Filgrastim and biosimilars side-by-side comparison

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Executive Summary

Introduction

Health care organizations have a choice among several GCSF products for formulary inclusion. Tbo-filgrastim was approved via a new BLA for prevention of chemotherapy-induced neutropenia in adult patients and subsequently for pediatric patients via a supplemental application, while filgrastim-sndz, filgrastim-aafi, and filgrastim-ayow were approved via the biosimilar pathway. Filgrastim-sndz and filgrastim-aafi are FDA approved for 5 of 6 indications of US filgrastim while filgrastim-ayow is approved for 4 of 6 indications.

Efficacy and safety

The approval of tbo-filgrastim was based on its comparison against placebo, although clinical trial evidence also demonstrated equivalency to EU filgrastim for the prevention of chemotherapy-induced neutropenia in nonmyeloid malignancies. Filgrastim-sndz, -aafi, and -ayow were approved based on the demonstration of high similarity to US filgrastim in analytical, nonclinical, and clinical studies. Filgrastim-sndz's clinical program consisted of single- and multiple-dose PK/PD studies conducted in healthy volunteers and a phase 3, noninferiority trial conducted in breast cancer patients receiving myelosuppressive chemotherapy. The clinical programs of filgrastim-aafi and filgrastim-ayow consisted of single- and multiple-dose PK/PD studies conducted in healthy volunteers.

Immunogenicity

Filgrastim has limited immunogenicity because it is a nonglycosylated protein administered mostly to immunocompromised populations. The immunogenicity of tbo-filgrastim, filgrastim-sndz, filgrastim-aafi, and filgrastim-ayow also appear limited and similar in magnitude to that of filgrastim based on immunogenicity data generated in respective clinical programs.

Guidelines

Guidelines recommend primary prophylactic use of GCSFs when the risk of FN exceeds 20%. NCCN, ASCO and ESMO guidelines suggest that any licensed GCSF biosimilar is an appropriate substitute for a reference GCSF. NCCN and the World Bone Marrow Association suggest that filgrastim biosimilars may be considered in place of filgrastim for allogeneic or autologous stem cell transplants.

Convenience Factors

Filgrastim, tbo-filgrastim, filgrastim-aafi, and filgrastim-ayow are available as a single-dose prefilled syringe and vial, while filgrastim-sndz is only available as a single-dose prefilled syringe. The prefilled syringe for filgrastim biosimilars cannot be used to directly administer doses of less than 180 mcg; therefore, the availability of single-dose vials may make it easier to prepare and administer smaller filgrastim doses. The needle cap of the prefilled syringes of filgrastim and filgrastim-sndz contain rubber latex and should be avoided in persons with latex allergies. Finally, in contrast to other filgrastim products, unopened tbo-filgrastim can remain at room temperature for up to 5 days before use and the prefilled syringe may be used to directly administer doses as small as 0.1 mL.

SUMMARY POINTS

- There are 5 FDA-approved filgrastim products: originator filgrastim (Neupogen), 3 filgrastim biosimilars (Zarxio, Nivestym, Releuko), and tbo-filgrastim (Granix).
- Filgrastim-sndz, -aafi, and -ayow were submitted and approved for licensure through the 351(k) pathway. Approval was based on a demonstration of high similarity to US filgrastim in analytical, nonclinical, and clinical studies. Filgrastim-sndz and filgrastim-aafi are approved for 5 of the 6 indications of originator filgrastim and filgrastim-ayow is approved for 4 indications.
- Tbo-filgrastim was submitted and approved for licensure through the 351(a) pathway based on a full complement of safety and efficacy data for a single indication.
- Professional organizations endorse the use of tbo-filgrastim and biosimilars as appropriate substitutes for originator filgrastim.
- None of the biosimilars are designated as interchangeable.
- Except for filgrastim-sndz, all filgrastim products are supplied as a pre-filled syringe (PFS) and a single-dose vial. Filgrastim-sndz is supplied as a PFS.
- Some products' PFS cannot administer doses less than 0.3 mL.

Summary

Data on the real-world use of tbo-filgrastim and the filgrastim biosimilars are rapidly becoming available and most professional organizations support the use of GCSF biosimilars in place of US filgrastim for most approved indications. Although data supports that alternating between filgrastim-sndz and US filgrastim preserves at least 50% of the efficacy of US filgrastim, none of the GCSF biosimilars have been approved as an interchangeable biosimilar. Therefore, a therapeutic interchange policy is necessary for substitution. In practice, it is likely that acquisition cost and reimbursement will be important considerations in the decision to use tbo-filgrastim or the filgrastim biosimilars.

Filgrastim and biosimilars side-by-side comparison

	Generic name (brand name)				
	Filgrastim (Neupogen)	**Filgrastim-sndz (Zarxio)**	**Filgrastim-aafi (Nivestym)**	**Filgrastim-ayow (Releuko)**	**Tbo-filgrastim (Granix)**
Manufacturer	Amgen	Sandoz	Pfizer	Amneal	Teva
Approval year (approval pathway)	1991 (351a)	2015 (351k)	2018 (351k)	2022 (351k)	2012 (351a)
Interchangeable	Reference	No	No	No	No
Market share (2022)	≅ 20%	≅ 50%	≅ 15%	NA	≅ 15%
FDA-approved indications	≥ Birth: • Decrease the incidence of infection, as manifested by FN, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever. • Reduce the time to neutrophil recovery and the duration of fever following induction or consolidation chemotherapy for AML. • Reduce the duration of neutropenia and neutropenia-related clinical sequelae in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT. • Reduce the incidence and duration of sequelae of severe neutropenia in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.				≥ 1 mo old: • Reduction in the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of FN.
	Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.			NA	
	Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).				
Dosage	• Receipt of myelosuppressive chemotherapy or induction/consolidation chemotherapy for AML: Starting dose is 5 mcg/kg/d subcutaneous injection, short IV infusion (15-30 min), or continuous IV infusion. See prescribing information for dose adjustments. • BMT: 10 mcg/kg/d given as an IV infusion no longer than 24 h. See prescribing information for dose adjustments and timing of administration. • Autologous PBPC collection and therapy: 10 mcg/kg/d subcutaneous injection. Administer for at least 4 d before first procedure and continue until last leukapheresis. • Congenital neutropenia: Starting dose is 6 mcg/kg subcutaneous injection twice daily. • Patients with cyclic or idiopathic neutropenia: Starting dose is 5 mcg/kg subcutaneous injection daily.				5 mcg/kg per day until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range.

