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REVIEW ARTICLE

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.

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®/Zarxio®) 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 suitably 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 (doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2) (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/m^2, doxorubicin 50 mg/m^2, and cyclophosphamide 500 mg/m^2 [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 settings [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 $< 500/\mu L$, 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/III studies	CIN post-approval studies	SCM post-approval studies
Accofil (Accord Healthcare)/ Grastofil (Apotex)	KWI-300-104: Phase III, non-comparative, multicenter, repeat-dose safety study in pts with breast cancer receiving TAC ($n = 120$) [56] • Mean ± SD DSN in cycle 1: 1.40 ± 1.07 days • Severe neutropenia reported in 77.5% of pts in cycle 1 • Most AEs were mild (748 events, 61.51%) or moderate (368 events, 30.26%) • Most common AE, bone pain: 267 events in 80 (66.67%) pts	Multicenter, non-interventional, epidemiological study of Accord/Apotex biosimilar filgrastim as PP and SP for FN ($n = 170$) [57] • PP 60.0%; SP 40.0% • Six CT cycles administered to 40.6% of pts • > 90% of pts received CT according to initial recommended dose • No FN reported after final CT cycle in most pts • Median neutrophil count at first visit 2.2×10^3/μL and did not fall below that level • No treatment-related AEs reported	Retrospective, single-center study of Accord/Apotex biosimilar filgrastim ($n = 47$) vs. ref filgrastim ($n = 170$) for autologous SCM [58] • Successful harvest in 92.4% of ref filgrastim and 100.0% of Accord/Apotex biosimilar filgrastim pts • Median total CD34⁺ cells collected was 6.2 (IQR 5.6–7.2) with ref filgrastim and 5.8 (IQR 5.3–7.0) $\times 10^6$ cells/kg with Accord/Apotex biosimilar filgrastim ($p = 0.53$) • Median time to neutrophil and platelet engraftment was 12 and 13 days with ref filgrastim vs. 12 and 14 days with Accord/Apotex biosimilar filgrastim ($p = 0.23$ and $p = 0.29$, respectively)
Nivestim (Hospira)	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] • Mean DSN in cycle 1 was 1.6 days with Hospira biosimilar filgrastim and 1.3 days with ref filgrastim; 95% CI for the difference was within the predefined equivalence limit (− 1 to + 1 day) • Severe neutropenia in cycle 1 occurred in 77.6% of Hospira biosimilar filgrastim and 68.2% of ref filgrastim pts • Any grade AEs occurred in 86.9% of Hospira biosimilar filgrastim and 84.2% of ref filgrastim pts • The most common any grade TEAE was bone pain, reported in 14.2% of Hospira biosimilar filgrastim and 9.5% of ref filgrastim pts • No neutralizing antibodies detected	Prospective, non-interventional, non-comparative, multicenter study of Hospira biosimilar filgrastim as PP for FN in pts with solid or hematological malignancies ($n = 171$) [60] • Increases in mean ANC between 3.3 and 6.2×10^9/L reported in the first three cycles • No cases of neutropenia, and only one event of FN reported (female aged ≤ 65 years and G-CSF-naïve) • In total, 15 events of infection occurred in 14 pts; 3 infections were serious • Overall, 40 ADRs reported in 34 (19.9%) pts, 5 considered serious • Discontinuation of Hospira biosimilar filgrastim occurred due to 8 ADRs; no AE or ADR had a fatal outcome Prospective, multicenter study assessing the tolerability, safety, and efficacy of Hospira biosimilar filgrastim in pts with cancer receiving CT ($n = 386$) [61] • PP 64.0%; SP 36.0% • At follow-up, 95.6% of pts had no change in CT dose due to FN • CT discontinued due to FN in 2 pts (0.5%) and CT dose reduced due to FN in 4 pts (1.0%) • CT cycle following first dose of Hospira biosimilar filgrastim was not delayed due to FN in 96.9% of pts • ≥ 1 AE potentially related to Hospira biosimilar filgrastim reported in 29.8% of pts Retrospective study comparing the efficacy of Hospira biosimilar filgrastim ($n = 134$), ref filgrastim ($n = 147$), and pegfilgrastim ($n = 139$) as PP for FN in pts with breast cancer receiving TAC [62] • FN rates (per pt) were 16.0% (95% CI 10.2–22.5) with ref filgrastim, 9.0% (95% CI 4.5–14.6) with pegfilgrastim, and 16.0% (95% CI 10.0–22.9) with Hospira biosimilar filgrastim • FN episodes with ANC < 100 cells/μL were reported in 50.0% of Hospira biosimilar filgrastim pts, 4.0% of ref filgrastim pts, and 6.0% of pegfilgrastim pts • No differences reported in terms of FN complications, except for more CT delays with Hospira biosimilar filgrastim vs. pegfilgrastim NEXT: prospective, non-interventional, longitudinal, multicenter study assessing safety of Hospira biosimilar filgrastim for CIN prophylaxis ($n = 2103$) [63] • PP 91.0%; SP 7.3% • FN reported in 4.9% of pts and infections in 3.1% of pts • Overall, 4.9% of pts were hospitalized for FN and/or infection at a median of 5.5 (range 0–64.0) days after initiating Hospira biosimilar filgrastim • Reduced CT dose due to FN and/or infection occurred in 4.7% of pts • ≥ 1 AE occurred in 20.4% of pts; muscle and/or bone disorders occurred in 12.7% of pts	Retrospective, single-center study evaluating the efficacy and safety of Hospira biosimilar filgrastim vs. ref filgrastim for autologous SCM ($n = 365$ pts) [64] • Mean total CD34⁺ cells collected was 4.75 ± 4.41 with ref filgrastim and 6.35 ± 6.42 $\times 10^6$ cells/kg with Hospira biosimilar filgrastim ($p = 0.01$) • Mean number of aphereses was 1.39 ± 0.65 vs. 1.24 ± 0.45 with ref filgrastim and Hospira biosimilar filgrastim, respectively ($p = 0.02$) • 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 • 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 ($n = 138$) [65] • < 3.0% of pts were poor mobilizers in both arms • Mean number CD34⁺ cells collected was 10.5 with ref filgrastim and 11.1 $\times 10^6$ cells/kg with Hospira biosimilar filgrastim ($p = 0.323$) Retrospective, single-center study comparing Hospira biosimilar filgrastim ($n = 60$) with ref filgrastim ($n = 38$) for autologous SCM in pts with MM [66] • Average total number CD34⁺ cells collected was 5.37 with Hospira biosimilar filgrastim and 4.59 $\times 10^6$ cells/kg with ref filgrastim ($p = 0.22$) • Median number of leukaphereses required was 1 with Hospira biosimilar filgrastim and 2 with ref filgrastim ($p = 0.0007$) • Overall, 51 Hospira biosimilar filgrastim pts and 30 ref filgrastim pts were transplanted • 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) Retrospective, single-center analysis comparing Hospira biosimilar filgrastim ($n = 66$), ref filgrastim ($n = 85$), and lenograstim ($n = 50$) for autologous SCM [67] • No significant differences reported, except for total number of aphereses per mobilization (lowest, Hospira biosimilar filgrastim [1.7]; highest, ref filgrastim [2.1]; $p = 0.009$) • Average CD34⁺ cells collected was similar with all three biologics ($p = 0.38$) • Transplant performed in 103 (51%) pts; no differences in infused CD34⁺ cells, days to neutrophil recovery, and days to platelet recovery observed Retrospective, single-center study evaluating efficacy and safety of Hospira biosimilar filgrastim vs. ref filgrastim for allogeneic SCM ($n = 217$ healthy sibling donors) [64] • No serious AEs reported • Mean total CD34⁺ cells collected was 7.6 ± 3.45 with Hospira biosimilar filgrastim and 6.26 ± 2.71 $\times 10^6$ cells/kg with ref filgrastim ($p = 0.002$) • Optimal cell dose not achieved in 8.5% and 13.0% of donors with Hospira biosimilar filgrastim and ref filgrastim, respectively • All recipients successfully transplanted; no differences in neutrophil and platelet engraftment reported

