

EXPERT OPINION

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Clinical safety of biosimilar recombinant human granulocyte colony-stimulating factors

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Introduction: A 'biosimilar', or 'similar biological medicinal product', is a biologic agent that is similar in terms of quality, safety and efficacy to an authorized reference biological medicine. Since the expiration of the filgrastim patent in Europe, three agents have received marketing authorization from the EMA: Tenvagrastim, Zarzio and Nivestim. Tenvagrastim has also been approved as a biologic by the FDA as tbo-filgrastim.

Areas covered: Using the EMA dossiers (all three agents), the FDA dossier (Tenvagrastim), and journal publications, this article reviews clinical safety data for these products with emphasis on serious/severe adverse events and special consideration of immunogenicity, bone pain, splenomegaly, allergic reactions, acute respiratory distress syndrome and mortality.

Expert opinion: All three agents have similar safety profiles. None were statistically higher on safety parameters to what is known about originator filgrastim (Neupogen). What is known about filgrastim in general regarding safety can be extended to biosimilar filgrastim. Safety profiles may become more differentiated once long-term product-specific safety data are available. Large-sample, long-term, observational studies of real-world practice will provide the heterogeneity and statistical power to demonstrate product-specific safety profiles. Current evidence indicates that statistically no one product is less and no one product is more safe.

Keywords: biosimilar pharmaceuticals, biosimilars, drug safety, granulocyte colony-stimulating factor, recombinant proteins, safety

Expert Opin. Drug Saf. (2013) 12(2):235-246

1. Introduction

Human granulocyte colony-stimulating factor (GCSF) is a granulopoietic growth factor produced by various immune cells in the body. As a cytokine for neutrophil precursors in the bone marrow, endogenous GCSF regulates neutrophil production and thus stimulates white blood cell production [1,2]. Human GCSF was cloned in 1986 [3,4]. Exogenous GCSF is synthesized by means of recombinant DNA technology in either an *Escherichia coli* expression system (filgrastim, the agent under consideration in this article) or in Chinese hamster ovary cells (lenograstim). Following two successful trials [5,6], filgrastim (Neupogen, Amgen, Thousand Oaks, CA, USA) was the first agent in the class of GCSFs approved for clinical use by the Food and Drug Administration (FDA).

The main indication for GCSFs is in the cancer setting. This class of agents is used in first place to reduce the duration of neutropenia and the incidence of febrile neutropenia in patients undergoing cytotoxic chemotherapy (Table 1). In the cancer setting, it is also approved to reduce the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation who are at risk of prolonged severe neutropenia; and in the mobilization of peripheral blood

Article highlights.

- A biosimilar is a biologic agent that is similar in terms of quality, safety and efficacy to an authorized reference biological medicine. Three biosimilar recombinant granulocyte colony-stimulating factors (GCSFs) have been approved by the European Medicines Agency (EMA): Tenvagrastim (Teva), Zarzio (Sandoz) and Nivestim (Hospira). Tenvagrastim has also been approved by the Food and Drug Administration (FDA) as a biologic under the name tbo-filgrastim.
- Manufacturing processes influence the quality, purity, biological parameters and clinical activity of the final product, which in turn affects efficacy and safety.
- Bone pain is the most frequent adverse event (AE). The incidence of immunogenicity reactions is low, as is the incidence of splenomegaly, allergic reactions and acute respiratory distress syndrome (ARDS). Detail of safety reporting in the documents reviewed is variable.
- The safety profiles of Tenvagrastim, Zarzio and Nivestim are consistent with what is known about the clinical safety of filgrastim; and, importantly, when compared among themselves. Statistically, no one product is less and no one product is more safe.

This box summarizes key points contained in the article.

progenitor cells (PBPC). Secondary indications include neutropenic patients with human immunodeficiency virus (HIV) or with a history of severe, repeated infections. Prophylactic use of GCSF reduces the relative risk of febrile neutropenia. GCSF use is associated with a reduction in early death, including infection-related deaths. Whether GCSF treatment directly impacts being cancer-free or surviving longer is unknown, as this has never been a specific end point in clinical studies [7].

The patent for filgrastim expired in Europe in 2006 and will expire in the USA in 2013. The European Medicines Agency (EMA) has approved several biosimilar versions, three of which are commercially available. In chronological order of approval and using their most common commercial name, these include Tenvagrastim (Teva; approved 24 July 2008; also known as Biograstim, Filgrastim ratiopharm and Ratio-grastim; code XM02), Zarzio (Sandoz; approved 20 November 2008; also known as Filgrastim Hexal; code EP2006) and Nivestim (Hospira; approved 18 March 2010; no code found, therefore GCF used in accordance with trial code numbers). One of these, Tenvagrastim, has been approved in the USA (29 August 2012) as a biologic agent as there was no approval pathway for biosimilars at that time.

Referred to legally in Europe as a 'similar biological medicinal product', a biosimilar is a biologic agent that is similar in terms of quality, safety and efficacy to an authorized reference biological medicine. The EMA requires manufacturers of biosimilars to provide the quality data required for any biotechnology product as well as comparability data that demonstrate the high similarity of the proposed biosimilar product to the originator reference product [8].

Being biologicals, biosimilar GCSFs are structurally complex proteins with significant micro-heterogeneity, produced by genetically modified living cells, and difficult to produce and purify [9]. This makes for complex manufacturing processes in terms of choice of cell type, and production, purification and formulation methods. Manufacturing processes influence the quality, purity, biological parameters and clinical activity of the final product, which in turn affects efficacy and safety. As Schellekens pointed out, 'even if the biosimilar product has the same gene sequence, vector, host cell line, culture conditions and purification methods' as the reference protein, 'it can still differ substantially in its biological and clinical properties' [9].

