Biosimilars

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REVIEW

Critical appraisal of biosimilar filgrastim (Nivestim™) for febrile and chemotherapy-induced neutropenia

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Abstract: Recombinant granulocyte colony-stimulating factor (filgrastim) stimulates the proliferation and differentiation of hematopoietic stem and progenitor cells committed to neutrophil and granulocyte lineages. Filgrastim has been used as an adjunct to chemotherapy for ameliorating neutropenia, one of the major side effects of chemotherapy in cancer patients. Its use has led to reduction of infections and hospital admissions for patients with cancer undergoing chemotherapy. In addition, filgrastim has multiple other indications in hematology and oncology. Following the European Union patent expiry of Neupogen® (filgrastim; Amgen Inc) in 2006, a biosimilar filgrastim has been developed (Nivestim™; Hospira). In accordance with the requirements of the European Medicines Agency, Nivestim has been studied in a development program that included preclinical studies, two Phase I clinical trials, and one Phase III clinical study. Preclinical studies showed pharmacodynamic as well as pharmacokinetic bioequivalence with the original product, Neupogen. Two randomized, single-center, Phase I trials compared both the pharmacokinetic, pharmacodynamic, and safety profiles of Nivestim and Neupogen in healthy volunteers. In both studies, 90% confidence intervals for the primary endpoints were within the predefined range (0.80–1.25) necessary to demonstrate bioequivalence. Nivestim was well tolerated, with no additional safety concerns over Neupogen. Bioequivalence was demonstrated in a randomized, double-blind multicenter Phase III trial of 279 patients with breast cancer receiving myelosuppressive chemotherapy. The mean duration of severe neutropenia in cycle 1, the primary endpoint, was similar between Nivestim (1.6 days, n = 165) and Neupogen (1.3 days, n = 85), meeting predefined criteria for bioequivalence. Secondary endpoints supporting bioequivalence included the mean time to recovery of absolute neutrophil count and incidence of febrile neutropenia. The most common treatment-related adverse event with Nivestim was grade 1–2 bone pain. As a result of these preclinical and clinical trials, Nivestim was approved by the European Medicines Agency and in Australia for prevention of febrile neutropenia and treatment of neutropenia in cancer patients treated with cytotoxic chemotherapy (except in patients with myelodysplastic syndromes and chronic myelogenous leukemia). Nivestim is also indicated for the treatment of myelosuppression after bone marrow transplantation, of neutropenia in patients with human immunodeficiency virus, and of severe congenital, cyclic, or idiopathic neutropenia.

Keywords: filgrastim, biosimilar, granulocyte colony-stimulating factor, neutropenia, Nivestim™

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Introduction

Due to the patent expiry of a number of first-generation innovator "biologics" in recent years, several "biosimilars," or follow-on biopharmaceuticals, have been developed.

However, in comparison with the relatively straightforward production of a generic equivalent of an original chemical-based drug, the process of developing a biosimilar to an innovator product is far more complex.[1–4] Because of their production by cells in culture or whole organisms, the manufacturing processes for biopharmaceuticals are very complex and cannot be replicated exactly.[5] As a result, it is impossible to generate an exact copy of an innovator product. However, legislation has enabled the development of biologically similar medicinal products, so-called "biosimilars," or follow-on biopharmaceuticals.[1]

Owing to the complex nature of the manufacturing process of these compounds and the potential for heterogeneity between the reference product and a biosimilar, strict guidelines are in place for the regulatory assessment of biosimilars in terms of quality, safety, and efficacy.[6] According to these guidelines, biosimilars may have an acceptable level of minor differences from the reference product. In addition, there may be qualitative differences between the process-related impurities present in biosimilars and their reference products.[7–9]

Granulocyte colony-stimulating factor (G-CSF) is a naturally occurring cytokine produced by endothelial cells, macrophages, and other immune cells. It stimulates the proliferation and differentiation of hematopoietic stem and progenitor cells committed to the neutrophil lineages in a dose-dependent manner. Fully differentiated neutrophilic granulocytes are functionally activated by G-CSF.[10–12]

Filgrastim, a recombinant human G-CSF, was first approved in 1991 in both Europe and the US as Neupogen® (Amgen Inc, Thousand Oaks, CA). Neupogen is a 175-amino acid recombinant protein with a molecular weight of 18.8 kDa. While human G-CSF is glycosylated, Neupogen is a nonglycosylated protein, produced in genetically modified *Escherichia coli*. Its amino acid sequence is identical to that of human G-CSF, except for an additional N-terminal methionine. In light of the hematopoietic activity of human G-CSF, filgrastim is primarily used to reduce the incidence and duration of neutropenia and associated complications.[13–18]

Following the patent expiry of Neupogen in 2006, a biosimilar version of filgrastim has been developed (Nivestim™; Hospira Ltd, Royal Leamington Spa, UK), which could potentially provide a clinically effective alternative to Neupogen.

Guidance issued by the European Medicines Agency (EMA) states that new biosimilar medicinal products containing filgrastim should demonstrate comparability with the reference product, Neupogen.[19] The EMA recommends that extensive preclinical and clinical studies be conducted. These should include pharmacokinetic, pharmacodynamic, and safety investigations as well as a clinical trial demonstrating comparability between the test and reference product for prophylaxis of severe neutropenia after cytotoxic chemotherapy in a homogenous population of patients. In addition, a risk-management program/pharmacovigilance plan needs to be presented within the authorization procedure.[19]

A number of filgrastim biosimilars have been approved recently for medicinal use or are in development.[20–22] If quality, safety, and efficacy comparable with that of Neupogen can be demonstrated, these agents could provide cost-effective alternatives. This review will focus on the development of Nivestim.

Preclinical data of Nivestim

The similarity of Nivestim and Neupogen with respect to their physicochemical profile was demonstrated using a wide range of rigorous analytical techniques.[5,23–26] These experiments showed that Nivestim and Neupogen were equivalent with respect to appearance, pH, molecular mass, protein concentration, isoelectric focus, secondary protein structure, amino acid sequence, purity, biologic activity, and degradation impurity profile (Figure 1). Further studies on the effect of different environmental conditions on Nivestim were performed. It could be demonstrated that Nivestim is unaffected by cyclical changes in temperature between the refrigerator and 25°C ± 2°C, and is also unaffected by exposure either to room temperature for 7 days or to freezing for 3 days. This indicates that Nivestim remains active and stable during the environmental conditions commonly encountered in transport and handling during general use.[23]

In addition to in vitro studies, preclinical in vivo investigations were performed. These included a standard rat model of neutropenia to evaluate the efficacy of both filgrastims. In addition, toxicology studies were conducted in rabbits as well as in rats. No biologically relevant differences were detected between Nivestim and Neupogen.