Table 1 (continued)

Biosimilar filgrastim	CIN phase I/III studies	CIN post-approval studies	SCM post-approval studies
Ratiograstim (Ratiopharm)/ Tevagrastim (Teva Generics) [R/T]	XM02-02-INT: Phase III, multinational, multicenter RCT comparing R/T biosimilar filgrastim, ref filgrastim, and placebo in pts with breast cancer receiving docetaxel/ doxorubicin CT ($n = 348$) [68] • Mean DSN in cycle 1 was 1.1 days with R/T biosimilar filgrastim, 1.1 days with ref filgrastim, and 3.9 days with placebo • 95% CI for difference was within the predefined equivalence limit (− 1 to + 1 day) • No significant difference in incidence of FN was found between R/T biosimilar filgrastim and ref filgrastim • Safety profiles were similar; incidence of drug-related AEs was lower with R/T biosimilar filgrastim (25.7%) than ref filgrastim (39.7%) • No neutralizing antibodies detected XM02-03-INT: Phase III, multinational, multicenter, randomized, controlled study comparing R/T biosimilar filgrastim with ref filgrastim in pts with SCLC or NSCLC ($n = 240$) [69] • Mean DSN in cycle 1 was 0.5 days with R/T biosimilar filgrastim and 0.3 days with ref filgrastim • 95% CI for the difference was within the predefined equivalence limit (− 1 to + 1 day) • 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 • No significant differences in AEs were observed between the two groups XM02-04-INT: Phase III, multinational, multicenter RCT comparing R/T biosimilar filgrastim with ref filgrastim in CT-naïve pts with aggressive NHL ($n = 92$) [70] • Mean DSN in cycle 1 was 0.5 days with R/T biosimilar filgrastim and 0.9 days with ref filgrastim ($p = 0.1055$) • Incidence of FN in cycle 1 was 11.1% with R/T biosimilar filgrastim and 20.7% with ref filgrastim ($p = 0.1232$) • Safety profile of R/T biosimilar filgrastim was similar to that of ref filgrastim	Prospective, international, multicenter study assessing R/T biosimilar filgrastim in pediatric pts receiving ≥ 1 cycle of myelosuppressive CT ($n = 50$) [71] • Mean ± SD number of doses administered: 9.2 ± 2.83 in children, 7.3 ± 1.88 in adolescents • Treatment-related AEs observed in 18.0% of pts, most commonly musculoskeletal and connective tissue disorders (8.0%) • Incidence of severe neutropenia was 52.0% (95% CI 0.374–0.663) • Incidence of FN was 26% (95% CI 0.146–0.403) • No deaths or study withdrawals Open-label, multicenter, prospective, observational survey in pts with cancer receiving CT and R/T biosimilar filgrastim for prevention of FN ($n = 354$) [72] • PP 65.8%; SP 34.2% • Median delivered dose of SC R/T biosimilar filgrastim was 30 million IU/kg/day for median duration of 5.4 days per cycle • Characteristics of FN leading to SP were grade 3–4 neutropenia (grade 4: 47.7%), median fever 38.6 °C, median duration of fever 2 days • MASCC score was < 21 (high risk) for 39.0% of pts (PP 35.8%; SP 44.3%)	Prospective, randomized, open-label, non-inferiority study comparing R/T biosimilar filgrastim ($n = 46$) with ref filgrastim ($n = 51$) plus plerixafor for autologous SCM in pts with MM or NHL [73] • Mean CD34$^+$ cell collection on day 5 was 11.6 ± 6.7 with R/T biosimilar filgrastim and 10.0 ± 6.8 cells/kg with ref filgrastim • Trend toward increased mobilization with R/T biosimilar filgrastim, not statistically significant • R/T biosimilar filgrastim and ref filgrastim similar for all secondary endpoints Retrospective single-center study of R/T biosimilar filgrastim ($n = 14$) vs. filgrastim/lenograstim ($n = 57$) for autologous SCM in pts with lymphoma or MM • No significant difference between R/T biosimilar filgrastim and filgrastim/lenograstim in terms of CD34$^+$ cell numbers collected, frequencies of AEs, time to engraftment, and incidence of complications after transplant Retrospective 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 plasma cell disorders [74] • Median yield of CD34$^+$ cells collected 5.56 with ref filgrastim and 5.85 × 10^6 cells/kg with R/T biosimilar filgrastim ($p = 0.58$) • Neutrophil and platelet recovery occurred after mean 11.5 and 17.7 days with R/T biosimilar filgrastim vs. 11.7 and 18.5 days with ref filgrastim ($p = 0.31$ and 0.20, respectively) • No 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 ($n = 24$) or ref filgrastim ($n = 25$) for autologous SCM in adult pts with MM or NHL [75] • Median CD34$^+$ cell yield 10.9 with R/T biosimilar filgrastim and 12.0 × 10^6 cells/kg for filgrastim ($p = 0.889$) • Toxicity similar in both groups • 18 R/T biosimilar filgrastim and 21 ref filgrastim pts transplanted • 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 $p = 0.238$, respectively) Retrospective, single-center study of R/T biosimilar filgrastim ($n = 154$) vs. ref filgrastim ($n = 131$) for autologous SCM in pts with cancer [76] • Median CD34$^+$ cell yield 4.5 (range 0.2–43.0) with R/T biosimilar filgrastim and 4.4 (range 0.5–56) × 10^6 cells/kg with ref filgrastim ($p = 0.65$) • In total, 111 R/T biosimilar filgrastim and 84 ref filgrastim pts proceeded to high-dose therapy and autologous transplant • Median days to neutrophil and platelet recovery: 13 and 12 with R/T biosimilar filgrastim vs. 13 and 12 with ref filgrastim 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 [77] • Mean number of leukaphereses: 1.3 for both groups • Median yield of CD34$^+$ cells collected 10.2 (range 2.52–35.4) with R/T biosimilar filgrastim and 9.35 (range 3.7–30.6) × 10^6 cells/kg with ref filgrastim • AEs were mild and transient, with no difference between 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 Prospective study of R/T biosimilar filgrastim ($n = 11$) vs. ref filgrastim ($n = 11$) for allogeneic SCM in healthy donors [32] • Mean number of leukaphereses 1.45 with R/T biosimilar filgrastim, 1.27 with ref filgrastim • Median CD34$^+$ cells collected 4.4 (range 2.0–7.3) with R/T biosimilar filgrastim and 4.2 (range 2.1–7.9) × 10^6 cells/kg with ref filgrastim • No allergic reactions or changes in kidney/liver function were reported in any donor; 6 pts in both groups experienced arthralgias • 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

