BREAST CANCER

original reports

Biosimilar Versus Originator Pegfilgrastim for Preventing Chemotherapy-Induced Neutropenia: A Phase III Randomized, Multicenter, Evaluator-Blinded, Noninferiority Study

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abstract

PURPOSE This study evaluated the efficacy, safety, and immunogenicity of biosimilar pegfilgrastim (PegFilBS) and originator pegfilgrastim (PegFilOR) in patients with stage 2-4 breast cancer.

METHODS This phase III randomized, multicenter, evaluator-blinded, noninferiority study recruited women with stage 2-4 breast cancer in Argentina who were scheduled to receive chemotherapy. Stratification was based on the breast cancer stage. The primary end point was the duration of severe neutropenia (DSN, noninferiority margin: 1 day) in the first chemotherapy cycle. Secondary end points assessed were incidence of severe neutropenia, grade 3 neutropenia, febrile neutropenia, infections, postchemotherapy hospitalization and duration, and the incidence of adverse drug reactions (ADRs).

RESULTS A total of 120 patients were randomly assigned to receive PegFilBS (58 patients) or PegFilOR (62 patients). Severe neutropenia occurred in 52 of 283 cycles (18.4%) for 27 patients who received PegFilBS and in 48 of 297 cycles (16.2%) for 20 patients who received PegFilOR ($P = .48$). During the first cycle, severe neutropenia occurred in 16 patients who received PegFilBS (DSN: 0.78 ± 1.53 days) and in 11 patients who received PegFilOR (DSN: 0.53 ± 1.25 days; 95% CI, –0.26 to 0.76 days). In the intention-to-treat analysis, the mean DSN values were 0.90 ± 1.79 days for the PegFilBS group and 0.50 ± 1.21 for the PegFilOR group (95% CI, –0.15 to 0.95 days). No significant differences were observed for the secondary efficacy end points. Three patients experienced seven ADRs in the PegFilBS group while 10 patients experienced 31 ADRs in the PegFilOR group. The most common ADR was myalgia.

CONCLUSION Relative to PegFilOR, PegFilBS provided noninferior efficacy outcomes in Argentinian women with stage 2-4 breast cancer who were treated using myelosuppressive chemotherapy.

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ASSOCIATED CONTENT

Data Sharing Statement
Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Neutropenia is common in patients with cancer who receive myelosuppressive chemotherapy and contributes to cancer-associated morbidity. Moreover, neutropenia is associated with an increased risk of infection, which can be life-threatening and requires aggressive treatment using intravenously administered antibiotics. Neutropenia-related infection often manifests as febrile neutropenia and can lead to hospitalization, morbidity, and mortality in up to 10% of patients.[1]

Granulocyte colony-stimulating factor (G-CSF) is a glycoprotein that acts on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation‘ differentiation, commitment‘ and some end-cell functions.[2] Human G-CSF is a single polypeptide chain protein (174 amino acids) with *O*-glycosylation at a single threonine residue. Endogenous G-CSF is a lineage-specific colony-stimulating factor that is produced by monocytes, fibroblasts, and endothelial cells. Furthermore, G-CSF regulates neutrophil production within the bone marrow and affects neutrophil progenitor proliferation[3] and differentiation.[4] Moreover, G-CSF activates select end-cell functions, such as enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory bursts,[5,6] antibody-dependent killing, and increases in some cell surface antigen-associated functions. Various methods are used to produce recombinant forms

CONTEXT

Key Objective

Are the efficacy, safety, and immunogenicity results obtained with a proposed biosimilar pegfilgrastim similar to the results obtained with the originator pegfilgrastim in patients with stage 2-4 breast cancer? To the best of our knowledge, this is the first clinical trial to evaluate a biosimilar pegfilgrastim that was developed in this region.

Knowledge Generated

Duration of severe neutropenia in the first chemotherapy cycle was similar with the two drugs (0.78 ± 1.53 days and 0.53 ± 1.25 days; CI for the difference, –0.26 to 0.76 days for 1 day noninferiority margin). An equivalence analysis was conducted as a sensitivity analysis. For both per-protocol and intention-to-treat populations, the Schuirmann two one-sided test showed equivalence.

Relevance

These results may help improve access to biologic drugs in Latin America.

of G-CSF. Filgrastim is one form, which is produced by *Escherichia coli* that expresses the human gene for G-CSF, and the product can be conjugated to monomethoxypolyethylene glycol (pegfilgrastim). This product has been approved by health authorities as prophylactic treatment to decrease the incidence of febrile neutropenia in patients with nonmyeloid malignancies who are receiving myelosuppressive anticancer drugs that are associated with a clinically significant incidence of febrile neutropenia.