In this article, the second in a series of reviews and appraisals of the evidence base on the safety of biosimilar agents [10], the authors review the clinical safety of the three biosimilar recombinant human GCSFs that have received marketing authorization from the EMA. These authorizations cover the use of these GCSFs in the prophylaxis of (febrile) neutropenia. Over the years, these three products and their manufacturers may have had different names as manufacturers and product lines were acquired. Products are reviewed in chronological order of EMA marketing authorization. Brand names are used mainly because all three products are referred to as filgrastim; product codes could only be identified for Tenvagrastim (XM02) and Zarzio (EP2006); and in keeping with the EMA's safety guidance to assure traceability. This need for traceability, the fact that the efficacy and safety evidence bases for biosimilar GCSFs are still evolving, and interchangeability of innovator and biosimilar products in practice warrant the use of commercial names instead of international non-proprietary names (INN), even if this may be counter to the prevailing trend in biomedical journals to use the latter. This clinical safety review is limited to adults as information on pediatric populations is insufficient. The focus being on clinical safety, this review assumes that the efficacy of the three products has been established. Efficacy is not addressed here, and neither are any preclinical activities. Safety data for each product are presented in absolute terms. No comparisons with other products are made as the focus is on an independent analysis of the safety of each agent.

The primary sources of evidence are the EMA's European Public Assessment Report (EPAR) documents, mainly the Scientific Discussion document but also the accompany Summary of Product Characteristic (SmPC) annexes and any related regulatory document, as posted on the EMA website [11-13]. For Tenvagrastim, the authors also used the FDA review documents as available on the FDA website [14]. In addition, they used articles published in peer-reviewed biomedical journals. Abstracts and posters were excluded because of constraints in the depth of reporting. The EMA and FDA approval processes may be considered at least equal to typical journal peer review and, in addition, includes detailed regulatory review of study processes, methods and analytics. Manufacturers were not approached for information.

Table 1. Therapeutic indications for each biosimilar GCSF as approved by the EMA.

		Zarzio	Tevagrastim	Nivestim
Cancer	Reduction in the duration of neutropenia and incidence of febrile neutropenia in patients with established cytotoxic chemotherapy for malignancy	✓	✓	✓
	Reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia	✓	✓	✓
	Mobilization of PBPC	✓	✓	✓
HIV	Treatment of persistent neutropenia in patients with advanced HIV infection and to reduce risk of bacterial infections if other treatments not appropriate	✓	✓	✓
Infections	Increase levels of neutrophils and reduce risk of infections in patients with neutropenia who have history of severe, repeated infections	✓	✓	✓

EMA: European Medicines Agency; GCSF: Granulocyte colony-stimulating factor; HIV: Human immunodeficiency virus; PBPC: Peripheral blood progenitor cells.

This article follows the structure of the recent review on biosimilar erythropoietins [10]. Following an overview of factors relevant to the clinical safety of biosimilar GCSFs, the authors review the safety findings obtained in the clinical (i.e., in human) development program of each of the three biosimilar GCSFs. Non-serious and non-severe safety issues known to be common in GCSFs are not reviewed in detail. Special emphasis is given to immunogenicity, bone pain, splenomegaly, allergic reactions, acute respiratory distress syndrome (ARDS) and mortality. Following a discussion, the authors offer an opinion on the clinical safety of the three products.

Note that the occasional similarities in text between this and the authors' recent article [10] is on purpose to provide a set of consistent papers that can be used readily in the evaluation of the safety of biosimilars by clinicians, regulators and payers.

2. Major clinical safety issues for recombinant human GCSFs

Immunogenicity refers to the ability of a protein antigen to elicit an immune response in a human or animal and the production of antibodies. A recombinant protein, even if similar to the endogenously produced protein, may stimulate the production of anti-product antibodies [15-17]. There are three potential responses. First, the antibodies may not have any observable effect on either the endogenous or exogenous protein. Second, the antibodies may bind to and thus attenuate or inactivate the exogenous protein, resulting in hypersensitivity reactions. Third, the antibodies may neutralize the endogenous protein. *Bone pain* is a common adverse event (AE) associated with GCSFs. As used in this review, the term refers not only to bone pain but also encompasses arthralgia; myalgia; neck, back, sacral, pelvic and musculo-skeletal pain; jaw pain and pain in extremity. *Splenomegaly* is relatively common and often expressed as abdominal pain. It may evolve into splenic rupture. *Allergic reactions* may include general drug hypersensitivity and general allergic reactions, as well as more specific reactions such as

angioneurotic edema, allergic dermatitis, rash, pruritic rash and urticaria. *ARDS* may be expressed as acute respiratory failure and respiratory failure.

3. Clinical safety of Tevagrastim

3.1 Summary of clinical development program

The clinical development program of XM02, as submitted to the EMA [11] and the FDA [14], comprised two Phase I pharmacokinetic and pharmacodynamic studies in 200 healthy volunteers (studies XM02-01-LT and XM02-05-DE) and three Phase III studies in breast cancer (XM-02-02-INT), lung cancer (XM-02-03-INT) and non-Hodgkin's lymphoma (XM-02-04-INT) involving in total 677 patients. Though the search was not exhaustive, publications were found for studies XM02-01-LT [18], XM02-05-DE [19], XM02-02-INT [20], XM02-03-INT [21] and XM02-04-INT [22]. In addition, one publication reported on a meta-analysis involving studies XM02-02-INT, XM02-03-INT and XM02-04-INT [23] and one article presented the findings of a single-center experience study of 14 patients receiving plerixafor and XM02 for peripheral blood stem cell mobilization [24].

As per the authors' count, 733 subjects were exposed to XM02 in the clinical development program. An additional 14 patients were exposed to XM02 in later studies, for a total of 747 patients.

