# Biosimilar granulocyte–colony-stimulating factor for healthy donor stem cell mobilization: need we be afraid?

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Biosimilars are approved biologics with comparable quality, safety, and efficacy to a reference product. Unlike generics, which are chemically manufactured copies of small-molecule drugs with relatively simple chemical structures, the biosimilar designation is applied to drugs that are produced by living organisms, implying much more difficult to control manufacturing and purification procedures. To account for these complexities, the European Medicines Agency (EMA), the US Food and Drug Administration, the Australian Therapeutic Goods Administration, and other regulatory authorities have devised and implemented specific, markedly more demanding pathways for the evaluation and approval of biosimilars. To date, several biosimilars have been approved, including versions of somatropin, erythropoietin, and granulocyte–colony-stimulating factor (G-CSF), and several biosimilar monoclonal antibodies are currently in development. The reference G-CSF product (Neupogen, Amgen) has been used for many years for prevention and treatment of neutropenia and also for mobilization of peripheral blood stem cells (PBSCs). However, concerns have been raised about the safety and efficacy of biosimilar G-CSF during PBSC mobilization procedures, especially in healthy donors. This article reviews the available evidence on the use of biosimilar G-CSF in this setting. Aggregate clinical evidence supports the assessment by the EMA of biosimilar and originator G-CSF as highly biologically similar, with respect to desired and undesired effects.



Biosimilars are approved biologics with comparable quality, safety, and efficacy to a reference product for which patent protection has expired. Biosimilar regulatory approval is provided on the basis of a robust comparability exercise demonstrating similarity with the original product, rather than on the need to show a positive risk-benefit assessment per se, which it is assumed has already been proven. Similarity must be demonstrated through biochemical characterization (purity, chemical identity, i.e., primary, secondary, and tertiary protein structure and receptor on–off kinetics); biologic activity in vitro, if applicable; and clinical similarity for at least one indication.

Depending on the extent of the evidence of preclinical similarity, the degree of clinical similarity required to achieve biosimilar status is considered on a case-by-case basis by the regulatory authorities. Since 2006, several biosimilars, including the first biosimilar monoclonal antibodies, have been approved by the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), and the Australian Therapeutic Goods

**ABBREVIATIONS:** AE(s) = adverse event(s); EMA = European Medicines Agency; PBSC(s) = peripheral blood stem cell(s); PD = pharmacodynamic; PK = pharmacokinetic; WMDA = World Marrow Donor Association.

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Administration. These health authorities have developed abbreviated approval pathways for biosimilars, provided that these products are proven to be "highly similar" to an already-approved biologic (known as the "reference" product).[1-3]

Biosimilars of recombinant human granulocyte–colony-stimulating factor (rHuG-CSF), based on the original filgrastim product (Neupogen), have been available for more than 5 years now and are widely used in Europe. Four biosimilars of filgrastim have been approved by the EMA, these being Zarzio/Filgrastim Hexal (Sandoz Biopharmaceuticals), Tevagrastim/Ratiograstim (Teva), Nivestim (Hospira), and Grastofil (Stada). In many countries, use of biosimilar filgrastim products now exceeds that of the original.

In addition to these "true" biosimilars, copies of original products are available in some less highly regulated markets, such as parts of South America, India, and South-East Asia. These copies of biopharmaceuticals cannot, however, be considered to be biosimilars, as they have not been approved through a stringent regulatory process.[4,5] These biologic copies can differ widely in composition, do not always meet self-declared specifications, exhibit considerable batch-to-batch variation, and may lack adequate clinical data to show comparability.[6] This difference is beginning to be noted in more recent treatment guidelines, which recommend that only "true" biosimilar products should be used (i.e., those that have received approval by official regulatory bodies).[5]

Unlike generics, biosimilars cannot automatically claim all indications of the reference product and any extrapolation of data requires sound scientific justification; that is, the mechanism of action and the receptor(s) involved need to be identical.[7] For the currently approved biosimilar G-CSFs, extrapolation to all indications of the reference product has been granted, given that comparable receptor site kinetics for each product indicate that their mode of action is the same, that is, direct stimulation of marrow cells through the G-CSF cell surface receptor. As such, biosimilar G-CSFs have been approved for the treatment of chemotherapy-induced neutropenia, severe chronic neutropenia, and persistent neutropenia in patients with advanced HIV infections. In addition, biosimilar G-CSFs are approved for the mobilization of peripheral blood stem cells (PBSCs) in patients undergoing myelosuppressive or myeloablative therapy followed by autologous hematopoietic stem cell transplantation, as well as for stem cell mobilization in patients and healthy donors.