Some medical organizations have suggested that systematic use of hematopoietic growth factors, including G-CSF and pegfilgrastim, is not justified as prophylaxis for chemotherapy-induced neutropenia unless the risk of febrile neutropenia exceeds 20% or there are special circumstances.[7,8] Regimens used to treat breast cancer in the adjuvant, neoadjuvant, or metastatic setting are associated with more than 20% risk of febrile neutropenia.[9-11] In addition to the risk associated with the specific chemotherapy regimen and malignancy, additional risk factors need to be considered. For example, the risk of febrile neutropenia is increased among older patients (especially those who are ≥ 65 years), patients who have received previous chemotherapy or radiotherapy, patients with preexisting neutropenia or tumor involvement in the bone marrow, and patients with pre-existing conditions (eg, neutropenia, infection/open wound, recent surgery, poor performance status, poor renal function, and liver dysfunction, especially elevated bilirubin concentrations).[12,13]

Biosimilars (or similar biotherapeutic products) are biotherapeutic agents that are considered similar in terms of quality, safety, and efficacy, relative to a currently licensed reference biotherapeutic product. Market approval of biosimilars may be granted after the patent for the reference product expires,[14] and Latin America is currently undergoing a full consolidation of regulatory procedures for biosimilars. As the region moves toward a stronger biosimilar registration program, the status and strictness of its regulations are evolving and consolidating.[15] A biosimilar form of pegfilgrastim (PegFilBS; Peg-Neutropine, Gema Biotech SAU, CABA, Argentina) has been developed in reference to the originator pegfilgrastim (PegFilOR; Roche, Chile). Analytical comparability and preclinical studies have shown that PegFilBS and PegFilOR are structurally similar and provide similar therapeutic results (Protocol). Therefore, this phase III study aimed to compare the efficacy, safety, and immunogenicity of PegFilBS and PegFilOR in patients who were receiving myelosuppressive chemotherapy for stage 2-4 breast cancer.

METHODS

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and the Council for Harmonization Good Clinical Practice Guidelines. The study protocol (ClinicalTrials.gov identifier: NCT03404752) was approved by the institutional ethics committee at each site. The study protocol, research sites, and investigators were also approved by the local Argentinean health authorities. All patients provided written informed consent before enrollment.

Study Design

This randomized, multicenter, evaluator-blinded, noninferiority, parallel group, controlled study was conducted at 12 sites in Argentina. The study was designed on the basis of the European Medical Association recommendations for biosimilar G-CSF products that were in effect when the study protocol was prepared and written.[2] The study was not conducted as a double-blind study because of regulatory constraints; it is not possible to modify the original one to make it the same as the biosimilar. However, bias was avoided because at each site, only the pharmacist and physician/nurse in charge of drug administration were not blinded. All evaluators were blinded when evaluating the laboratory test results, clinical efficacy, safety end points, and the causality of adverse events (AEs). A safety monitoring committee performed two interim analyses

