Extrapolation in Practice: Lessons from 10 Years with Biosimilar Filgrastim

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Abstract
Biosimilar filgrastim (Sandoz) was approved in Europe in 2009 and, in 2015, was the first biosimilar approved in the USA. These authorizations were based on the “totality of evidence” concept, an approach that considers data from structural and functional characterization and comparability analysis and non-clinical and clinical studies. For biosimilar filgrastim, phase III confirmatory clinical studies were performed in the most sensitive population, patients with breast cancer undergoing myelosuppressive chemotherapy. In Europe and the USA, approval was granted for all indications of the reference biologic. Hence, stem cell mobilization and severe chronic neutropenia indications were approved on the basis of extrapolation, with no clinical data available at the time of market authorization in the EU. Although extrapolation is well-accepted in biologic development and regulatory contexts, it remains a misunderstood part of the biosimilarity concept in the medical community. Since approval, more than a decade of obtained clinical experience supports the totality of evidence and reassures clinicians regarding the efficacy and safety of biosimilar filgrastim. This includes real-world data from MONITOR-GCSF, a multicenter, prospective, observational study describing treatment patterns and clinical outcomes of patients with cancer \( n = 1447 \) receiving biosimilar filgrastim for the prophylaxis of chemotherapy-induced neutropenia in solid tumors and hematological malignancies. Evidence is also available from unrelated healthy donors and those with severe chronic neutropenia. Together, the experience from a decade of use of biosimilar filgrastim includes over 24 million patient-days of exposure, which can help reassure oncologists that extrapolation is based on strong scientific evidence and works in practice.

1 Introduction

In 2006, the European Medicines Agency (EMA) approved the first biosimilar in Europe (Omnitrope®, Sandoz), followed in 2009 by approval of the granulocyte colony-stimulating factor (G-CSF), Sandoz biosimilar filgrastim (Zarzio®, Sandoz GmbH). Since then, the EMA has approved more than 50 other biosimilars [1, 2]. Sandoz biosimilar filgrastim was the first biosimilar approved by the US FDA in 2015, with 20 subsequent approvals of biosimilars to date [3, 4]. The increasing number of approved biosimilars in the oncology field, including bevacizumab, rituximab, and trastuzumab, may improve the sustainability of cancer care.

Key Points

| Biosimilar filgrastim (Sandoz) has been approved in Europe since 2009 and in the USA since 2015, when it became the first biosimilar approved by the US FDA. |
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| Phase III confirmatory clinical studies supporting the authorization of biosimilar filgrastim were performed in the most sensitive population, patients with breast cancer undergoing myelosuppressive chemotherapy. Approval was then granted for all indications of the reference biologic. Hence, other indications were approved on the basis of extrapolation. |
| Although extrapolation is well-accepted in biologic development and regulatory contexts, it remains a misunderstood part of the biosimilarity concept in the medical community. |
| More than a decade of clinical experience obtained since approval supports the totality of evidence and can reassure clinicians as to the efficacy and safety of biosimilar filgrastim. |

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through expansion of available therapeutic options and the potential for reinvestment of funds [5–8]. For simplicity, we refer to Sandoz biosimilar filgrastim (Zarzio®/Zarxiò®) as biosimilar filgrastim in this review.

Biosimilars are biologic medicines that have been shown to match an authorized reference biologic with regards to quality, primary and higher-order structure, biological activity and function, clinical efficacy, safety, and immunogenicity. Biosimilar approval by the EMA and FDA is highly regulated based on the concept of totality of evidence from evaluation of physicochemical and functional characteristics, pharmacokinetic/pharmacodynamic studies, and phase III confirmatory clinical studies [9]. Importantly, phase III confirmatory studies are required to be performed in an indication that is suitable and sensitive in order to identify any potential differences in safety, efficacy, or immunogenicity between the biosimilar and reference biologic [9]. Once the safety and efficacy has been confirmed in a sensitive indication, a biosimilar may then be approved for all the licensed indications of the reference medicine without the need to perform clinical studies in each indication, a concept known as extrapolation [10, 11]. It is important that a biosimilar does not automatically receive approval for each indication of the reference medicine; each extrapolated indication must undergo a separate assessment and have solid scientific rationale and justification.

