N	%	E	N	%	E	
All TEAEs										
At least one TEAE	40	63.5	138	21	72.4	52	61	66.3	190	p= 0.4806
At least one severe TEAE	7	11.1	9	2	6.9	3	9	9.8	12	p= 0.7142
At least one serious TEAE	6	9.5	8	2	6.9	2	8	8.7	10	p= 1.0000
Discontinued drug due to TEAE	1	1.6	1	0	0.0	0	1	1.1	1	p= 1.0000
Deaths	0	0.0	0	0	0.0	0	0	0.0	0	p= -
Possibly study drug related TEAEs										
At least one TEAE	10	15.9	13	5	17.2	6	15	16.3	19	p= 1.0000
At least one severe TEAE	0	0.0	0	0	0.0	0	0	0.0	0	p= -
At least one serious TEAE	0	0.0	0	0	0.0	0	0	0.0	0	p= -
Discontinued drug due to TEAE	0	0.0	0	0	0.0	0	0	0.0	0	p= -
Deaths	0	0.0	0	0	0.0	0	0	0.0	0	p= -
Possibly CTX related TEAEs										
At least one TEAE	33	52.4	86	14	48.3	30	47	51.1	116	p= 0.8232
At least one severe TEAE	7	11.1	9	2	6.9	3	9	9.8	12	p= 0.7142
At least one serious TEAE	6	9.5	8	2	6.9	2	8	8.7	10	p= 1.0000
Discontinued drug due to TEAE	1	1.6	1	0	0.0	0	1	1.1	1	p= 1.0000
Deaths	0	0.0	0	0	0.0	0	0	0.0	0	p= -

* TEAEs starting in cycle 1 with outcome death after cycle 1
N = number of patients exposed to study drug or number of patients affected by TEAEs
% = 100 * (N affected / N exposed)
E = number of events for the N patients.
p: 2-sided p-value of Fisher's exact test

Study XM-04. NHL Individual adverse events in Cycle 1

Table 34. Commonly reported TEAEs by Preferred Term (Cycle 1). Safety set.

	XM02 [N=63]			Filgrastim [N=29]			Overall [N=92]		
	N	%	E	N	%	E	N	%	E
NAUSEA	11	17.5	13	2	6.9	2	13	14.1	15
ALOPECIA	11	17.5	11	2	6.9	2	13	14.1	13
NEUTROPENIA	8	12.7	9	2	6.9	2	10	10.9	11
VOMITING	6	9.5	6	1	3.4	2	7	7.6	8
HEADACHE	4	6.3	5	2	6.9	2	6	6.5	7
PYREXIA	4	6.3	4	2	6.9	2	6	6.5	6
BONE PAIN	6	9.5	6	0	0.0	0	6	6.5	6
DIARRHOEA	3	4.8	3	2	6.9	3	5	5.4	6
ASTHENIA	1	1.6	4	3	10.3	4	4	4.3	8
ANAEMIA	2	3.2	2	2	6.9	4	4	4.3	6
FEBRILE NEUTROPENIA	2	3.2	2	2	6.9	2	4	4.3	4
ARTHRALGIA	2	3.2	2	2	6.9	2	4	4.3	4
BACK PAIN	2	3.2	2	2	6.9	2	4	4.3	4
TACHYCARDIA	3	4.8	3	0	0.0	0	3	3.3	3
CONSTIPATION	2	3.2	2	1	3.4	1	3	3.3	3
STOMATITIS	1	1.6	1	2	6.9	2	3	3.3	3
ANOREXIA	3	4.8	3	0	0.0	0	3	3.3	3
INSOMNIA	2	3.2	2	1	3.4	1	3	3.3	3
HYPERTENSION	2	3.2	2	1	3.4	1	3	3.3	3
DEHYDRATION	1	1.6	3	1	3.4	1	2	2.2	4
THROMBOCYTOPENIA	1	1.6	2	1	3.4	1	2	2.2	3
ABDOMINAL PAIN	2	3.2	2	0	0.0	0	2	2.2	2
DYSPEPSIA	1	1.6	1	1	3.4	1	2	2.2	2
DYSPHAGIA	2	3.2	2	0	0.0	0	2	2.2	2
FATIGUE	1	1.6	1	1	3.4	1	2	2.2	2
INFLUENZA LIKE ILLNESS	1	1.6	1	1	3.4	1	2	2.2	2
BODY TEMPERATURE INCREASED	1	1.6	1	1	3.4	1	2	2.2	2
WEIGHT DECREASED	1	1.6	1	1	3.4	1	2	2.2	2
MUSCULOSKELETAL PAIN	1	1.6	1	1	3.4	1	2	2.2	2
PARAESTHESIA	2	3.2	2	0	0.0	0	2	2.2	2
COUGH	2	3.2	2	0	0.0	0	2	2.2	2
DYSPHONIA	2	3.2	2	0	0.0	0	2	2.2	2

Cut-off at incidence >1 patient overall
N = number of patients exposed to study drug or number of patients affected by TEAEs
% = 100 * (N affected / N exposed)
E = number of events for the N patients. Adverse events were coded using MedDRA 7.1

Immunogenicity

As indicated in the EMA guideline (annex regarding G-CSF[4]), the development of antibodies to the Neupogen brand of filgrastim occur infrequently and these have not been associated with major consequences for efficacy or safety. However, slight differences in filgrastim molecular structure between Neupogen and Tevagrastim may translate into differences in the incidence or severity of immune reactions.

Patients enrolled in three efficacy studies were tested for anti-GCSF antibodies at screening, within 24 hours before each cycle, at the end of the study and at a further follow-up visit approximately 6 months after study start. Results for neutralising antibodies are summarised in Table 35 below.

Table 35. Immunogenicity. Time to onset for positive neutralising antibodies. Test results (excluding tests with implausible results). Cancer patients set.

	XM02 only (N=356)		Filgrastim only (N=134)		Filgrastim/ XM02 (N=115)		Placebo/ XM02 (N=72)		Overall (N=677)	
Number and percentage of patients with positive neutralising antibody test results										
	n	%	n	%	n	%	N	%	n	%
Tests excluded	24	6.7	9	6.7	5	4.3	4	5.6	42	6.2
Missing	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
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
Before cycle 2	1	0.3	0	0.0	0	0.0	0	0.0	1	0.1
Before cycle 3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Before cycle 4	1	0.3	0	0.0	0	0.0	0	0.0	1	0.1
Before cycle 5	1	0.3	0	0.0	0	0.0	0	0.0	1	0.1
Before cycle 6	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
End of study	1	0.3	0	0.0	0	0.0	0	0.0	1	0.1
Antibody follow-up	2	0.6	2	1.5	0	0.0	2	2.8	6	0.9
No positive result	326	91.6	123	91.8	110	95.7	66	91.7	625	92.3

Abbreviations: n = number of patients, NAB = neutralising antibodies
Note: In case of negative antibody testing no NAB tests were planned. Therefore, if the antibody test was negative, then missing NAB status was also set to negative.

The incidence of positive tests for neutralising antibodies was comparable in the Tevagrastim and Neupogen arms. Positive results were not associated with clinical signs.

Risk Management Plan

The sponsor's risk management plan was found to be generally acceptable to the TGA's Office of Product Review.

Risk-Benefit Analysis

Delegate Considerations

1. Overall risk-benefit
   The data package submitted complies with the requirements of the EMA guideline adopted by the TGA. Subject to resolution of the issues raised by the PSC, the submitted studies have demonstrated that Tevagrastim has comparable pharmacokinetics, pharmacodynamic effects, efficacy and safety compared to Neupogen. Given that the two products have comparable efficacy and safety, it can be concluded that Tevagrastim has a favourable risk-benefit ratio and the Delegate proposed to approve the application.

2. Extrapolation to other indications
   The submission included data on use in chemotherapy-induced neutropaenia. In Australia, Neupogen is also registered for several other indications.

   The EMA guideline adopted by the TGA[2] allows demonstration of efficacy and safety in chemotherapy induced neutropaenia to be extrapolated to other indications approved for the innovator (that is, approval of such indications without data), provided that the mechanism of action is the same across indications. As the

mechanism of action for all indications is the interaction between filgrastim and the G-CSF receptor, the Delegate proposed to allow these indications.

The Delegate proposed to approve the application. The advice of the Advisory Committee for Prescription medicines (ACPM) was requested.

Response from Sponsor

The sponsor agreed with the Delegate's summary and proposed action and therefore had no comments to make.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

In expressing its view that this submission for filgrastim (Tevagrastim) solution 300 µg in 0.5 mL and 480 µg in 0.8 mL was suitable to be considered for approval, the ACPM agreed with the Delegate that the evidence of safety and efficacy provided supported a positive risk-benefit profile in the indications sought. The ACPM considered the following matters:

Despite the lack of clear data on pharmacokinetic bioequivalence with the currently registered product in Australia, including the lack of information on the bioanalytical method used, the pharmacodynamic data does show the required equivalence, providing reassurance.

The data submitted from the single pivotal and two supportive trials demonstrated clear efficacy equivalent to that of the active comparator in the treatment of chemotherapy-induced neutropenia. It was noted that the trials also fulfilled requirements in the EMA guidelines. The adverse event profiles of Tevagrastim and Neupogen appeared broadly comparable.

In line with the TGA-adopted EMA guideline, the ACPM agreed with the Delegate's proposal to use the demonstration of efficacy and safety in chemotherapy-induced neutropenia to extrapolate to other indications approved for the innovator.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Tevagrastim injection in pre-filled syringes containing filgrastim 300 micrograms/0.5mL and 480 micrograms/0.8mL indicated:

- To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs in doses not usually requiring bone marrow transplantation.
- To reduce the duration of neutropenia and clinical sequelae in patients undergoing induction and consolidation chemotherapy for acute myeloid leukaemia.
- For the mobilisation of autologous peripheral blood progenitor cells alone, or following myelosuppressive chemotherapy, in order to accelerate neutrophil and platelet recovery by infusion of such cells after myeloablative or myelosuppressive therapy in patients with nonmyeloid malignancies.
- For the mobilisation of peripheral blood progenitor cells, in normal volunteers, for use in allogeneic peripheral blood progenitor cell transplantation.
- In patients receiving myeloablative chemotherapy, to reduce the duration of neutropenia and clinical sequelae following autologous or allogeneic bone marrow transplantation.