However, some groups have raised concerns over the use of biosimilar GCSFs in healthy donors, given the unarguable scarcity of long-term clinical safety data. While the overall evidence suggests a positive risk-benefit ratio, stem cell mobilization with G-CSF is not without short-term and long-term adverse effects. Thus far, all adverse events (AEs) of G-CSF have generally been considered class effects and therefore tend to be analyzed together, irrespective of the G-CSF formulation. In fact, the product sheet for biosimilar G-CSFs warns of AEs that were originally observed with the originator product. In other words, all evidence currently points to the observed short- and long-term AEs as being class effects; that is, these are intrinsic, on-target (G-CSF receptor-mediated) effects, rather than off-target effects.

Currently recognized short-term AEs of G-CSF include activation of myelopoiesis, bone metabolism and bone pain, flu-like symptoms, and alteration of T-cell responsiveness.[8-10] Rare cases of splenic rupture due to excessive extramedullary hematopoiesis, pulmonary hemorrhage, and capillary leakage syndrome have also been reported.[11-13] Possible long-term effects may include activation of autoimmune diseases, as well as proposed but highly uncertain consequences like epigenetic or genetic changes that might result in the development of myelodysplasia, myeloid leukemia, or other hematologic malignancies.[9,14-18]

Donor outcome databases currently do not differentiate between filgrastim- and lenograstim (Granocyte)-mobilized donors; thus, large-scale retrospective differential analyses are not possible. However, comparison of reports on individual cohorts mobilized with lenograstim[19] or filgrastim[10,20] indicate that the combining of all healthy donor mobilization outcome data is likely justified, given their highly similar AEs, including their frequency and severity. However, with the advent of biosimilar G-CSF preparations, this attitude has changed somewhat, and a differential approach has been taken to biosimilar versus originator G-CSFs. Thus, the European Group for Blood and Bone Marrow Transplantation has recommended against the use of biosimilar G-CSFs in healthy donors until more efficacy and safety data have been collected.[21] This view is endorsed by the World Marrow Donor Association (WMDA), which stated that biosimilars should not be used in normal donors outside of a clinical study and long-term registry context.[22] Other national professional organizations have issued similar statements.[23-25] However, these articles must be weighed against the views expressed by European regulators such as the Working Party on Similar Biological (Biosimilar) Medicinal Products, who have highlighted that all biosimilars go through a rigorous and methodical approval process before marketing authorization and can safely be considered biologically similar.[7]

## HOW SIMILAR IS BIOSIMILAR G-CSF: BIOCHEMICAL AND CLINICAL EVIDENCE LEADING TO BIOSIMILAR APPROVAL

For the regulatory approval of biosimilar G-CSF, evidence of a high degree of biochemicophysical similarity was

provided through comparisons of their primary protein sequences, mass spectrometry analyses, and receptor on- and off-rates.[26] Clinical development programs for the different biosimilar G-CSFs varied. For Tevagrastim/Ratiograstim, clinical development included two pharmacokinetic (PK) and pharmacodynamic (PD) studies and three Phase III studies (in breast cancer, lung cancer, and non-Hodgkin's lymphoma),[27-31] while the development of Nivestim involved two PK and PD studies and a single Phase III study in patients with breast cancer.[32] For Zarzio, bioequivalence with Neupogen was demonstrated in four comparative studies in adult volunteers (n = 146),[26] with near-identical PD and PK within a dose range from 1 to 10 μg/kg, 10 μg/kg being the dose typically needed for stem cell mobilization. Further data were provided by a noncomparative study in 170 patients with breast cancer.[26] There were no reports of immunogenicity and the majority of G-CSF–related AEs were of mild intensity.