3.2 Phase I studies

3.2.1 Study designs

- XM02-01-LT was a randomized, single dose, two-period crossover, two-arm study of 56 healthy volunteers with a 14-day washout period of XM02 compared with Neupogen in doses of 5 and 10 µg/kg administered subcutaneously (s.c.).
- XM02-05-DE was a randomized single-dose, single-blind, two-period crossover study of both intravenous (i.v.) and s.c. formulations of XM02 in doses of 5 and 10 µg/kg compared with similar i.v. and s.c. doses of Neupogen enrolling 140 healthy volunteers.

3.2.2 Safety results

The safety population in the Phase I studies comprised 192 healthy volunteers exposed to XM02: 56 in XM01-01-LT and 136 in XM02-05-DE. In XM02-01-LT, 75 AEs were reported in 31 out of 56 subjects. No serious adverse events (SAEs) were recorded. There were six AE reports of myalgia. There were no other reports of bone pain, nor of immunogenicity, splenomegaly, allergic reactions, ARDS and death. In XM02-02-DE, 81 of 136 XM02-exposed subjects experienced an AE: 47 reported bone pain, mainly mild ($n = 40$) or moderate ($n = 6$). The one subject with severe back pain, who also exhibited moderate sweating during infusion of the 5 $\mu\text{g}/\text{kg}$ i.v. formulation, was withdrawn. Both events were judged to be probably related to XM02. They were not serious and resolved without intervention. The AEs in other subjects who were withdrawn were not related to study medication. Two subjects experienced rhinitis and three nasopharyngitis, that is, possibly allergic reactions. There were no cases of immunogenicity, splenomegaly, ARDS or death in association with exposure to XM02.

3.3 Phase III studies

3.3.1 Study designs

- XM02-02-INT was a randomized, placebo- and active-controlled trial in breast cancer patients treated with docetaxel/doxorubicin chemotherapy. A total of 348 patients were randomized in a 2:2:1 scheme to the XM02 ($n = 140$), Neupogen ($n = 136$) or placebo ($n = 72$) arms. Patients in the placebo arm were converted to XM02 therapy after completion of cycle 1. Dosing was 5 $\mu\text{g}/\text{kg}$ s.c. for a minimum of 5 and a maximum of 14 days.
- XM02-03-INT was a randomized active-controlled trial in lung cancer patients receiving platinum-based chemotherapy and designed specifically to evaluate the safety of XM02. In total, 240 patients were randomized 2:1 to XM02 ($n = 160$) or Neupogen ($n = 80$) treatment in cycle 1 of chemotherapy. All patients were treated with XM02 in subsequent chemotherapy cycles. Dosing was 5 $\mu\text{g}/\text{kg}$ s.c. for a minimum of 5 and a maximum of 14 days.
- XM02-04-INT was a randomized active-controlled trial in patients with non-Hodgkin's lymphoma receiving chemotherapy. It was designed specifically to evaluate the safety of XM02. A total of 92 patients were randomized 2:1 to XM02 ($n = 63$) or Neupogen ($n = 29$) treatment in cycle 1 of chemotherapy. All patients were treated with XM02 in subsequent cycles. Dosing was 5 $\mu\text{g}/\text{kg}$ s.c. for a minimum of 5 and a maximum of 14 days.

3.3.2 Safety results

Across the three studies, 356 patients were exposed to XM02 only and 134 to Neupogen only. Of patients switched

later to XM02, 115 were previously treated with Neupogen and 72 received a placebo. There are some discrepancies between the EMA EPAR document and the FDA medical review document in the detail with which efficacy results and safety data are reported.

Immunogenicity was investigated in the three studies using the following predefined characterization cascade of antibody assays using XM02 as test antigen. As per the EMA EPAR document, screening was done with anti-XM02 IgG enzyme-linked immunosorbent assay (ELISA) and anti-XM02 IgG-IgM Luminex assay. If the result was positive or questionable, IgG-specific and IgM-specific western blot confirmation assays were performed. If these were positive or questionable, the following three assays were done in parallel: quantitative anti-XM02 IgG Luminex assay using polyclonal calibrator sera and relative assay units (RU-MFI IgG); neutralizing antibodies using a GCSF-dependent NFS-60 cell-based assay and binding antibodies using a BIACORE total antibody assay. Among the 356 patients treated with XM02 only, 12 had positive antibody results at screening, 4 before cycle 1, 7 at subsequent visits, 2 at end of study and 2 at antibody follow-up. Excluding 33 cases with implausible results, there were no patients with positive antibodies at screening or before cycle 1, 3 at subsequent visits, and 1 at end of study and antibody follow-up. One patient was positive for neutralizing antibodies in later cycles and one borderline positive (23% inhibition with cut-off set at 23%) at antibody follow-up. This patient was still borderline positive after excluding implausible results.

Among the 115 patients first treated with Neupogen and subsequently with XM02, 2 had positive antibody results at screening, 1 before cycle 1 and 2 at antibody follow-up. Excluding seven cases with implausible results, there were no patients with positive antibodies at screening, before cycle 1, subsequent visits and at end of study, but one case at antibody follow-up. No patients were positive for neutralizing antibodies at any time point in this subsample.

Among the 72 patients first administered placebo and subsequently treated with XM02, 2 had positive antibody results at screening, 2 at visits after cycle but not at cycle 1, 1 at end of study and 2 at antibody follow-up. Excluding six cases with implausible results, there were no patients with positive antibodies at screening, before cycle 1, and one case at end of study and at antibody follow-up. No patients were positive for neutralizing antibodies at any time point in this subsample.