Table 1 (continued)

Biosimilar filgrastim	CIN phase I/III studies	CIN post-approval studies	SCM post-approval studies
Biosimilar filgrastim (Zarzio/ Zarxio, Hexal AG/ Sandoz Inc.), Filgrastim Hexal (Sandoz)	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/docetaxel CT ($n=170$) [13] • Mean ANC curves with biosimilar filgrastim were congruent for all cycles from day 1 to 11 • Depth of ANC nadir greater in cycle 1 than following 3 cycles • In cycle 1, 6% of pts experienced FN • Incidence of musculoskeletal pain 21.0%, bone pain 8.8% • No ADA detected Phase III, randomized, double-blind, parallel-group, multicenter study of efficacy and safety of biosimilar filgrastim vs. US licensed ref filgrastim in pts with breast cancer receiving TAC ($n=218$) [12] • Mean ± SD DSN 1.18 ± 1.12 days with biosimilar filgrastim, 1.20 ± 1.02 days with ref filgrastim • Lower bound of 97.5% CI was above the predefined equivalence limit of − 1 day • TEAEs potentially related to study drug occurred in 20.6% of biosimilar filgrastim and 19.6% of ref filgrastim pts • 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 myelosuppressive CT ($n=1496$) [21] • PP 72.3%; SP 27.7% • 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 5.9% across study • CT was disturbed in 9.5% of pts MONITOR-GCSF subanalysis: pts with stage III–IV DLBCL ($n=245$) [28] • In all cycles, ≥ 1 any grade event of CIN was experienced by 35.5% of pts • Incidence of any grade FN was 9.8% across the study • Overall, 5.9% of pts discontinued prophylaxis • Most commonly observed AEs: bone pain (2.9%), arthralgia (0.8%), and back pain (0.8%) MONITOR-GCSF subanalysis: pts with stage III–IV breast cancer ($n=466$) [30] • In all cycles, ≥ 1 any grade event of CIN experienced by 32.8% of pts • Incidence of FN 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 ($n=345$) [29] • In all cycles, ≥ 1 any grade event of CIN was experienced by 36.5% of pts • Incidence of FN 5.2% across study • 19.1% of pts discontinued prophylaxis • 80.0% of pts had a change to CT regimen • AEs included arthralgia, bone pain, cough, gastroenteritis, and myalgia (1 pt each)	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 ($p=0.10$) • Median CD34$^+$ cells collected with first leukapheresis 5.5 (range 1.1–20.0) with biosimilar filgrastim and 4.49 (range 0.9–25.0) × 10^6 cells/kg with ref filgrastim ($p=0.26$) • With biosimilar filgrastim at 5 and 10 μg/kg doses, bone pain and/or headache was observed in 3 and 11 pts, respectively • 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 ($n=80$) vs. ref filgrastim ($n=61$) for autologous SCM [36] • Median number of aphereses, 1 with both biosimilar filgrastim and ref filgrastim • Median CD34$^+$ cells collected per apheresis day was 3.6 (range 0–47) with biosimilar filgrastim and 3.4 (range 0.1–45) × 10^6 cells/kg with ref filgrastim • 42.5% of donors contacted experienced AEs, including bone and lower back pain Retrospective study of biosimilar filgrastim for autologous SCM ($n=209$) [39] • Median harvest days needed, 1 • Median CD34$^+$ cell yield, 4.08 (range 0.36–57.42) × 10^6 cells/kg • 191 pts received high-dose CT and transplant • Median 12 days to both neutrophil and platelet engraftment • After median follow-up 31 months, 30.6% of pts experienced bone or muscle pain; no serious AEs reported Retrospective study of biosimilar filgrastim ($n=131$) vs. ref filgrastim ($n=74$) vs. lenograstim ($n=45$) for autologous SCM in pts with MM [38] • Median number of leukaphereses, 1 in all 3 groups • Median number CD34$^+$ cells harvested, 10.5 (range 2.7–40.4) with ref filgrastim, 9.9 (range 0.2–26.0) with biosimilar filgrastim, 10.7 (range 3.1–27.9) × 10^6 cells/kg with lenograstim Prospective, multicenter, long-term study of biosimilar filgrastim for allogeneic SCM in healthy donors ($n=244$) [51] • 91% of donors underwent 1 and 9% underwent 2 aphereses • Median yield of CD34$^+$ cells, 7.9 (range 3.0–52.0) × 10^6 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 for allogeneic SCM in healthy donors ($n=51$) [78] • Median number of aphereses needed, 1 • Median CD34$^+$ cells collected, 5.6 (range 1.3–13.9) × 10^6 cells/kg • In transplanted pts, median days to neutrophil and platelet engraftment was 16 and 5 days, respectively • AEs reported in 17 biosimilar filgrastim pts and 15 ref filgrastim pts, including bone pain, headache, and/or neutropenic fever Prospective study of biosimilar filgrastim ($n=85$) vs. lenograstim ($n=121$) and ref filgrastim ($n=107$) for allogeneic SCM [48] • Proportion of donors requiring only 1 apheresis for collection, 93% for both biosimilar filgrastim and ref filgrastim, 87% for lenograstim • Mean CD34$^+$ cells collected, 7.6 for biosimilar filgrastim, 6.2 for lenograstim, 7.3 × 10^6 cells/kg for ref filgrastim ($p=0.129$) • No mobilization failures reported Retrospective comparative analysis of biosimilar filgrastim ($n=45$) and ref filgrastim ($n=41$) for allogeneic SCM in healthy donors [49] • With both biosimilar filgrastim and ref filgrastim, 4 days of G-CSF required; all donors collected > 2 × 10^6 cells/kg • Median number of aphereses required, 1 in both groups • Median number CD34$^+$ cells harvested with first apheresis, 4.02 (range 0.6–12.9) with biosimilar filgrastim and 4.53 (range 1.3–12.1) × 10^6 cells/kg with ref filgrastim ($p=0.666$) • No AEs or serious AEs were observed in either group

Table 1 (continued)

ADA antidrug antibodies, *ADR* antidrug reaction, *AE* adverse event, *ANC* absolute neutrophil count, *CD34+* cluster of differentiation 34 positive, *CI* confidence interval, *CIN* chemotherapy-induced neutropenia, *CT* chemotherapy, *DLBLC* diffuse large B-cell lymphoma, *DSN* duration of severe neutropenia, *EORTC* European Organisation for Research and Treatment of Cancer, *FN* febrile neutropenia, *G-CSF* granulocyte colony-stimulating factor, *HLA* human leukocyte antigen, *IQR* interquartile range, *IU* international units, *MASCC* Multinational Association for Supportive Care in Cancer, *MM* multiple myeloma, *NHL* non-Hodgkin lymphoma, *NSCLC* non-small-cell lung cancer, *PP* primary prophylaxis, *pt(s)* patient(s), *RCT* randomized controlled trial, *SC* subcutaneous, *SCLC* small-cell lung cancer, *SCM* stem cell mobilization, *SD* standard deviation, *SP* secondary prophylaxis, *TAC* docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2, *TEAE* treatment-emergent adverse event

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 to benefit. This support must be continued to maintain clinical confidence in biosimilars in oncology.

5 Conclusion

The stringent processes for biosimilar development, including the totality of evidence approach based on solid scientific evidence, and the review and approval by regulatory bodies such as the EMA and FDA, should reassure HCPs and patients that approved biosimilars are efficacious and safe. Biosimilar filgrastim provides a practical example of how a decade of clinical experience can reassure HCPs regarding the extrapolation concept and the safety and efficacy of biosimilars in different indications.

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Compliance with Ethical Standards