	Generic name (brand name)														
	Filgrastim (Neupogen)			**Filgrastim-sndz (Zarxio)**			**Filgrastim-aafi (Nivestym)**			**Filgrastim-ayow (Releuko)**			**Tbo-filgrastim (Granix)**		
Administration															
Subcutaneous	HCP or patient			HCP or patient			HCP or patient			HCP or patient			HCP or patient		
Intravenous	• Dilute in 5% dextrose injection to concentrations between 5 mcg/mL and 15 mcg/mL. • Filgrastim diluted to concentrations from 5 mcg/mL to 15 mcg/mL should be protected from adsorption to plastic materials by the addition of albumin (human) to a final concentration of 2 mg/mL. • Diluted solution can be stored at room temperature for up to 24 h (this includes the duration of the infusion and the time during room temperature storage). • Filgrastim and biosimilars are compatible with glass bottles, polyvinyl chloride and polyolefin IV bag, and polypropylene syringes.												NA		
Dosage forms and strengths															
Prefilled syringe	Single dose (contains latex): • 300 mcg/0.5 mL • 480 mcg/0.8 mL			Single dose (contains latex): • 300 mcg/0.5 mL • 480 mcg/0.8 mL			Single dose (latex-free): • 300 mcg/0.5 mL • 480 mcg/0.8 mL			Single dose • 300 mcg/0.5 mL • 480 mcg/0.8 mL			Single dose (latex-free): • 300 mcg/0.5 mL • 480 mcg/0.8 mL		
Vial	Single dose: • 300 mcg/1 mL • 480 mcg/1.6 mL			NA			Single dose: • 300 mcg/1 mL • 480 mcg/1.6 mL			Single dose: • 300 mcg/mL • 480 mcg/1.6 mL			Single dose: • 300 mcg/1 mL • 480 mcg/1.6 mL		
Product composition (Prefilled syringe)	Filgrastim (mcg)	300	480	Filgrastim (mcg)	300	480	Filgrastim (mcg)	300	480	Filgrastim (mcg)	300	480	Filgrastim (mcg)	300	480
	Acetate (mg)	0.295	0.472	Glutamic acid (mg)	0.736	1.178	Acetate (mg)	0.295	0.472	Acetic acid (mg)	0.302	0.483	Glacial acetic acid (mg)	0.3	0.48
	PS-80	0.02	0.032	PS-80 (mg)	0.02	0.032	PS-80 (mg)	0.02	0.032	PS-80 (mg)	0.02	0.032	PS-80 (mg)	0.0275	0.044
	Sorbitol	25	40	Sorbitol	25	40	Sorbitol	25	40	Sorbitol	25	40	Sorbitol	25	40
	Sodium	0.0175	0.028	Sodium hydroxide (mg)	q.s.	q.s.	Sodium (mg)	0.0175	0.028	Sodium hydroxide (mg)	0.028	0.045	Sodium hydroxide	q.s. to pH 4.2	q.s. to pH 4.2
Contraindications	History of serious allergic reactions to human GCSF (filgrastim or pegfilgrastim)														

	Generic name (brand name)				
	Filgrastim (Neupogen)	**Filgrastim-sndz (Zarxio)**	**Filgrastim-aafi (Nivestym)**	**Filgrastim-ayow (Releuko)**	**Tbo-filgrastim (Granix)**
Warnings and precautions	• Fatal splenic rupture: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture. • ARDS: Evaluate patients who develop fever and lung infiltrate or respiratory distress for ARDS. • If serious allergic reactions occur (including anaphylaxis), discontinue permanently. • Fatal sickle cell crises have occurred. Discontinue if sickle cell crisis occurs. • Glomerulonephritis has occurred with use, but usually resolves after dose reduction or discontinuation. • Capillary leak syndrome may occur. Monitor and administer standard symptomatic treatment if symptoms occur. • The potential for tumor growth stimulatory effect on malignant cells exists. • May cause transient positive bone-imaging changes. Consider when interpreting bone-imaging results. • Simultaneous use with chemotherapy and radiation therapy is not recommended. • May cause cutaneous vasculitis, thrombocytopenia, or leukocytosis. • Aortitis has been reported as early as the first week after start of therapy. Discontinue therapy in patients with suspected aortitis. • Alveolar hemorrhage manifesting as pulmonary infiltrates and hemoptysis requiring hospitalization have been reported in filgrastim-treated healthy donors undergoing PBPC collection mobilization. This is not an approved indication.				
	Confirm the diagnosis of SCN before initiating filgrastim. Although MDS and AML may occur in the natural history of congenital neutropenia, transformation to MDS and AML have also been observed in patients treated with filgrastim for SCN. MDS and AML have also been observed in the setting of filgrastim-treated patients with breast or lung cancer.				--
Adverse reactions	Most common adverse reactions in patients: • Nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs: pyrexia, pain, rash, cough, and dyspnea. • AML: Pain, epistaxis and rash. • Nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT: rash. • PBPC collection: bone pain, pyrexia and headache. • SCN: pain, anemia, epistaxis, diarrhea, hypoesthesia and alopecia.				Bone pain
Special populations					
Pediatric	May directly administer doses ≥ 0.1 mL	The prefilled syringe may not accurately measure volumes less than 0.3 mL. Direct administration of a volume less than 0.3 mL (180 mcg) is not recommended due to the potential for dosing errors.	For direct administration of doses less than 0.3 mL (180 mcg), use single-dose vial.		May directly administer doses ≥ 0.1 mL

	Generic name (brand name)				
	Filgrastim (Neupogen)	**Filgrastim-sndz (Zarxio)**	**Filgrastim-aafi (Nivestym)**	**Filgrastim-ayow (Releuko)**	**Tbo-filgrastim (Granix)**
Drug interactions	Not reported				
Pharmacology	GCSF stimulates neutrophil progenitor cells, which increases production and activity of neutrophils.				
Storage/stability					
Refrigeration	Store at 2°C to 8°C in the carton to protect from light.	Store at 2°C to 8°C in the carton to protect from light.	Store at 2°C to 8°C in the carton to protect from light.	Store at 2°C to 8°C in the carton to protect from light.	Store at 2°C to 8°C in the carton to protect from light.
Room temperature	May store up to 24 h	May store up to 24 h	May store up to 24 h	May store up to 24 h	• May be removed from refrigeration for a single period of up to 5 d. • If not used within 5 d, the product may be returned to 2°C to 8°C up to expiration date.
Assistance programs	• Amgen First Step – Commercial Co-Pay Program • Patient Assistance Program – The Safety Net Foundation	Sandoz One Source • Commercial Co-Pay Program (medical and pharmacy benefits) • Patient Assistance Program	Pfizer Oncology Together • Injectables Commercial Co-Pay Program • Patient Assistance Program	Unknown	• Commercial Co-Pay Program (pharmacy benefit) • Patient Assistance Program
HCPS/CPT code	J1442	Q5101	Q5110	C9399	J1447
APC status indicator (start date)	K	K	G (4/1/2019)	N	K
Clinical studies					