In this review, we discuss the clinical evidence for biosimilar filgrastim, including the phase III confirmatory studies assessing filgrastim as primary prophylaxis to reduce duration of chemotherapy-induced febrile neutropenia [12–14]. Following approval, clinical experience and real-world evidence have demonstrated the safety and efficacy of biosimilar filgrastim in patients with different tumor types undergoing myelosuppressive chemotherapy and in both autologous and allogeneic stem cell mobilization and severe chronic neutropenia. Evidence in these extrapolated indications is also included in this review.

2 Biosimilar Filgrastim Phase III Clinical Data

Biosimilar filgrastim was approved by the EMA in 2009 and by the FDA in 2015. The submission to the EMA included confirmatory clinical data from an open-label, single-arm, phase III study performed in patients with breast cancer undergoing myelosuppressive chemotherapy [13, 15, 16]. Other indications, including stem cell mobilization and severe chronic neutropenia, were approved on the basis of extrapolation [17], with no data available at the time of the regulatory review and approval. FDA authorization of biosimilar filgrastim was based on results from PIONEER, a randomized, double-blind, multicenter, phase III confirmatory study that compared biosimilar filgrastim with the US-marketed reference biologic. PIONEER was conducted between December 2011 and June 2013 and thus contributed to the post-EU-approval body of evidence for biosimilar filgrastim [12, 14–16].

2.1 EU Registration Study

The EU registration study was a phase III confirmatory study that evaluated biosimilar filgrastim as primary prophylaxis for neutropenia in 170 patients with breast cancer receiving cytotoxic chemotherapy (dorozubicin 60 mg/m² and docetaxel 75 mg/m²) (Table 1) [13]. In this single-arm study, the primary endpoint, mean duration of severe neutropenia (DSN) in cycle 1 with biosimilar filgrastim (1.8 days) was comparable to previously published results for reference filgrastim (1.6–1.8 days) [13, 18, 19]. Regarding safety, treatment-emergent adverse events that were considered to be treatment related were generally mild and in line with those historically known for G-CSF therapy [13]. No patient developed antidrug binding or neutralizing antibodies.

2.2 US Registration Study

The US registration study was PIONEER, a randomized, double-blind, multicenter, phase III confirmatory study performed in patients with breast cancer (n = 218) receiving up to six cycles of chemotherapy (docetaxel 75 mg/m², doxorubicin 50 mg/m², and cyclophosphamide 500 mg/m² [TAC regimen]) (Table 1) [12]. Biosimilar filgrastim was considered non-inferior to the reference filgrastim, since the mean treatment difference for DSN was 0.02 days, with a lower limit of the 97.5% confidence interval of −0.27 days, which was entirely above the predefined margin of −1 day [12]. There were also no clinically meaningful differences in safety and immunogenicity between biosimilar filgrastim and the reference filgrastim [12].

PIONEER also provided the first published clinical evidence in oncology patients regarding repeated switching between a reference biologic and a biosimilar [12, 14, 20]. The results showed no clinically meaningful differences regarding efficacy, safety, or immunogenicity when patients were switched from reference to biosimilar filgrastim, or vice versa [14].

3 Biosimilar Filgrastim Post-Approval Evidence

3.1 Chemotherapy-Induced Neutropenia

Clinical experience in the use of biosimilar filgrastim since the original EU approval has provided further evidence of
its efficacy and safety profile [17]. Real-world evidence is available from the MONITOR-GCSF study, a multicenter, prospective, observational study performed in 12 European countries describing the treatment patterns and clinical outcomes of patients with cancer (n = 1447) who received biosimilar filgrastim for the prophylaxis of chemotherapy-induced neutropenia (Table 1) [21]. The real-world data from MONITOR-GCSF showed that biosimilar filgrastim was effective, with a safety profile consistent with historical data for the reference filgrastim and with what is expected for biosimilar filgrastim based on the totality of evidence. In addition, several non-interventional clinical studies with biosimilar filgrastim, conducted post-approval, showed outcomes in accordance with the MONITOR-GCSF study [21], confirming the efficacy and safety of biosimilar filgrastim in real-world clinical practice [22–27].

Subanalyses of MONITOR-GCSF have provided evidence for the efficacy and safety profile of biosimilar filgrastim in hematological and solid malignancies [17]. The study enrolled patients with different tumor types, including diffuse large B-cell lymphoma (n = 245) [28], non-small-cell lung cancer (n = 345) [29], and breast cancer (n = 466) [30]. Overall, the results from these subgroup analyses showed that, in real-world clinical practice in these tumor types, biosimilar filgrastim demonstrated similar efficacy and safety to published data for reference filgrastim, expanding on the evidence for the efficacy, safety, and tolerability from the clinical development program.