Clinical evaluation of Nivestim

According to the EMA guidance, two randomized Phase I trials were performed comparing the pharmacokinetic, pharmacodynamic, and safety profiles of Nivestim with those of standard recombinant human G-CSF (Amgen filgrastim) in healthy volunteers. The primary objective of study 1 (GCF061) was to compare the pharmacokinetic profiles of

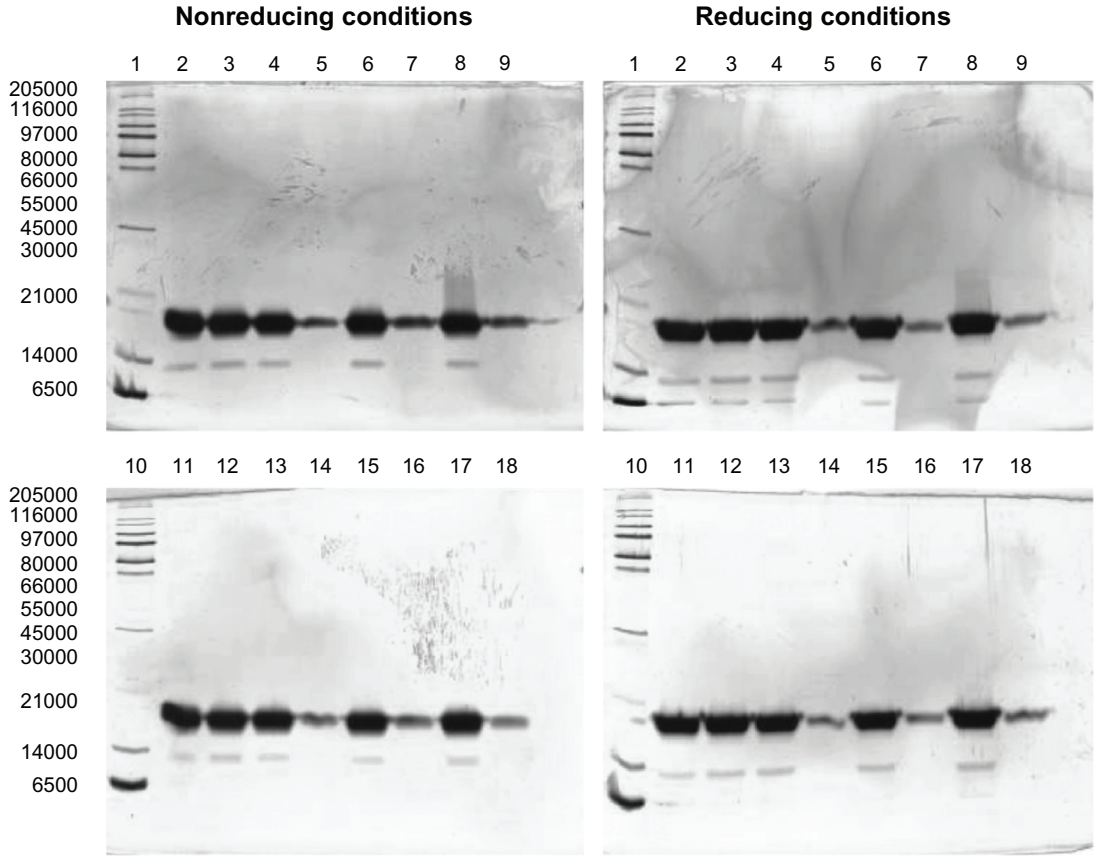

Figure 1 Impurity analysis of Nivestim and comparators using reducing and nonreducing silver-stained SDS-PAGE. Molecular weight marker masses are in Daltons. (**1**) Molecular mass standard, (**2**) Neupogen® 480 μg/0.5 mL, 1006625, (**3**) Filgrastim reference substance 1920, (**4**) Hospira filgrastim PFS 480 μg/0.5 mL 4626067 (100%), (**5**) Hospira filgrastim PFS 480 μg/0.5 mL 4626067 (2%), (**6**) Hospira filgrastim PFS 300 μg/0.5 mL 4623107 (100%), (**7**) Hospira filgrastim PFS 300 μg/0.5 mL 4623107 (2%), (**8**) Neupogen 300 μg/0.5 mL, 1000574 (100%), (**9**) Neupogen 300 μg/0.5 mL, 1000574 (2%), (**10**) molecular mass standard, (**11**) Neupogen 480 μg/0.5 mL, 1006625, (**12**) Filgrastim reference substance 1920, (**13**) Neupogen 480 μg/0.5 mL, 1003937 (100%), (**14**) Neupogen 480 μg/0.5 mL, 1003937 (2%), (**15**) Neupogen 480 μg/0.5 mL, 1006625 (100%), (**16**) Neupogen 480 μg/0.5 mL, 1006625 (2%), (**17**) Hospira filgrastim PFS 480 μg/0.5 mL 4621067 (100%), (**18**) Hospira filgrastim PFS 480 μg/0.5 mL 4621067 (2%).

Abbreviations: SDS-PAGE, sodium dodecyl sulfate polyacrylamide gel electrophoresis; PFS, prefilled syringe.