- For chronic administration to increase neutrophil counts and to reduce the incidence and duration of infections in patients with severe chronic neutropenia.
- In patients with HIV infection, for reversal of clinically significant neutropenia and subsequent maintenance of adequate neutrophil counts during treatment with antiviral and/or other myelosuppressive medications.

It is a condition of registration that the first five independent batches of Tevagrastim imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION
TEVAGRASTIM

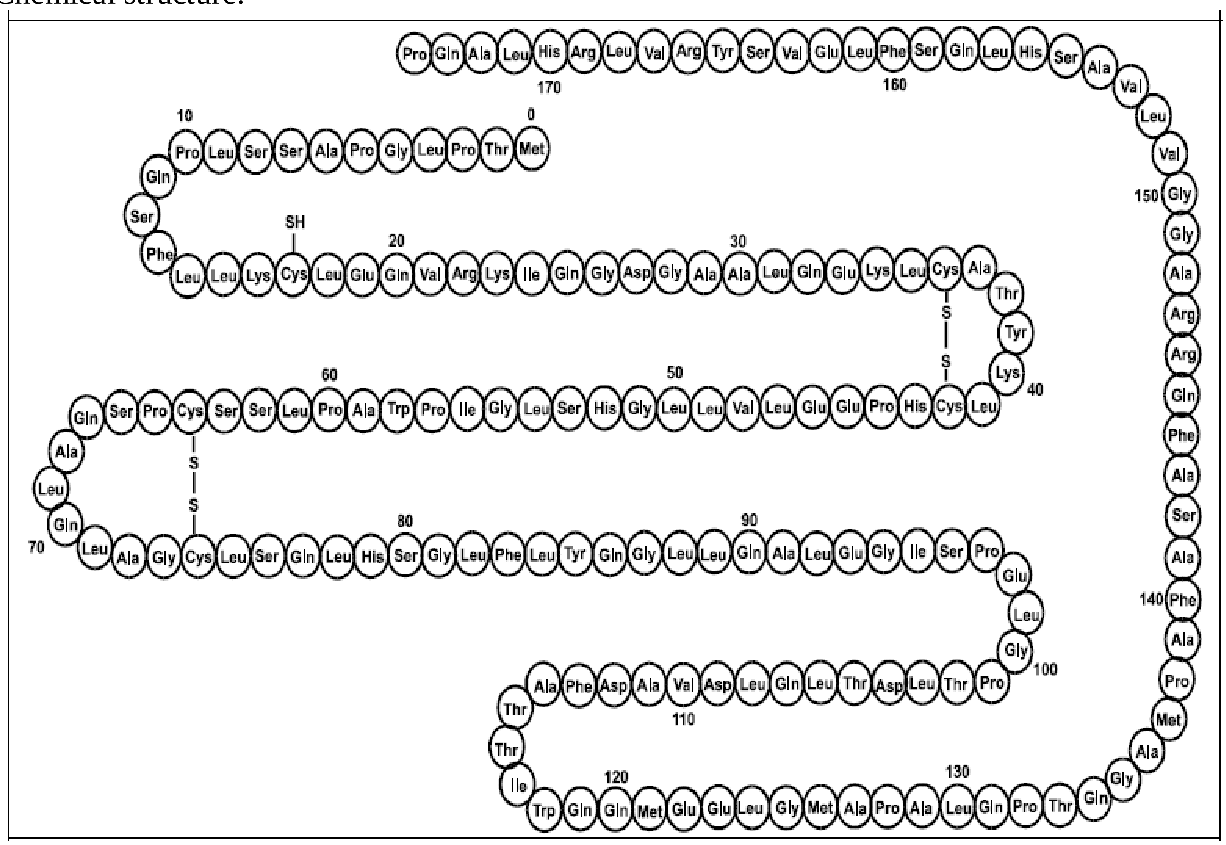
NAME OF THE MEDICINE

Filgrastim (recombinant methionyl human granulocyte colony stimulating factor)

Filgrastim is a 175 amino acid protein manufactured by recombinant DNA technology. It is produced by *Escherichia coli* bacteria into which has been inserted the human granulocyte colony stimulating factor gene. Filgrastim is unglycosylated and contains an N-terminal methionine necessary for expression in *E. coli*.

Molecular weight: 18,800
CAS no. 121181-53-1

Chemical structure:



DESCRIPTION

TEVAGRASTIM Injections contain 600mg/mL of filgrastim as the active ingredient. Excipients include glacial acetic acid, polysorbate 80, sodium hydroxide, sorbitol and water for injections.

PHARMACOLOGY

Actions: Colony stimulating factor.

Colony stimulating factors are glycoproteins which act on haemopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation commitment, and some end-cell functional activation.

Endogenous filgrastim (ie. granulocyte-colony stimulating factor) is a lineage specific colony stimulating factor with selectivity for the neutrophil lineage. Filgrastim is not species specific and has been shown to primarily affect neutrophil progenitor proliferation, differentiation and selected end-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).

The pH of filgrastim is 4.12.

Preclinical studies - The results of all preclinical studies indicate that the pharmacological effects of filgrastim are consistent with its predominant role as a regulator of neutrophil production and function.

Comparison of Tevagrastim with Neupogen
Comparability assessment of primary pharmacodynamic *in vitro* studies on receptor binding and biological activity between Tevagrastim and Neupogen, as well as *in vivo* studies in neutropenic mice, healthy rats and monkeys support similar/equivalent pharmacological activity of Tevagrastim compared to Neupogen.

Studies *in vitro*
A comparability study on the binding affinity of Tevagrastim and Neupogen to the human G-CSF receptor using BIAcore analysis demonstrated that the binding of human G-CSF receptor and Tevagrastim or Neupogen was specific and dose dependent, and the results confirmed that the binding affinities of Tevagrastim and Neupogen to the receptor were similar.

A comparison of the biological activity of Tevagrastim relative to that of Neupogen was performed in the murine M-NFS-60 leukaemia cell line. The data indicated that both, Tevagrastim 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.

Secondary pharmacodynamic study *in vitro* for determination of proliferation promoting effects of Tevagrastim in comparison to Neupogen on five human malignant cell lines demonstrated that no effect on cell proliferation by both products was found.

Studies *in vivo*
In an *in vivo* cyclophosphamide-induced neutropenic mouse model, the ability of Tevagrastim relative to that of Neupogen in increasing the absolute neutrophil count (ANC) was investigated

on days 3 and 5 in two studies. The results of meta-analysis showed that Tevagrastim and Neupogen induced neutrophilia to a similar extent and there was a tendency towards comparable potencies in terms of the *in vivo* biological activity. *In vivo* studies in neutropenic and non-neutropenic animals, Tevagrastim and Neupogen showed similar primary pharmacological response i.e. increase in ANC.

The pharmacodynamic effects of Tevagrastim and Neupogen in ANC levels were investigated in two phase I studies in healthy volunteers after single dose administration of 5 µg/kg or 10 µg/kg. The first study included only subcutaneous (SC) administration, the second both SC and IV (intravenous) infusion. In both studies, equivalence between Tevagrastim and Neupogen was demonstrated for both the doses after IV or SC administration (Table 1).

Table 1

Treatment Group	Mean ANC AUC_{0-t} [h*10^9/L]		90% CI	Point estimate [%]
	Tevagrastim	Neupogen		
Phase I study (1st)				
5 µg/kg SC (n=24)	901.68	901.57	97.8-102.5	100.1
10 µg/kg SC (n=26)	1199.66	1187.85	97.2-104.9	101.0
Phase I study (2nd)				
5 µg/kg SC (n=33)	956.93	983.14	88.23-107.92	97.58
10 µg/kg SC (n=30)	1305.93	1245.18	91.22-120.58	104.88
5 µg/kg IV (n=31)	738.37	776.67	87.47-108.13	97.25
10 µg/kg IV (n=30)	916.96	958.90	80.07-116.45	96.56
Abbreviations: SC = subcutaneous; IV = intravenous				

In the second phase I study there was demonstrated equivalence of Tevagrastim and Neupogen with regard to the pharmacodynamic variable CD34+ count in both the 5 and 10 µg/kg dose groups after single SC injection and IV infusion (Table 2).

Table 2

Treatment Group	Mean CD34+ AUC_{0-t} [h*/µL]		90% CI	Point estimate [%]
	Tevagrastim	Neupogen		
Phase I study (2nd)				
5 µg/kg SC (n=33)	1462.63	1448.61	93.29-109.26	100.96
5 µg/kg IV (n=31)	1451.35	1545.21	87.02-101.05	93.77
10 µg/kg SC (n=30)	1860.82	2063.90	84.79-95.87	90.16
10 µg/kg IV (n=30)	1644.85	1525.62	101.37-114.44	107.71
Abbreviations: SC = subcutaneous; IV = intravenous				

Pharmacokinetics

In normal volunteers, serum filgrastim concentrations declined monoexponentially following a single intravenous infusion, exhibiting a half-life of approximately three hours. Clearance and volume of distribution averaged 0.6 mL/minute/kg and 163 mL/kg. Following a single subcutaneous injection, peak serum concentrations of filgrastim occurred at approximately four to six hours. The absorption phase can be fitted to either a zero order or a first order model whereas the elimination phase observed a monoexponential decline. No difference in half-lives

was observed following intravenous and subcutaneous doses. The bioavailability was estimated to be approximately 50% following subcutaneous administration.

In cancer patients, clearance and volume of distribution of filgrastim were found to be lower than in normal volunteers, averaging approximately 0.12 to 0.34 mL/minute/kg and 56 to 127 mL/kg, respectively. However, the elimination half-life appeared to be similar when compared to normal volunteers, averaging three to four hours. Following single subcutaneous injections of 3.45 microgram/kg and 11.5 microgram/kg, peak serum concentrations occurred at approximately four to five hours and averaged 4 nanogram/mL and 49 nanogram/mL, respectively. Continuous subcutaneous infusion of filgrastim 23 microgram/kg over 24 hours in cancer patients resulted in a steady-state concentration of approximately 50 (30 to 70) nanogram/mL. No evidence of drug accumulation was observed over 11 to 20 days of continuous infusion. When single intravenous doses (1.73 to 69 microgram/kg) were administered to cancer patients, the area under the serum concentration-time curves (AUC) increased proportional to the dose. Serum concentrations of filgrastim were found to decrease in paediatric cancer patients who were dosed at 5 to 15 microgram/kg/day for ten days. The decrease of serum concentrations may be associated with a change in the clearance of filgrastim due to increasing neutrophil counts.