Filgrastim-sndz (EP2006)

- **PIONEER study**. ***Ann Oncol*. 2015;26(9):1948-1953**.[a] In a noninferiority, double-blind study, patients with breast cancer scheduled to receive chemotherapy with docetaxel, doxorubicin, and cyclophosphamide (TAC regimen) were randomized to 4 treatment arms in a 1:1:1:1 manner. Two treatment arms received the same filgrastim product for all 6 cycles and 2 treatment arms alternated between filgrastim products (biosimilar then reference or vice versa). Both the biosimilar and reference US filgrastim were administered subcutaneously at a dose of 5 mcg/kg of body weight starting from day 2 of each cycle until the ANC recovered to 10 x10^9/L after its nadir or a maximum of 14 d. The primary efficacy outcome — mean DSN during cycle 1 in the per-protocol set — was 1.17 ± 1.11 d with the biosimilar (n = 101) and 1.20 ± 1.02 d with the reference product (n = 103). The lower limit of the 97.5% CI for the treatment difference was -0.26 d, which was greater than the noninferiority margin of -1 d. The median depth of the ANC nadir (biosimilar: 0.30 x 10^9/L vs reference: 0.25 x 10^9/L), median time to ANC nadir (7 d in both groups),

and median time to ANC recovery (2 d in both groups) were similar between treatment arms. At least 1 episode of FN was reported in 6 patients (6.7%) in the pooled alternating arm and in 2 patients in the pooled non-alternating arm. No patient developed ADAs.

- ***Ann Oncol*. 2018;29(1): 244-249**.[b] In an analysis of the PIONEER study, the incidence of FN was compared between treatment arms (n = 107) that received alternating filgrastim products (biosimilar then reference or vice versa) during cycles 2 through 6 and the treatment arm (n = 51) that received reference filgrastim for all 6 cycles. The incidence of FN was 3.4% (n = 3) across treatment arms that alternated and 0% in the reference filgrastim treatment arm (difference: -3.4%; 95% CI, -9.65%-4.96%), which did not exceed the predefined noninferiority margin of -15%. One patient in the alternating cohort was hospitalized due to FN. The rate of infections was similar between groups, with a reported incidence of 9.3% and 9.9% in the alternating and reference arms, respectively. Study-drug related TEAEs occurred in 42.1% of patients who alternated filgrastim products and 39.2% of patients who remained on reference filgrastim.
- ***Oncologist*. 2018;23(4):403-409**.[c] The safety of EP2006 was evaluated in a combined analysis of the PIONEER study and the EU registration trial. Study details of the PIONEER trial are summarized above. Briefly, the EU registration trial was an open-label, single-arm trial that evaluated the safety and efficacy of EP2006 administered as a weight-based dose (300 mcg in patients who weighed less than 60 kg and 480 mcg in patients who weighed greater than 60 kg) over 4 cycles in women with stage II-IV breast cancer. In the EU trial, women were treated with a combination of doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2. Overall, 277 women were included in the combined analysis. The most frequently reported serious TEAE was FN (cycle 1: n = 16; 7.2%). No serious TEAEs were suspected to be related to EP2006 use. A total of 46 (20.6%) EP2006-treated patients had a TEAE suspected to be related to EP2006 use over cycles 1-4. The most frequent TEAEs were musculoskeletal and connective tissue disorder (n = 34; 15.2%) including bone pain (n = 16; 7.2%), myalgia (n = 16; 7.2%), musculoskeletal pain (n = 4; 1.8%), and arthralgia (n = 4; 1.8%). No patient developed neutralizing or binding antibodies.

Filgrastim-aafi (filgrastim Hospira)

- ***Onkologie.* 2010;33(10):504-511**.[d] In a double-blind phase 3 equivalency trial, females aged 18 to 70 years with invasive breast cancer appropriate for treatment with doxorubicin and docetaxel combination therapy in the neoadjuvant, adjuvant, or first-line metastatic setting were randomized 2:1 to treatment with EU filgrastim-aafi (n = 184) or EU reference filgrastim (n = 95), both administered subcutaneously at a dose of 5 mcg/kg daily until ANC was greater than 3 x 10^9/L or for 14 days, whichever came first. In the primary analysis population (n = 250), EU filgrastim-aafi was equivalent to EU reference filgrastim for DSN based on an equivalency margin of ±1 d during cycle 1 (adjusted mean: 1.85 d vs 1.47 d, respectively; difference: 0.38 d [95% CI, 0.08-0.68]). The incidence of FN during cycle 1 was 1.8% and 2.4% with EU filgrastim-aafi and EU reference filgrastim, respectively. In both groups, nausea, fatigue, and bone pain were the most frequent events, but bone pain was more frequent with EU filgrastim-aafi (14.2% vs 9.5% for EU reference filgrastim).
- ***Support Care Cancer*. 2016;24(2):597-603**.[e] In a retrospective, noninterventional comparative study, females with early breast cancer who underwent treatment with TAC (docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2, and cyclophosphamide 500 mg/m^2) received prophylaxis with 1 of 3 GCSFs based on treatment year: EU reference filgrastim (2004-2006, n = 147); pegfilgrastim (2007-2008, n = 139); and EU filgrastim-aafi (2011-2012, n = 134). Filgrastim and its biosimilar were administered at a daily dose of 300 mcg in patients who weighed 75 kg or less and at a dose of 480 mcg in those that weighed greater than 75 kg. Pegfilgrastim was administered as a single 6-mg dose. The median relative dose intensity (average dose intensity per week divided by reference dose intensity per week) was 100% for each chemotherapy drug in each cohort. Febrile neutropenia (body temperature ≥ 38°C and ANC ≤ 500 cells/µL) occurred in 16%, 9%, and 16% of patients who received EU reference filgrastim, pegfilgrastim, and EU filgrastim-aafi, respectively, and the FN rate per cycle was 3%, 2%, and 4%, respectively. In an exploratory analysis, the incidence of FN among cohorts did not differ significantly, but there was a greater incidence of profound neutropenia (ANC < 100 cells/µL) at FN diagnosis in the EU filgrastim Hospira group compared with other cohorts (50% vs 4-6%, respectively). Subjects in the EU filgrastim-aafi group were younger and more likely to receive ciprofloxacin as a component of an FN prophylaxis regimen.
- ***BioDrugs*. 2019;33:207-220**.[f] In an open-label, 2-period parallel trial, 256 healthy male and female subjects aged 18 to 65 y were randomized to receive filgrastim-aafi or US reference filgrastim, both administered as a 5 mcg/kg subcutaneous injection. In each treatment arm, subjects received at least 5 daily doses of the assigned treatment during period 1 followed by a single 5 mcg/kg dose in period 2. There was at least a 26-d washout between treatment periods. The primary endpoint — proportion of patients with a negative ADA at baseline and a confirmed positive ADA test result at any time after the first dose — occurred in 7.4% (9/121) in the filgrastim-aafi group and in 4.9% (6/123) in the US filgrastim group (90% CI, -2.717%-8.096%). The upper bound of the 90% CI was below the noninferiority margin of 10%. No neutralizing antibodies were detected in either treatment arm. The most commonly reported adverse reactions in the filgrastim-aafi and reference filgrastim groups were musculoskeletal events (34% vs 35%, respectively) and injection site reactions (1.6% vs 10.2%, respectively).
- **ZIN-FIL 1502 trial. *BioDrugs*. 2019;33:207-220**.[f] In an open-label, single-dose crossover trial, 24 healthy male and female subjects aged 18 to 65 y were randomized to 1 of 2 treatment sequences: filgrastim-aafi followed by US reference filgrastim or US reference filgrastim followed by filgrastim-aafi. During each treatment period,