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References

1. Generics and Biosimilars Initiative (GaBi). Biosimilars approved in Europe. December 2018. http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe. Accessed 02 May 2019.
2. Generics and Biosimilars Initiative (GaBI). EMA accepts application for pegfilgrastim biosimilar from Cinfa. October 2017. http://www.gabionline.net/Biosimilars/News/EMA-accepts-application-for-pegfilgrastim-biosimilar-from-Cinfa. Accessed 02 May 2019.
3. US Food and Drug Administration (FDA). FDA Briefing Document—Oncologic Drugs Advisory Committee Meeting. January 2015. http://patentdocs.typepad.com/files/briefing-document.pdf. Accessed 02 May 2019.
4. US Food and Drug Administration (FDA). Biosimilar product information. FDA-approved biosimilar products. https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm580432.htm. Accessed 28 June 2019.
5. Zelenetz AD, Ahmed I, Braud EL, Cross JD, Davenport-Ennis N, Dickinson BD, et al. NCCN biosimilars white paper: regulatory, scientific, and patient safety perspectives. J Natl Compr Canc Netw. 2011;9(Suppl 4):S1–22.
6. Cornes P. The economic pressures for biosimilar drug use in cancer medicine. Target Oncol. 2012;7(Suppl 1):S57–67.
7. Curigliano G, O'Connor DP, Rosenberg JA, Jacobs I. Biosimilars: extrapolation for oncology. Crit Rev Oncol Hematol. 2016;104:131–7.
8. Tkaczuk KHR, Jacobs IA. Biosimilars in oncology: from development to clinical practice. Semin Oncol. 2014;41(Suppl 3):S3–12.
9. Weise M, Kurki P, Wolff-Holz E, Bielsky MC, Schneider CK. Biosimilars: the science of extrapolation. Blood. 2014;124(22):3191–6.
10. European Medicines Agency (EMA). Guideline on similar biological medicinal products. CHMP/437/04 Rev 1. Oct 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf. Accessed 02 May 2019.
11. European Medicines Agency and European Commission. Biosimilars in the EU. Information guide for healthcare professionals. April 2017. https://www.ema.europa.eu/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf. Accessed 02 May 2019.
12. Blackwell K, Semiglazov V, Krasnozhon D, Davidenko I, Nelyubina L, Nakov R, et al. Comparison of EP2006, a filgrastim biosimilar, to the reference: a phase III, randomized, double-blind clinical study in the prevention of severe neutropenia in patients with breast cancer receiving myelosuppressive chemotherapy. Ann Oncol. 2015;26(9):1948–53.
13. Gascón P, Fuhr U, Sörgel F, Kinzig-Schippers M, Makhson A, Balser S, et al. Development of a new G-CSF product based on biosimilarity assessment. Ann Oncol. 2010;21(7):1419–29.
14. Blackwell K, Gascón P, Krendyukov A, Gattu S, Li Y, Harbeck N. Safety and efficacy of alternating treatment with EP2006, a filgrastim biosimilar, and reference filgrastim: a phase III, randomised, double-blind clinical study in the prevention of severe neutropenia in patients with breast cancer receiving myelosuppressive chemotherapy. Ann Oncol. 2018;29(1):244–9.
15. Harbeck N, Gascón P, Krendyukov A, Hoebel N, Gattu S, Blackwell K. Safety profile of biosimilar filgrastim (Zarzio/Zarxio): a combined analysis of phase III studies. Oncologist. 2018;23(4):403–9.
16. Harbeck N, Yau L, Mathieson N, Krendyukov A. Comparison of efficacy and safety of biosimilar filgrastim in a RCT (PIONEER) and real-world practice (MONITOR-GCSF). J Clin Oncol. 2018;36(15_suppl):111–111.
17. Gascón P, Tesch H, Verpoort K, Rosati MS, Salesi N, Agrawal S, et al. Clinical experience with Zarzio® in Europe: what have we learned? Support Care Cancer. 2013;21(10):2925–32.
18. Holmes FA, O'Shaughnessy JA, Vukelja S, Jones SE, Shogan J, Savin M, 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(3):727–31.