Subcutaneous injections of filgrastim solutions containing either sorbitol or mannitol resulted in similar pharmacokinetic profiles and response in absolute neutrophil counts (ANC). When single 5 microgram/kg subcutaneous doses were administered to normal subjects using three concentrations of filgrastim solution (300, 600 and 960 microgram/mL), the three concentrations were found to be equivalent in elevating ANC. Although increased maximum serum concentration and AUC were observed with increasing filgrastim concentrations, these pharmacokinetic differences did not correlate with biological response.

Comparison of Tevagrastim with Neupogen
Bioequivalence of Tevagrastim and Neupogen was demonstrated in healthy volunteers at doses of 5 µg/kg and 10 µg/kg bodyweight via either SC injection or IV infusion.
Mean AUC_{0-t} and C_{max} values were similar between treatment groups following SC and IV administration of Tevagrastim and Neupogen in both phase I studies (Table 3 and 4).

Table 3

Treatment Group	AUC_{0-t} [h*ng/mL]		90% CI	Point estimate [%]
	Tevagrastim	Neupogen		
Phase I study (1st)				
5 µg/kg SC (n=24)	158.45	143.10	102.7-119.0	110.5
10 µg/kg SC (n=26)	473.91	475.20	93.9-105.9	99.7
Phase I study (2nd)				
5 µg/kg SC (n=33)	157.585	159.426	92.05-105.66	98.63
10 µg/kg SC (n=30)	1056.472	990.996	104.02-115.03	109.39
5 µg/kg IV (n=31)	480.201	470.373	96.55-107.01	101.65
10 µg/kg IV (n=30)	471.148	430.717	102.14-111.30	106.62
Abbreviations: SC = subcutaneous; IV = intravenous				

Table 4

Treatment Group	C_{max} [ng/mL]		90% CI	Point estimate [%]
	Tevagrastim	Neupogen		
Phase I study (1st)				
5 µg/kg SC (n=24)	23.54	21.23	102.2-120.1	110.8
10 µg/kg SC. (n=26)	55.74	56.28	92.1-106.5	99.0
Phase I study (2nd)				
5 µg/kg SC (n=33)	17.976	18.416	87.22-109.10	97.55
5 µg/kg IV (n=31)	129.786	126.124	97.44-107.55	102.37
10 µg/kg SC (n=30)	231.142	221.562	99.30-115.66	107.17
10 µg/kg IV (n=30)	46.239	43.145	100.88-108.41	104.58
Abbreviations: SC = subcutaneous; IV = intravenous				

CLINICAL TRIALS

Cancer patients receiving myelosuppressive chemotherapy

In all clinical studies, administration of filgrastim resulted in a dose dependent rise in neutrophil counts. Following termination of filgrastim therapy, circulating neutrophil counts declined by 50% within one to two days, and to pretreatment levels within one to seven days. Isolated neutrophils displayed normal phagocytic and chemotactic activity in vitro.

In a study of the effects of filgrastim in patients with carcinoma of the urothelium, repeated daily intravenous dosing with filgrastim resulted in a linear dose dependent increase in circulating neutrophil counts over the dose range of 1 to 70 microgram/kg/day. The effects of filgrastim therapy reversed within 24 hours of the termination of administration, and neutrophil counts returned to baseline, in most cases within four days.

In a phase I study of patients with a variety of malignancies, including lymphoma, multiple myeloma and adenocarcinoma of the lung, breast and colon, filgrastim induced a dose dependent increase in neutrophil counts. This increase in neutrophil counts was observed whether filgrastim was administered intravenously (1 to 70 microgram/kg twice daily), subcutaneously (1 to 3 microgram/kg once daily) or by continuous subcutaneous infusion (3 to 11 microgram/kg/day).

These results were consistent with a phase I study of patients with small cell lung cancer who were administered filgrastim prior to chemotherapy. All patients responded to filgrastim (1 to 45 microgram/kg/day), given for five days, with a dose dependent increase in median neutrophil count from a baseline of 9.5 x 10^9/L to a maximum response of 43 x 10^9/L.

In a randomised, double blind, placebo controlled phase III study of small cell lung cancer patients receiving combination chemotherapy (cyclophosphamide, doxorubicin and etoposide), treatment with filgrastim resulted in clinically and statistically significant reductions in both the incidence and duration of infection, as manifested by febrile neutropenia. The incidence, severity and duration of severe neutropenia (absolute neutrophil count (ANC) < 0.5 x 10^9/L) following chemotherapy were all significantly reduced, as were the requirements for inpatient hospitalisation and antibiotic use (see Adverse Reactions). With other myelosuppressive

regimens (e.g. M-VAC, melphalan), a dose dependent increase in neutrophil counts was observed, as well as a decrease in the duration of severe neutropenia.

In a randomised, double blind placebo controlled phase III study of patients with acute myeloid leukaemia (AML), the median duration of neutropenia (ANC < 0.5 x 10^9/L) during the first induction cycle was significantly reduced, from 19 days in the placebo group to 14 days in the filgrastim group. The duration of hospitalisation during induction therapy was also significantly reduced in the filgrastim group, from 29 days to 23 days, as were the duration of fever and incidence of intravenous antibiotic use. Filgrastim had a similar impact on the durations of neutropenia, hospitalisation, fever and intravenous antibiotic use in subsequent cycles of chemotherapy.

The absolute monocyte count was reported to increase in a dose dependent manner in most patients receiving filgrastim. The percentage of monocytes in the differential count was within the normal range. In all studies to date, absolute counts of both eosinophils and basophils were within the normal range following administration of filgrastim. Small non-dose dependent increases in lymphocyte counts following filgrastim administration have been reported in normal subjects and cancer patients.

Peripheral blood progenitor cell (PBPC) collection and therapy
Use of filgrastim, either alone or after chemotherapy, mobilises haemopoietic progenitor cells into the peripheral blood. These PBPCs may be harvested and infused after high dose chemotherapy, either in place of, or in addition to, bone marrow transplantation. Infusion of PBPCs accelerates the rate of neutrophil and platelet recovery, reducing the risk of haemorrhagic complications and the need for platelet transfusions.

In a randomised phase III study of patients with Hodgkin's disease or non-Hodgkin's lymphoma undergoing myeloablative chemotherapy, 27 patients received autologous filgrastim mobilised peripheral blood progenitor cell transplantation (PBPCT) followed by filgrastim 5 microgram/kg/day and 31 patients received autologous bone marrow transplantation (ABMT) followed by filgrastim 5 microgram/kg/day. Patients randomised to the filgrastim mobilised PBPCT group, compared to the ABMT group, had significantly fewer median days of platelet transfusions (six versus ten days), a significantly shorter median time to a sustained platelet count > 20 x 10^9/L (16 versus 23 days), a significantly shorter median time to recovery of a sustained ANC greater than or equal to 0.5 x 10^9/L (11 versus 14 days) and a significantly shorter duration of hospitalisation (17 versus 23 days).

In all clinical trials of filgrastim for the mobilisation of PBPCs, filgrastim 5 to 24 microgram/kg/day was administered following infusion of the cells until a sustainable ANC (greater than or equal to 0.5 x 10^9/L) was reached.

Overall, infusion of filgrastim mobilised PBPCs, supported by filgrastim post-transplantation, provided rapid and sustained haematological recovery. Long-term (approximately 100 days) follow-up haematology data from patients treated with autologous PBPCT alone or in combination with bone marrow were compared to historical data from patients treated with ABMT alone. This retrospective analysis indicated that engraftment is durable.

In a randomised trial comparing filgrastim mobilised allogeneic PBPCT with allogeneic BMT in patients with acute leukaemia, chronic myelogenous leukaemia or myelodysplastic syndrome, filgrastim was given at 10 microgram/kg/day to 163 healthy volunteers for four to five days followed by leukapheresis beginning on day 5. Another 166 healthy volunteers donated bone marrow. The number of CD34+ cells in the leukapheresis product was generally sufficient to support a transplant, with over 80% of donors achieving the target yield of 4 x 106/kg recipient bodyweight. In the vast majority of donors (95%) sufficient PBPCs (2 x 10^6 CD34+ cells/kg of recipient) were obtained in less than or equal to 2 leukaphereses. The median number of CD34+ cells in the leukapheresis product (5.8 x 10^6/kg) was higher than that of bone marrow product (2.7 x 10^6/kg); however, the product from both procedures was sufficient to allow each recipient to receive a transplant. Following transplant, all recipients received filgrastim at 5 microgram/kg/day until neutrophil recovery (up to 28 days). Recipients of allogeneic PBPC had a shorter median time to platelet recovery of greater than or equal to 20 x 10^9/L (15 versus 20 days) and shorter median time to ANC recovery of greater than or equal to 0.5 x 10^9/L (12 versus 15 days). There was no difference in leukaemia free survival at a median follow-up of 12 months.

Patients with severe chronic neutropenia (SCN)
In a randomised, controlled, open label phase III trial of 123 patients with idiopathic, cyclic and congenital neutropenia, untreated patients had a median absolute neutrophil count (ANC) of 0.21 x 10^9/L. Filgrastim therapy was adjusted to maintain the median ANC between 1.5 x 10^9/L and 10 x 10^9/L. A complete response (defined as a median ANC greater than or equal to 1.5 x 10^9/L) was seen in 88% of patients over five months of filgrastim therapy. Overall, the response to filgrastim therapy for all patients was observed in one to two weeks. The median ANC after five months of filgrastim therapy for all patients was 7.46 x 10^9/L (range 0.03 to 30.88 x 10^9/L). In general, patients with congenital neutropenia responded to filgrastim therapy with lower median ANC than patients with idiopathic or cyclic neutropenia.

Overall, daily treatment with filgrastim resulted in clinically and statistically significant reductions in the incidence and duration of fever, infections and oropharyngeal ulcers. As a result, there were also substantial decreases in requirements for antibiotic use and hospitalisation. Additionally, patients treated with filgrastim reported fewer episodes of diarrhoea, nausea, fatigue and sore throat.