filgrastim-aafi or reference filgrastim was administered as a single 5 mcg/kg subcutaneous dose. Cross-over to treatment period 2 occurred after a 28 d washout period. The GMRs (90% CIs) of filgrastim-aafi to US reference filgrastim for the primary PK endpoints of C_{max} (1.11 (1.02-1.21)) and $AUC_{0\text{-}inf}$ (1.14 (1.05-1.23)) were within the predefined equivalence range of 0.80 to 1.25. Similarly, the GMRs (90% CIs) of filgrastim-aafi to US reference filgrastim for the primary PD endpoints of ANC_{max} (0.98 (0.93-1.02)) and $AUEC_{ANC}$ (0.99 (0.95-1.02)) were within the predefined equivalence range of 0.80 to 1.25.

- **ZIN-FIL 1501 trial. *BioDrugs*. 2019;33: 207-220.**[f] In an open-label, multiple-dose crossover trial, 60 healthy male and female subjects aged 18 to 65 y were randomized to 1 of 2 treatment sequences: filgrastim-aafi followed by US reference filgrastim or US reference filgrastim followed by filgrastim-aafi. During each treatment period, participants received filgrastim-aafi or US reference filgrastim administered subcutaneously at a dose of 5 mcg/kg once daily for 5 d and then crossed over to the alternate treatment after a washout period of 28 d. The GMRs (90% CI) of filgrastim-aafi to US reference filgrastim for the primary PD endpoints of $CD34^{+}{}_{max}$ (1.06 (0.95-1.19)) and $AUEC_{CD34+}$ (1.06 (0.98-1.15)) were within the predefined equivalence range of 0.80 to 1.25.

Filgrastim-ayow (TPI-G-CSF)

- **TPI-CL-106*. Biosimilars.* 2015;5:93-101**.[g] In a double-blind, single-dose, cross-over trial, 58 healthy male and female subjects aged 19 to 55 y were randomized to 1 of 2 treatment sequences: filgrastim-ayow followed by US reference filgrastim or US reference filgrastim followed by filgrastim-ayow. At day 1 of each 10 ± 3 d treatment periods, participants received filgrastim-ayow or reference filgrastim as a single 5 mcg/kg dose given as a subcutaneous injection and then crossed over to alternate filgrastim product after a washout period of 14 d. Sampling for PK and PD profiling occurred at regular intervals up to 36 h and 72 h, respectively after each dose. The point estimates of the GMRs (%) of filgrastim-ayow to reference filgrastim for the primary PK endpoints of $AUC_{0\text{-}inf}$ and C_{max} were 91.53 (95% CI, 85.92-97.50) and 89.57 (95% CI, 83.53-96.05), respectively. The 90% CIs (data not provided) were within the equivalence limits of 80% to 125% in favor of biosimilarity. The point estimates of the GMRs (%) of filgrastim-ayow to reference filgrastim for the primary PD endpoints of $AUEC_{0\text{-}t}$ and E_{max} were 108.14 (95% CI, 100.44-116.43) and 106.52 (101.15-112.17) and similar to PD endpoints, the 90% CIs (data not provided) were within the equivalence limits of 80% to 125%. No subject was determined to have anti-rhG-CSF. TEAEs occurring in ≥ 10% of subjects included mild injection-site erythema, injection-site pain, headache, and myalgia. There were no significant differences between filgrastim products in the occurrence of treatment-emergent AEs.
- **TPI-CL-110**.[h] In a single-blind, single-center, multiple-dose, noninferiority, parallel trial, 134 healthy male and female subjects aged 18 to 55 y were randomized 1:1 to filgrastim-ayow or US reference filgrastim. In each treatment arm, participants received 2 treatment cycles separated by 4 wks. During treatment cycle 1, the assigned filgrastim product was given as a 5 mcg/kg subcutaneous injection once daily for 5 d. During treatment cycle 2, the assigned filgrastim product was given as a single 5 mcg/kg dose on day 33. During the study period, no neutralizing antibodies were detected. One patient in the filgrastim-ayow group tested positive for post-dose ADAs vs. no patients in the US reference filgrastim group, for a between group difference in ADA rate of 1.5% (upper bound of the 95% CI of 6.9% fell below the noninferiority margin of 10%).