The above immunogenicity rates were statistically not different from those observed in the 134 patients treated exclusively with Neupogen. None of the immunogenicity findings were of clinical relevance and were believed to have major consequences for efficacy and safety.

As per the EPAR, 541 patients were treated with XM02 in some form (as per the authors' count 543). Of the XM02-exposed patients, 77.4% experienced at least one AE/SAE during treatment in cycle 1. In 13.9% of patients, the AE/SAE was drug-related. The AEs were rated severe in 19.8%

and serious in 10.9% of patients. Study drug was stopped in 2.0% of patients. Seven patients died as a consequence of an AE experienced during XM02 treatment; the percentage (1.3%) was statistically similar to the percentage among patients treated only with Neupogen (1.5%). Still in cycle 1, 9.9% of patients experienced AEs classified under bone pain and in 6.6% this was attributed to XM02; 3.7% reported abdominal pain and therefore possible splenomegaly, which was rated as related to XM02 in 0.6% of patients. Another 0.6% possibly exhibited an allergic reaction, but in none this was attributed to XM02. There were no cases of ARDS in cycle 1.

Reporting of AEs across all cycles was not as systematic as for cycle 1 in the EPAR document and the authors relied on the FDA medical review document instead. Among XM02-exposed patients, the FDA document cites 59 patients experiencing a non-fatal SAE, of which 2 cases were related to study drug in cycle 1. Across all cycles, non-fatal SAEs occurred on 118 patients and in 5 patients these were attributed to XM02. Among the XM02-exposed patients, 11 discontinued study participation prematurely but this was not attributed to XM02 treatment. Across all cycles, 27 patients discontinued study participation; for 2 patients, this was rated to be related to study drug. Rates for XM02-exposed patients were statistically not different from patients treated only with Neupogen.

As per the FDA document, among XM02-exposed patients, AEs classifiable as bone pain occurred in 65 patients (12.0%) during cycle 1, including one case of grade 3. In 27 (5.0%) of these patients the bone pain was attributed to study drug. Across all cycles, 130 patients (24.0%) experienced bone pain, including the one case of grade 3 observed in cycle 1. Fifty-four (10.0%) cases were related to study drug. Thirty-seven patients (6.8%) treated with XM02 reported abdominal pain, none with splenic rupture. Across all cycles, allergic reactions were reported in 3.7% of XM02-exposed patients. One patient had bronchospasm allergic reaction in cycle 1 after the 10th dose of XM02. Treatment with corticosteroids was effective and the patient received subsequent doses of XM02.

The FDA report cites one case of ARDS in cycle 1, which was not related to study drug. Across all cycles, three cases of ARDS were identified, all in study XM02-03-INT in the lung cancer setting, all in the XM02-only study arm, but none attributed to study drug.

Other non-fatal SAEs attributed to XM02 included one case of syncope in cycle 3 in the placebo/XM02 arm in study XM02-02-INT; and one case of myocardial infarction in cycle 3 and one case of thrombocytopenia in cycle 5 in the Neupogen/XM02 arm in study XM02-03-INT. In the same study, one patient in the XM02-only arm experienced thrombocytopenia in cycle 1 and hyperuricemia in cycle 2.

According to the EPAR and the three journal publications [20-22], 26 patients died across the three cancer studies. In the FDA medical review report, 27 deaths are cited, the difference being a death in study XM02-04-INT.

Twenty-two deaths occurred in study XM02-03-INT, which was in the lung cancer setting. None of the deaths were attributed to study medication.

3.4 Other study

One article reported on a single-center experience of plerixafor and Tevagrastim combination therapy as first-line peripheral blood stem cell mobilization strategy in eight patients with multiple myeloma and six patients with lymphoma candidate to autologous bone marrow transplantation [24]. Bone pain was reported to be the most common side effect, but no data are presented for this or other AEs. No mention is made of SAEs. None of the patients died during the observation period.

4. Clinical safety of Zarzio

4.1 Summary of clinical development program

The clinical development program of Zarzio (EP2006) submitted to the EMA for marketing authorization [12] included Phase I four pharmacokinetic and pharmacodynamic studies in 146 healthy volunteers (EP06-101; EP06-102; EP06-103; EP06-104) as well as one Phase III trial involving 170 breast cancer patients (EP06-301).

A thorough but non-exhaustive search identified one publication related to the above-referenced studies [25]. In addition, two reports of prospective single-center experience studies were found, one on 48 patients with solid tumors treated with cyclical chemotherapy [26] and one involving 40 patients with hematological malignancies treated with autologous peripheral blood stem cell mobilization [27]. One article reported on a retrospective review of 77 chemotherapy-treated patients with solid tumors or hematological malignancies and receiving primary or secondary prophylaxis with Zarzio [28]. Two articles described the background and methodology of an observational study of Zarzio in patients with selected solid tumors and hematological malignancies [29,30].

As per the authors' count, 316 subjects were exposed to XM02 in the clinical development program. An additional 88 patients were exposed to XM02 in later studies, for a total of 404 patients.

4.2 Phase I studies

4.2.1 Study designs

- EP06-101 was a randomized, double-blind, two-way crossover study involving 40 healthy volunteers with a 28-day washout period of multiple s.c. doses of 10 µg/kg XM02 compared with Neupogen.
- EP06-102 was a randomized, double-blind, two-way crossover study involving 26 healthy volunteers with a 12- to 18-day washout period treated with a single i.v. infusion of 5 µg/kg XM02 compared with Neupogen.
- EP06-103 was a randomized, double-blind, two-way crossover, two-dose-group study involving 56 healthy

volunteers with a 28- to 40-day washout period of multiple s.c. doses of 2.5 and 5 µg/kg XM02 compared with Neupogen.