Nivestim and Neupogen, following a single intravenous or subcutaneous 10 μg/kg body weight dose. The primary objective of study 2 (GCF062) was to compare the pharmacodynamic profiles of Nivestim and Neupogen, following administration of multiple consecutive subcutaneous doses at two dose levels (5 or 10 μg/kg).[27,28]

Study 1

A Phase I, single-center, open-label, randomized comparator-controlled, two-way crossover trial was undertaken to investigate the equivalence of the pharmacokinetic characteristics of Nivestim and Neupogen. Forty-eight healthy volunteers were randomized to receive intravenous or subcutaneous dosing and were then further randomized to order of treatment. Volunteers in each of the two dosing groups received a single 10 μg/kg dose of Nivestim or Neupogen, with subsequent crossover. Bioequivalence was evaluated by analysis of variance. Bioequivalence was concluded if the estimated 90% confidence intervals (CI) for the ratio of "test" to "reference" treatment means were within the conventional equivalence limits of 0.80–1.25. All pharmacokinetic parameters examined were found to be similar following a single dose of Nivestim or Neupogen, regardless of administration route (intravenous or subcutaneous, Table 1). Therapeutic bioequivalence was demonstrated for the primary endpoint $AUC_{0-tlast}$ for intravenous and subcutaneous application. Furthermore, $AUC_{0-infinity}$, maximum observed plasma concentration (C_{max}), and $T_{1/2}$ were equivalent between intravenous or subcutaneous dosing. The 90% CI were within the predefined range necessary to demonstrate bioequivalence. Bioavailability of Nivestim and Neupogen was lower when administered subcutaneously than intravenously, as has been shown previously for Neupogen.[29]

Table 1 Summary of pharmacokinetic data from study GCF061

PK parameter	Geometric mean (range)		Ratio	90% CI
	Nivestim 10 µg/kg	Neupogen 10 µg/kg		
Intravenous route (n = 20)				
$AUC_{0-tlast}$, pg·h/mL	1,259,808 (827,253–1,882,329)	1,316,067 (914,165–1,864,730)	0.96	0.90–1.02*
C_{max}, pg/mL	288,450 (194,944–479,154)	305,687 (198,410–935,835)	0.94	0.84–1.07*
T_{max}, hours	0.62 (0.50–1.00)	0.71 (0.50–3.00)	–	–
$T_{1/2}$, hours	7.57 (3.22–15.37)	8.06 (3.36–13.68)	0.95	0.81–1.12*
$AUC_{0-infinity}$, pg·h/mL	1,264,255 (832,227–1,888,906)	1,319,602 (916,022–1,868,352)	0.96	0.91–1.02*
λ_z	0.092 (0.045–0.216)	0.086 (0.051–0.206)	–	–
Clearance, mL/h/kg	7.910 (5.294–12.016)	7.578 (5.352–10.917)	–	–
Subcutaneous route (n = 26)				
$AUC_{0-tlast}$, pg·h/mL	946,611 (426,566–1,340,753)	929,670 (671,388–1,248,375)	1.02	0.95–1.09*
C_{max}, pg/mL	94,765 (49,602–159,675)	90,754 (62,633–119,410)	1.04	0.97–1.13*
T_{max}, hours	5.11 (3.00–8.00)	5.06 (3.05–8.00)	–	–
$T_{1/2}$, hours	7.01 (5.29–11.26)	6.91 (5.30–9.98)	1.01	0.94–1.09*
$AUC_{0-infinity}$, pg·h/mL	950,955 (427,687–1,344,385)	933,847 (676,427–1,252,249)	1.02	0.95–1.09*
λ_z	0.099 (0.062–1.131)	0.100 (0.069–1.131)	–	–
Clearance, mL/h/kg	10.516 (7.438–23.382)	10.708 (7.986–14.784)	–	–

Notes: *90% CI was within the predefined equivalence range of 0.80–1.25, demonstrating bioequivalence between the two agents.

Abbreviations: $AUC_{0-infinity}$, area under the curve from time 0 extrapolated to infinity; $AUC_{0-tlast}$, AUC from time 0 to the last time point; CI, confidence interval; C_{max}, maximum observed plasma concentration; PK, pharmacokinetic; T_{max}, time at which C_{max} occurred; $T_{1/2}$, elimination half life; λ_z, terminal elimination rate constant; –, not reported.

Furthermore, bioequivalence could be demonstrated for all pharmacodynamic parameters except ANC_{min}, irrespective of the administration route. There was some slight variation in time to peak plasma concentration (T_{max}) between the two drugs. However, these minor differences are unlikely to be of clinical relevance. Tolerability was similar between Nivestim and Neupogen, and no additional safety concerns were noted.

Study 2

The primary objective of the second randomized, double-blind, comparator-controlled, two-way crossover Phase I trial was comparison of the pharmacodynamic profiles of Nivestim and Neupogen following administration of multiple consecutive subcutaneous doses at two dose levels (5 or 10 µg/kg). Pharmacokinetic and safety assessments were secondary objectives of the study. Bioequivalence of the two filgrastims was demonstrated for the primary pharmacodynamic endpoint of absolute neutrophil count $AUC_{0-tlast}$, as well as for all other pharmacodynamic parameters tested at 5 or 10 µg/kg doses (Figure 2 and Table 2). A slight difference between the two filgrastims was that the absolute neutrophil count T_{max} at day 5 in the 10 µg/kg dose group occurred slightly earlier with Nivestim than with Neupogen, which is unlikely to have any clinical significance.

Data on mobilization of $CD34^+$ cells also demonstrated that Nivestim is bioequivalent to Neupogen (Figure 3). These data indicate that Nivestim has potential for use as a growth factor to support autologous and allogeneic peripheral blood progenitor cell transplantation, indications where Neupogen has been used successfully for many years.[30–32] Pharmacokinetic analyses, which were the secondary endpoint of the study, further supported the bioequivalence of Nivestim and Neupogen. However, for several pharmacokinetic parameters, bioequivalence could only be concluded when outliers (as are commonly observed in these type of studies) were excluded.[33,34] Bioequivalence could not be shown for C_{max} at day 5, even when outliers were excluded. There was also some slight variability between the two agents in terms of T_{max} at day 5 at both dose levels. In this context, it should be considered that study GCF062 was primarily designed to