Tbo-filgrastim (XM02)

- ***BMC Cancer*. 2008;8:332**.[i] In a multicenter, investigator-blinded study, patients with high-risk breast cancer (stage II-IV) treated with docetaxel/doxorubicin chemotherapy were randomized in a 2:2:1 ratio to treatment with XM02 5 mcg/kg/d (n = 140), filgrastim 5 mcg/kg/d (n = 136), or matching placebo (n = 72), starting 1 d after chemotherapy and continuing for 5 to 14 d. After the first cycle, placebo-treated patients received XM02 during the remaining cycles. The primary endpoint — mean DSN, defined as the number of days with an ANC less than 0.5 x 10^9/L — was 1.1, 1.1, and 3.9 d in the XM02, filgrastim, and placebo groups, respectively. The 95% CI for the difference between XM02 and filgrastim did not exceed the predefined criteria of ± 1 d for equivalence. The secondary endpoint — observed or protocol-defined FN — was significantly lower with XM02 and filgrastim (12.1% and 12.5%, respectively, vs placebo (36.1%)). The incidence of drug-related adverse events across all cycles was greater with filgrastim (39.7%) than XM02 (25.7%; *P* = .0149).
- ***Leuk Lymphoma*. 2009;50(3):374-379**.[j] In a multicenter, investigator-blinded study, patients with aggressive NHL treated with the CHOP regimen were randomized on a 2:1 basis to receive XM02 (n = 63) or filgrastim (n = 29) in the first chemotherapy cycle. In subsequent cycles, all patients received XM02. Study drugs were started 1 d after chemotherapy and administered as a subcutaneous injection of 5 mcg/kg/day for at least 5 d and up to 14 d. There were no differences between XM02 and filgrastim in cycle 1 in the DSN (0.5 d vs 0.9 d; *P* = .1055), in the incidence of observed or protocol-defined FN (11.1% vs 20.7%; *P* = .1232), mean ANC nadir values (1.7 x 10^9/L vs 1.1 x 10^9/L; *P* =.1531), or in the mean time to ANC recovery (6 vs 6.7 days; *P* = .4939). Bone pain and arthralgias were the most common adverse events and did not differ between treatment arms.
- ***J Thorac Oncol*. 2009;4(6):736-740**.[k] In a multicenter trial, patients with small or non–small-cell lung cancer with planned receipt of platinum-based myelosuppressive chemotherapy were randomized on a 2:1 basis to receive XM02 (n = 160) or filgrastim (n = 80) administered as a daily 5 mcg/kg subcutaneous injection for at least 5 d up to a maximum of 14 d. After cycle 1, all patients received XM02. The DSN was 0.5 and 0.3 d in the XM02 and filgrastim groups, respectively (difference: 0.157 d;

95% CI, -0.114-0.428 days fell within the prespecified equivalence range). Observed or protocol-defined FN did not differ significantly between groups (XM02: 15% vs filgrastim: 8.8%; *P* = .2347). The mean ANC nadir value (2.1 x 10^9/L vs 2.9 x 10^9/L) and mean time to ANC recovery (6.3 vs 4.5 days) were similar between XM02 and filgrastim, respectively. The most frequent drug-related adverse events were anemia (2.1%), myalgia (2.1%), back pain (2.1%), and headache (2.1%), and did not differ significantly between groups.

- ***Onkologie*. 2009;32(10):599-604**.[l] A meta-analysis of phase 3 studies was conducted to determine the comparative incidence of FN (observed or protocol defined) between XM02 and filgrastim during chemotherapy cycle 1. A total of 608 patients (XM02, n = 363; filgrastim, n = 245) were included in the analysis. The majority had breast cancer (45.4%) and received chemotherapy associated with a mean DSN of 1.1 d (45.4%) or 0.6 d (43.1%). Across all 3 studies, the odds ratio of FN (XM02 divided by filgrastim) was 1.08 (95% CI, 0.66-1.77). Chemotherapy regimens were placed into 3 myelotoxic potency categories based on DSN. The odds ratio of FN (XM02 divided by filgrastim) adjusted by myelotoxic potency category was 1.08 (95% CI, 0.66-1.78).
- ***Bioanalysis*. 2018;10(15):1221-1228**.[m] Immunogenicity results from 3 independent phase 3 studies conducted in breast cancer, lung cancer, and NHL were pooled. The overall immunogenicity rate was 1.6% (7/436) in cancer patients. In the breast, lung, and NHL cohorts, treatment-emergent ADA occurred in 3/213 (1.4%), 2/160 (1.3%), and 1/63 (1.6%) patients, respectively. None of the treatment-emergent ADA demonstrated neutralizing activity and none of the patients with treatment-emergent ADA had evidence of hypersensitivity or anaphylactic reactions or loss of efficacy.

Evidence Summary

Introduction: Filgrastim (Neupogen), tbo-filgrastim (Granix), filgrastim-sndz (Zarxio), filgrastim-aafi (Nivestym), filgrastim-ayow (Releuko), pegfilgrastim (Neulasta), pegfilgrastim-jmdb (Fulphila), pegfilgrastim-cbqv (Udenyca), pegfilgrastim-bmez (Ziextenzo), pegfilgrastim-apgf (Nyvepria), and pegfilgrastim-pbbk (Fylnetra) are FDA-approved GCSFs. The filgrastim products are the focus of this evidence summary. All filgrastim biosimilars – filgrastim-sndz, -aafi, and -ayow – are approved for 4 of the 6 indications of reference filgrastim: for use to decrease the incidence and duration of neutropenia including clinical sequelae in patients with nonmyeloid cancers receiving myelosuppressive chemotherapy; patients with AML who receive induction or consolidation chemotherapy; patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT; and patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.[n-q] Filgrastim-sndz and filgrastim-aafi are also indicated for mobilization of autologous hematopoietic progenitor cells.[o,p] The manufacturer of filgrastim-ayow did not request authorization for this indication. Due to an orphan designation, reference filgrastim is the only GCSF approved for the treatment of acute radiation syndrome secondary to a nuclear disaster.[n] Although tbo-filgrastim was approved as a biosimilar in the EU in 2008, the 351(k) biosimilar pathway was not established when tbo-filgrastim was submitted for licensure in the US and Teva submitted a BLA through the 351(a) pathway. As a result, tbo-filgrastim was ineligible for indication extrapolation as outlined in the 351(k) pathway and was approved for the submitted indication based on a full complement of safety and efficacy data.[r] In contrast, biosimilars filgrastim-sndz, filgrastim-aafi, and filgrastim-ayow were authorized for multiple indications based on extrapolation.