## HOW SIMILAR ARE THE ORIGINATORS: DIFFERENCES BETWEEN BATCHES AND DRIFT OVER TIME

All biopharmaceuticals undergo production changes over time, which may result in slight alterations to their molecular structure and biologic activity.[33] These may be more abrupt changes, arising from modifications to manufacturing processes (and might require new clinical studies to show comparability), or may be a simple "drift" in characteristics over time. This is a normal aspect of manufacturing biologics and is highly regulated. A study analyzing different commercial batches of darbepoetin alfa (Aranesp), rituximab (Rituxan/Mabthera), and etanercept (Enbrel) revealed substantial variations in glycosylation patterns, C- or N-terminus heterogeneity, and biologic activity between older and newer batches.[33] Nonetheless, despite all these alterations over time, it was concluded by regulators and manufacturers that these changes did not result in evidently altered clinical profiles for these products, and hence their label was unaffected, with all adverse effects observed with these biochemically drifting compounds being grouped together.[33] Rarely, a new Phase III study may be requested by the regulatory authorities, but there has not been a single case to date where new clinical data have been requested in every indication after a manufacturing change.

While molecular drift data are not available for G-CSF, it is reasonable, given the lesser complexity of the molecule, to assume a less pronounced interbatch drift, but some differences would be inherent to the manufacturing processes. Moreover, although filgrastim and lenograstim are often used interchangeably in the clinic, they are different molecules (unlike filgrastim, lenograstim is glycosylated) and much more dissimilar to each other than biosimilar filgrastim is to original filgrastim. The same pharmacovigilance requirements for any biologic medicine are also applied to biosimilars; that is, the manufacturers must develop a comprehensive risk management plan for these products.[1-3]

## CLINICAL EXPERIENCE WITH BIOSIMILAR G-CSF IN STEM CELL MOBILIZATION

The overall evidence points to a very high degree of biochemical similarity between the approved biosimilar G-CSFs and the originator product. As to whether this can reasonably be interpreted to predict a high degree of similarity in long-term safety has been answered affirmatively by international regulators (EMA, Therapeutic Goods Administration), but currently the medical community has not universally subscribed to this view.

Given the previous lack of direct clinical evidence to support biosimilar G-CSF use in PBSC mobilization, there has been considerable interest in testing its effectiveness, and a body of data now exists in autologous and allogeneic settings (Table 1). The majority of reports so far focus on autologous mobilization, but its use in healthy (primarily related) donors has also been described.

### Autologous PBSC mobilization

Since its approval, the overall effectiveness of biosimilar G-CSF has been evaluated in several open-label studies, some of which have included the reference product as a comparator (Table 1). All these studies have measured the ability of biosimilar or originator G-CSF to mobilize sufficient CD34+ cells into the peripheral blood in patients with hematologic malignancies. Side effects of treatment have also been recorded.

Collectively, these studies have shown that there are no significant differences between biosimilar versus originator G-CSF in the median number of CD34+ cells mobilized (frequency in peripheral blood or dose of apheresed CD34+ cells by body weight) or in the number of G-CSF injections and leukapheresis procedures required to harvest the target CD34+ cell dose.[34-45] Furthermore, the side effect profiles of biosimilar versus originator G-CSF were comparable, with a similar incidence and severity of common AEs such as bone or muscle pain and headache[34,35,40,45] and no severe or unexpected AEs.

While the majority of the biosimilar studies are small and lack long-term follow-up, it is reassuring to see comparable efficacy with a similar short-term safety profile to the original product, and the limited longer-term follow-up has not reported any major long-term AEs (e.g., leukemia, capillary leakage syndrome, autoimmune disease, myelodysplastic syndrome, or splenic rupture) or unexpected (i.e., not previously described) AEs in these patients.[45]