3.2 Stem Cell Mobilization

3.2.1 Autologous Stem Cell Mobilization

Beyond the wealth of available data in chemotherapy-induced neutropenia, a large body of evidence is also available from clinical studies for stem cell mobilization in both the autologous and the allogeneic setting [31, 32]. A recent systematic review reported data from 1019 patients undergoing autologous transplantation in a total of 27 studies [33]. Generally, data from studies of stem cell mobilization in the autologous setting demonstrated that the efficacy and safety of biosimilar filgrastim were consistent with the known profile of reference filgrastim. Furthermore, similar results were observed when reference filgrastim was included as a comparator [34–44]. Representative studies of autologous stem cell mobilization with biosimilar filgrastim are summarized in Table 1.

3.2.2 Allogeneic Stem Cell Mobilization

Importantly, although most data in stem cell mobilization are in the autologous setting, evidence is also emerging in allogeneic stem cell mobilization. A recent systematic review discussed the evidence for biosimilar filgrastim in the allogeneic setting, including 331 patients in eight studies [33, 45–50]. This included real-world evidence, including data from the largest healthy volunteer donor cohort (n = 244) of allogeneic stem cell mobilization reported to date [51], a long-term ongoing safety surveillance study with a planned duration of 10 years. An interim data analysis from a mean follow-up of 433 days (range 2–1528) showed that the safety profile and the efficacy of biosimilar filgrastim in allogeneic stem cell mobilization were consistent with previously reported data for biosimilar filgrastim [51]. A full analysis will be performed at the completion of the 10-year planned study duration period. Representative studies of allogeneic stem cell mobilization with biosimilar filgrastim are summarized in Table 1. Based on the comprehensive evidence for the safety and efficacy of biosimilars of filgrastim, the World Marrow Donor Association recently recommended their use in healthy donors [52].

3.3 Severe Chronic Neutropenia

As a part of the EMA post-approval commitment to address potential safety concerns for biosimilar filgrastim (e.g., osteoporosis, severe splenomegaly/splenic rupture, acute respiratory distress syndrome, cutaneous vasculitis), a study was performed in patients with severe chronic neutropenia, a group of very rare hematological disorders that may present at birth or later in life. Patients with severe chronic neutropenia have blood neutrophil counts of <500/μL, lasting for months or years, whereas other blood cell counts remain normal or close to normal. The European Branch of the Severe Chronic Neutropenia International Registry (SCNIR) includes patients in 26 European countries, Israel, Russia, and Turkey. This study included data that had been collected by SCNIR since 1994 on the long-term follow-up of patients with severe chronic neutropenia. Patients who received biosimilar filgrastim between 1 July 2011 and 31 March 2018 were separately analyzed as follow-up of a Sandoz study. Final analysis is ongoing, but no serious adverse events have been reported so far in patients receiving biosimilar filgrastim [53]. The number of treated patients was small because of the rarity of this disease, but the absence of any significant safety findings in this registry analysis led to the EMA’s decision to remove this surveillance activity from the pharmacovigilance plan, indicating that the major safety concerns in this indication with biosimilar filgrastim had been addressed.

4 Extrapolation in Clinical Practice

The experience from a decade of use of biosimilar filgrastim includes over 24 million patient-days of exposure and 10 years of real-world clinical evidence, indicating
Table 1 Summary of phase III and representative post-approval data for EU-approved biosimilars of filgrastim