Tbo-filgrastim and filgrastim-sndz, -aafi, and -ayow are highly similar to reference filgrastim; however, the products are not identical copies; all are manufactured using proprietary processes. The primary amino acid sequence is identical among the products and all products are expressed in *E. coli*.[n-r] The final formulations have minor differences. For example, the pH of the final formulations of tbo-filgrastim and filgrastim-sndz is more basic than the pH of reference filgrastim. Additionally, tbo-filgrastim has a higher polysorbate concentration than filgrastim and the filgrastim-sndz formulation uses a different buffer than filgrastim.[n,o,r,s] In spite of these differences, results from studies performed in healthy volunteers demonstrate that the GMRs of tbo-filgrastim, filgrastim-sndz, -aafi, and -ayow to reference filgrastim for PD endpoints (ANC, CD34+ cell) and PK endpoints (AUC, Cmax) lay within the accepted bioequivalence range of 80 to 125%.[f,g,t,u] The PK curves of tbo-filgrastim and filgrastim are nearly superimposable, while filgrastim-sndz has a slightly lower Cmax than filgrastim, which is likely attributable to the differences in buffers.[t]

Chemotherapy-induced neutropenia: Guidelines from the NCCN, ASCO, EORTC, and ESMO recommend primary prophylactic use of GCSFs when the risk of FN exceeds 20%.[v-y] ASCO, EORTC, ESMO, and NCCN guidelines do not recommend a preferential GCSF, but rather advise that the choice of agent depends on convenience, cost, and clinical situation.[v-y] NCCN, ASCO and ESMO guidelines suggest that any licensed GCSF biosimilar is an appropriate substitute for a reference GCSF.[v,w,y]

Tbo-filgrastim: The tbo-filgrastim phase 3 clinical development program consisted of 3 trials that evaluated 680 cancer patients. In all 3 trials, EU filgrastim was the active comparator.[i-k] In the pivotal FDA registration trial, tbo-filgrastim was compared with both placebo and EU filgrastim in 348 patients with high-risk breast cancer.[i] Although equivalence was established between tbo-filgrastim and EU filgrastim by demonstrating that the difference in mean DSN during cycle 1 did not differ by greater than 1

day, the FDA's review and subsequent approval of tbo-filgrastim was based only on its significant reduction in mean DSN compared with placebo. Secondary endpoints that included incidence of FN, mean ANC nadir, and median time to ANC recovery were similar between tbo-filgrastim and EU filgrastim, but only descriptive statistics were performed.[i] The primary objective of the remaining 2 trials — 1 conducted in patients with lung cancer and the other in patients with NHL — was to demonstrate the safety of tbo-filgrastim compared with EU-filgrastim.[j,k] Efficacy endpoints in both trials were exploratory. No unexpected adverse events occurred in the tbo-filgrastim treatment arms. In lung cancer patients, the incidence of FN favored EU filgrastim over tbo-filgrastim while in NHL patients, the opposite occurred.[j,k] These discordant results prompted a meta-analysis of phase 3 trials to be conducted, the results of which showed no significant difference between tbo-filgrastim and EU filgrastim in the incidence of FN. However, it is important to note that almost half of the patients included in the meta-analysis were enrolled in the breast cancer study and the incidence of FN was similar between treatment arms in this trial.[l] To date, there are no formal evaluations of switching from filgrastim to tbo-filgrastim during a chemotherapy course, though in 2 of the 3 phase 3 trials, patients assigned to receive EU filgrastim during the first chemotherapy cycle received tbo-filgrastim during subsequent cycles. Results from these trials indicate no significant difference in efficacy outcomes, but formal statistical analyses were not conducted.

Filgrastim-sndz: The filgrastim-sndz clinical development program consisted of a single-dose PK/PD study in healthy volunteers and a phase 3 trial that compared filgrastim-sndz to US filgrastim in 218 patients with breast cancer undergoing myelosuppressive chemotherapy.[a,t] Results of the phase 3 trial established that filgrastim-sndz was noninferior to US filgrastim for the mean DSN during cycle 1. The lower limit of the 97.5% CI for the difference between treatment arms did not exceed the a priori noninferiority margin of 1 day. A number of secondary outcomes were compared descriptively between filgrastim-sndz and US filgrastim that included fever episodes, FN episodes, median depth of ANC nadir, time of ANC nadir, time to ANC recovery, hospitalization, and infections. Although results of these secondary outcomes appeared numerically similar between treatment arms, owing to the small occurrence of some of the secondary endpoints and the lack of inferential statistics, the statistical or clinical significance of the observed differences is unknown.[a] Approximately half of the participants were treated with the same filgrastim product throughout all 6 chemotherapy cycles whereas approximately half alternated between biosimilar and US filgrastim during cycles 2 through 6. The incidence of FN during cycles 2 through 6 in the pooled alternating treatment arms was noninferior to the incidence in the non-alternating US filgrastim arm; however, the selected noninferiority margin of 15% only guaranteed maintenance of 50% of the effect of US-filgrastim.[b] Sandoz has not applied for a designation of interchangeability. A number of postapproval studies of EU and US filgrastim-sndz are published that evaluate its use in the prevention of chemotherapy-induced neutropenia.[z-bb] In a pooled analysis of 5 observational studies, data generated from 1,302 patients — mostly with breast cancer, lung cancer, or lymphoma/leukemia — demonstrated overall rates of FN and grade 4 neutropenia of 2.2% and 8.5%, respectively, with EU-filgrastim-sndz.[bb]

Filgrastim-aafi: The clinical development program of filgrastim-aafi was the first to be conducted entirely in a healthy population without a phase 3 comparative study in the intended population. For biosimilar approval, the FDA does not require a clinical study to be conducted in an intended population unless there is residual uncertainty about the clinical meaningfulness of differences in analytical, nonclinical, and clinical pharmacology studies. The selected population for evaluation in clinical pharmacology studies must be sensitive to detecting differences between the proposed biosimilar and reference product. In general, healthy volunteers are considered the most sensitive for evaluating PK/PD differences because they are least likely to demonstrate PK/PD variability. Additionally, healthy volunteers are likely to be immunocompetent and differences in immunogenicity are most likely to be detected in a healthy population. Pfizer conducted 3 phase 1 trials in healthy volunteers to support biosimilarity: a single-dose, crossover, PK/PD equivalence study in support of neutropenia; a multiple-dose, crossover, PK/PD equivalence study in support of PBPC mobilization; and a parallel, noninferiority, comparative immunogenicity study. Filgrastim-aafi was equivalent to US filgrastim for the PK endpoints of C_{max} and $AUC_{0\text{-}inf}$ in the single-dose, crossover trial and for the PD endpoints of ANC (C_{max} and AUC) and CD34+ (C_{max} and AUC) in the single-dose and multiple-dose crossover studies, respectively.[f] While filgrastim-aafi was initially approved in Europe in June 2010, Pfizer did not conduct 3-way bridging studies to establish a scientific bridge among filgrastim-aafi, EU filgrastim, and US filgrastim; therefore, it is unknown if results of studies conducted in Europe can be extrapolated. However, most of the published literature evaluates filgrastim-aafi vs. EU filgrastim; therefore, the main findings of the European experience with filgrastim-aafi are briefly summarized.