**TABLE 1. Summary of studies with biosimilar G-CSF in patients undergoing autologous PBSC mobilization**

| Study design and number of patients | Mean/median duration of G-CSF (days) | Mean/median number of leukapheresis* | Mean/median number of CD34+ cells mobilized by body weight ($\times 10^6$/kg) | Mean/median number of CD34+ cells mobilized in PB ($\times 10^{12}$/L)† | Safety/AEs |
|---|---|---|---|---|---|
| Prospective comparative study of biosimilar (n = 40) vs. historical originator (n = 41) (5 or 10 μg/kg)[34] | Biosimilar, 5 (5-12)<br>Originator, 5 (5-9)<br>(p = 0.62) | Biosimilar, 1 (1-3)<br>Originator, 1 (1-3)<br>(p = 0.10) | Biosimilar, 5.50 (1.1-20)<br>Originator, 4.49 (0.9-25)<br>(p = 0.26) | Biosimilar, 55.5 (1-196)<br>Originator, 60.0 (13-432)<br>(p = 0.71) | *Bone pain and/or headache:*<br>Biosimilar 5 μg, n = 3<br>Biosimilar 10 μg, n = 11<br>Originator, NA |
| Prospective comparative study of biosimilar (n = 54) vs. originator (n = 54) (10 g/kg)[35] | Biosimilar, 8 (4-17)<br>Originator, 8 (4-14) | Biosimilar, 1<br>Originator, 1 | Biosimilar, 9.1 (0-23)<br>Originator, 9.4 (6-48) | Biosimilar, 62.0 (2-394)<br>Originator, 47.5 (2-370) | *Bone pain:*<br>Biosimilar, n = 8; originator, n = 6<br>*Neutropenic fever:*<br>Biosimilar, n = 9; originator, n = 11 |
| Prospective comparative study of biosimilar (n = 55) vs. originator (n = 35), 5 μg/kg[36] | Biosimilar, 12 (10-13)<br>Originator, 12 (10-21)<br>(until ANC recovery, $>0.5 \times 10^9$/L) | Biosimilar, NA<br>Originator, NA | Biosimilar, 6.7 ± 3<br>Originator, 3.9 ± 3 | Biosimilar, NA<br>Originator, NA | *Infections (Grade 3 or 4)*<br>Biosimilar, n = 9; originator, n = 11 (p = 0.09)<br>*Neutropenic fever:*<br>Biosimilar, n = 3; originator, n = 7 (p = 0.03) |
| Prospective comparative multicenter study of biosimilar (n = 38) vs. historical originator (n = 50)[37] | Biosimilar,<br>7 (4-12)‡<br>7.8 (1-16)‡<br>Originator,<br>7.5 (6-10)‡<br>6.9 (5-9)‡ | Biosimilar, NA<br>Originator, NA | Biosimilar,<br>4 (1.3-7.36)‡<br>3.2 (2.24-5.03)‡<br>Originator,<br>3.8 (1.74-12.3)‡<br>3.6 (1.61-7.35)‡ | NA | Biosimilar, one patient died from transplantation-related mortality<br>Originator, NA |
| Retrospective noncomparative study of biosimilar (n = 23)[38] | Biosimilar, 14.4 (6-23) | NA | Biosimilar, 10.1 ± 4 | NA | *Neutropenic events:*<br>Biosimilar, n = 5 |
| Prospective noncomparative multicenter study of biosimilar (n = 21), 10 μg/kg[39] | Biosimilar, 12 (9-27) | NA | Biosimilar, 5.83 (2.22-24.7) | Biosimilar, 51 (8-393) | NA |
| Prospective comparative single-center study of biosimilar (n = 26) vs. historical originator (n = 48), 10 μg/kg[40] | Biosimilar, 16.5 (11-44)<br>Originator, 15.0 (9-23)<br>(p = 0.078)<br>(until neutrophil engraftment, >500/μL) | NA | Biosimilar, 9.7<br>Originator, 8.0<br>(p = 0.437) | Biosimilar, $92 \times 10^6$/L (Day 5)<br>Originator, $88 \times 10^6$/L (Day 5)<br>(p = 0.713) | The occurrence and intensity of bone pain was similar in both groups |
| Prospective study of biosimilar (n = 44), 5 μg/kg bd[41] | Biosimilar, 8.2† | Biosimilar, 1.45† | Biosimilar, 4.3 (0.8-6.2)/kg | Biosimilar, 58.3 (10-503.5) | NA |
| Retrospective comparative study of biosimilar (n = 154) vs. historical originator (n = 131)[42] | Biosimilar, NA<br>Originator, NA | Biosimilar, 1 (1-4)<br>Originator, 1 (1-4) | Biosimilar, 4.5 (0.2-43)/kg<br>Originator, 4.4 (0.5-56)/kg | Biosimilar, 0.038 (0-0.516) $\times 10^9$/L<br>Originator, 0.031 (0.002-0.802) $\times 10^9$/L | NA |
| Retrospective comparative study of biosimilar (n = 104) vs. historical lenograstim (n = 155), ~5 μg/kg[43] | Biosimilar, 13-14§<br>Lenograstim, 12-13§<br>(until ANC recovery, $>0.5 \times 10^9$/L) | Biosimilar, 1-2 (1-3)§<br>Lenograstim, 1-2 (1-3)§ | Biosimilar, 3.9-8.7 (0.5-29.9)§<br>Lenograstim, 3.1-5.1 (1.1-33.7)§ | Biosimilar, 25.9-66.7 (6.6-577.7)§<br>Lenograstim, 20.5-32.5 (5.1-412.9)§ | NA |
| Prospective comparative study of biosimilar (n = 10) vs. historical originator (n = 10), 15 μg/kg[44] | Biosimilar, 12 (10-16)<br>Originator, 14 (10-17)<br>(time to white blood cell engraftment) | Biosimilar, 1 (1-3)<br>Originator, 1 (1-2) | Biosimilar, 4.10 (0.25-4.84)<br>Originator, 2.71 (1.22-10.3) | NA | |
| Prospective comparative study of biosimilar (n = 36) vs. historical originator (n = 36), 5 or 10 μg/kg[45] | Biosimilar, 5 (5-6)<br>Originator, 5 (5-6) | Biosimilar, 1 (1-3)<br>Originator, 1 (1-3) | Biosimilar, 4.76 (2.04-13.42)<br>Originator, 4.36 (1.04-10.98)<br>(p = NS) | Biosimilar, 58.8 (3.2-256.5)<br>Originator, 31.3 (1.8-119.1)<br>(p = 0.01) | Mild bone or muscle pain in both groups |