- EP06-104 was a randomized, double-blind, two-way crossover study involving 24 healthy volunteers with a 14-day washout period treated with a single s.c. injection of 1 µg/kg XM02 compared with Neupogen.

4.2.2 Safety results

In the four Phase I studies, immunogenicity was evaluated before each period and at study end using a three-step procedure: screening for binding of ¹²⁵I-rhG-CSF by IgG present in the serum, that is, screening radio immune-precipitation (RIP) assay; specificity of the binding (confirmatory RIP assay) and inhibitory effect (neutralizing antibody assay). Three samples, all from the same subject in EP06-102, tested positive for binding antibodies, including the baseline sample. This indicates that this subject was positive prior to exposure to EP2006. No increase was detected during treatment and no neutralizing antibodies developed. Thus, no Phase I subjects developed binding and neutralizing antibodies during the studies and concurrent with exposure to EP2006.

No specific data were reported for drug-related AEs. Frequently observed, though in line with those observed in normal subjects in Neupogen studies, AEs were musculoskeletal pain, leukocytosis, thrombocytopenia and headaches. No SAEs were observed in these subjects, including no splenomegaly, allergic reactions and ARDS. No deaths occurred during the four Phase I studies.

4.3 Phase III study

4.3.1 Study design

EP06-301 was designed as an open, single-arm, multicenter study in 170 chemotherapy-naïve breast cancer patients being treated with docetaxel/doxorubicin chemotherapy and receiving primary prophylaxis with EP2006. EP2006 was administered from day 2 of up to four chemotherapy cycles for up to 14 days or through absolute neutrophil count (ANC) nadir and ANC reaching $10 \times 10^9/l$. Dose was 30 MIU for women weighing less than 60 kg and 48 MIU for women weighing 60 kg or more. Planned study participation was 3 months of active treatment (4 cycles) and 3 months of follow-up after the last cycle. Of the 170 patients in whom treatment was initiated, 153 completed the study. Results were compared with published data from Neupogen trials [31,32].

4.3.2 Safety results

Fourteen screening RIP (RNP Immunoprecipitation Assay) assays were above the study-specific cut-off of 2.27% total binding values, including 2 at baseline or cycle 1, 4 at cycle 2, 1 at cycle 4 or end of treatment and 7 at 90-day follow-up. Re-analysis in a confirmatory RIP assay yielded no samples with depletion rates $\geq 20\%$ and thus were classified as negative. Thus, no patients in EP06-301 developed binding and neutralizing antibodies.

Thirty-nine patients experienced a total of 89 EP2006-associated AEs and 168 a total of 1494 AEs not related to study drug. Of the 89 related AEs, 79 were mild and 10 were moderate; none were severe, life threatening or fatal. As AEs could be related to both filgrastim and chemotherapy, 45 of the 89 events were not suspected to be related to EP2006, 44 suspected to be EP2006-related and 48 were attributed to chemotherapy.

Thirty-five patients experienced a total of 85 AEs classifiable as bone pain. There were no reports of splenomegaly, allergic reactions or ARDS.

There were no deaths during the active treatment phase, however, three patients died during the follow-up period. Two deaths were attributed to disease progression as they occurred in patients with stage IV breast cancer at screening. The third death was due to injuries from an automobile accident.

4.4 Other studies

4.4.1 Prospective single-center study in cancer (Italy)

This study followed 48 patients receiving cyclical chemotherapy for solid tumors. Thirty-seven patients with breast (n = 10), lung (n = 17), stomach (n = 6) and prostate cancer (n = 4) received primary prophylaxis with Zarzio, whereas 11 patients with colorectal cancer were given Zarzio as secondary prophylaxis. Apart from the statement that Zarzio 'was well tolerated with no unexpected adverse effect being reported', no safety data are provided.

4.4.2 Prospective single-center study in peripheral blood stem cell mobilization (France)

Forty patients with a hematological malignancy and receiving chemotherapy for treatment and autologous peripheral blood stem cell mobilization were treated with Zarzio and followed prospectively. Safety reporting was limited to 14 patients experiencing bone pain and/or headache, but no separate results were reported. No other safety data were reported either.

4.4.3 Retrospective single-center study in cancer (Germany)

This was a retrospective review of 77 patients with hematological malignancies (n = 17) or solid tumors (n = 60) treated undergoing cyclical chemotherapy. Forty received Zarzio as primary and 37 as secondary prophylaxis. Safety reporting was limited to the statement that 'no unexpected safety findings were observed'; yet that, not being a prospective study, 'adverse events were not formally recorded' but that 'it is likely that any severe or serious events were recorded' in the patient medical file.

5. Clinical safety of Nivestim

5.1 Summary of clinical development program

The clinical development program of Nivestim submitted as part of the evidence base for EMA approval [13] included two Phase I pharmacokinetic and pharmacodynamic studies

involving 98 healthy volunteers (studies GCF061 and GCF062); and one Phase III trial in 278 breast cancer patients receiving a docetaxel/doxorubicin chemotherapy regimen (study GCF071).

Journal publications were found for studies GCF061 [33], GCF062 [34] and GCF071 [35], as was an article summarizing these three studies [36]. This was a thorough but not exhaustive search and the possibility of other publications cannot be excluded.

As per the authors' count, 281 subjects were exposed to Nivestim in the clinical development program.

5.2 Phase I studies

5.2.1 Study designs

- GCF061 was a randomized, open-label, single dose (10 µg/kg), active comparator-controlled (Neupogen), two-way crossover study. Forty-eight healthy subjects were randomized to i.v. or s.c. administration of Nivestim and further randomized to treatment sequence. Washout period was 13 days.
- GCF062 was a randomized, open-label, multiple dose, active comparator-controlled (Neupogen), two-way crossover study. Fifty healthy volunteers were randomized to 5 s.c. injections of 5 or 10 µg/kg Nivestim or Neupogen before further randomization to treatment sequence. Washout period was 13 days.