A phase 3 clinical trial conducted in patients with invasive breast cancer was submitted to the EMA as a component of the clinical data package.[d] As with other GCSF biosimilars, DSN in cycle 1 was the primary endpoint and filgrastim-aafi was equivalent to EU filgrastim based on the predefined equivalency margin of ± 1 day. In cycles 1 and 2, a greater proportion of patients in the filgrastim-aafi group experienced severe neutropenia than those in the EU filgrastim group (77.6% vs 68.2% in cycle 1 and 48.7% vs 34.9% in cycle 2). In cycle 3, the proportion of patients who experienced severe neutropenia was similar between treatment groups. Although the EMA was concerned about the between group differences in cycles 1 and 2, there were no differences between treatment groups in documented infections or proportion of patients administered prophylactic antibiotics. Thus, the agency concluded that the difference in the incidence of severe neutropenia was likely not clinically meaningful. The agency also noted that bone pain was more frequently reported with filgrastim-aafi (n = 26, 14.2%) than with EU filgrastim (n = 9; 9.5%). Results of other investigations

have also suggested a difference between filgrastim-aafi and comparators in the proportion of patients with severe neutropenia. In a noninterventional cohort study, a higher proportion of patients in the filgrastim-aafi cohort had profound neutropenia (ANC < 0.1 x 10^9) at FN diagnosis than patients in the EU filgrastim and pegfilgrastim cohorts (50% vs 4-6%, respectively).[e] Although the filgrastim-aafi group reported more FN-related chemotherapy delays than the reference cohorts, there were no differences among the cohorts in FN complications (hospitalization rate and duration, septic shock, and death) or FN-related chemotherapy reductions. As with the results of the clinical trial, the difference between the biosimilar and its reference in ANC nadir did not appear to be clinically meaningful. Lastly, results of a pharmacovigilance study that retrospectively evaluated adverse events reported to VigiBase, the World Health Organization's global individual case safety report database, showed that the most commonly reported adverse event with filgrastim-aafi was neutropenia, which was different from the most commonly reported adverse event(s) with filgrastim-sndz (drug ineffective) and EU filgrastim (bone pain, pyrexia, and dyspnea).[cc] Due to imitations inherent with cohort studies and spontaneous adverse drug reaction reports, it is unclear if a causal relationship exists.

Filgrastim-ayow: Filgrastim-ayow is the first approved biosimilar from Amneal and has a long review history, undergoing 4 review cycles prior to approval. Amneal did not seek licensure for autologous PBPC mobilization because of the requirement for additional clinical CD34+ evaluations;[h] it is the only biosimilar not approved for this indication. Similar to filgrastim-aafi, the clinical development program for filgrastim-ayow compared filgrastim-aafi to US filgrastim in healthy volunteers. A total of 3 studies were conducted to support biosimilarity that included 2 single-dose, crossover, PK/PD equivalence studies in support of neutropenia indication and a multi-dose, parallel, noninferiority, comparative immunogenicity study. The first PK/PD study failed to meet its primary PK endpoint and was included in the application for licensure as supportive data only.[h] Filgrastim-ayow was equivalent to US filgrastim for the PK endpoints of C_{max} and $AUC_{0\text{-}inf}$ and for the PD endpoints of ANC ($AUEC_{0\text{-}t}$ and E_{max}) in the single-dose, crossover trial.[g] Because the US approval of filgrastim-ayow is its first approval, there are no clinical studies in the real-world setting.

Hematopoietic cell transplant setting: NCCN guidelines provide recommendations for the use of GCSFs for PBPC mobilization.[dd] NCCN recommends filgrastim, tbo-filgrastim, or an FDA-approved biosimilar for the mobilization of autologous hematopoietic progenitor cells (as a single agent or as a part of a chemomobilization regimen, category 2A) or as supportive care after autologous transplantation. Single-agent filgrastim, tbo-filgrastim or an FDA-approved biosimilar (category 2A) are recommended for allogeneic hematopoietic cell mobilization.

Mobilization in the autologous setting is an FDA-approved indication of US filgrastim. Due to a common mechanism of action across indications, the biosimilars filgrastim-sndz and filgrastim-aafi were approved for mobilization of autologous hematopoietic progenitor cells based on extrapolation of results from clinical data generated in healthy patients (filgrastim-sndz, filgrastim-aafi) and breast cancer patients (filgrastim-sndz) that showed high similarity of the biosimilars to filgrastim. As noted, filgrastim-ayow did not seek licensure for PBPC mobilization. Approved as a new biological entity in the US, the use of tbo-filgrastim for autologous mobilization is not an approved indication. The majority of evidence that confirms the safety and effectiveness of tbo-filgrastim or filgrastim-sndz in the hematopoietic cell transplant setting is derived from retrospective, single-center experiences that compared use of a biosimilar to historical experience with reference filgrastim.[ee-nn] Outcomes were not consistent across studies, but the most commonly reported outcomes were the number of CD34+ cells mobilized, the number of leukapheresis sessions required to mobilize the minimum number of CD34+ cells, and the number of mobilization failures. A meta-analysis combined results from 30 studies that evaluated autologous stem cell mobilization using a biosimilar GCSF (tbo-filgrastim or filgrastim-sndz). In the included studies, 1,541 patients underwent stem cell mobilization with use of a biosimilar GCSF — 463 with tbo-filgrastim and 1,078 with filgrastim-sndz.[oo] Although the combined studies were heterogeneous (GCSF dose, cancer types, and mobilization regimens), results of the combined analysis demonstrated no differences between biosimilars (tbo-filgrastim and filgrastim-sndz, collectively) and reference filgrastim for the number of apheresis sessions (P = .57), the CD34+ cell count (P = .17), time to recovery of neutrophil count to greater than 0.5 x 10^9/L after engraftment (P = .22), or time to recovery of platelet count to greater than 20 x 10^9/L after engraftment (P = .16).[oo] A small phase 2 trial demonstrated that tbo-filgrastim was noninferior to US filgrastim for the median number of CD34+ cells collected on day 5.[hh]