* Ranges not provided.
† Doses not provided.
‡ For lymphoma and myeloma patients, respectively.
§ Depending on indication and age: lymphoma or myeloma patients aged less than and 60 or more years. In myeloma patients less than 60 years old, all variables were significantly superior in the biosimilar group compared with lenograstim, including the need for one rather than two apheresis procedures. In all studies, biosimilar is Zarzio, except in Ianotto et al.,[37] where it was not defined, and Publicover et al.,[42] who used Ratiograstim.
ANC = absolute neutrophil count; NA = data not available; NS = non significant; PB = peripheral blood.

### Allogeneic PBSC mobilization

The safety considerations for healthy donors differ from those for patients, since donors do not benefit from the treatment, whereas patients generally do. Therefore, the safety threshold for donors is extremely low and, hence, even the aggregate experience with G-CSF since its inception has not satisfied the medical community as to its definitive safety profile. Although there are fewer reports of biosimilar G-CSF use for PBSC mobilization in healthy donors (which may reflect the less frequent use of G-CSF in this setting), some data are now emerging (Table 2).

Altogether, the main findings from these healthy donor studies report that biosimilar G-CSFs are effective and well tolerated, with similar mobilization outcomes in comparison to Neupogen; for example, the median number of circulating CD34+ cells in peripheral blood or harvested by body weight was similar with either treatment.[43,46-48] In terms of safety, side effects included mild bone or muscle pain in most patients, with no clinically significant differences between groups.[46-48]

Moreover, interim results from a large, post-authorization study of 200 healthy unrelated donors indicated that biosimilar G-CSF (Zarzio) was highly effective, with the majority of donors achieving the target CD34+ cell dose of $5 \times 10^6$/kg body weight of the recipient with a median of one apheresis. The acute-phase safety profile of biosimilar G-CSF was in line with the known toxicities of G-CSF and no cases of splenic rupture occurred.[49] This is an ongoing, long-term safety study over 10 years which will contribute data for up to 2000 person-years and thus add to the cumulative assessment of the long-term safety of G-CSF as a mobilizing agent.[49]

## HOW SAFE IS G-CSF IN THE LONG TERM?

To date, extensive reviews of safety data in healthy volunteers and cancer patients have uncovered no differences between the biosimilars and the reference product in the frequency, type, or severity of AEs.[13,50,51] Furthermore, none of the reported infrequent but more severe AEs associated with G-CSF in volunteer donors have been observed with the biosimilars. This observation, however, is most likely due to the lesser experience with the biosimilars in general. Greater experience with G-CSF overall has led to the identification of risk factors for such AEs (e.g., autoimmune disease), as a result of which donors with an established risk profile for any of these AEs are deferred; that is, G-CSF has actually become safer over time. Bearing in mind the special responsibility toward stem cell donors, national and international guidelines (WMDA and Foundation for the Accreditation of Cellular Therapy/Joint Accreditation Committee) recommend a very conservative approach to donor clearance.[52,53]