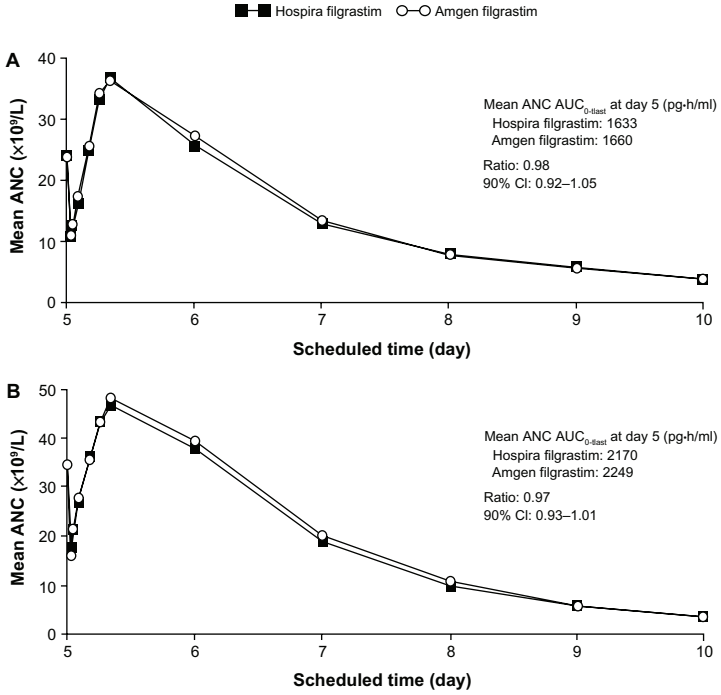

Figure 2 Mean ANC over time in subjects given Nivestim or Neupogen in study 2 for (**A**) 5 μg/kg dose group and (**B**) 10 μg/kg dose group.
Note: Data shown are geometric means. Samples taken outside each schedule time point window have been excluded.

Abbreviations: ANC, absolute neutrophil count; $AUC_{0-tlast}$, area under the curve from time 0 to the last time point; CI, confidence interval.

evaluate pharmacodynamic characteristics and differences in pharmacokinetics. Furthermore, it has been shown previously that there are pharmacodynamic-pharmacokinetic interactions between neutrophils and G-CSF, given that neutrophils appear to contribute to G-CSF clearance, which could have confounded the pharmacokinetic data.[35] Therefore, it is not surprising that bioequivalence of Nivestim and Neupogen was not demonstrated by all pharmacokinetic parameters.

Toxicity of Nivestim and Neupogen in Phase I studies

Nivestim was generally well tolerated in both Phase I studies, with no unexpected toxicities (Table 3).[28] All adverse events

Table 2 Summary of the pharmacodynamic profiles from study GCF062

PD parameter	Geometric mean (range)		Ratio	90% CI
	Nivestim	Neupogen		
5 μg/kg dose (n = 24)				
ANC $AUC_{0-tlast}$, pg·hour/mL	1633 (918–2633)	1660 (696–2535)	0.98	0.92–1.05*
ANC C_{max}, × 10^9·hour/L	36.09 (24.12–52.19)	35.66 (18.14–58.17)	1.01	0.96–1.07*
ANC C_{min}, × 10^9·hour/L	3.39 (1.01–8.32)	3.82 (1.71–7.83)	0.89	0.80–0.98*
ANC T_{max}, hours	7.81 (6.00–8.00)	7.80 (6.00–24.00)	–	–
$CD34^+$ count, cells/μL	47.2 (14.0–158.0)	46.0 (12.0–187.0)	1.03	0.85–1.24*
10 μg/kg dose (n = 23)				
ANC $AUC_{0-tlast}$, pg·hour/mL	2170 (1091–3341)	2249 (1099–3970)	0.97	0.93–1.01*
ANC C_{max}, × 10^9·hour/L	46.10 (30.53–69.65)	47.20 (25.09–66.44)	0.98	0.95–1.01*
ANC C_{min}, × 10^9·hour/L	3.01 (1.86–6.11)	3.24 (1.69–4.90)	0.93	0.83–1.04*
ANC T_{max}, hours	7.85 (4.00–24.00)	9.45 (6.00–24.07)	–	–
$CD34^+$ count, cells/μL	82 (19–184)	78 (28–232)	1.06	0.90–1.24*

Notes: *90% CI was within the predefined equivalence range of 0.80–1.25, demonstrating bioequivalence between the two agents.

Abbreviations: ANC, absolute neutrophil count; $AUC_{0-tlast}$, area under the curve from time 0 to the last time point; CI, confidence interval; C_{max}, maximum observed plasma concentration; C_{min}, minimum observed plasma concentration; PD, pharmacodynamic; T_{max}, time at which C_{max} occurred; – not reported.