| Biosimilar filgrastim | CIN phase I/II studies | CIN post-approval studies | SCM post-approval studies |
|-----------------------|------------------------|---------------------------|---------------------------|
| Accellin (Accord Healthcare)/Grastofil (Apotex) | KW130-104: Phase III, non-comparative, multicenter, repeat-dose safety study in pts with breast cancer receiving TAC (n = 120) [56] | Six CT cycles administered to 40.6% of pts | Retrospective, single-center study of Accord/Apotex biosimilar filgrastim (n = 47) vs. ref filgrastim (n = 170) for autologous SCM [58] |
| | (Accord Healthcare)/Grastofil (Apotex) | > 90% of pts received CT according to initial recommended dose | Mean total CD34+ cells collected was 6.2 (IQR 5.6–7.2) with ref filgrastim and 5.8 (IQR 5.3–7.0) × 106 cells/kg with Accord/Apotex biosimilar filgrastim (p = 0.53) |
| | | Median CT cycle following first dose of Hospira biosimilar filgrastim was not delayed due to FN vs. 13.5 and 18 days with ref filgrastim (p = 0.09 and 0.01, respectively) | Median time to neutrophil and platelet engraftment was 12 and 14 days with ref filgrastim vs. 12 and 14 days with Accord/Apotex biosimilar filgrastim (p = 0.23 and p = 0.29, respectively) |
| | | CT cycle following first dose of Hospira biosimilar filgrastim was not delayed due to FN in 96.9% of pts | No differences reported, except for total number of aphereses per mobilization (lowest, Hospira biosimilar filgrastim = 0.323) |
| | | All recipients successfully transplanted; no differences in neutrophil and platelet recovery observed | No significant differences reported, except for total number of aphereses per mobilization (lowest, Hospira biosimilar filgrastim = 0.323) |
| | | No neutralizing antibodies detected | Retrospective, single-center study evaluating the efficacy and safety of Hospira biosimilar filgrastim vs. ref filgrastim for autologous SCM (n = 367 pts) [64] |
| | | Prospective, multicenter study assessing the tolerability, safety, and efficacy of Hospira biosimilar filgrastim in pts with cancer receiving CT (n = 171) [67] | Mean total CD34+ cells collected was 4.75 ± 4.41 with ref filgrastim and 6.35 ± 6.42 × 106 cells/kg with Hospira biosimilar filgrastim (p = 0.01) |
| | | No cases of neutropenia, and only one event of FN reported (female aged ≤ 65 years and G-CSF-naïve) | Mean number of aphereses was 1.39 ± 0.65 vs. 1.24 ± 0.45 with ref filgrastim and Hospira biosimilar filgrastim, respectively (p = 0.02) |
| | | In total, 15 events of infection occurred in 14 pts; 3 infections were serious | Overall, 87.0% of Hospira biosimilar filgrastim pts and 92.0% of ref filgrastim pts underwent transplant; no differences in hematopoietic recovery or transplant-related toxicity observed |
| | | No cases of neutropenia, and only one event of FN reported (female aged ≤ 65 years and G-CSF-naïve) | Prospective, single-center study of pts with hematological malignancies receiving Hospira biosimilar filgrastim (n = 49) for autologous SCM vs. historical cohort of pts receiving ref filgrastim (n = 136) [65] |
| | | Nivestim (Hospira) | Overall, 87.0% of Hospira biosimilar filgrastim pts and 92.0% of ref filgrastim pts underwent transplant; no differences in hematopoietic recovery or transplant-related toxicity observed |
| | | GCF071: Phase III, multicenter, randomized, double-blind therapeutic equivalence study of Hospira biosimilar filgrastim vs. ref filgrastim in pts with invasive breast cancer (n = 250) [59] | No significant differences reported, except for total number of aphereses per mobilization (lowest, Hospira biosimilar filgrastim = 0.323) |
| | | Increases in mean ANC between 3.3 and 6.2 × 10^9/L reported in the first three cycles | Retrospective, single-center analysis comparing Hospira biosimilar filgrastim (n = 85), ref filgrastim (n = 134), and lenograstim (n = 38) for autologous SCM [67] |