Several long-term safety studies in healthy volunteer donors have recently come forth. While the typical acute

**TABLE 2. Summary of studies with biosimilar G-CSF in healthy donors undergoing allogeneic PBSC mobilization**

| Study design and number of donors | Mean/median duration of G-CSF (days) | Mean/median number of leukapheresis procedures | Mean/median number of CD34+ cells mobilized by body weight ($\times 10^6$/kg) | Mean/median number of CD34+ cells mobilized in PB ($\times 10^{12}$/L) | Safety/AEs |
|---|---|---|---|---|---|
| Prospective noncomparative study of biosimilar (n = 48), ~5 µg/kg[43] | Biosimilar, 16 (10-28) (until ANC recovery, >0.5 × $10^9$/L) | Biosimilar, 1-3 | Biosimilar, 6.1 | NA | NA |
| Prospective study of biosimilar (n = 21), 10 µg/kg[46] | Biosimilar, 5 (4-7) | Biosimilar, 1.5 (1-3) | Biosimilar, 6.0 (2.6-9.2) | Biosimilar, 72 (16-145) | Bone pain, n = 8 |
| Prospective comparative study of biosimilar (n = 9) vs. historical originator (n = 9), 5 µg/kg[47] | Biosimilar, 5 (5-6) | Biosimilar, 1 (1-2) | Biosimilar, 7.2 (4-9.2)<br>Originator, 9.0 (6-14.3)<br>(p = 0.12) | Biosimilar, 70.2 (24-114) × $10^9$/L<br>Originator, 86.3 (42.3-146.4) × $10^9$/L | Mild bone or muscle pain in all patients in both groups |
| Prospective comparative study of biosimilar (n = 11) vs. originator (n = 11), 10 µg/kg[48] | Biosimilar, 5 (5-6)<br>Originator, 5 (5-6) | Biosimilar, 1.45*<br>Originator, 1.27* | Biosimilar, 4.4 (2.0-7.3)<br>Originator, 4.2 (2.1-7.9) | Biosimilar, 65.8 (19.3-114.6) $mm^3$<br>Originator, 50.9 (13.6-122.4) $mm^3$ | 6/11 donors reported arthralgias in both groups |
| Prospective long-term study of biosimilar (n = 84), 10 µg/kg[49] | Biosimilar, 5 (5-6) | Biosimilar, 1 (1-2) | Biosimilar, 9.5 (4.6-19.9) | Biosimilar, 111 (34-284) | Bone pain, 89%<br>Headache, 29%<br>Back pain, 12% |

* Ranges not provided. In all studies, biosimilar is Zarzio, except Schmitt et al.,[48] in which they used Tevagrastim.
ANC = absolute neutrophil count; NA = data not available.

adverse effects of G-CSF are observed frequently, irrespective of the G-CSF preparation used, the studies confirm the overall safety of G-CSF.[10,20,54,55] Of note, no evidence for an increased propensity for cancer, autoimmune disease, or thromboembolic complications was found,[55] nor were changes in immune function observed.[20]

A recent expert report evaluating the safety of biosimilar G-CSF has concluded that all these agents have safety profiles similar to one another[51] and the available data so far indicate that efficacy profiles of biosimilar filgrastim products are also the same as those of the original; therefore, no major differences in biologic activity or long-term side effects are expected.

The observation of rare and possibly grave AEs should not be overlooked. For instance, some of the severe acute as well as long-term AEs attributed to G-CSF in donors include splenic rupture, lung hemorrhage, capillary leakage syndrome, autoreactive T-cell activation, aneuploidy, and epigenetic changes.[9,11-18] Some of these AEs will be discussed in the next section and have also been reviewed in more detail elsewhere.[9,51]

## BIOSIMILAR G-CSF FOR HEALTHY DONOR MOBILIZATION: IS THERE REASON FOR CONCERN?

Most concerns over the use of growth factors focus on their long-term safety, in particular the possibility of an increased risk of developing de novo hematologic malignancies, although the rationale for the concern is not stated in any of the publications so this is inherently difficult to debate or challenge. Nonetheless, the potential causes for concern for biosimilar G-CSF are described below.