19. Green MD, Koelbl H, Baselga J, Galid A, Guillem V, Gascon P, 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(1):29–35.
20. Aapro M. Biosimilars in oncology: much ado about nothing? Ann Oncol. 2018;29(1):25–6.
21. Gascón P, Aapro M, Ludwig H, Bokemeyer C, Boccadoro M, Turner M, et al. Treatment patterns and outcomes in the prophylaxis of chemotherapy-induced (febrile) neutropenia with biosimilar filgrastim (the MONITOR-GCSF study). Support Care Cancer. 2016;24(2):911–25.
22. Roché H, Eymard JC, Radji A, Prevost A, Diab R, Lamuraglia M, et al. Biosimilar filgrastim treatment patterns and prevention of febrile neutropenia: a prospective multicentre study in France in patients with solid tumours (the ZOHé study). BMC Cancer. 2018;18(1):1127.
23. Damaj GL, Benbrahim O, Hacini M, Voronina I, Benabed K, Soumoudronga RF, et al. ZOHé: a prospective study of the use of biosimilar filgrastim Zarzio in clinical practice in patients treated with chemotherapy for lymphoid malignancies. Clin Lymphoma Myeloma Leuk. 2017;17(6):362–9.e2.
24. Salesi N, Di Cocco B, Colonna M, Veltri E. Biosimilar medicines in oncology: single-center experience with biosimilar G-CSF. Future Oncol. 2012;8(5):625–30.
25. Verpoort K, Möhler TM. A non-interventional study of biosimilar granulocyte colony-stimulating factor as prophylaxis for chemotherapy-induced neutropenia in a community oncology centre. Ther Adv Med Oncol. 2012;4(6):289–93.
26. Nahon S, Rastkhah M, Ben Abdelghani M, Soumoudronga RF, Gasnereau I, Labourey JL. Zarzio®, biosimilar of filgrastim, in prophylaxis of chemotherapy-induced neutropenia in routine practice: a French prospective multicentric study. Support Care Cancer. 2016;24(5):1991–8.
27. Tesch H, Ulshöfer T, Vehling-Kaiser U, Ottillinger B, Bulenda D, Turner M. Prevention and treatment of chemotherapy-induced neutropenia with the biosimilar filgrastim: a non-interventional observational study of clinical practice patterns. Oncol Res Treat. 2015;38(4):146–52.
28. Gascón P, Krendyukov A, Höbel N, Aapro M. MONITOR-GCSF DLBCL subanalysis: treatment patterns/outcomes with biosimilar filgrastim for chemotherapy-induced/febrile neutropenia prophylaxis. Eur J Haematol. 2018;100(3):241–6.
29. Aapro M, Krendyukov A, Höbel N, Gascón P. Treatment patterns and outcomes in patients with non-small cell lung cancer (NSCLC) receiving biosimilar filgrastim for prophylaxis of chemotherapy-induced (febrile) neutropenia: results from the MONITOR-GCSF study. Eur J Cancer Care (Engl). 2019:e13034.
30. Aapro M, Bokemeyer C, Ludwig H, Gascón P, Boccadoro M, Denhaerynck K, et al. Chemotherapy-induced (febrile) neutropenia prophylaxis with biosimilar filgrastim in elderly versus non-elderly cancer patients: patterns, outcomes, and determinants (MONITOR-GCSF study). J Geriatr Oncol. 2017;8(2):86–95.
31. Schmitt M, Hoffmann JM, Lorenz K, Publicover A, Schmitt A, Nagler A. Mobilization of autologous and allogeneic peripheral blood stem cells for transplantation in haematological malignancies using biosimilar G-CSF. Vox Sang. 2016;111(2):178–86.
32. Schmitt M, Publicover A, Orchard KH, Görlach M, Wang L, Schmitt A, et al. Biosimilar G-CSF based mobilization of peripheral blood hematopoietic stem cells for autologous and allogeneic stem cell transplantation. Theranostics. 2014;4(3):280–9.
33. Agrawal S, Mathieson N, Krendyukov A. Sandoz biosimilar filgrastim in stem cell mobilization—a decade of clinical experience. Bone Marrow Transplant. 2018. https://doi.org/10.1038/s41409-018-0312-4.
34. Czerw T, Kruzel T, Sadus-Wojciechowska M, Najda J, Holowiecki J, Giebel S. Comparison of two formulations of filgrastim, Neupogen® (Amgen) and Zarzio® (Sandoz), used to accelerate neutrophil recovery after autologous peripheral blood stem cell transplantation. Bone Marrow Transplant. 2012;47(Suppl 1):S316 (Abstract P872).