Patients with HIV infection
In an open label noncomparative study involving 200 HIV positive patients with neutropenia (ANC < 1.0 x 10^9/L), filgrastim reversed the neutropenia in 98% of patients (ANC greater than or equal to 2 x 10^9/L) with a median time to reversal of two days (range 1 to 16) and a median dose of 1 microgram/kg/day (range 0.5 to 10). 96% of patients achieved reversal of neutropenia with a dose of less than or equal to 300 microgram/day. Normal ANCs were then maintained with a median dose frequency of three 300 microgram vials/week (range 1 to 7). Ganciclovir, zidovudine, co-trimoxazole and pyrimethamine were the medications most frequently considered to be causing neutropenia and 83% of patients received one or more of these on-study. During the study, 84% of these patients were able to increase or maintain dosing of these four medications or add them to their therapy. The number of these four medications received per patient increased by more than 20% (from 0.98 to 1.18) during filgrastim therapy. The median

duration of filgrastim treatment was 191 days (range 2 to 815). 153 patients received long-term maintenance therapy (greater than 58 days) and the frequency of dosing was similar to that in the first 30 days of maintenance therapy (71% of patients were receiving two to three vials/week).

Overall, in patients with HIV infection filgrastim rapidly reverses neutropenia and is subsequently able to maintain normal neutrophil counts during chronic administration.

Comparison of Tevagrastim with Neupogen
Biosimilarity between Tevagrastim and Neupogen was demonstrated through the clinical program composed of 5 clinical studies showing the clinical equivalence of both medicinal products. The clinical pharmacology was observed in two phase I studies; clinical efficacy and safety in a pivotal phase III study in patients with breast cancer. Lung cancer and NHL studies in patients focused on safety.

Breast Cancer Study
This was a multinational, multicentre, randomised, controlled phase III study with a total of 348 patients with breast cancer treated with cytotoxic chemotherapy. The study aimed to demonstrate therapeutic equivalence of Tevagrastim and Neupogen.

The primary objective of the study was to compare the effect of Tevagrastim, Neupogen and placebo on the duration of severe neutropenia (DSN) in cycle 1. Secondary endpoints included the incidence of observed neutropenia, the incidence of protocol-defined neutropenia, DSN in cycles 2-4, depth of ANC nadir in cycles 1 to 4, time to ANC recovery in cycles 1 to 4, and safety.

Chemotherapy consisted of a maximum of four cycles of docetaxel 75 mg/m^2 on day 1 and doxorubicin 60 mg/m^2 IV on day 1, repeated every 3 weeks.

The patients were randomised in a ratio 2:2:1 to Tevagrastim, Neupogen, or placebo. The study drugs were injected daily SC from the day after chemotherapy for 5 to a maximum of 14 days or until the ANC reached $\geq 10 \times 10^9/L$ post-nadir. Placebo patients were switched to filgrastim after completion of first cycle. Blood samples for the determination of ANC were collected within 24 hours prior to chemotherapy and then daily from day 2 to 15 or longer until ANC reached $\geq 2 \times 10^9/L$. In cycle 1 mean of DSN was statistically significantly longer for the placebo group than for the Tevagrastim and Neupogen groups and confirmed the significantly superior activity of Tevagrastim compared with placebo and equivalence to Neupogen.

The incidence of febrile neutropenia (FN) in cycle 1 was considerably lower in Tevagrastim and Neupogen groups compared with placebo (12.1 % vs. 12.5 % vs. 36.1 %). There were no relevant differences between Tevagrastim and Neupogen in the incidence of FN in cycle 1 or across all cycles.

ANC over time in cycle 1 in Tevagrastim and Neupogen study groups increased abruptly after day 2 to achieve a maximum on day 3, then fell to a mean ANC nadir $0.7 \times 10^9/L$ on day 7 and reached a second maximum on day 11. In placebo group, there was no initial increase, but ANC decreased steadily from day 2 and fell to a considerably deeper mean nadir of $0.2 \times 10^9/L$ on day

11. In cycle 1, the median time to ANC recovery was similar in the Tevagrastim and Neupogen groups (8.0 days) and shorter in the placebo group (15.0 days). In cycles 2 to 4, the mean ANC nadir was not as deep as in the first cycle and similar for all study groups (1.0 x 10^9/L). Median time to ANC recovery was also similar (8.0 days). Full analysis set for the study is presented in Table 7.

In this phase III trial Tevagrastim was shown to be superior to placebo and as effective as Neupogen in reducing the duration of chemotherapy-induced severe neutropenia, the depth of the ANC nadir, and time to ANC recovery. Both medicinal products were equally effective in reducing the incidence of febrile neutropenia, had low immunogenicity and were well tolerated with no un-expected drug-related adverse events.

Lung cancer study
Multinational, multicentre, randomized Phase III clinical trial was conducted in 240 patients with lung cancer treated with cytotoxic chemotherapy.

The primary objective of the trial was to assess safety in cycle 1 in comparison with Neupogen. Efficacy endpoints included the DSN, the incidence of FN, and the depth of ANC nadir (ANC_{min}) in cycles 1 and 4; and time to ANC recovery (t_{rec}) in cycles 1 and 4.

The patients received a maximum of 6 cycles of chemotherapy every 3 or 4 weeks, depending on the regimen. Chemotherapy was started on day 1 of each cycle. The most common chemotherapy regimen used was cisplatin plus etoposide or gemcitabine. Other regimens included cisplatin plus vinorelbine and combinations of carboplatin with vinorelbine, etoposide, gemcitabine, or paclitaxel.

The patients were randomised in a 2:1 ratio to primary filgrastim prophylaxis with Tevagrastim or Neupogen during cycle 1, administrating of 5 μg/kg/day. Patients in the reference group were switched to Tevagrastim after completion of cycle 1. The study drugs were injected daily SC for at least 5 days to a maximum of 14 days, starting 24 hours after the last chemotherapy. Filgrastim prophylaxis discontinued when ANC of≥10 x 10^9/L was reached.

In this phase III trial primary prophylaxis with Tevagrastim and Neupogen was shown to be equally effective and safe. ANC profiles were very similar. Minor, non significant differences between both drugs were noticed in the time to ANC recovery and the incidence of FN, which explained by differences in patient characteristics. The typical side effects reported occurred with either preparation. The full analysis set for the study is presented in Table 7.

Non-Hodgkin Lymphoma
This was multinational, multicenter, investigator-blinded, randomized phase III trial of Tevagrastim versus Neupogen in patients with aggressive non-Hodgkin lymphomas.

The study aimed to compare Tevagrastim with Neupogen with regard to safety and clinical efficacy in the treatment of chemotherapy induced neutropenia. Efficacy endpoints included DSN, the incidence of observed or protocol-defined FN, depth of ANC nadir in cycles 1 and 4,

and time to ANC recovery in cycles 1 and 4. The safety evaluation was assessed based on AEs, laboratory tests, physical examination, and vital signals.

Patients received a maximum of 6 cycles of Cyclophosphamide-Hydroxydaunomycin (Adriamycin)-Oncovin (Vincristine)-Prednisolon (CHOP) chemotherapy every 3 weeks. Additional treatment with the anti-CD20 monoclonal antibody rituximab was at the discretion of the treating physician.

The patients were randomised to treatment with Tevagrastim or Neupogen during cycle 1, administrating 5 μg/kg/day. The study drugs were injected daily SC for at least 5 days to a maximum of 14 days, starting 24 hours after the last chemotherapy. Study drugs were discontinued when ANC of $\geq 10 \times 10^9$/L was reached.

The study data confirmed that primary prophylaxis with Tevagrastim is as effective as the Neupogen in reducing the duration of severe neutropenia and the incidence of febrile neutropenia. The ANC profiles were similar over the course of 1 chemotherapy cycle. The safety profiles were comparable. Full analysis set for the study is presented in Table 7.

Table 7: Duration of Severe Neutropenia and Incidence of Febrile Neutropenia Across Studies: Full Analysis Set

Study Name Indication	**Breast Cancer Study**			**Lung Cancer Study**		**Non-Hodgkin Lymphoma Study**	
Treatment Group	**T**	**N**	**P***	**T**	**N**	**T**	**N**
[n]	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
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

Abbreviations: T = Tevagrastim, N = Neupogen, P = Placebo.
DSN = duration of severe neutropenia; FN = Observed or protocol-defined febrile neutropenia; ANCOVA = analysis of covariance; CI = confidence interval;
* - patients in this groups received Tevagrastim in all cycles after cycle 1
# ANCOVA estimate and 2-sided 95% confidence interval for difference Tevagrastim-Neupogen in cycle 1

INDICATIONS

To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs in doses not usually requiring bone marrow transplantation.

To reduce the duration of neutropenia and clinical sequelae in patients undergoing induction and consolidation chemotherapy for acute myeloid leukaemia.

For the mobilisation of autologous peripheral blood progenitor cells alone, or following myelosuppressive chemotherapy, in order to accelerate neutrophil and platelet recovery by infusion of such cells after myeloablative or myelosuppressive therapy in patients with nonmyeloid malignancies.

For the mobilisation of peripheral blood progenitor cells, in normal volunteers, for use in allogeneic peripheral blood progenitor cell transplantation.

In patients receiving myeloablative chemotherapy, to reduce the duration of neutropenia and clinical sequelae following autologous or allogeneic bone marrow transplantation.
For chronic administration to increase neutrophil counts and to reduce the incidence and duration of infections in patients with severe chronic neutropenia.

In patients with HIV infection, for reversal of clinically significant neutropenia and subsequent maintenance of adequate neutrophil counts during treatment with antiviral and/or other myelosuppressive medications.

CONTRAINDICATIONS

Known hypersensitivity to *E. coli* derived products, filgrastim, or any other component of the product.

WARNINGS

Splenic rupture has been reported in both healthy donors and patients with cancer following administration of filgrastim; some of these cases were fatal. Left upper abdominal pain and/or shoulder tip pain accompanied by rapid increase in spleen size should be carefully monitored due to the rare but serious risk of splenic rupture.

Sickle cell disease
Clinicians should exercise caution and monitor patients accordingly when administering filgrastim to patients with sickle cell disease because of the reported association of filgrastim with sickle cell crisis (in some cases fatal). Use of filgrastim in patients with sickle cell disease should be considered only after careful evaluation of the potential risks and benefits.