| | | Overall, 40 ADRs reported in 34 (19.9%) pts, 5 considered serious | Average total number CD34+ cells collected was 5.37 with Hospira biosimilar filgrastim and 4.59 × 10^6 cells/kg with ref filgrastim (p = 0.23) |
| | | In total, 15 events of infection occurred in 14 pts; 3 infections were serious | Median number of leukaphereses required was 1 with Hospira biosimilar filgrastim and 2 with ref filgrastim (p = 0.007) |
| | | No cases of neutropenia, and only one event of FN reported (female aged ≤ 65 years and G-CSF-naïve) | Overall, 51 Hospira biosimilar filgrastim pts and 30 ref filgrastim pts were transplanted |
| | | No cases of neutropenia, and only one event of FN reported (female aged ≤ 65 years and G-CSF-naïve) | Median time to neutrophil and platelet engraftment was 15 and 20 days with Hospira biosimilar filgrastim vs. 13.5 and 18 days with ref filgrastim (p = 0.09 and 0.01, respectively) |
| | | No cases of neutropenia, and only one event of FN reported (female aged ≤ 65 years and G-CSF-naïve) | Retrospective, single-center analysis comparing Hospira biosimilar filgrastim (n = 66), ref filgrastim (n = 85), and lenograstim (n = 50) for autologous SCM [67] |
| | | No cases of neutropenia, and only one event of FN reported (female aged ≤ 65 years and G-CSF-naïve) | Average total number CD34+ cells collected was 5.37 with Hospira biosimilar filgrastim and 4.59 × 10^6 cells/kg with ref filgrastim (p = 0.23) |
| | | No cases of neutropenia, and only one event of FN reported (female aged ≤ 65 years and G-CSF-naïve) | Overall, 87.0% of Hospira biosimilar filgrastim pts and 92.0% of ref filgrastim pts underwent transplant; no differences in hematopoietic recovery or transplant-related toxicity observed |
| | | No cases of neutropenia, and only one event of FN reported (female aged ≤ 65 years and G-CSF-naïve) | No significant differences reported, except for total number of aphereses per mobilization (lowest, Hospira biosimilar filgrastim = 0.323) |
| | | No cases of neutropenia, and only one event of FN reported (female aged ≤ 65 years and G-CSF-naïve) | Retrospective, single-center study evaluating the efficacy and safety of Hospira biosimilar filgrastim vs. ref filgrastim for autologous SCM (n = 367 pts) [64] |
| | | No cases of neutropenia, and only one event of FN reported (female aged ≤ 65 years and G-CSF-naïve) | Mean total CD34+ cells collected was 4.75 ± 4.41 with ref filgrastim and 6.35 ± 6.42 × 10^6 cells/kg with Hospira biosimilar filgrastim (p = 0.01) |
| | | No cases of neutropenia, and only one event of FN reported (female aged ≤ 65 years and G-CSF-naïve) | Mean number of aphereses was 1.39 ± 0.65 vs. 1.24 ± 0.45 with ref filgrastim and Hospira biosimilar filgrastim, respectively (p = 0.02) |
| | | No cases of neutropenia, and only one event of FN reported (female aged ≤ 65 years and G-CSF-naïve) | Overall, 87.0% of Hospira biosimilar filgrastim pts and 92.0% of ref filgrastim pts underwent transplant; no differences in hematopoietic recovery or transplant-related toxicity observed |
| | | No cases of neutropenia, and only one event of FN reported (female aged ≤ 65 years and G-CSF-naïve) | No cases of neutropenia, and only one event of FN reported (female aged ≤ 65 years and G-CSF-naïve) |
| | | No cases of neutropenia, and only one event of FN reported (female aged ≤ 65 years and G-CSF-naïve) | No cases of neutropenia, and only one event of FN reported (female aged ≤ 65 years and G-CSF-naïve) |
| | | No cases of neutropenia, and only one event of FN reported (female aged ≤ 65 years and G-CSF-naïve) | No cases of neutropenia, and only one event of FN reported (female aged ≤ 65 years and G-CSF-naïve) |
Table 1 (continued)