5.2.2 Safety results

Immunogenicity was monitored in study GCF062 using an unspecified screening antibody assay and a cell-based neutralizing antibody assay. Two subjects showed a positive antibody response following treatment with Nivestim. Three Nivestim-exposed patients had one or more post-treatment samples with a borderline positive result; none were positive for neutralizing antibodies. None of the borderline positive results had a clinical effect on efficacy or safety.

In study GCF061, 30 patients experienced at least one AE during treatment with Nivestim and 37 during treatment with Neupogen. Nineteen patients reported bone pain during Nivestim therapy and 16 during Neupogen therapy. No cases of splenomegaly, allergic reactions, ARDS or other SAEs were observed. No deaths were recorded. Observed differences between Nivestim and Neupogen therapy were statistically non-significant.

In addition to the immunogenicity events summarized above, the following AEs were observed in GCF062. Thirty-nine patients experienced at least one AE during Nivestim treatment and 43 during Neupogen treatment. For bone pain, these numbers were 29 and 30, respectively. Eight patients reported skin and subcutaneous tissue AEs during Nivestim treatment compared with three during Neupogen treatment. Though not specified as such, these may be allergic reaction cases. No instances of splenomegaly or ARDS were

observed. No patients died. Differences between drugs were statistically non-significant.

5.3 Phase III study

5.3.1 Study design

Study GCF071 was a Phase III randomized, double-blind therapeutic equivalence trial comparing 5 µg/kg s.c. Nivestim with Neupogen during up to six cycles of chemotherapy in breast cancer patients receiving docetaxel/doxorubicin chemotherapy; with extended follow-up at 28 days following last dose of GCSF and again at 6 months. Patients were randomized 2:1 to Nivestim (n = 183 with n = 149 at cycle 6) versus Neupogen (n = 95 with n = 78 at cycle 6).

5.3.2 Safety results

No patients tested positive for neutralizing antibodies. Data on binding antibodies were not reported.

A total of 159 patients (86.9%) in the Nivestim and 80 (84.2%) in the Neupogen study arms experienced at least one AE; including, respectively, 45 (24.6%) and 22 (23.2%) treatment-related AEs. Eighty-six patients (47.0%) treated with Nivestim reported events classifiable as bone pain, compared with 31 (32.6%) among those on Neupogen. Nineteen patients reported bone pain during Nivestim therapy and 16 during Neupogen therapy. Severe (grade 4) AEs were reported by 15 patients (8.2%) in the Nivestim arm and 10 patients (10.5%) in the Neupogen arm. Eight patients (4.4%) treated with Nivestim and two patients (2.1%) administered Neupogen experienced life threatening or disabling AEs. None of these SAEs was attributed to study treatments. One patient in the control arm treated with Neupogen died from unknown causes but the investigator classified this death as unlikely to be related to the treatment but that infection could not be ruled out. No cases of splenomegaly, allergic reactions, ARDS or other SAEs were observed. Observed differences between Nivestim and Neupogen therapy were statistically non-significant.

6. Summary tables

Table 1 presents the therapeutic indications for Tevagrastim, Zarzio and Nivestim as approved by the EMA on the basis of efficacy and safety data. These indications cover cancer (cytotoxic chemotherapy, myeloablative therapy followed by bone marrow transplantation and mobilization of PBPC), HIV and infections. Note that the FDA label specifies that Tevagrastim is limited to patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. Table 2 lists the contraindications for each product as specified by the EMA. FDA label does not list any contraindications. Lastly, EMA warnings for the three products are summarized in Table 3. The FDA label for Tevagrastim warns about splenic rupture, ARDS, allergic reactions (angioneurotic edema, allergic dermatitis, drug

Table 2. Contraindications for each biosimilar GCSF as approved by the EMA.

	Zarzio	Tevagrastim	Nivestim
Hypersensitivity to the active substance or to any of the excipients	✓	✓	✓

EMA: European Medicines Agency; GCSF: Granulocyte colony-stimulating factor.

hypersensitivity, general hypersensitivity, rash, pruritic rash and urticaria) and sickle cell crisis.

7. Comments and conclusions

Registration studies seldom have the statistical power to detect low-frequency safety issues and this should be kept in mind in the evaluation of biosimilar agents. However (and with the exception of immunogenicity where the process is the drug) by virtue of being second-generation products of agents (and hence being part of the classes of these agents), prior safety knowledge about originators and their classes can be extended. This is implicit in this present review as the authors chose not to focus in detail on common and known side effects. This does not imply that such side effects are not important. They should be monitored clinically and, as with any potential safety issue, patients should be educated about their relative likelihood. Further, it is imperative to monitor for clusters of symptoms, as they may be predictive of more serious conditions; for instance, the relationship between headaches, dizziness, hypertension and vascular events. Seemingly isolated side effects may be part of a pattern of a more serious safety concern.

It is assuring that, statistically, the incidence of known AEs was not higher than what is known about originator filgrastim in general. Similarly, the incidence rates of safety issues of greater significance did, statistically, not exceed known rates for originator filgrastim. They do exist and clinicians should be vigilant and patients should be educated about them. A challenge at this time, however, concerns the known serious and severe safety events for GCSFs for which the frequency for Tevagrastim, Zarzio and Nivestim is as of yet unknown. Therefore, pharmacovigilance remains a priority with an emphasis on safety studies and signal detection analyses in various data sources, such as drug safety databases; prospective observational studies with heterogeneity of patients, providers and settings and electronic health records. The signal detection studies require greater market penetration than what the three biosimilar filgrastim currently have.