35. Pavone V, Ostuni A, Morciano MR, Mele A, Fina M, Greco G, et al. Stem cell mobilization with Zarzio® plus chemotherapy in patients with hematological diseases candidated to autologous stem cell transplantation (ASCT). Bone Marrow Transplant. 2014;49(Suppl 1):S524–5 (Abstract PH-AB202).
36. Michael MD, Stylianou C, Konstantelos I, Tsitskari T, Elena L, Antoniades M, et al. Biosimilar G-CSF (filgrastim) is (cost) effective for peripheral blood stem-cell mobilization before autologous transplantation—a single centre experience. Bone Marrow Transplant. 2014;49(Suppl 1):S212 (Abstract PH-P233).
37. Garcia Gala JM, Martinez Revuelta E, Rodriguez Gonzalez RD, Garcia Menendez Tevar F, Colado Vareta E, Solario Tovar J. Use of Zarzio® with plerixafor in mobilization of peripheral blood stem cells. Bone Marrow Transplant. 2014;49(Suppl 1):S525 (Abstract PH-AB203).
38. Lisenko K, Baertsch MA, Meiser R, Pavel P, Bruckner T, Kriegsmann M, et al. Comparison of biosimilar filgrastim, originator filgrastim, and lenograstim for autologous stem cell mobilization in patients with multiple myeloma. Transfusion. 2017;57:2359–65.
39. Martín-Sánchez G, Amunarriz C, Sanchez M, Aranzazu Bermudez M, Yañez L, Colorado M, Richard C, et al. Efficacy and safety of a biosimilar granulocyte-colony stimulating factor for stem cell mobilization before autologous hematopoietic stem cell transplantation. Blood. 2016;128:5737.
40. Manko J, Walter-Croneck A, Jawniak D, Grzasko N, Gorska-Kosicka M, Cioch M, et al. A clinical comparison of the efficacy and safety of biosimilar G-CSF and originator G-CSF in haematopoietic stem cell mobilization. Pharmacol Rep. 2014;66:239–42.
41. Vokurka S, Jungova A, Brandejsová R, Jindra P, Dvorak J, Steinerova K. Efficacy of filgrastim biosimilar Zarzio® in autologous stem cells transplantation setting. Bone Marrow Transplant. 2015;50(Suppl 1):S441 (Abstract P641).
42. Marchesi F, Vacca M, Gumenyuk S, Pandolfi A, Renzi D, Palombi F, et al. Biosimilar filgrastim (Zarzio®) vs. lenograstim (Myelostim®) for peripheral blood stem cell mobilization in adult patients with lymphoma and myeloma: a single center experience. Leuk Lymphoma. 2016;57(2):489–92.
43. Marchesi F, Vacca M, Renzi D, Pandolfi A, Gumenyuk S, Palombi F, et al. Efficacy and safety of biosimilar filgrastim (Zarzio®) after autologous stem cell transplant: a prospective study with historical comparison with lenograstim and peg-filgrastim. Bone Marrow Transplant. 2017;52(Suppl 1):S145–6 (Abstract P330).
44. Nasillo V, Paolini A, Riva G, Morselli M, Potenza L, Coluccio V, et al. Effectiveness of originator (Neupogen) and biosimilar (Zarzio®) filgrastim in autologous peripheral blood stem cell mobilization in adults with acute myeloid leukemia: a single-center retrospective study. Leuk Lymphoma. 2018;59:225–8.
45. Azar N, Choquet S, Garnier A, et al. Use of a biosimilar G-CSF in allogeneic stem cell mobilisation. Bone Marrow Transplant. 2012;47(Suppl 1):S244 (Abstract P727).
46. Uddin S, Russell P, Farrell M, et al. Use of biosimilar G-CSF compared with lenograstim in autologous hematopoietic stem cell transplant and in sibling allogeneic transplant. Blood. 2013;122:2170.
47. Lefrère F, Brignier AC, Elie C, Ribeil JA, Bernimoulin M, Aoun C, et al. First experience of autologous peripheral blood stem cell mobilization with biosimilar granulocyte colony-stimulating factor. Adv Ther. 2011;28(4):304–10.
48. Farhan R, Urbanowska E, Zborowska H, Król M, Król M, Torosian T, et al. Biosimilar G-CSF versus filgrastim and lenograstim