| Biosimilar filgrastim | CIN phase I/II studies | CIN post-approval studies | SCM post-approval studies |
|-----------------------|-----------------------|---------------------------|---------------------------|
| Ratiop-harmo/Tevarastim (Teva Generics) [R/T] | XM02-02-INT: Phase II, multinational, multicenter RCT comparing R/T biosimilar filgrastim, ref filgrastim, and placebo in pts with breast cancer receiving docetaxel/carboplatin CT (n=348) [68] | Mean DSN in cycle 1 was 1.1 days with R/T biosimilar filgrastim, 1.2 days with ref filgrastim, and 1.6 days with placebo. | Mean 95% CI for difference was within the predefined equivalence limit (−1 to +2 days) |
| • Mean number of doses administered: 9.2 ± 2.83 in children, 7.3 ± 1.88 in adolescents | No significant difference in incidence of FN was found between R/T biosimilar filgrastim and ref filgrastim | No deaths or study withdrawals |
| • No significant difference in incidence of FN was found between R/T biosimilar filgrastim and ref filgrastim | No significant difference in incidence of FN was found between R/T biosimilar filgrastim and ref filgrastim for all secondary endpoints |
| Safety profiles were similar; incidence of drug-related AEs was lower with R/T biosimilar filgrastim (25.7%) than ref filgrastim (39.7%) | Retrospective single-center study of R/T biosimilar filgrastim (n=99) vs. ref filgrastim (n=86), with or without plerixafor, for autologous SCM in pts with lymphoma or MM |
| • No neutralizing antibodies detected | No significant difference in FN events (p=0.21) or length of hospital stay (p=0.87) Phase II, single-center, randomized study of R/T biosimilar filgrastim (n=24) vs ref filgrastim (n=25) for autologous SCM in adult pts with MM or NHL | No difference in FN events (p=0.21) or length of hospital stay (p=0.87) |
| XM02-03-INT: Phase II, multinational, multicenter, randomized, controlled study comparing R/T biosimilar filgrastim with ref filgrastim in pts with SCLC or NSCLC (n=240) [69] | Toxoid similar in both groups | No difference in FN events (p=0.21) or length of hospital stay (p=0.87) |
| • Mean DSN in cycle 1 was 0.5 days with R/T biosimilar filgrastim and 3.0 days with ref filgrastim | 18 R/T biosimilar filgrastim and 21 ref filgrastim pts transplanted | Phase II, single-center, randomized study of R/T biosimilar filgrastim (n=24) vs ref filgrastim (n=25) for autologous SCM in adult pts with MM or NHL |
| • 95% CI for the difference was within the predefined equivalence limit (−1 to +1 day) | Median time to neutrophil and platelet engraftment 12 and 17 days for R/T biosimilar filgrastim vs. 11 and 17 days for ref filgrastim (p=0.178 and p=0.1055) | Median CD34+ cell yield 10.9 with R/T biosimilar filgrastim and 12.0 × 10^6 cells/kg for filgrastim (p=0.889) |
| • Incidence of FN across all cycles was 33.1% in the R/T biosimilar filgrastim and 23.8% in the ref filgrastim/R/T biosimilar filgrastim group | Retrospective, single-center study of R/T biosimilar filgrastim (n=154) vs. ref filgrastim (n=131) for autologous SCM in pts with cancer | Toxicity similar in both groups |
| • No significant differences in AEs were observed between the two groups | In total, 111 R/T biosimilar filgrastim and 84 ref filgrastim pts proceeded to high-dose therapy and autologous transplant | 18 R/T biosimilar filgrastim and 21 ref filgrastim pts transplanted |
| XM02-04-INT: Phase II, multinational, multicenter RCT comparing R/T biosimilar filgrastim with ref filgrastim in CT-naive pts with aggressive NHL (n=92) [70] | Median days to neutrophil and platelet recovery: 13 and 12 with R/T biosimilar filgrastim vs. 13 and 13 with ref filgrastim | Median CD34+ cell yield 10.9 with R/T biosimilar filgrastim and 12.0 × 10^6 cells/kg for filgrastim (p=0.889) |
| • Mean DSN in cycle 1 was 0.5 days with R/T biosimilar filgrastim and 0.9 days with ref filgrastim (p=0.1055) | Prospective, single-center study of HLA-matched healthy sibling donors receiving R/T biosimilar filgrastim (n=24) vs historical controls receiving ref filgrastim (n=24) for allogeneic SCM | Toxicity similar in both groups |
| • Incidence of FN in cycle 1 was 11.5% with R/T biosimilar filgrastim and 20.7% with ref filgrastim (p=0.1232) | • Mean number of leukaphereses: 1.3 for both groups | All but one R/T biosimilar filgrastim pt were engrafted, median time to neutrophil and platelet recovery was 13 and 14 days with R/T biosimilar filgrastim vs. 12 and 13 days with ref filgrastim |
| Safety profile of R/T biosimilar filgrastim was similar to that of ref filgrastim | Median yield of CD34+ cells collected 10.2 (range 2.5–35.4) with R/T biosimilar filgrastim and 9.35 (range 3.7–30.6) × 10^6 cells/kg with ref filgrastim | Prospective study of R/T biosimilar filgrastim (n=11) vs. ref filgrastim (n=11) for allogeneic SCM in healthy donors |
| • No allergic reactions or changes in kidney/liver function were reported in any donor; 6 pts in both groups experienced arthralgias | AEs were mild and transient, with no difference between groups | • Mean number of leukaphereses: 1.45 with R/T biosimilar filgrastim, 1.27 with ref filgrastim |
| • Median time to neutrophil and platelet recovery was 14 and 6 days with R/T biosimilar filgrastim vs. 17 and 8 days with ref filgrastim | All but one R/T biosimilar filgrastim pt were engrafted, median time to neutrophil and platelet recovery was 13 and 14 days with R/T biosimilar filgrastim vs. 12 and 13 days with ref filgrastim | Median time to neutrophil and platelet recovery was 14 and 6 days with R/T biosimilar filgrastim vs. 17 and 8 days with ref filgrastim |
Prospective study comparing biosimilar filgrastim (n = 40) with ref filgrastim (n = 41) at 5 or 10 μg/kg doses for autologous SCM [47]