The low incidence of anti-GCSF antibodies and neutralizing antibodies in particular should not detract from the need for continued pharmacovigilance. Cases of immunogenicity were identified in the clinical development programs of all three agents. The source materials for this review were

inconsistent in specifying the assays used and the detail with which immunogenicity data were reported. It is possible that different assays might have been used to evaluate similar safety parameters for the three products reviewed. Especially differences in antidrug antibody assays may introduce differences in immunogenicity results, even when testing samples of the same patient. Hence, it is possible that studies may have yielded different immunogenicity outcomes. This underscores the need to standardize immunogenicity assays in general and antidrug antibody assays in particular [10].

The relationship between GCSF treatment and mortality is more difficult to establish because of the disease state cancer patients and cancer-associated mortality. The mortality cases in the clinical development programs of Tevagrastim, Zarzio and Nivestim are consistent in trend and statistical inference with what is known for originator filgrastim.

AEs classifiable as bone pain (bone pain itself, but also arthralgia; myalgia; neck, back, sacral, pelvic and musculoskeletal pain; jaw pain and pain in extremity) are the most frequently observed AEs. Rates were comparable with those known for originator filgrastim.

There were significant differences in safety reporting across the three sets of documents reviewed in terms of organization and presentation, detail, differentiation and enumeration. This merits regulatory attention. Objective safety reporting about biosimilar filgrastim is also an issue for journal publications. Safety issues should be reported consistently and openly. The implicit concern that disclosing safety data, whether about an originator or biosimilar, may reflect negatively on the product is intrinsically invalid. Within the perspective that no drug has a perfect safety (or, for that matter, efficacy) profile, the emphasis should be on disclosure, analysis and clinical guidance [10].

There were also differences between products in the scope and design of Phase III studies submitted for regulatory review. The Tevagrastim dossier included three randomized Phase III trials. Zarzio was approved on the basis of data from a single-arm Phase III study compared with those from published Neupogen trials. The Nivestim submission included one randomized Phase III trial.

While in the Phase III studies for Tevagrastim, Zarzio and Nivestim, these biosimilars were used as primary prophylaxis of chemotherapy-induced (febrile) neutropenia, the occasional experience studies evidenced both primary and secondary prophylaxis. Secondary prophylaxis trials may be indicated.

8. Expert opinion

Review of the safety evidence of Tevagrastim, Zarzio and Nivestim as documented in EMA documents (for Tevagrastim, FDA documents as well) and published scientific literature shows that, as with originator filgrastim, immunogenicity risk must be considered. Immunogenicity monitoring, preferably using standardized assays, continues to be important in the use of biosimilar or originator GCSFs. Mortality must be

Table 3. Summary of key EMA special warnings and precautions for biosimilar GCSF.

			Zarzio	Tevagrastim	Nivestim
General	Malignant cell growth	GCSF can promote growth of myeloid cells <i>in vitro</i> and similar effects may be seen on some non-myeloid cells <i>in vitro</i> and should be administrated with caution	✓	✓	✓
Cancer patients	Leukocytosis	Though no undesirable effects attributable to degree of leukocytosis have been reported, a white blood cell count should be performed at regular intervals during filgrastim therapy. If leukocyte count is over $50 \times 10^9/l$ after expected nadir, filgrastim should be discontinued	✓	✓	✓
	Chemotherapy	Special caution should be used in patients receiving high-dose chemotherapy because improved tumor outcome has not been demonstrated. Intensified doses of chemotherapeutic agents can lead to increased toxicities including cardiac, pulmonary and dermatologic effects	✓	✓	✓
	Thrombocytopenia and anemia	Patient may be at greater risk for thrombocytopenia and anemia because of potential of receiving higher doses of chemotherapy	✓	✓	✓
	GvHD	Monitor patients receiving GCSF after allogeneic bone marrow transplantation as incidence of GvHD and fatalities have occurred	✓	✓	✓
Patients undergoing peripheral blood progenitor cell mobilization	Method of treatment	Degree of variation between individual patients and laboratory assays of CD34 ⁺ cells means direct comparison between studies is difficult and choice of mobilization method should be considered in relation of overall objectives of treatment for individual patient	✓	✓	✓
	Prior exposure to cytotoxic agents	Patients who have undergone extensive myelosuppressive therapy may not show sufficient mobilization of PBPC to achieve recommended minimum yield of 2.0×10^6 CD34 ⁺ cells/kg or acceleration of platelet recovery	✓	✓	✓
	Assessment	Recommendation of minimum yield of 2.0×10^6 CD34 ⁺ cells/kg based on published experience and yields excess to this correlate with rapid recovery and yields below correlate to slower recovery	✓	✓	✓
Normal donors undergoing PBPC mobilization	Thrombocytopenia	Transient thrombocytopenia (platelets $< 100 \times 10^9$) occurred in 35% of subjects studied following filgrastim administration and leukapheresis	✓	✓	✓
	Administration of filgrastim	Filgrastim administration should be discontinued or reduced if leukocyte counts rise to $> 70 \times 10^9/l$ and donors who receive GCSF should be monitored until hematological indices return to normal	✓	✓	✓
	Splenomegaly/splenic rupture	Spleen size should be monitored and if donors or patients report left upper abdominal pain or shoulder tip pain, diagnosis of splenic rupture should be considered as asymptomatic cases of splenomegaly and rare cases of splenic rupture have been reported following administration of GCSFs	✓	✓	✓

ANC: Absolute neutrophil count; EMA: European Medicines Agency; GCSF: Granulocyte colony-stimulating factor; GvHD: Graft-versus-host disease; MDS: Myelodysplastic syndrome; PBPC: Peripheral blood progenitor cells; SCN: Severe chronic neutropenia.