### Immunogenicity

As a protein, the general risk of immunogenicity of G-CSF must be considered. Hypothetically speaking, if neutralizing antibodies were induced, a profound neutropenia could ensue as a result of neutralization of endogenous G-CSF. Risk factors for (neutralizing) antibody induction include G-CSF deficiency in the recipient, long-term or chronic use (as opposed to short-term), physiologic substitution dose (as opposed to pharmacologic), complex structure, and glycosylation.[56] The type and dosage of G-CSF used for PBSC mobilization do not meet any of these criteria and can thus be considered immunologically innocuous. Indeed, induction of autoantibodies by G-CSF has not been observed, despite significant vigilance. A rationale to propose differential immunogenic risks for biosimilar rHuG-CSF is thus not apparent. The relatively high alert is possibly explained by the case of Eprex (epoetin alfa), of note not a biosimilar, but an originator compound that had undergone changes in its production process that then led to the development of autoantibodies and pure red blood cell aplasia in some patients.[57]

### Acute AEs

Acute AEs due to G-CSF treatment are very common, albeit rarely limiting and include bone pain, fatigue, and flu-like symptoms (see above and articles by Miller et al.,[8] Anderlini,[9] and Pulsipher et al.[10]). There is ample evidence that severe acute AEs are infrequent during short-term treatment with G-CSF. Certain acute-phase AEs, such as splenic rupture, may be a concern, although such events are rare and whether they are attributable or coincidental may be difficult to discern.[51] Other rare AEs include capillary leakage syndrome and pulmonary hemorrhage.[11-13] Treatment with G-CSF is not recommended in patients or donors with underlying autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus.[9,58] By careful donor evaluation, susceptible individuals can be largely identified and deferred, so that nowadays such issues rarely cause any problems.

There have been occasional reports of inflammatory bowel disease after administration of G-CSF in healthy donors; given the evidence provided of altered T-cell responsiveness, direct causality cannot be excluded, although this most likely arises in donors with subclinical inflammatory bowel disease at the time of G-CSF treatment. A few patients with sickle cell disease have died after G-CSF therapy,[51] so that nowadays at-risk individuals are screened and excluded, if applicable. A few reports have warned that G-CSF can activate the coagulation cascade and lead to a "hypercoagulable state" in some healthy donors.[9,59,60] However, this has been rarely observed in clinical practice.[61] Nonetheless, G-CSF therapy should be undertaken cautiously in healthy donors with underlying thrombotic risk factors.[62]

We must remember that these AEs were observed with both originator G-CSFs; no product-specific AEs have been observed to date. For the biosimilar G-CSFs, thus far none of the rarer AEs have been reported, which is likely a consequence of their cumulative lesser use and of greater experience (and donor exclusion) with G-CSF per se. The more common AEs have been observed with a similar frequency to reported data for the originator.

### Long-term AEs

#### *Epigenetic and genetic damage*

Previous studies have highlighted the potential for G-CSF to induce epigenetic and genetic damage in lymphocytes of healthy donors, which could predispose to an increased risk of hematologic malignancies.[14,15] A systematic review of 25 randomized controlled trials in which patients with solid tumors or lymphoma were randomly assigned to

chemotherapy with or without G-CSF support for at least 2 years indeed found an increased risk of acute myeloid leukemia or myelodysplastic syndrome.[16] However, the authors concluded that it was not possible to distinguish between the effects of G-CSF and the effects of a higher dose of chemotherapy (facilitated by G-CSF support).[16] In addition, these patients are at greater risk for leukemia or myelodysplastic syndrome because of their genetic make-up and also the chemotherapy treatment. So, whether G-CSF on its own increases susceptibility to leukemia or lymphoma cannot be answered today; the available data neither suggest such an effect nor are they extensive enough to rule it out.[10,19]

Reports of prolonged effects of G-CSF on hematopoietic stem cells, including genetic, epigenetic, and gene expression changes keep resurfacing, although evidence to the contrary has also been put forth. Thus while a recent report describes protracted changes in microRNA expression and several putative targets in circulating CD34+ cells from healthy donors mobilized with G-CSF, the clinical relevance of these findings remains to be fully elucidated.[63]