Mobilization in the allogeneic setting is an unapproved use for filgrastim, tbo-filgrastim, and the filgrastim biosimilars. In 2011, the WMDA issued a position paper that GCSF biosimilars should not be used for mobilization in healthy donors unless the donor is followed for long-term toxicity and both the donor and recipient consent to use of a biosimilar.[pp] At the time of the report, there were no long-term safety data with the use of biosimilars in healthy donors. Since 2011, multiple published reports have described the use of filgrastim biosimilars for allogeneic mobilization.[qq-vv] The results of these studies (n = 1,287 donors) and a meta-analysis (n = 351 donors) collectively suggest no differences exist between filgrastim and its biosimilars regarding CD34+ mobilization efficacy, transplant results, or donor safety.[ss,ww] Although only short-term results are available, the WMDA revised its position in 2018 and recommends that biosimilars be considered in place of filgrastim in healthy donors as long as the donor and recipient are followed for adverse events and the biosimilars are approved by a regulatory agency.[ww]

Immunogenicity: Filgrastim has limited immunogenicity because it is a nonglycosylated protein administered mostly to immunocompromised populations. The immunogenicity of tbo-filgrastim, filgrastim-sndz, filgrastim-aafi, and filgrastim-ayow also appear limited and similar in magnitude to that of filgrastim based on immunogenicity data generated in respective clinical programs. In the phase 3 clinical program of tbo-filgrastim, the incidence of treatment-emergent ADAs in patients with breast, lung, or NHL cancer was 1.6% (7 of 436) and none of the treatment-emergent ADAs had neutralizing activity.[m] In a combined analysis of the US and EU phase 3 trials conducted in 223 patients with breast cancer, no patients treated with filgrastim-sndz developed binding or neutralizing antibodies against GCSF at any time.[c] Similarly, no neutralizing antibodies were detected in healthy patients who received filgrastim-sndz during phase 1 trials.[t] Filgrastim-aafi and filgrastim-ayow were not associated with the development of neutralizing antibodies in healthy volunteers that received 2 treatment cycles (5-day cycles followed by a single-dose cycle) of the biosimilar and both were noninferior to US filgrastim at a noninferiority margin of 10% for the development of treatment-emergent ADAs in their respective studies.[e,g,h]

Other issues: Filgrastim, tbo-filgrastim, filgrastim-aafi, and filgrastim-ayow are available as a single-dose prefilled syringe and vial, while filgrastim-sndz is only available as a single-dose prefilled syringe.[n-r] The prefilled syringe for filgrastim biosimilars cannot be used to directly administer doses of less than 180 mcg[o-q]; therefore, the availability of single-dose vials may make it easier to prepare and administer smaller filgrastim doses. The needle cap of the prefilled syringes of filgrastim and filgrastim-sndz contain rubber latex and should be avoided in persons with latex allergies.[n,o] Finally, in contrast to other filgrastim products, unopened tbo-filgrastim can remain at room temperature for up to 5 days before use and the prefilled syringe may be used to directly administer doses as small as 0.1 mL.[r]

Summary: Health care organizations have a choice among several GCSF products for formulary inclusion. Tbo-filgrastim was approved via a new BLA for prevention of chemotherapy-induced neutropenia in adult patients and subsequently for pediatric patients via a supplemental application, while filgrastim-sndz, filgrastim-aafi, and filgrastim-ayow were approved via the biosimilar pathway. Filgrastim-sndz and filgrastim-aafi are FDA approved for 5 of 6 indications of US filgrastim while filgrastim-ayow is approved for 4 of 6 indications. The approval of tbo-filgrastim was based on its comparison against placebo, although clinical trial evidence also demonstrated equivalency to EU filgrastim for the prevention of chemotherapy-induced neutropenia in nonmyeloid malignancies. Filgrastim-sndz was approved based on the demonstration of high similarity to US filgrastim in analytical, nonclinical, and PK/PD studies as well as demonstration of noninferiority to filgrastim for prevention of chemotherapy-induced neutropenia in breast cancer patients receiving myelosuppressive chemotherapy. Filgrastim-aafi also demonstrated high similarity to US filgrastim in analytical, nonclinical, and PK/PD studies and is the first filgrastim biosimilar to be approved by the FDA without submission of clinical data in an intended population. However, filgrastim-aafi has demonstrated equivalence to EU filgrastim for prevention of chemotherapy-induced neutropenia in breast cancer patients receiving myelosuppressive chemotherapy. Filgrastim-ayow's clinical program was also conducted in a healthy population and the US approval represents the first approval; therefore, there is no published real-world experience with filgrastim-ayow. Data on the real-world use of tbo-filgrastim and the filgrastim biosimilars are rapidly becoming available and most professional organizations support the use of GCSF biosimilars in place of US filgrastim for most approved indications. Although data supports that alternating between filgrastim-sndz and US filgrastim preserves at least 50% of the efficacy of US filgrastim, none of the GCSF biosimilars have been approved as an interchangeable biosimilar. Therefore, a therapeutic interchange policy is necessary for substitution. In practice, it is likely that acquisition cost and reimbursement will be important considerations in the decision to use tbo-filgrastim or the filgrastim biosimilars.

Abbreviations: Abbreviations: ADA = anti-drug antibodies; AML = acute myeloid leukemia; ANC = absolute neutrophil count; ANC_{max} = maximum observed absolute neutrophil count; ARDS = acute respiratory distress syndrome; ASCO = American Society of Clinical Oncology; $AUC_{0\text{-}inf}$ = area under the serum concentration versus time curve from zero to infinity; $AUEC_{0}$-t = baseline-corrected area under the effect curve from time zero to the last non-zero cell count data; $AUEC_{ANC}$ = area under the effect curve for absolute neutrophil count; $AUEC_{CD34+}$ = area under the effect curve for CD34+ count from day 1 through 120 h post-dose on day 5; BLA = biological licenses application; BMT = bone marrow transplantation; CHOP = cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone; CI = confidence interval; C_{max} = maximum serum concentration; DSN = duration of severe neutropenia; EMA = European Medicines Administration; E_{max} = maximum observed effect; EORTC = European Organization for Research and Treatment of Cancer; ESMO = European Society for Medical Oncology; EU = European Union; FDA = US Food and Drug Administration; FN = febrile neutropenia; GCSF = granulocyte-colony stimulating factor; GMR = geometric mean ratio; HCP = health care provider; IV = intravenous; MDS = Myelodysplastic Syndrome; NHL = non-Hodgkin's lymphoma; NCCN = National Comprehensive Cancer Network; PBPC = peripheral blood progenitor cell; PD = pharmacodynamic; pH = potential hydrogen; PK = pharmacokinetic; PS-80 = polysorbate 80; q.s. = quantum sufficit; SCN = severe chronic neutropenia; TEAE = treatment-related adverse events; WMDA = World Marrow Donor Association.

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