- Median number of leukaphereses was 1 with both biosimilar filgrastim and ref filgrastim (p = 0.10)
- No ADA detected

MONITOR-GCSF: International, multicenter, prospective, observational, open-label, pharmacoepidemiologic study of biosimilar filgrastim as PP or SP for FN in pts with cancer receiving myelo-suppressive CT (n = 1496) [21]

- According to EORTC guidelines, 17.4% of pts were under-, 56.6% were correctly, and 26.0% were over-prophylacted
- In all cycles, ≥ 1 any grade event of CIN was experienced by 34.8% of pts
- Incidence of any grade FN was 5.9% across study
- CT was disturbed in 9.7% of pts

MONITOR-GCSF subanalysis: pts with stage III–IV DLBCL (EP06-301: Phase III, open-label, single-arm study assessing safety, efficacy, and immunogenicity of biosimilar filgrastim for CIN prophylaxis in pts with breast cancer receiving 4 cycles of doxorubicin/doxetaxel (n = 170) [13]

- Median days to neutrophil and platelet recovery 14 and 12 days with biosimilar filgrastim vs. 15 and 11 days with ref filgrastim

Prospective study of biosimilar filgrastim vs. ref filgrastim (n = 61) for autologous SCM [30]

- Median CD34+ cells collected per apheresis day was 3.6 (range 0.5–47) with biosimilar filgrastim and 3.4 (range 0.3–54) × 10⁶ cells/kg with ref filgrastim
- 42.5% of donors contacted reported AEIs, including bone and lower back pain

Retrospective study of biosimilar filgrastim as PP or SP for FN in pts with breast cancer receiving 4 cycles of doxorubicin/docetaxel CT (n = 245) [33]

- In all cycles, ≥ 1 any grade event of CIN experienced by 35.5% of pts
- Incidence of FN was 6.2% across study
- CT disturbed in 9.7% of pts
- Most frequent AEs: bone pain (1.9%), arthralgia (0.6%), back pain (0.6%)

MONITOR-GCSF subanalysis: pts with stage III–IV NSCLC (n = 345) [49]

- 91% of donors underwent 1 and 9% underwent 2 aphereses
- Median yield of CD34+ cells, 7.9 (range 3.0–52.0) × 10⁶ cells/kg
- All 244 donors experienced ≥ 1 AE; in 98.8% of donors, at least 1 AE was considered related to biosimilar filgrastim
- Bone pain was the most common drug-related AE, occurring in 93.9% of donors

Retrospective study of biosimilar filgrastim in pts with MM (n = 244) [51]

- 91% of donors underwent 1 and 9% underwent 2 aphereses
- Median yield of CD34+ cells, 7.9 (range 3.0–52.0) × 10⁶ cells/kg
- All 244 donors experienced ≥ 1 AE; in 98.8% of donors, at least 1 AE was considered related to biosimilar filgrastim
- Bone pain was the most common drug-related AE, occurring in 93.9% of donors

Retrospective study of biosimilar filgrastim as PP or SP for FN in pts with breast cancer receiving myelo-suppressive CT (n = 245) [33]

- In all cycles, ≥ 1 any grade event of CIN experienced by 35.5% of pts
- Incidence of FN was 6.2% across study
- CT disturbed in 9.7% of pts
- Most frequent AEs: bone pain (1.9%), arthralgia (0.6%), back pain (0.6%)

MONITOR-GCSF subanalysis: pts with stage III–IV NSCLC (n = 345) [49]

- 91% of donors underwent 1 and 9% underwent 2 aphereses
- Median yield of CD34+ cells, 7.9 (range 3.0–52.0) × 10⁶ cells/kg
- All 244 donors experienced ≥ 1 AE; in 98.8% of donors, at least 1 AE was considered related to biosimilar filgrastim
- Bone pain was the most common drug-related AE, occurring in 93.9% of donors