in healthy unrelated volunteer hematopoietic stem cell donors. Ann Hematol. 2017;96:1735–9.
49. Anguita J, Balsalobre P, González-Arias E, Redondo S, Pérez-Corral A, Pascual C, et al. Mobilisation of PBSC for allogenic transplantation by the use of G-CSF biosimilar Zarzio® in healthy donors. Blood. 2014;124:5824.
50. Antelo M, Zabalza A, Sánchez Antón MP, et al. Mobilization of hematopoietic progenitor cells from allogenic healthy donors using a new biosimilar G-CSF (Zarzio®). J Clin Apher. 2016;31:48–52.
51. Becker P, Schwebig A, Brauninger S, Bialleck H, Luxembourg B, Schulz M, et al. Healthy donor hematopoietic stem cell mobilization with biosimilar granulocyte-colony-stimulating factor: safety, efficacy, and graft performance. Transfusion. 2016;56(12):3055–64.
52. Pahnke S, Egeland T, Halter J, Hägglund H, Shaw BE, Woolfrey AE, et al. Current use of biosimilar G-CSF for haematopoietic stem cell mobilisation. Bone Marrow Transplant. 2018 Oct 3. **(Epub ahead of print)**.
53. Data on file, Sandoz.
54. Lyman GH, Balaban E, Diaz M, Ferris A, Tsao A, Voest E, et al. American Society of Clinical Oncology Statement: biosimilars in oncology. J Clin Oncol. 2018;36(12):1260–5.
55. Tabernero J, Vyas M, Giuliani R, Arnold D, Cardoso F, Casali PG, et al. Biosimilars: a position paper of the European Society for Medical Oncology, with particular reference to oncology prescribers. ESMO Open. 2017;1(6):e000142.
56. Jilma B, Jagiełło-Gruszfeld A, Tomczak P, Gadgil H, Orlik G, Desai K, et al. Demonstration of clinical comparability of the biosimilar filgrastim to Neupogen, in terms of safety and efficacy, in healthy volunteers and patients receiving myelosuppressive chemotherapy. Eur Oncol Haematol. 2014;10(2):107–15.
57. Kraj L, Krawczyk-Lipiec J, Górniewska J, Orlik G. Efficacy and safety of biosimilar filgrastim in primary and secondary prevention of febrile neutropenia. Biomed Rep. 2017;7(2):143–7.
58. Stakiw J, Sabry W, Elemary M, Bosch MJ, Danyluk P, Aggarwal V, Mondal P. Biosimilar G-CSF versus originator G-CSF for autologous peripheral blood cell mobilization: a comparative analysis of mobilization and engraftment. Blood. 2018;132(Suppl. 1):3345.
59. 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(10):504–11.
60. Otremba B, Hielscher C, Petersen V, Petrik C. Home administration of filgrastim (Nivestim) in primary prophylaxis of chemotherapy-induced febrile neutropenia. Patient Prefer Adherence. 2018;12:2179–86.
61. Fruehauf S, Otremba B, Stötzer O, Rudolph C. Compatibility of biosimilar filgrastim with cytotoxic chemotherapy during the treatment of malignant diseases (VENICE): a prospective, multicenter, non-interventional, longitudinal study. Adv Ther. 2016;33(11):1983–2000.
62. Brito M, Esteves S, André R, Isidoro M, Moreira A. Comparison of effectiveness of biosimilar filgrastim (Nivestim™), reference Amgen filgrastim and pegfilgrastim in febrile neutropenia primary prevention in breast cancer patients treated with neo(adjuvant) TAC: a non-interventional cohort study. Support Care Cancer. 2016;24(2):597–603.
63. Maloisel F, Leprêtre S, Kamioner D, Berthou C, Albrand H. 1615 Safety and efficacy of prophylactic and curative biosimilar filgrastim in patients undergoing neutropenia-inducing chemotherapy: the NEXT study. Eur J Cancer. 2015;51(Suppl. 3):S243.
64. López-Parra M, Baile M, Dávila J, Caballero JC, Veiga A, Arratibel N, et al. Efficacy and safety of filgrastim biosimilar compared to filgrastim originator in the stem cell mobilization and hematopoietic engraftment in patients undergoing stem cell transplantation. Haematologica. 2017;102(Suppl 2):1–882 (Abstract E1543).
65. Brunello L, Giaccone L, Fornaro MJ, Scaldaferri M, Redoglia V, Omedè P, et al. A comparative study of biosimilar filgrastim versus originator G-CSF for CD34 + cells mobilization and autografting in hematological malignancies. Blood. 2016;128:2183.
66. Pham T, Patil S, Fleming S, Avery S, Walker P, Wei A, et al. Comparison of biosimilar filgrastim with originator filgrastim for peripheral blood stem cell mobilization and engraftment in patients with multiple myeloma undergoing autologous stem cell transplantation. Transfusion. 2015;55(11):2709–13.
67. Soria B, Martín-Martín A, Rodríguez-López J, De Bonis C, Iglesias A, Mesa J, Tapia M, Hernández-García MT, Raya JM. Factors related to the final number of cd34 + cells obtained by apheresis for autologous stem cell transplantation: experience in 181 consecutive procedures in a single center. Haematologica 2015;100:1-804(PB2047).
68. 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.
69. Gatzemeier U, Ciuleanu T, Dediu M, Ganea-Motan E, Lubenau H, Del Giglio A. XM02, the first biosimilar G-CSF, is safe and effective in reducing the duration of severe neutropenia and incidence of febrile neutropenia in patients with small cell or non-small cell lung cancer receiving platinum-based chemotherapy. J Thorac Oncol. 2009;4(6):736–40.
70. Engert A, Griskevicius L, Zyuzgin Y, Lubenau H, del Giglio A. XM02, the first granulocyte colony-stimulating factor biosimilar, is safe and effective in reducing the duration of severe neutropenia and incidence of febrile neutropenia in patients with non-Hodgkin lymphoma receiving chemotherapy. Leuk Lymphoma. 2009;50(3):374–9.
71. Federman N, Dragomir MD, Kizyma Z, Lebedev V, Roganovic J, Bias P, et al. A phase 2, international, multicenter, prospective clinical trial of subcutaneous tbo-filgrastim in pediatric patients with solid tumors undergoing chemotherapy. Blood. 2017;130(Suppl. 1):2271.
72. Lotz J. Use of a granulocyte-colony stimulating factor (G-CSF) as primary or secondary prophylaxis for chemo-induced febrile neutropenia (FN): results of the ObStim French survey. Ann Oncol. 2012;23(suppl_9):Abstract 1556P.
73. Bhamidipati PK, Fiala MA, Grossman BJ, DiPersio JF, Stockerl-Goldstein K, Gao F, et al. Results of a prospective randomized, open-label, noninferiority study of tbo-filgrastim (Granix) versus filgrastim (Neupogen) in combination with plerixafor for autologous stem cell mobilization in patients with multiple myeloma and non-Hodgkin lymphoma. Biol Blood Marrow Transplant. 2017;23(12):2065–9.
74. Elayan MM, Horowitz JG, Magraner JM, Shaughnessy PJ, Bachier C. TBO-filgrastim versus filgrastim during mobilization and neutrophil engraftment for autologous stem cell transplantation. Biol Blood Marrow Transplant. 2015;21(11):1921–5.
75. Fiala MA, Schwab D, Vij R, Cashen AF, Stockerl-Goldstein K, Abboud C. A randomized trial of tbo-filgrastim versus filgrastim for autologous stem cell mobilization in patients with multiple myeloma or non-Hodgkin lymphoma. Blood. 2015;126:516.
76. Publicover A, Richardson DS, Davies A, Hill KS, Hurlock C, Hutchins D, et al. Use of a biosimilar granulocyte colony-stimulating factor for peripheral blood stem cell mobilization: an analysis of mobilization and engraftment. Br J Haematol. 2013;162(1):107–11.
77. Danylesko I, Sareli R, Bloom-Varda N, Yerushalmi R, Shem-Tov N, Shimoni A, et al. Biosimilar filgrastim (tevagrastim, XM02)