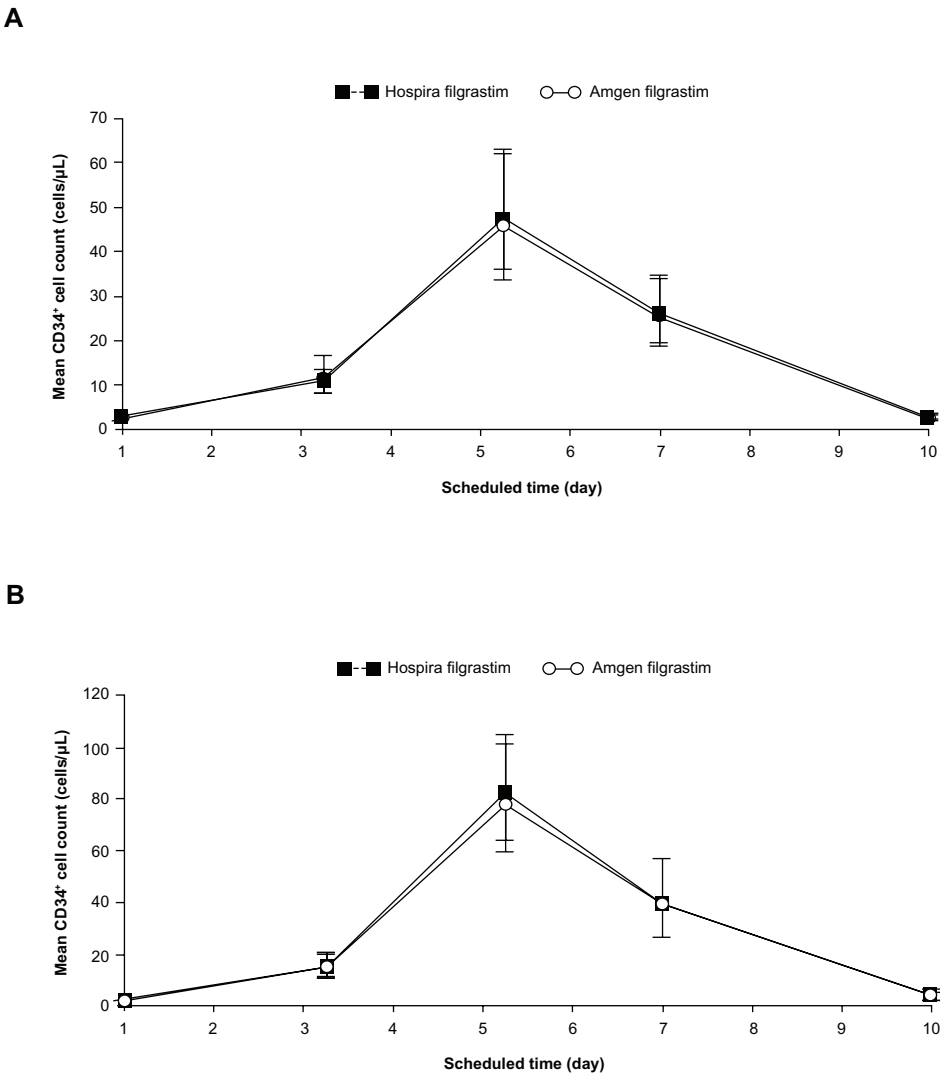

Figure 3 Mean CD34$^+$ cell count over time in subjects given Nivestim or Neupogen in study 2 for (**A**) 5 μg/kg dose group and (**B**) 10 μg/kg dose group.
Note: Data shown are geometric mean values with lower and upper 95% confidence intervals**.**

were mild or moderate in intensity. No serious adverse events were reported, except for one individual receiving Neupogen who experienced severe headache and one individual receiving Nivestim who suffered severe back spasms. The most common adverse events related to the study drug were back pain, headache, pain in the extremities, and nausea. In all treatment groups in both studies, biochemical changes observed with both filgrastims included increased levels of lactate dehydrogenase and alkaline phosphatase which were reversible. The adverse event profiles of Nivestim and Neupogen were comparable in terms of their nature and intensity, and similar to those reported previously for recombinant G-CSF in healthy volunteers.[30] The biochemical abnormalities were not considered to be related to study medication.

Study 3 (GCF071)

In addition to the abovementioned Phase I trials, a randomized, multicenter, double-blind, therapeutic equivalence study was performed to demonstrate the bioequivalence of Neupogen and Nivestim. A total of 279 patients with breast cancer, suitable for treatment with doxorubicin and docetaxel in the neoadjuvant, adjuvant, or first-line metastatic setting, were enrolled at 37 European centers.

Study endpoints were chosen according to the guidelines for the clinical development of biosimilar filgrastims issued by the EMA Committee for Medicinal Products for Human Use[19] and following consultation with the EMA. In addition, the study endpoints were consistent with those used in previous Phase III bioequivalence studies of filgrastim in patients

Table 3 Treatment-emergent adverse events occurring in more than five volunteers across all treatment groups (study GCF062)

Adverse event	5 μg/kg dose, n (%)		10 μg/kg dose, n (%)	
	Nivestim (n = 24)	Neupogen (n = 24)	Nivestim (n = 26)	Neupogen (n = 25)
Any event	19 (79.2)	20 (83.3)	20 (76.9)	23 (92.0)
Gastrointestinal disorders	5 (20.8)	6 (25.0)	3 (11.5)	6 (24.0)
Nausea	2 (8.3)	3 (12.5)	3 (11.5)	2 (8.0)
General disorders and administration site conditions	5 (20.8)	6 (25.0)	5 (19.2)	8 (32.0)
Chest pain	2 (8.3)	4 (16.7)	2 (7.7)	3 (12.0)
Infections and infestations	3 (12.5)	4 (16.7)	0 (0)	5 (20.0)
Nasopharyngitis	2 (8.3)	3 (12.5)	0 (0)	4 (16.0)
Musculoskeletal and connective tissue disorders	12 (50.0)	13 (54.2)	17 (65.4)	17 (68.0)
Arthralgia	4 (16.7)	4 (16.7)	3 (11.5)	2 (8.0)
Back pain	11 (45.8)	9 (37.5)	16 (61.5)	15 (60.0)
Neck pain	1 (4.2)	2 (8.3)	4 (15.4)	4 (16.0)
Pain in extremity	4 (16.7)	4 (16.7)	5 (19.2)	6 (24.0)
Nervous system disorders	12 (50.0)	15 (62.5)	15 (57.7)	11 (44.0)
Headache	11 (45.8)	14 (58.3)	14 (53.8)	11 (44.0)
Respiratory, thoracic and mediastinal disorders	7 (29.2)	4 (16.7)	3 (11.5)	7 (28.0)
Epistaxis	2 (8.3)	2 (8.3)	0 (0)	3 (12.0)
Skin and subcutaneous tissue	3 (12.5)	1 (4.2)	5 (19.2)	2 (8.0)

receiving chemotherapy for breast cancer.[36,37] The primary efficacy endpoint was duration of severe neutropenia (absolute neutrophil count $< 0.5 \times 10^9$/L) in treatment cycle 1. The analysis of variance least-square mean duration of severe neutropenia (adjusted for treatment setting) was calculated for each treatment group, and bioequivalence was assumed if the two-sided 95% CI for the difference in the adjusted mean duration of severe neutropenia values was entirely within the range of ±1 day. This bioequivalence criterion was defined following careful consideration of information from previous studies

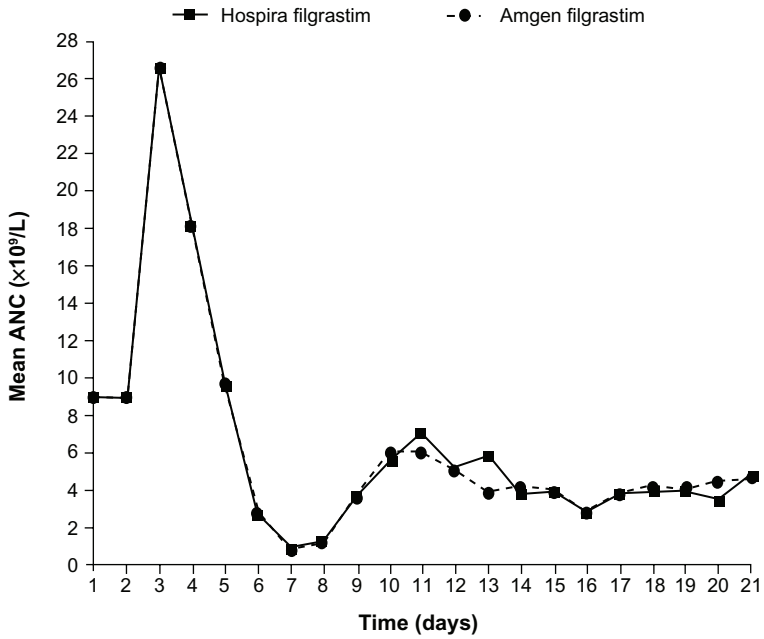

Figure 4 Mean ANC (×10⁹/L) over time in cycle 1 (per protocol population).