Severe chronic neutropenia
Cytogenetic abnormalities, transformation to myelodysplasia (MDS) and acute myeloid leukaemia (AML) have been observed in patients treated with filgrastim for severe chronic neutropenia (SCN). Myelodysplasia and AML have been reported to occur in the natural history of SCN without cytokine therapy. Based on available data including a postmarketing surveillance study, the risk of developing MDS and AML appears to be confined to the subset of patients with congenital neutropenia (see Adverse Reactions). Abnormal cytogenetics have been associated with the development of myeloid leukaemia. The effect of filgrastim on the development of abnormal cytogenetics and the effect of continued filgrastim administration in patients with abnormal cytogenetics or MDS are unknown. If a patient with SCN develops abnormal cytogenetics or MDS, the risks and benefits of continuing filgrastim should be carefully considered.

PRECAUTIONS

There have been occasional reports of the occurrence of adult respiratory distress syndrome (ARDS) in patients receiving filgrastim. 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 leading to respiratory failure or ARDS.

As with other haemopoietic growth factors, granulocyte colony stimulating factor (G-CSF) has shown in vitro stimulating properties on human endothelial cells. G-CSF can promote growth of myeloid cells, including malignant cells, in vitro and similar effects may be seen on some nonmyeloid cells in vitro.

Special warnings
TEVAGRASTIM should not be used to increase the dose of cytotoxic chemotherapy beyond established dosage regimens (see below).

TEVAGRASTIM should not be administered to patients with severe congenital neutropenia (Kostman's syndrome) with abnormal cytogenetics (see below).

Myelodysplasia and leukaemia
The safety and efficacy of filgrastim administration in patients with myelodysplasia or chronic myeloid leukaemia receiving myelosuppressive chemotherapy without stem cell support have not been established.

Randomised studies of filgrastim in patients undergoing chemotherapy for acute myeloid leukaemia demonstrate no stimulation of disease as measured by remission rate, relapse and survival.

Cancer patients receiving myelosuppressive chemotherapy
Concurrent use with chemotherapy and radiotherapy
The safety and efficacy of filgrastim given concurrently with cytotoxic chemotherapy have not been established. Because of the potential sensitivity of rapidly dividing myeloid cells to

cytotoxic chemotherapy, the use of filgrastim is not recommended in the period 24 hours before to 24 hours after the administration of chemotherapy (see Dosage and Administration).

No controlled study has been done to examine the combination of chemoradiotherapy and filgrastim on platelet count in a suitable oncology setting. Therefore, until more definitive data are available, simultaneous use of filgrastim with chemoradiation should be undertaken with caution.

Leucocytosis

White blood cell counts of 100 x 10^9/L or greater were observed in approximately 2% of patients receiving filgrastim at doses above 5 microgram/kg/day. There were no reports of adverse events associated with this degree of leucocytosis. In order to avoid the potential complications of excessive leucocytosis, a full blood count is recommended twice per week during filgrastim therapy (see Laboratory monitoring).

Premature discontinuation of filgrastim therapy

A transient increase in neutrophil counts is typically seen one to two days after initiation of filgrastim therapy. However, for a sustained therapeutic response, filgrastim therapy should be continued until the post nadir absolute neutrophil count reaches 10 x 10^9/L. Therefore, the premature discontinuation of filgrastim therapy, prior to the time of recovery from the expected neutrophil nadir, is generally not recommended (see Dosage and Administration).

Other

In studies of filgrastim administration following chemotherapy, most reported side effects were consistent with those usually seen as a result of cytotoxic chemotherapy (see Adverse Reactions). Because of the potential for receiving higher doses of chemotherapy (i.e. full doses on the prescribed schedule for a longer period), the patient may be at greater risk of thrombocytopenia, which should be monitored for carefully. Anaemia and nonhaematological consequences of increased chemotherapy doses (please refer to the prescribing information of the specific chemotherapy agents used) may also occur. Regular monitoring of the haematocrit and platelet count is recommended. Furthermore, care should be exercised in the administration of filgrastim in conjunction with drugs known to lower the platelet count and in the presence of moderate or severe organ impairment. Thrombocytopenia may be more severe than normal in later courses of chemotherapy.

The use of filgrastim mobilised peripheral blood progenitor cells has been shown to reduce the depth and duration of thrombocytopenia following myelosuppressive or myeloablative chemotherapy.

Peripheral blood progenitor cell collection and therapy

Mobilisation

There are no prospectively randomised comparisons of the two recommended mobilisation methods (filgrastim alone, or in combination with myelosuppressive chemotherapy) within the same patient population. The degree of variation between both different patient groups and results of laboratory assays of CD34+ cells means that direct comparison between different studies is difficult and an optimum method cannot yet be recommended. The choice of

mobilisation method should be considered in relation to the overall objectives of treatment for an individual patient.

Assessment of progenitor cell yields

In assessing the number of progenitor cells harvested in patients treated with filgrastim, particular attention should be paid to the method of quantitation. The results of flow cytometric analysis of CD34+ cell numbers vary depending on the precise methodology used. Recommendations for minimum acceptable progenitor cell yield based on studies using methods other than that of the reporting laboratory need to be interpreted with caution.

Statistical analysis of the relationship between the number of CD34+ cells infused and the rate of platelet recovery after high dose chemotherapy indicates a complex but continuous relationship, with the probability of more rapid platelet recovery increasing as the CD34+ cell yield increases. Currently, the minimum acceptable yield of CD34+ cells is not well defined. The recommendation of a minimum yield of greater than or equal to 2×10^6 CD34+ cells/kg is based on published experience resulting in adequate haematological reconstitution.

Prior exposure to cytotoxic agents

Patients who have undergone very extensive prior myelosuppressive therapy may not show sufficient mobilisation of peripheral blood progenitor cells to achieve the recommended minimum yield (greater than or equal to 2×10^6 CD34+ cells/kg) or acceleration of platelet recovery to the same degree. When peripheral blood progenitor cell transplantation is envisaged it is advisable to plan the stem cell mobilisation procedure early in the treatment course of the patient. Particular attention should be paid to the number of progenitor cells mobilised in such patients before the administration of high dose chemotherapy.

In one phase II study in heavily pretreated patients with acute lymphoblastic leukaemia, non-Hodgkin's lymphoma or Hodgkin's disease, no increased yield of progenitor cells was demonstrated by increasing the dose of filgrastim beyond that recommended.

If yields are inadequate, as measured by the criterion above, alternative forms of treatment not requiring progenitor cell support should be considered.

Some cytotoxic agents exhibit particular toxicities to the haemopoietic progenitor pool, and may adversely affect progenitor cell mobilisation. Agents such as melphalan, carmustine (BCNU) and carboplatin, when administered over prolonged periods prior to attempts at progenitor cell mobilisation, may reduce progenitor cell yield. Nevertheless, the administration of melphalan, carboplatin or BCNU together with Neupogen has been shown to be effective for progenitor cell mobilisation.

Leucocytosis

During the period of administration of filgrastim for peripheral blood progenitor cell mobilisation in cancer patients, discontinuation of filgrastim is appropriate if the leucocyte count rises to $> 100 \times 10^9$/L. (See Sickle Cell disease).

Tumour contamination of bone marrow and leukapheresis products

Some studies of patient bone marrow and leukapheresis products have demonstrated the presence of malignant cells. While the possibility exists for tumour cells to be released from the marrow during mobilisation of peripheral blood progenitor cells and subsequently collected in the leukapheresis product, in most of the studies, leukapheresis products appear to be less contaminated than bone marrow from the same patient. The effect of reinfusion of tumour cells has not been well studied, and the limited data available are inconclusive.

Normal donors undergoing peripheral blood progenitor cell mobilisation

Mobilisation of PBPC does not provide a direct clinical benefit to normal donors and should only be considered for the purposes of allogeneic stem cell transplantation.

PBPC mobilisation should be considered only in donors who meet normal clinical and laboratory eligibility criteria for stem cell donation with special attention to haematological values and infectious disease.

The safety and efficacy of filgrastim has not been assessed in normal donors < 16 years or > 60 years.

Transient thrombocytopenia (platelets < 100 x 10^9/L) following filgrastim administration and leukapheresis was observed in 35% of subjects studied. Among these, two cases of platelets < 50 x 10^9/L were reported and attributed to the leukapheresis procedure.

If more than one leukapheresis is required, particular attention should be paid to donors with platelets < 100 x 10^9/L prior to leukapheresis; in general apheresis should not be performed if platelets are < 75 x 10^9/L.

Leukapheresis should not be performed in donors who are anticoagulated or who have known defects in haemostasis.

Filgrastim administration should be discontinued or its dosage should be reduced if the leukocyte counts rise to > 100 x 10^9/L.

Donors who receive filgrastim for PBPC mobilisation should be monitored until haematological indices return to normal.

Insertion of a central venous catheter should be avoided where possible, therefore consideration should be given to the adequacy of venous access when selecting donors.

Long-term safety follow-up of donors is ongoing. For up to four years, there have been no reports of abnormal haemopoiesis in normal donors. Nevertheless, a risk of promotion of a malignant myeloid clone cannot be excluded. It is recommended that the apheresis centre perform a systematic record and tracking of the stem cell donors to ensure monitoring of long-term safety.

There have been rare cases of splenic rupture reported in healthy donors following administration of G-CSFs. In donors experiencing left upper abdominal pain and/or shoulder tip pain and rapid increase in spleen size, the risk of splenic rupture should be considered and carefully monitored.

In normal donors, pulmonary adverse events (haemoptysis, pulmonary infiltrates) have been reported very rarely (< 0.01%).

Recipients of allogeneic peripheral blood progenitor stem cells mobilised with filgrastim
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 (GvHD) when compared with bone marrow transplantation.

Severe chronic neutropenia
Diagnosis
Care should be taken to confirm the diagnosis of severe chronic neutropenia (SCN), which may be difficult to distinguish from myelodysplasia, before initiating filgrastim therapy. The safety and efficacy of filgrastim in the treatment of neutropenia or pancytopenia due to other haemopoietic disorders (e.g. myelodysplastic disorders or myeloid leukaemia) have not been established.

It is therefore essential that serial full blood counts, with differential and platelet counts, and an evaluation of bone marrow morphology and karyotype be performed prior to initiation of filgrastim therapy. The use of filgrastim prior to diagnostic confirmation of SCN may mask neutropenia as a diagnostic sign of a disease process other than SCN and prevent adequate evaluation and appropriate treatment of the underlying condition causing the neutropenia.

Patients with HIV infection
Risks associated with increased doses of myelosuppressive medications
Treatment with filgrastim alone does not preclude thrombocytopenia and anaemia due to myelosuppressive medications. As a result of the potential to receive higher doses or a greater number of medications with filgrastim therapy, the patient may be at higher risk of developing thrombocytopenia and anaemia. Regular monitoring of blood counts is recommended (see Laboratory monitoring, Patients with HIV infection).