Retrospective study of biosimilar filgrastim in pts with MM (n = 244) [51]

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Retrospective study of biosimilar filgrastim as PP or SP for FN in pts with breast cancer receiving myelo-suppressive CT (n = 245) [33]

- In all cycles, ≥ 1 any grade event of CIN experienced by 35.5% of pts
- Incidence of FN was 6.2% across study
- CT disturbed in 9.7% of pts
- Most frequent AEs: bone pain (1.9%), arthralgia (0.6%), back pain (0.6%)

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MONITOR-GCSF subanalysis: pts with stage III–IV NSCLC (n = 345) [49]
successful extrapolation. Together, this experience can help reassure clinicians, other healthcare professionals (HCPs), and patients that the concept of extrapolation is based on strong scientific evidence and principles. Furthermore, other biosimilars of filgrastim are available and, alongside biosimilars of epoetin alfa and recently approved biosimilars of pegfilgrastim, offer HCPs and patients several options for improved sustainability of supportive cancer care. Table 1 highlights the abundance of data available for these biosimilars of filgrastim, with phase III confirmatory studies performed in patients undergoing cytotoxic chemotherapy receiving G-CSF for prevention of neutropenia. The availability of clinical data is just one approach to provide reassurance about biosimilars and must be complemented by patient education, clinical practice recommendations, regulatory guidance, and positioning statements such as those recently published by the American Society of Clinical Oncology and the European Society for Medical Oncology [54, 55], if the full potential of biosimilars in oncology is to be realized.

A total of 14 types of biosimilars approved in the EU, and nine types approved in the USA, indicates the level of uptake of biosimilars. Acceptance of biosimilars is also reflected by the inclusion of biosimilars of filgrastim and biosimilars of epoetin in international clinical practice guidelines [79–82]. This adoption of biosimilars has been driven by several factors, including the experience with established biosimilars such as filgrastim and epoetin alfa, which has in turn improved understanding of the biosimilar concept and totality of evidence and confidence in the extrapolation concept [83]. A recent survey by the European Society for Medical Oncology assessed oncology specialists’ level of understanding and comfort with using biosimilars [84]. The survey reported that nearly half of responding prescribers used biosimilars in their clinical oncology practice, and ~ 80% reported an average to very high level of biosimilar knowledge [84], showing an encouraging level of understanding of biosimilars and comfort in their use in oncology. However, switching was identified as an area in which prescribers were less confident at the time of survey. Nonetheless, the latest publication of switching studies in oncology [12, 14, 20] and other therapeutic areas [85–88] has contributed to acceptance of biosimilars, including those more recently approved. In addition, a recent systematic review assessed whether switching could lead to altered clinical outcomes. It included data from 90 studies that enrolled 14,225 subjects and reported that the vast majority of studies did not show differences in efficacy or safety after multiple switches [89]. Systematic reviews such as this, and publication of real-world evidence, will help further reassure physicians and drive acceptance of biosimilars. Finally, the efforts of international medical oncology societies in providing guidance on using biosimilars [54, 55] have also paved the way for acceptance of newer biosimilars, allowing more patients
Conflict of interest

MA has been a consultant for Amgen, BMS, Celgene, Clinigen, Eisai, Genomic Health, GSK, Helsinn, Hospira, Johnson & Johnson, Novartis, Merck, Merck Serono, Mundipharma, Pfizer, Pierre Fabre, Roche, Sandoz, Tesaro, Teva, Vifor, G1 Therapeutics, and Lilly. MN and NM are receiving consulting fees/honoraria and payment for lectures (including service on speaker’s bureaus) from Amgen, Pfizer, and Sandoz. PG has received consulting fees/honoraria and payment for lectures (including service on speaker’s bureaus) from Amgen, Bayer Schering, Cephalon, Chugai, Eisai, Genomic Health, GSK, Helsinn, Hospira, Ipsen, Johnson & Johnson, OrthoBiotech, Kyowa Hakko Kirin, Merck, Merck Serono, Mundipharma, Novartis, Pfizer, Pierre Fabre, Roche, Sandoz, Sanofi, Tesaro, Taiho, Teva, Vifor, G1 Therapeutics, and Lilly. PG has received consulting fees/honoraria and payment for lectures (including service on speaker’s bureaus) from Amgen, Pfizer, and Sandoz. MN and NM are employees of Hexal AG. AK was an employee of Hexal AG at the time of manuscript development.

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