Abbreviation: ANC, absolute neutrophil count.

Table 4 Duration of severe neutropenia in **(A)** cycle 1, **(B)** cycle 2, and **(C)** cycle 3 as per protocol population

	A		B		C	
	Nivestim (n = 165)	**Neupogen (n = 85)**	**Nivestim (n = 154)**	**Neupogen (n = 83)**	**Nivestim (n = 154)**	**Neupogen (n = 78)**
Patients with severe neutropenia, n (%)	128 (77.6)	58 (68.2)	75 (48.7)	29 (34.9)	60 (39.0)	33 (42.3)
DSN, days						
Mean (range)	1.6 (0–5)	1.3 (0–3)	0.8 (0–4)	0.6 (0–4)	0.7 (0–4)	0.7 (0–3)
Adjusted mean DSN	1.85	1.47	0.89	0.75	0.93	0.90
95% CI	1.63–2.08	1.19–1.75	0.69–1.08	0.52–0.98	0.74–1.12	0.67–1.14
Comparison of filgrastim treatments						
Difference of adjusted means	0.38		0.14		0.02	
95% CI	0.08–0.68		–0.12–0.39		–0.23–0.28	

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Abbreviations: DSN, duration of severe neutropenia; CI, confidence interval.

of patients treated with doxorubicin and docetaxel, with or without colony-stimulating factors, and agreed with the EMA Committee for Medicinal Products for Human Use.[19] Secondary endpoints included duration of severe neutropenia in cycles 2 and 3; time to absolute neutrophil count recovery (absolute neutrophil count $>3 \times 10^9$/L) in cycles 1–3; incidence of febrile neutropenia (absolute neutrophil count $<0.5 \times 10^9$/L and body temperature of ≥38.5°C) in cycles 1–3; incidence of documented infection in cycles 1–3; and cumulative dose of filgrastim. The incidence of adverse events and incidence

Table 5 Summary of treatment-emergent adverse events in study GCF071 (safety population) frequency more than 5% of patients in either treatment group

	Nivestim (n = 183)		**Neupogen (n = 95)**	
	Any grade n (%)	**Grade 3–4 n (%)**	**Any grade n (%)**	**Grade 3–4 n (%)**
Any adverse event	159 (86.9)	23 (12.6)	80 (84.2)	12 (12.6)
Gastrointestinal disorders				
Nausea	94 (51.4)	–	47 (49.5)	–
Diarrhea	28 (15.3)	2 (1.1)	15 (15.8)	2 (2.1)
Vomiting	22 (12.0)	–	13 (13.7)	–
Stomatitis	19 (10.4)	–	12 (12.6)	–
Upper abdominal pain	3 (1.6)	–	5 (5.3)	–
General disorders				
Fatigue	75 (41.0)	1 (0.5)	34 (35.8)	0 (0.0)
Asthenia	18 (9.8)	0 (0.0)	5 (5.3)	1 (1.1)
Pyrexia	10 (5.5)	–	5 (5.3)	–
Skin and subcutaneous tissue disorders				
Alopecia	86 (47.0)	–	43 (45.3)	–
Musculoskeletal and connective tissue disorders				
Bone pain	48 (26.2)	–	16 (16.8)	–
Myalgia	26 (14.2)	–	9 (9.5)	–
Arthralgia	12 (6.6)	–	6 (6.3)	–
Vascular disorders				
Hyperemia	13 (7.1)	–	7 (7.4)	–
Hypotension	14 (7.7)	1 (0.5)	3 (3.2)	0 (0.0)
Respiratory, thoracic and mediastinal disorders				
Dyspnea	5 (2.7)	–	5 (5.3)	–
Metabolism and nutrition disorders				
Anorexia	12 (6.6)	–	5 (5.3)	–
Ear and labyrinth disorders				
Vertigo	12 (6.6)	–	5 (5.3)	–

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and duration of hospitalization due to febrile neutropenia were recorded as part of the safety assessment.

A total of 184 patients were randomized to Nivestim and 95 to Neupogen at a dose of 5 µg/kg/day after the end of chemotherapy. Mean duration of severe neutropenia in cycle 1 was similar between Nivestim (1.6 days, n = 165) and Neupogen (1.3 days, n = 85). The 95% CI for the difference in adjusted mean duration of severe neutropenia in cycle 1 between Nivestim and Neupogen (primary endpoint) was 0.08–0.68 and thus within the predefined range (±1 day) required to demonstrate bioequivalence (Figure 4). Secondary endpoints supporting bioequivalence included mean time to absolute neutrophil count recovery (Table 4) and incidence of febrile neutropenia. The incidence of febrile neutropenia in cycles 1–3 was similar in patients receiving Nivestim (2.4%) and Neupogen (2.4%).

The most common treatment-emergent adverse events of any grade in both treatment groups were nausea, fatigue, and bone pain,[22] while the incidence of treatment-emergent bone pain was higher with Nivestim (26.2%) than with Neupogen (16.8%, Table 5). However, the number of patients with skeletal pain of any kind (bone pain, back pain, arthralgia, musculoskeletal chest pain, musculoskeletal pain or pain in extremities [limbs]) was similar between Nivestim (41.0%) and Neupogen (32.6%). Furthermore, the proportion of patients requiring treatment for bone pain was similar in both groups (Nivestim 13.1%, Neupogen 10.5%). The incidence of grade 3–4 treatment-emergent adverse events was almost identical with Nivestim (12.57%) and Neupogen (12.63%).