Table 3. Summary of key EMA special warnings and precautions for biosimilar GCSF (continued).

			Zarzio	Tevagrastim	Nivestim
SCN	Blood cell counts	Platelet counts should be monitored closely during first few weeks of filgrastim therapy so that platelets are consistently $< 100 \times 10^9/l$ or $< 100,000/mm^3$	✓	✓	✓
	Leukemia/MDS	SCN may develop abnormal cytogenetics and risks and benefits of continuing filgrastim should be considered. If MDS or leukemia occurs filgrastim should be discontinued	✓	✓	✓
	Hematuria/proteinuria	Regular urinalysis should be performed to monitor for hematuria and proteinuria occurring	✓	✓	✓
Patients with HIV infection	ANC	ANC should be monitored daily for first 2 – 3 days of filgrastim administration and blood samples taken for ANC measurement prior to scheduled dosing with filgrastim	✓	✓	✓
	Dose increase	Patient may be at higher risk for developing thrombocytopenia and anemia and regular monitoring of blood count as listed above should be completed	✓	✓	✓
	Infections and malignancies	Consider appropriate therapy for treatment of underlying condition in addition to administration of filgrastim for treatment of neutropenia for patients with infection or malignancy	✓	✓	✓
Sickle cell disease	Evaluation	Exercise caution with potential risks and benefits when considering use of filgrastim in patients with sickle cell disease as sickle cell crises have been reported with use of filgrastim in subjects with sickle cell disease	✓	✓	✓
Excipients	Sorbitol	Patients with rare hereditary problems of fructose intolerance should not use medicinal product	✓	✓	✓

ANC: Absolute neutrophil count; EMA: European Medicines Agency; GCSF: Granulocyte colony-stimulating factor; GvHD: Graft-versus-host disease; MDS: Myelodysplastic syndrome; PBPC: Peripheral blood progenitor cells; SCN: Severe chronic neutropenia.

assessed in light of major and comorbid disease, in particular tumor type and disease stage.

Within the constraints of what can be known from registration trials and inherently small sample sizes, all three agents reviewed had similar safety profiles. None were statistically higher on safety parameters to what is known about originator filgrastim or GCSFs as a class. Hence, what is known about originator filgrastim and GCSFs in general regarding safety can be extended to biosimilar filgrastim at this time.

By combining safety signals from the clinical development programs of Tevagrastim, Zarzio and Nivestim as well as the few follow-on studies in the public domain, the safety profiles of three products reviewed here are consistent with what is known in terms of the clinical safety of GCSFs in general; and, importantly, when compared among themselves. Statistically, no one product is less and no one product is more safe.

This is a reassuring conclusion *ad interim*, however with significant caveats as to the safety signals that are statistically detectable from the limited size and relatively homogeneous samples from carefully selected centers typically found in registration studies. To enable broader safety signal detection,

follow-on observational studies with larger samples and greater heterogeneity of patients, clinicians and centers are necessary. As they accumulate, drug safety databases should be analyzed for possible signals using novel signal detection methods. Electronic health records may prove to be a critical source of drug safety information as well. At this stage, the bioequivalence, biosimilarity and relative efficacy of the three biosimilar molecules have been documented; and safety signals detectable within the statistical parameters permitted by the sample sizes employed have been recorded. The probability of serious and severe safety problems has not been established for the three agents reviewed here because registration studies are powered in function of efficacy and not safety.

One avenue to address this gap is to commission (costly) safety trials where large samples of relatively homogeneous patients treated by carefully selected clinicians from known centers are randomized to various treatment options. Another avenue, in the authors' opinion much more informative, is to conduct longitudinal observational studies characterized by high heterogeneity in patients, clinicians and centers to capture the real-world safety and effectiveness of biosimilar GCSFs.

Since biosimilars are unique, complex biological molecules, safety profiles may evolve from common to differentiated profiles once accrual of long-term product-specific safety data is available. Large-sample, long-term, observational studies of real-world practice will provide the heterogeneity and statistical power to demonstrate product-specific effectiveness and safety profiles, as well as drug safety databases and electronic health records.

Clinicians should weigh the benefit of stimulation with any one of the three biosimilars reviewed here with the associated risks, under consideration of patient characteristics and disease features that may put a given patient at greater risk for serious or severe AEs. Patients should be educated about these AEs, but also about the less severe AEs known for product and class.

Scientifically, long-term vigilance studies of biosimilar GCSFs are necessary. Clinically, assessment of tolerability and safety should be part of routine clinical practice.

Acknowledgments

I Abraham was supported as Director of the AzAHEC Inter-professional Fellowship Program in Clinical Outcomes and Comparative Effectiveness Research funded by the Bureau

of Health professions, US Department of Health and Human Services; and as Director of the Postdoctoral Fellowship Program in Clinical Research and Human Therapeutics funded by King Abdulaziz University, Jeddah, Saudi Arabia.

Declaration of interest

No funding was received in preparation of this manuscript. I Abraham and K MacDonald are employees of, and S Tharmarajah was an intern at, Matrix45, which has received research grants and contracts related to GCSFs Sandoz/Novartis (Zarzio). By company policy, employees cannot hold equity in sponsor organizations except through mutual funds and cannot receive direct personal benefits, financial or otherwise, from sponsor organizations. Matrix45 is currently contracted for scientific consulting services with Sandoz/Novartis on an observational study on Zarzio in the oncology and hematology settings, I Abraham and K MacDonald are involved in this work. Matrix45 provides similar services to other biopharmaceutical companies without exclusivity constraints. Manufacturers of the products reviewed here were not contacted for data, publications or other sources of information, nor did they have any input on the review activities or the preparation of the manuscript.

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