Infections and malignancies causing myelosuppression
Neutropenia may also be due to bone marrow infiltrating opportunistic infections such as Mycobacterium avium complex or malignancies such as lymphoma. In patients with known bone marrow infiltrating infection or malignancy, consideration should be given to appropriate therapy for treatment of the underlying condition. The effects of filgrastim on neutropenia due to bone marrow infiltrating infection or malignancy have not been been well established.

Effect on laboratory tests
Cancer patients receiving myelosuppressive chemotherapy
A full blood count, haematocrit and platelet count should be obtained prior to chemotherapy and at regular intervals (twice per week) during TEVAGRASTIM therapy. Following cytotoxic

chemotherapy, the neutrophil nadir occurred earlier during cycles when filgrastim was administered, and white blood cell differentials demonstrated a left shift, including the appearance of promyelocytes and myeloblasts. In addition, the duration of severe neutropenia was reduced, and was followed by an accelerated recovery in the neutrophil counts. Therefore, regular monitoring of white blood cell counts, particularly at the time of the recovery from the postchemotherapy nadir, is recommended in order to avoid excessive leucocytosis (see Dosage and Administration).

Peripheral blood progenitor cell collection and therapy

After four days of TEVAGRASTIM treatment for peripheral blood progenitor cell mobilisation, neutrophil counts should be monitored. Frequent complete blood counts and platelet counts are recommended following infusion of peripheral blood progenitor cells, at least three times per week until haemopoietic recovery.

The mobilisation and apheresis procedures should be performed in collaboration with an oncology/ haematology centre with acceptable experience in this field and where the monitoring of haemopoietic progenitor cells can be appropriately performed and interpreted (see Precautions, Peripheral blood progenitor cell collection and therapy).

Severe chronic neutropenia

During the initial four weeks of TEVAGRASTIM therapy and for two weeks following any dose adjustment, a full blood count (FBC) with differential count should be performed twice weekly. Once a patient is clinically stable, a full blood count with differential count and platelet determination should be performed monthly during the first year of treatment. Thereafter, if clinically stable, routine monitoring with regular FBCs (i.e. as clinically indicated but at least quarterly) is recommended. Additionally, for those patients with congenital neutropenia, annual bone marrow and cytogenetic evaluations should be performed throughout the duration of treatment (see Warnings, Adverse Reactions).

In clinical trials, the following laboratory results were observed:
Cyclic fluctuations in the neutrophil counts were frequently observed in patients with congenital or idiopathic neutropenia after initiation of filgrastim therapy.

Platelet counts were generally at the upper limits of normal prior to filgrastim therapy. With filgrastim therapy, platelet counts decreased but generally remained within normal limits (see Adverse Reactions).

Early myeloid forms were noted in peripheral blood in most patients, including the appearance of metamyelocytes and myelocytes. Promyelocytes and myeloblasts were noted in some patients. Relative increases were occasionally noted in the number of circulating eosinophils and basophils. No consistent increases were observed with filgrastim therapy.

HIV infection

Absolute neutrophil count should be monitored closely, especially during the first few weeks of TEVAGRASTIM therapy. Some patients may respond very rapidly with a considerable increase in neutrophil count after initial doses of TEVAGRASTIM. It is recommended that the ANC is

measured daily for the first two to three days of TEVAGRASTIM administration. Thereafter, it is recommended that the ANC is measured at least twice per week for the first two weeks and subsequently once per week or once every other week during maintenance therapy. During intermittent dosing with TEVAGRASTIM 300 microgram, there will be wide fluctuations in the patient's ANC over time. In order to determine a patient's trough or nadir ANC, it is recommended that blood samples for ANC measurement are obtained immediately prior to any scheduled dosing with TEVAGRASTIM.

Carcinogenesis, genotoxicity, effects on fertility

The carcinogenic potential of filgrastim has not been studied. In either the presence or absence of a drug enzyme metabolising system, filgrastim failed to induce chromosomal aberrations (in Chinese hamster lung cells in vitro) or bacterial gene mutations. Filgrastim was negative in an in vivo mouse micronuclear test. Filgrastim failed to induce bacterial gene mutations in either the presence or absence of a drug metabolising enzyme system. Filgrastim had no observed effect on the fertility of male or female rats, or gestation at doses up to 500 microgram/kg.

No human data are available.

Use in pregnancy (Category B3)

There are no company sponsored studies of the use of TEVAGRASTIM in pregnant women. However, there are cases in the literature where the transplacental passage of filgrastim has been demonstrated. TEVAGRASTIM should not be used during pregnancy unless the potential benefit outweighs the potential risk to the fetus.

Reproductive studies in pregnant rats have shown that filgrastim was not associated with lethal, teratogenic or behavioural effects on fetuses when administered by daily intravenous injection during the period of organogenesis at dose levels up to 575 microgram/kg/day. The administration of filgrastim to pregnant rabbits during the period of organogenesis at doses of 20 microgram/kg/day intravenously, or greater, was associated with an increased incidence of embryonic loss, urogenital bleeding and decreased food consumption. External abnormalities were not observed in the fetuses of treated does, but there was a significant increase in the incidence of fusion of sternebrae at an 80 microgram/kg/day dose. The administration of filgrastim to pregnant rabbits at a dose of 5 microgram/kg/day intravenously was not associated with observable adverse effects to the doe or fetus.

Use in lactation

It is not known whether filgrastim is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised in the use of TEVAGRASTIM in breastfeeding women.

Use in children

Long-term follow-up data are available from a postmarketing surveillance study in SCN patients including 32 infants, 200 children and 68 adolescents. The data suggest that height and weight are not adversely affected in paediatric patients who received up to five years of filgrastim treatment. Limited data from patients who were followed in a phase 3 study to assess the safety

and efficacy of filgrastim in SCN for 1.5 years did not suggest alterations in sexual maturation or endocrine function.

Paediatric patients with congenital types of neutropenia (Kostmann's syndrome, congenital agranulocytosis or Schwachman Diamond syndrome) have developed cytogenetic abnormalities and have undergone transformation to MDS and AML while receiving chronic filgrastim treatment. The relationship of these events to TEVAGRASTIM administration is unknown (see Warnings, Adverse Reactions).

Although use in children with acute myeloid leukaemia is not excluded, published experience is limited and safety has not been clearly established.

Use in elderly
Clinical trials with filgrastim have included a small number of elderly patients but special studies have not been performed in this group and therefore specific dosage recommendations cannot be made.

Patients with renal or hepatic impairment
Studies of filgrastim in patients with severe impairment of renal or hepatic function demonstrate that it exhibits a similiar pharmacokinetic and pharmacodynamic profile to that seen in normal individuals. Dose adjustment is not required in these circumstances.

Interactions with other medicines
Increased haemopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging changes. This should be considered when interpreting bone imaging results.

Since lithium promotes the release of neutrophils, it is likely to potentiate the effect of filgrastim. Although this interaction has not been formally investigated, there is no evidence that such an interaction is harmful.

Cancer patients receiving myelosuppressive chemotherapy
Chronic administration
No evidence of interaction of filgrastim with other drugs was observed in the course of clinical trials (see Precautions, Myelosuppressive chemotherapy, Concurrent use with chemotherapy and radiotherapy).

ADVERSE REACTIONS

Cancer patients receiving myelosuppressive chemotherapy
In clinical trials involving over 200 patients receiving filgrastim following cytotoxic chemotherapy, most adverse experiences were the sequelae of the underlying malignancy or cytotoxic chemotherapy. In all phase II/III trials, medullary bone pain was the only consistently observed adverse reaction attributed to filgrastim therapy, reported in 24% of patients. This bone pain was generally reported to be of mild to moderate severity, and could be controlled in most

patients with non-narcotic analgesics; infrequently, bone pain was severe enough to require narcotic analgesics. Bone pain was reported more frequently in patients treated with higher doses (20 to 100 microgram/kg/day) administered intravenously, and less frequently in patients treated with lower subcutaneous doses of filgrastim (3 to 10 microgram/kg/day).

In the randomised, double blind, placebo controlled trial of filgrastim therapy following combination chemotherapy in patients with small cell lung cancer, the adverse events shown in Table 1 were reported to be possibly, probably or definitely related to the double blind study medication (placebo or filgrastim at 4 to 8 microgram/kg/day).

Table 8 – Clinical adverse events reported to be related to double blind study medication

Body system	**Percentage of patients**	
	Placebo (n=68)	**Filgrastim (n=69)**
Musculoskeletal	1.5	12.0
Dermatological	6.0	6.0
Body as a whole	5.0	4.3
Neurological/psychiatric	3.0	4.3
Respiratory	1.5	3.0
Vascular disorders	1.5	3.0
Local reaction	1.5	1.4
Thrombocytopenia/coagulation	2.9	Not reported
Autonomic nervous system	Not reported	1.4
Special senses	Not reported	1.4

In this study, there were no serious, life threatening or fatal adverse reactions attributed to filgrastim therapy. Specifically, there were no reports of flu-like symptoms, pleuritis, pericarditis or other major systemic reactions to filgrastim.

Spontaneously reversible elevations in uric acid, lactate dehydrogenase and alkaline phosphatase occurred in 26 to 56% of patients receiving filgrastim following cytotoxic chemotherapy; these elevations were not reported to be associated with clinical adverse events.

The occurrence of stomatitis and diarrhoea in patients receiving allogeneic transplants is consistent with the use of myeloablative chemotherapy. In a study of 70 patients undergoing allogeneic bone marrow transplantation in which 33 patients were randomised to the placebo group and 37 to the filgrastim group, the incidence and severity of diarrhoea and stomatitis increased from the pretransplant to the post-transplant period in both the placebo and filgrastim treated patients. Prior to transplantation, 12 patients randomised to the placebo group and six patients randomised to filgrastim reported moderate to severe diarrhoea. Following transplantation, the incidence of moderate to severe diarrhoea increased to 23 and 14 patients respectively. No patients in either group experienced moderate or severe stomatitis prior to transplantation, while after transplantation, 19 patients in the placebo group and eight patients in the filgrastim group reported moderate to severe stomatitis.