for allogeneic hematopoietic stem cell transplantation in patients with acute myelogenous leukemia/myelodysplastic syndromes. Biol Blood Marrow Transplant. 2016;22(2):277–83.
78. Taylor JG, Seddon Alizadeh K, Agrawal C, Kempster L, Gribben JG, et al. Single centre experience of Zarzio™ biosimilar granulocyte-colony stimulating factor (GCSF) for the mobilisation of healthy donors demonstrates good leukapheresis yields and safety profile at 24 month median follow-up. Bone Marrow Transplant. 2017;52(S1):S145–6.
79. Aapro M, Beguin Y, Bokemeyer C, Dicato M, Gascón P, Glaspy J, et al. Management of anaemia and iron deficiency in patients with cancer: ESMO Clinical Practice Guidelines. Ann Oncol. 2018;29(Supplement_4):iv96–iv110.
80. Aapro MS, Bohlius J, Cameron DA, Dal Lago L, Donnelly JP, Kearney N, 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. 2011;47(1):8–32.
81. Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2015;33(28):3199–212.
82. NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors Version 2.2019. https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf. Accessed 28 June 2019.
83. Krendyukov A, Schiestl M. Biosimilars in oncology: a decade of experience with granulocyte colony-stimulating factor and its implication for monoclonal antibodies. Crit Rev Oncol Hematol. 2019. **(In press)**.
84. Giuliani R, Tabernero J, Cardoso F, McGregor KH, Vyas M, de Vries EGE. Knowledge and use of biosimilars in oncology: a survey by the European Society for Medical Oncology. ESMO Open. 2019;4(2):e000460.
85. Goll GL, Jørgensen KK, Sexton J, Olsen IC, Bolstad N, Haavardsholm EA, et al. Long-term efficacy and safety of biosimilar infliximab (CT-P13) after switching from originator infliximab: open-label extension of the NOR-SWITCH trial. J Intern Med. 2019;285(6):653–69.
86. Ye BD, Pesegova M, Alexeeva O, Osipenko M, Lahat A, Dorofeyev A, et al. Efficacy and safety of biosimilar CT-P13 compared with originator infliximab in patients with active Crohn's disease: an international, randomised, double-blind, phase 3 non-inferiority study. Lancet. 2019;393(10182):1699–707.
87. Park MC, Matsuno H, Kim J, Park SH, Lee SH, Park YB, et al. Long-term efficacy, safety and immunogenicity in patients with rheumatoid arthritis continuing on an etanercept biosimilar (LBEC0101) or switching from reference etanercept to LBEC0101: an open-label extension of a phase III multicentre, randomised, double-blind, parallel-group study. Arthritis Res Ther. 2019;21(1):122.
88. Weinblatt ME, Baranauskaite A, Dokoupilova E, Zielinska A, Jaworski J, Racewicz A, et al. Switching from reference adalimumab to SB5 (adalimumab biosimilar) in patients with rheumatoid arthritis: fifty-two-week phase III randomized study results. Arthritis Rheumatol. 2018;70(6):832–40.
89. Cohen HP, Blauvelt A, Rifkin RM, Danese S, Gokhale SB, Woollett G. Switching reference medicines to biosimilars: a systematic literature review of clinical outcomes. Drugs. 2018;78(4):463–78.