Relatively few adverse events were considered to be related to treatment with filgrastim. Consistent with previous studies of Neupogen, the most frequent treatment-related adverse event of any grade was bone pain (Nivestim 14.2%, Neupogen 9.5%).[37,38] No other treatment-related adverse event occurred in >5% of patients in either treatment group.

Serious adverse events were reported in 6.6% of patients receiving Nivestim and 4.2% of patients receiving Neupogen (including one death), although none was considered related to the study treatment. The frequency of hospitalization due to febrile neutropenia was low in both groups (1.1%).

There were no clinically significant differences in vital signs between the treatment groups, including blood pressure, heart rate, tympanic temperature, electrocardiogram results, or weight. Importantly, no neutralizing antibodies to G-CSF were recorded in any patient. Changes in laboratory evaluation results for hematology, biochemistry, and urinalysis were transient and returned to baseline levels by the time of the follow-up visits.

Conclusion

All stages of the preclinical and clinical development of Nivestim were carefully designed in accordance with EMA guidelines and after guidance by the EMA.[6,7,9,19] As a result, a series of rigorous analyses have now demonstrated the bioequivalence of Nivestim and Neupogen in terms of their physicochemical properties, pharmacokinetic, and pharmacodynamic characteristics, as well as their clinical efficacy and safety profiles.[5,22,27,28] EMA guidelines support the extrapolation of clinical data from one therapeutic indication to another, assuming that reasonable justification can be made following consideration of clinical experience, current literature, similarity of the mechanisms of action, and any possible safety issues in different patient subpopulations. Therefore, Nivestim may become a valuable and cost-effective treatment option for clinical scenarios, other than chemotherapy-induced neutropenia, where Neupogen is currently used, including severe chronic neutropenia and peripheral blood progenitor cell mobilization.[39]

Due to the reduced costs involved in the development of biosimilars and the clinical trials program, they are likely to offer health economic benefits and improve patient access to medication.[40] It has been postulated that if biosimilar medicines were used as alternatives to only seven conventional biopharmaceuticals within the European Union, savings of more than €2 billion could be achieved. A cost-efficiency study of recombinant G-CSF was conducted across the G5 European countries (France, Germany, Italy, Spain, and the UK) to compare various regimens of filgrastim (Neupogen), biosimilar filgrastim (Zarzio™), and pegfilgrastim (Neulasta®), a second-generation filgrastim with a sustained duration of action. The analysis showed that treatment with a biosimilar filgrastim product was the most cost-efficient approach to reduce the incidence of febrile neutropenia in chemotherapy-treated patients.[39] Other biosimilar filgrastim products, such as Nivestim, are expected to provide similar cost-saving benefits.

A growing number of biosimilars are in development or have been approved following the recent patent expiry of several biopharmaceuticals.[1,4,41,42] These biosimilars will have an increasing role in supportive care in oncology and other medical fields. Biosimilars are an important addition to the range of treatment options available to clinicians and

may provide cost-effective alternatives to their branded counterparts, potentially benefiting public health by improving access to these medications.[1,43–45]