In a randomised double blind placebo controlled phase III study of patients with acute myeloid leukaemia, there were three patients reported to have developed ARDS during the study (two filgrastim, one placebo). This is a rare but expected event in this patient population, and all three patients had recognised predisposing factors. As a causal relationship between the development of ARDS and filgrastim treatment has not been established, and as multiple risk factors are often present, any decision to discontinue filgrastim in this setting should be based on the overall assessment of contributing factors.

Extremely rare cases of capillary leak syndrome have been reported.

Rare cases (>0.01% and <0.1%) of Sweet's syndrome (acute febrile dermatosis) have been reported.

Very rare (estimated 0.03 cases per 100,000 exposures [0.00003%]) events of pseudogout have been reported in patients with cancer treated with filgrastim.

Chronic administration

With chronic administration, clinical splenomegaly has been reported in 30% of patients. Less frequently observed adverse events included exacerbation of some pre-existing skin disorders (e.g. psoriasis), cutaneous vasculitis (leucocytoclastic), alopecia, haematuria/ proteinuria, thrombocytopenia (platelets < 50 x 10^9/L) and osteoporosis. Patients receiving chronic treatment with TEVAGRASTIM should be monitored periodically for the appearance of these conditions.

No evidence of interaction of filgrastim with other drugs was observed in the course of clinical trials (see Precautions, Concurrent use with chemotherapy and radiotherapy). Since commercial introduction of filgrastim, there have been rare reports (< 1 in 100,000 administrations) of symptoms suggestive of allergic type reactions, such as anaphylaxis, dyspnoea, hypotension, skin rash and urticaria, but in which an immune component has not been demonstrated. Approximately half occurred following the initial dose; reactions occurred more frequently with intravenous administration. Symptoms recurred in some patients who were rechallenged. There have been rare reports (< 1 in 500,000 administrations) of cutaneous vasculitis. TEVAGRASTIM should be permanently discontinued in patients who experience a serious allergic reaction.

In chronically treated patients, including some who have received filgrastim daily for almost two years, there has been no evidence of the development of antibodies to filgrastim or a blunted or diminished response over time.

Peripheral blood progenitor cell collection and therapy

Filgrastim mobilised autologous peripheral blood progenitor cell collection

In clinical trials, 126 patients have received filgarstim for mobilisation of peripheral blood progenitor cells. During the mobilisation period, adverse events related to filgrastim consisted primarily of mild to moderate musculoskeletal symptoms, reported in 44% of patients. These symptoms were predominantly events of medullary bone pain (38%). Headache was reported related to filgrastim in 7% of patients. Mild to moderate transient increases in alkaline

phosphatase levels were reported related to filgrastim in 21% of the patients who had serum chemistries evaluated during the mobilisation phase.

All patients had increases in neutrophil counts consistent with the biological effects of filgrastim. Two patients had a white blood cell count greater than 100 x 10^9/L with white blood cell count increases during the mobilisation period ranging from 16.7 x 10^9/L to 138 x 10^9/L above baseline. 88% of patients had an increase in white blood cell count between 10 x 10^9/L and 70 x 10^9/L above baseline. No clinical sequelae were associated with any grade of leucocytosis.

65% of patients had downward shifts in haemoglobin, which were generally mild to moderate (59%), and 97% of patients had decreases in platelet counts related to the leukapheresis procedure. Only two patients had platelet counts less than 50 x 10^9/L.

Allogeneic peripheral blood progenitor cell mobilisation in normal donors
The most commonly reported adverse event was mild to moderate transient musculoskeletal pain. Leucocytosis (WBC > 50 x 10^9/L) was observed in 41% of donors and transient thrombocytopenia (platelets < 100 x 10^9/L) following filgrastim and leukapheresis was observed in 35% of donors.

Transient, minor increases in alkaline phosphatase, LDH, AST and uric acid have been reported in normal donors receiving filgrastim; these were without clinical sequelae.

Exacerbation of arthritic symptoms has been observed very rarely.

Symptoms suggestive of severe allergic reactions have been reported very rarely.

Headaches, believed to be caused by filgrastim, have been reported in PBPC donor studies.

There have been rare cases of splenic rupture reported in normal donors receiving G-CSFs (see Precautions).

Extremely rare cases of capillary leak syndrome have been reported.
In normal donors, pulmonary adverse events (haemoptysis, pulmonary infiltrates) have been reported very rarely (< 0.01%).

Peripheral blood progenitor cell transplantation supported by filgrastim
During the period of filgrastim administration after infusion of autologous peripheral blood progenitor cells, filgrastim was administered to 110 patients as supportive therapy and adverse events were consistent with those expected after high dose chemotherapy. Mild to moderate musculoskeletal pain was the most frequently reported adverse event related to filgrastim, reported in 15% of patients. In patients receiving allogeneic PBPCs, a similar incidence of musculoskeletal pain was reported.

Severe chronic neutropenia
The safety and efficacy of chronic daily administration of filgrastim in patients with severe chronic neutropenia have been established in phase I/II clinical trials of 74 patients treated for up to three years, and in a phase III trial of 123 patients treated for up to two years.

Mild to moderate bone pain was reported in approximately 33% of patients in clinical trials. This symptom was readily controlled with mild analgesics. General musculoskeletal pain was also noted in higher frequency in patients treated with filgrastim.

Palpable splenomegaly was observed in approximately 30% of patients. Abdominal or flank pain was seen infrequently and thrombocytopenia ($< 50 \times 10^9$/L) was noted in 12% of patients with palpable spleens. Less than 3% of all patients underwent splenectomy, and most of these had a prestudy history of splenomegaly. Less than 6% of patients had thrombocytopenia ($< 50 \times 10^9$/L) during filgrastim therapy, most of whom had a prestudy history. In most cases, thrombocytopenia was managed by filgrastim dose reduction or interruption. There were no associated serious haemorrhagic sequelae in these patients. Epistaxis was noted in 15% of patients treated with filgrastim, but was associated with thrombocytopenia in 2% of patients. Anaemia was reported in approximately 10% of patients, but in most cases appeared to be related to frequent diagnostic phlebotomy, chronic illness or concomitant medications.

Cytogenetic abnormalities, transformation to myelodysplasia and acute myeloid leukaemia have been observed in patients treated with filgrastim for severe chronic neutropenia (SCN) (see Precautions, Severe chronic neutropenia). Based on analysis of data from a postmarketing surveillance study of 531 SCN patients with an average follow-up of 4.0 years, the risk of developing these abnormalities (cytogenetic abnormalities, myelodysplasia and AML) appears to be confined to the subset of patients with congenital neutropenia. A life table analysis of these data revealed that the cumulative risk of developing leukaemia or MDS by the end of the eighth year of Neupogen treatment in a patient with congenital neutropenia was 16.5% which is an annual rate of approximately 2%.

Cytogenetic abnormalities, including monosomy 7, have been reported in patients treated with filgrastim who had previously documented normal cytogenetic evaluations. It is unknown whether the development of cytogenetic abnormalities, myelodysplasia or AML is related to chronic daily filgrastim administration or to the natural history of SCN. It is also unknown if the rate of conversion in patients who have not received filgrastim is different from that of patients who have received filgrastim. Routine monitoring through regular FBCs is recommended for all SCN patients. Additionally, annual bone marrow and cytogenetic evaluations are recommended in all patients with congenital neutropenia (see Precautions, Laboratory monitoring).

Other adverse events infrequently observed and possibly related to filgrastim therapy were injection site reaction, headache, hepatomegaly, arthralgia, osteoporosis, rash, alopecia, cutaneous vasculitis and haematuria/ proteinuria. Patients receiving chronic treatment with filgrastim should be monitored periodically for the appearance of these conditions.

HIV infection
In three clinical studies involving a total of 244 HIV positive patients, the only adverse events that were consistently considered related to filgrastim administration were musculoskeletal pain, predominantly mild to moderate bone pain and myalgia. In the largest of the three studies involving 200 patients, the event rate was 12%. This is consistent with the 14% incidence of musculoskeletal pain reported in clinical trials in other indications where doses of 0.35 to 11.5 microgram/kg/day were used. The incidence of severe musculoskeletal pain (3%) was identical to that reported in clinical trials in other indications.

In a small study of 24 patients, there were seven reports of treatment related splenomegaly, but in a larger study of 200 patients, there were no such reports. In the former study, no baseline measurements of spleen size were made for comparison with on-study measurements. In all cases, splenomegaly was mild or moderate on physical examination and the clinical course was benign; no patients had a diagnosis of hypersplenism and no patients underwent splenectomy. As splenic enlargement is a common finding in patients with HIV infection and is present to varying degrees in most patients with AIDS, the relationship to filgrastim treatment is unclear.

An analysis was performed on viral load data, as measured by HIV-1 RNA polymerase chain reaction (PCR), from a controlled randomised study of filgrastim for the prevention of grade 4 neutropenia. No clinically or statistically significant differences were seen between filgrastim treated groups and untreated groups for changes in viral load over a 24 week period. However, since the study was not powered to show equivalence between the groups, the possibility that filgrastim affects HIV-1 replication cannot be excluded. There was also no detrimental effect on immunological markers, which is important in a population of patients in whom a decline in CD4+ T-lymphocyte count is expected. There were no safety concerns with long-term administration of filgrastim in this setting.

DOSAGE AND ADMINISTRATION

Cancer patients receiving standard dose cytotoxic chemotherapy or induction/ consolidation chemotherapy for acute myeloid leukaemia
In adults and children receiving induction/ consolidation chemotherapy for AML, the recommended starting dose is 5 microgram/kg/day administered as a single daily subcutaneous injection.

In patients with nonmyeloid malignancies receiving standard dose cytotoxic chemotherapy, the recommended starting dose of TEVAGRASTIM is 5 microgram/kg/day, administered as a single daily subcutaneous injection or short intravenous infusion (over 15 to 30 minutes). In phase III trials efficacy was observed at doses of 4 to 8 microgram/kg/day.

TEVAGRASTIM should not be administered in the period 24 hours before to 24 hours after the administration of chemotherapy (see Precautions).

The duration of TEVAGRASTIM therapy needed to attenuate chemotherapy induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen

employed. In patients with nonmyeloid malignancies receiving standard dose cytotoxic chemotherapy, TEVAGRASTIM should be administered daily for up to two weeks, until the ANC has reached 10 x 10^9/L following the expected chemotherapy induced neutrophil nadir. In patients with AML receiving induction or consolidation chemotherapy, TEVAGRASTIM should be administered daily until the ANC has reached > 1.0 x 10^9/L for three consecutive days or > 10 x 10^9/L for one day following the expected chemotherapy induced neutrophil nadir.