#### *Abnormalities in lymphocyte function*

More recent studies have reported abnormalities in lymphocyte function, for example, a prolonged suppression of humoral immune responses through the loss of B cells in blood marrow, as observed in mice[64] and reduced immunoglobulin levels in healthy donors.[17] Evidence of aneuploidy in hematopoietic stem cells or T cells has been provided but could not be confirmed in subsequent studies.[65] Data from prospective studies and donor registries have also not supported these initial concerns.[8,20] The very low frequency of immunologic issues or malignancies after G-CSF, currently indistinguishable in frequency from that in the general population, certainly do not suggest clinical relevance, but a high level of vigilance remains appropriate. To date, no clear long-term AEs have been observed with either of the two G-CSF products that have been in clinical use for sufficient duration to draw preliminary conclusions.

#### *Hematologic malignancies*

Any increased likelihood of hematologic malignancies (or any of the AEs of G-CSF) is likely to be attributable to a pharmacologic class effect on mature or immature hematopoietic cells. The presumed mechanism is thought to be via G-CSF receptor–mediated effects,[14] as well as through the actions of inflammatory cytokines elicited by G-CSF.[66] Some authors consider the risk of hematologic malignancies to be higher in related donors and have warned that the contribution of filgrastim exposure to the development of acute leukemia and lymphoma needs to be monitored;[18] the WMDA supports this view.

### Overall clinical safety of biosimilar G-CSF

In clinical practice, compounds as dissimilar as filgrastim and lenograstim are considered interchangeable for all clinical indications and the list of observed or potential AEs are identical. Since highly comparable stimulation of the G-CSF receptor has been established for the biosimilar G-CSFs, any long-term safety issues are likely to be the same as for the original filgrastim. Given that biosimilar approval is based on rigorous demonstration of comparable quality, efficacy, and safety, there is no basis to believe that this risk would be any different for biosimilar products versus the original. Supplementary evidence is provided by a recent pooled analysis of five postapproval studies in chemotherapy-induced neutropenia (comprising >1300 patients). This analysis has shown that the safety profile of biosimilar G-CSF is consistent with safety data for Neupogen;[67] no additional safety concerns arising from the use of a biosimilar formulation were identified.

## CONCLUSION

When filgrastim was first used for autologous PBSC mobilization, only 3 years elapsed until it was also used for allogeneic mobilization in sibling donors. Again, only 1 year later, healthy donors started to receive filgrastim. Thus, at that time, long-term safety data for filgrastim in healthy donors were very limited and many contraindications were unknown,[68,69] unlike now, when we can at least be reasonably comfortable that, provided that donors are evaluated by physicians sufficiently knowledgeable about its risks and contraindications, filgrastim is safe per se,[9,10] and the only risk to which the donors are being exposed is the "added" risk, if any, of the biosimilar versus the original formulation.

Since the approval of biosimilar G-CSF, the reported clinical experience for this product in PBSC mobilization has suggested comparable efficacy and short-term tolerability as with the reference product (or, in fact, with all approved G-CSF preparations, whether glycosylated or not). While this does not directly support long-term safety, it can nevertheless be taken as additional reassurance as to biologic similarity. Therefore, the argument of donor safety as a reason to argue against biosimilar usage in healthy donors thus may appear as a pretextural argument. In any case, even though no additional safety concerns have been identified, ongoing studies will continue to be essential to monitor the safety and tolerability of biosimilar G-CSF in a variety of settings and patient or donor populations.

For all products in the G-CSF and GM-CSF class, it is recommended in the Summary of Product Characteristics that apheresis centers systematically monitor allogeneic donors for at least 10 years. Thus, many donor registries in the European Union have established safety follow-up procedures to record potential side effects of PBSC

mobilization with G-CSF. The WMDA requests long-term follow-up in their current practice standards, and Germany has rigorous national stem cell guidelines. In addition, the safety of biosimilar G-CSF in allogeneic mobilization is being specifically assessed in a 10-year follow-up study.[49] Given the robust approval process required for biosimilars, and the 5 years of cumulative clinical experience to date, there seems to be no reason to expect significant differences between biosimilar and originator products in their long-term safety profiles.

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#### CONFLICT OF INTEREST

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