Disclosure

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References

1. Jelkmann W. Biosimilar epoetins and other "follow-on" biologics: update on the European experiences. *Am J Hematol*. 2010;85:771–780.
2. Kramer I. Pharmacy and pharmacology of biosimilars. *J Endocrinol Invest*. 2008;31:479–488.
3. Schellekens H. Follow-on biologics: challenges of the "next generation". *Nephrol Dial Transplant*. 2005;20 Suppl 4:iv31–iv36.
4. Sekhon BS, Saluja V. Biosimilars: an overview. *Biosimilars*. 2011;1:1–11.
5. Skrlin A, Radic I, Vuletic M, et al. Comparison of the physicochemical properties of a biosimilar filgrastim with those of reference filgrastim. *Biologicals.* 2010;38:557–566.
6. European Medicines Agency (EMEA) Committee for Medicinal Products for Human Use (CHMP). Guidelines on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues. London, February 22, 2006. Doc Ref EMEA/CHMP/BMWP/49348/2005. Available at: http://www.emea.europa.eu/pdfs/human/biosimilar/4934805en_pdf. Accessed January 31, 2012.
7. European Medicines Agency (EMEA) Committee for Medicinal Products for Human Use (CHMP). Guidelines on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. London, February 22, 2006. Doc Ref EMEA/CHMP/BMWP/42832/2005. Available at: http://www.emea.europa.eu/pdfs/human/biosimilar/4283205en_pdf. Accessed February 1, 2012.
8. European Medicines Agency (EMEA) Committee for Medicinal Products for Human Use (CHMP). Annex to guidelines on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Guidance on similar medicinal products containing somatropin. London, February 22, 2006. Available at: http://www.emea.europa.eu/pdfs/human/biosimilar/9452805en_pdf. Accessed January 31, 2012.
9. European Medicines Agency (EMEA) Committee for Medicinal Products for Human Use (CHMP). Guideline on similar biological medicinal products. London, October 30, 2005. Doc Ref CHMP/437/04. Available at: http://www.emea.europa eu/pdfs/human/biosimilar/043704en_pdf. Accessed January 31, 2010.
10. Bronchud MH, Potter MR, Morgenstern G, et al. In vitro and in vivo analysis of the effects of recombinant human granulocyte colony-stimulating factor in patients. *Br J Cancer*. 1988;58:64–69.
11. Bronchud MH, Scarffe JH, Thatcher N, et al. Phase I/II study of recombinant human granulocyte colony-stimulating factor in patients receiving intensive chemotherapy for small cell lung cancer. *Br J Cancer*. 1987;56:809–813.
12. Roberts AW. G-CSF: a key regulator of neutrophil production, but that's not all! *Growth Factors*. 2005;23:33–41.
13. Dale DC. Colony-stimulating factors for the management of neutropenia in cancer patients. *Drugs*. 2002;62 Suppl 1:1–15.
14. Duhrsen U, Villeval JL, Boyd J, Kannourakis G, Morstyn G, Metcalf D. Effects of recombinant human granulocyte colony-stimulating factor on hematopoietic progenitor cells in cancer patients. *Blood*. 1988;72:2074–2081.
15. Gomez RC, Pinto MA, Gonzalez BM. Colony-stimulating factors: clinical evidence for treatment and prophylaxis of chemotherapy-induced febrile neutropenia. *Clin Transl Oncol*. 2006;8:729–734.
16. Welte K, Bonilla MA, Gillio AP, et al. Recombinant human granulocyte colony-stimulating factor. *J Exp Med*. 1987;165:941–948.
17. Welte K, Gabrilove J, Bronchud MH, Platzer E, Morstyn G. Filgrastim (r-metHuG-CSF): the first 10 years. *Blood*. 1996;88:1907–1929.
18. Aapro MS, Bohlius J, Cameron DA, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. *Eur J Cancer*. 2010;47:8–32.
19. European Medicines Agency (EMEA) Committee for Medicinal Products for Human Use (CHMP). Annex to guidelines on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor. London, February 22, 2006. Doc Ref EMEA/CHMP/BMWP/31329/2005. Available at: http://www.emea.europa.eu/pdfs/human/biosimilar/3132905en pdf. Accessed February 1, 2012.
20. Engert A, del Giglio A, Bias P, Lubenau H, Gatzemeier U, Heigener D. Incidence of febrile neutropenia and myelotoxicity of chemotherapy: a meta-analysis of biosimilar G-CSF studies in breast cancer, lung cancer, and non-Hodgkin's lymphoma. *Onkologie*. 2009;32:599–604.
21. Gascon P, Fuhr U, Sorgel F, et al. Development of a new G-CSF product based on biosimilarity assessment. *Ann Oncol*. 2009;21:1419–1429.
22. Waller CF, Semiglazov VF, Tjulandin S, Bentsion D, Chan S, Challand R. A Phase III randomized equivalence study of biosimilar filgrastim versus Amgen filgrastim in patients receiving myelosuppressive chemotherapy for breast cancer. *Onkologie*. 2010;33:504–511.
23. Burnett B, Radic Krleza I. Stability of Hospira filgrastim following changes to thermal and photic storage conditions. *Eur J Hosp Pharm*. 2011;17:50–57.
24. Hammerling U, Kroon R, Sjodin L. In vitro bioassay with enhanced sensitivity for human granulocyte colony-stimulating factor. *J Pharm Biomed Anal*. 1995;13:9–20.
25. Righetti PG, Verzola B. Folding/unfolding/refolding of proteins: present methodologies in comparison with capillary zone electrophoresis. *Electrophoresis*. 2001;22:2359–2374.
26. Sreerama N, Woody RW. Computation and analysis of protein circular dichroism spectra. *Methods Enzymol*. 2004;383:318–351.
27. Waller CF, Bronchud M, Mair S, Challand R. Pharmacokinetic profiles of a biosimilar filgrastim and Amgen filgrastim: results from a randomized, phase I trial. *Ann Hematol*. 2010;89:927–933.
28. Waller CF, Bronchud M, Mair S, Challand R. Comparison of the pharmacodynamic profiles of a biosimilar filgrastim and Amgen filgrastim: results from a randomized, Phase I trial. *Ann Hematol*. 2010;89:971–978.
29. Sugiura M, Yamamoto K, Sawada Y, Iga T. Pharmacokinetic/pharmacodynamic analysis of neutrophil proliferation induced by recombinant granulocyte colony-stimulating factor (rhG-CSF): comparison between intravenous and subcutaneous administration. *Biol Pharm Bull*. 1997;20:684–689.
30. Anderlini P. Effects and safety of granulocyte colony-stimulating factor in healthy volunteers. *Curr Opin Hematol*. 2009;16:35–40.
31. Bishop MR, Tarantolo SR, Geller RB, et al. A randomized, double-blind trial of filgrastim (granulocyte colony-stimulating factor) versus placebo following allogeneic blood stem cell transplantation. *Blood*. 2000;96:80–85.
32. Brugger W, Birken R, Bertz H, et al. Peripheral blood progenitor cells mobilized by chemotherapy plus granulocyte-colony stimulating factor accelerate both neutrophil and platelet recovery after high-dose VP16, ifosfamide and cisplatin. *Br J Haematol*. 1993;84:402–407.
33. Chow SC, Tse SK. Outlier detection in bioavailability/bioequivalence studies. *Stat Med*. 1990;9:549–558.
34. Liao JJ. A new approach for outliers in a bioavailability/bioequivalence study. *J Biopharm Stat*. 2007;17:393–405.
35. Kuwabara T, Kobayashi S, Sugiyama Y. Pharmacokinetics and pharmacodynamics of a recombinant human granulocyte colony-stimulating factor. *Drug Metab Rev*. 1996;28:625–658.

36. del Giglio A, Eniu A, Ganea-Motan D, Topuzov E, Lubenau H. XM02 is superior to placebo and equivalent to Neupogen in reducing the duration of severe neutropenia and the incidence of febrile neutropenia in cycle 1 in breast cancer patients receiving docetaxel/doxorubicin chemotherapy. *BMC Cancer*. 2008;8:332.
37. Green MD, Koelbl H, Baselga J, et al. A randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy. *Ann Oncol*. 2003;14:29–35.
38. Holmes FA, O'Shaughnessy JA, Vukelja S, et al. Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. *J Clin Oncol*. 2002;20:727–731.
39. Aapro M, Cornes P, Abraham I. Comparative cost-efficiency across the European G5 countries of various regimens of filgrastim, biosimilar filgrastim, and pegfilgrastim to reduce the incidence of chemotherapy-induced febrile neutropenia. *J Oncol Pharm Pract*. 2012;18:171–179.
40. European Generic Medicines Association. *Biosimilars Handbook*. 2nd ed. Brussels, Belgium: European Generic Medicines Association; 2011.
41. Mellstedt H, Niederwieser D, Ludwig H. The challenge of biosimilars. *Ann Oncol*. 2008;19:411–419.
42. Schellekens H. Assessing the bioequivalence of biosimilars: the Retacrit case. *Drug Discov Today*. 2009;14:495–499.
43. Fuhr JP. Biosimilars and follow-on biologics. *Expert Rev Pharmacoecon Outcomes Res*. 2009;9:149–150.
44. Genazzani AA, Biggio G, Caputi AP, et al. Biosimilar drugs : concerns and opportunities. *Bio Drugs*. 2007;21:351–356.
45. Kresse GB. Biosimilars – science, status, and strategic perspective. *Eur J Pharm Biopharm*. 2009;72:479–486.