Patients with nonmyeloid malignancies receiving high dose cytotoxic chemotherapy with autologous or allogeneic bone marrow or peripheral blood progenitor cell transplantation.
The recommended starting dose of TEVAGRASTIM is 10 microgram/kg/day given by continuous subcutaneous infusion or by intravenous infusion over 4 to 24 hours. TEVAGRASTIM should be diluted in 25 to 50 mL of glucose 5% solution. The first dose of TEVAGRASTIM should be administered not less than 24 hours following cytotoxic chemotherapy and within 24 hours of bone marrow or PBPC infusion.

Once the neutrophil nadir has been passed, the daily dose of TEVAGRASTIM should be titrated against the neutrophil response as follows.

If the ANC is > 1 x 10^9/L for three consecutive days, reduce the TEVAGRASTIM dose to 5 microgram/kg/day.*

Then, if the ANC remains > 1 x 10^9/L for three consecutive days, discontinue TEVAGRASTIM. If the ANC decreases to < 1 x 10^9/L, resume TEVAGRASTIM at 5 microgram/kg/day.

*If the ANC decreases to < 1 x 10^9/L at any time during the 5 microgram/kg/day administration, TEVAGRASTIM should be increased to 10 microgram/kg/day and the above steps should then be followed.

Patients with myeloid malignancies receiving high dose cytotoxic chemotherapy with autologous or allogeneic bone marrow or peripheral blood progenitor cell transplantation.
Following transplant, the recommended dose of TEVAGRASTIM to be given to the recipient is 5 microgram/kg/day until neutrophil recovery (up to 28 days). When given after transplantation, the first dose of TEVAGRASTIM should be administered at least 24 hours after cytotoxic chemotherapy and at least 24 hours after infusion of bone marrow or PBPCs.

Autologous peripheral blood progenitor cell collection and therapy.
The recommended dose of TEVAGRASTIM for peripheral blood progenitor cell mobilisation when used alone is 10 microgram/kg/day given as a single daily subcutaneous injection or a continuous 24 hour infusion. TEVAGRASTIM therapy should be given for at least four days before the first leukapheresis procedure, and should be continued through to the day of the last leukapheresis procedure. Collections should be commenced on day 5 and continued on consecutive days until the desired yield of haemopoietic progenitor cells is obtained. For peripheral blood progenitor cells mobilised with TEVAGRASTIM alone, a schedule of leukapheresis collections on days 5, 6 and 7 of a seven day treatment regimen has been found to be effective. In some patients with extensive prior chemotherapy, additional daily doses of TEVAGRASTIM may be required to support additional leukaphereses to reach the desired target

yield of cells (see Precautions, Peripheral blood progenitor cell collection and therapy, Prior exposure to cytotoxic agents).

The recommended dose of TEVAGRASTIM for peripheral blood progenitor cell mobilisation after myelosuppressive chemotherapy is 5 microgram/kg/day given daily by subcutaneous injection from 24 hours after completion of chemotherapy until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Leukapheresis should be commenced during the period when the ANC rises from $< 0.5 \times 10^9$/L to $> 5.0 \times 10^9$/L. Leukapheresis collection should be repeated on consecutive days until an adequate number of progenitor cells is obtained (see Precautions, Peripheral blood progenitor cell collection and therapy, Prior exposure to cytotoxic agents).

In all clinical trials of filgrastim for the mobilisation of peripheral blood progenitor cells, filgrastim was administered following infusion of the collected cells. In the randomised phase III study, patients received filgrastim 5 microgram/kg/day after transplantation until a sustainable ANC ($> 0.5 \times 10^9$/L) was reached (see Pharmacology, Peripheral blood progenitor cell collection and therapy). When given after transplantation, the first dose of TEVAGRASTIM should be administered at least 24 hours after cytotoxic chemotherapy and at least 24 hours after infusion of peripheral blood progenitor cells.

Allogeneic peripheral blood progenitor cell collection from normal donors.
For PBPC mobilisation in normal donors, TEVAGRASTIM should be administered at 10 microgram/kg/day subcutaneously for four to five consecutive days. Leukapheresis should be started on day 5 and daily collections continued on day 6 in order to collect a target yield of 4×10^6 CD34+ cells/kg recipient bodyweight.

Severe chronic neutropenia.
Diagnosis
Care should be taken to confirm the diagnosis of severe chronic neutropenia, which may be difficult to distinguish from myelodysplasia, before initiating TEVAGRASTIM therapy.
It is essential that serial full blood counts with differential and platelet counts, and an evaluation of bone marrow morphology and karyotype be performed prior to initiation of TEVAGRASTIM therapy.

Congenital neutropenia
The recommended daily starting dose is 12 microgram/kg subcutaneously every day (single or divided doses).

Idiopathic or cyclic neutropenia
The recommended daily starting dose is 5 microgram/kg subcutaneously every day (single or divided doses).

TEVAGRASTIM may be administered subcutaneously as a single daily injection to increase and sustain the average neutrophil count above 1.5×10^9/L. Chronic daily administration is required to maintain an adequate neutrophil count. After one to two weeks of therapy, the initial dose may be doubled or halved. Subsequently, the dose may be individually adjusted not more than every

one to two weeks to maintain the average neutrophil count between 1.5 and 10 x 10^9/L. The dose should be reduced if the ANC is persistently above 10 x 10^9/L for one to two weeks.

In clinical trials, 97% of patients who responded to treatment with filgrastim were treated at doses less than or equal to 24 microgram/kg/day. In the SCN postmarketing surveillance study, the reported median daily doses of filgrastim were 6.0 microgram/kg (congenital neutropenia), 2.1 microgram/kg (cyclic neutropenia) and 1.2 microgram/kg (idiopathic neutropenia). In rare instances, patients with congenital neutropenia have required doses of filgrastim greater than or equal to 100 microgram/kg/day.

HIV infection

For reversal of neutropenia

The recommended starting dose of TEVAGRASTIM is 1 microgram/kg/day administered daily by subcutaneous injection with titration up to a maximum of 5 microgram/kg/day until a normal neutrophil count is reached and can be maintained (ANC greater than or equal to 2.0 x 10^9/L). In clinical studies, 96% of patients responded to filgrastim at these doses, achieving reversal of neutropenia in a median of two days.

In a small number of patients (2%), doses of up to 10 microgram/kg/day were required to achieve reversal of neutropenia.

For maintaining neutrophil counts

When reversal of neutropenia has been achieved, the minimal effective dose of TEVAGRASTIM to maintain a normal neutrophil count should be established. Initial dose adjustment to three times weekly dosing with 300 microgram/day by subcutaneous injection is recommended. Further dose adjustment may be necessary, as determined by the patient's ANC, to maintain the neutrophil count at greater than or equal to 2.0 x 10^9/L. In clinical studies, dosing with 300 microgram/day on one to seven days per week was required to maintain the ANC greater than or equal to 2.0 x 10^9/L, with the median dose frequency being three days per week. Long-term administration may be required to maintain the ANC greater than or equal to 2.0 x 10^9/L. TEVAGRASTIM dosing should be reduced and then stopped if myelosuppressive medication is discontinued and there is no recurrence of neutropenia.

Dilution and sterile transfer

TEVAGRASTIM syringes should be used in one patient on one occasion only and any residue discarded.

If required, TEVAGRASTIM may be diluted in glucose 5%. TEVAGRASTIM diluted to concentrations below 15 microgram/mL should be protected from adsorption to plastic materials by addition of albumin (human) to a final concentration of 2 mg/mL. When diluted in glucose 5% or glucose 5% plus albumin (human), TEVAGRASTIM is compatible with glass and a variety of plastics including PVC, polyolefin and polypropylene.

Dilution to a final concentration of less than filgrastim 5 microgram/mL is not recommended at any time. Do not dilute with saline at any time; product may precipitate. Infusion should be complete within 24 hours of the sterile dilution and transfer.

To reduce microbiological hazard, TEVAGRASTIM should be used as soon as practicable after dilution. If it is not administered immediately, it must be stored in the refrigerator at 2-8°Cand infusion must be complete within 24 hours of dilution.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit; if particulates or discolouration are observed, the container should not be used.

OVERDOSAGE

The maximum tolerated dose of TEVAGRASTIM has not been determined. Twenty seven patients have been treated at filgrastim doses of greater than or equal to 69 microgram/kg/day. Of those, six patients have been treated at 115 microgram/kg/day with no toxic effects attributable to filgrastim. Efficacy has been demonstrated using much lower doses. (Doses of 4 to 8 microgram/kg/day showed efficacy in the phase III study.) Doses of TEVAGRASTRIM that increase the ANC beyond 10×10^9/L may not result in any additional clinical benefit.

In clinical trials of filgrastim in cancer patients receiving myelosuppressive chemotherapy, white blood cell counts > 100×10^9/L have been reported in less than 5% of patients, but were not associated with any reported adverse clinical effects.

It is recommended, to avoid the potential risks of excessive leucocytosis, that TEVAGRASTIM therapy should be discontinued if the ANC surpasses 10×10^9/L after the chemotherapy induced ANC nadir has occurred.

In cancer patients receiving myelosuppressive chemotherapy, discontinuation of TEVAGRASTRIM therapy usually results in a 50% decrease in circulating neutrophils within one to two days, with a return to pretreatment levels in one to seven days.

PRESENTATION AND STORAGE CONDITIONS

TEVAGRASTIM (solution for injection or infusion) is available in strengths of 300mcg/0.5mL prefilled syringes in packs of 1's, 5's and 10's.

TEVAGRASTIM (solution for injection or infusion) is available in strengths of 480mcg/0.8mL prefilled syringes in packs of 1's, 5's and 10's.

Store between 2 to 8°C. To reduce micro biological hazard, TEVAGRASTIM should be used as soon as practicable after dilution. If it is not administered immediately, it must be stored in the refrigerator at 2°C to 8°C and infusion must be complete within 24 hours of dilution.

NAME AND ADDRESS OF SPONSOR

Aspen Pharmacare Australia Pty Ltd
34-36 Chandos St
St Leonards NSW 2065
Australia

POISONS SCHEDULE

S4 (Prescription Only Medicine)

Date of approval: 16 August 2011

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au

Reference/Publication #