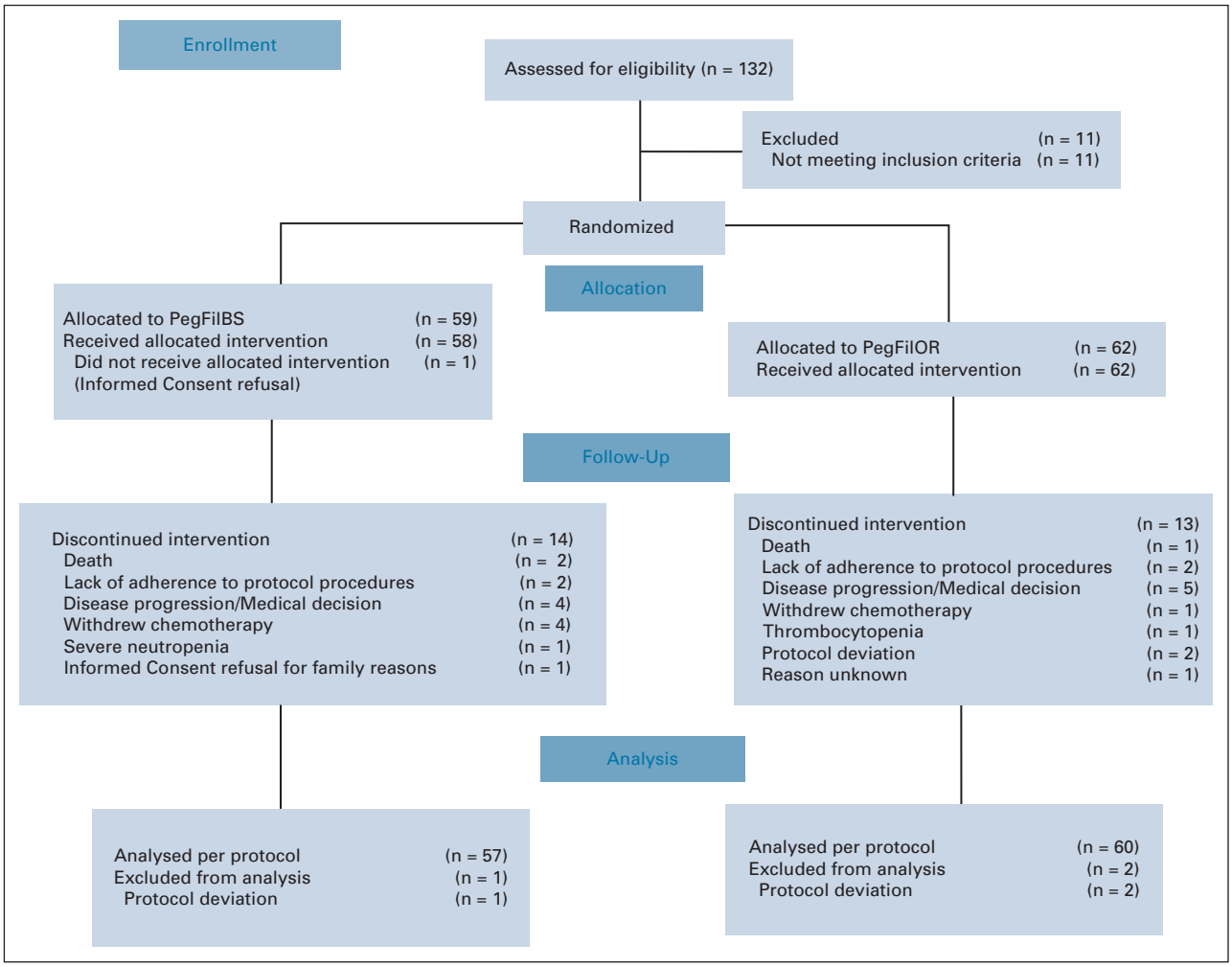

FIG 1. CONSORT diagram of patient disposition. PegFilBS, biosimilar pegfilgrastim; PegFilOR, originator pegfilgrastim.

when the study reached 48 and 100 randomly assigned participants. Both analyses were blinded to the safety monitoring committee. The difference in the duration of severe neutropenia (DSN) during the first analysis was 0 day (CI 95%, –0.6 to 0.6; $P = .500$), and for the second interim analysis, it was 0.13 days (CI 95%, –0.13 to 0.39), and the safety results were similar for both arms. There were no formal stopping rules planned for the interim analyses.

Patients

Women were considered eligible if they were age 18-70 years, had stage 2-4 breast cancer, were scheduled to receive four or six cycles of taxane-containing chemotherapy at 3-week intervals, had an ECOG performance status of 0-2, had a life expectancy of $>$ 6 months, and adequate bone marrow, renal, and hepatic functions. Targeted treatments using monoclonal antibodies were permitted in addition to the taxane-containing regimens. Sexually active premenopausal women were required to use an acceptable form of contraception, and fertile women were required to have monthly negative results from a serum pregnancy test while using the study drugs. A complete list of the inclusion and exclusion criteria is provided in the Protocol.

Random Assignment

Participants were enrolled at the study sites and randomly assigned 1:1 in blocks to receive either PegFilBS (Peg-Neutropine, GEMA BIOTECH S.A.U, Buenos Aires, Argentina) or PegFilOR (Roche). The sequence generated by the random assignment system was concealed until the treatments were assigned. Stratification was based on breast cancer stage, adjuvant chemotherapy, neoadjuvant chemotherapy, first-line chemotherapy for metastatic disease, and other lines of chemotherapy for metastatic disease.

Treatments

Unblinded physicians or nurses administered the treatments subcutaneously (dose: 6 mg) once per chemotherapy cycle for up to six cycles. All treatments were administered at 24-72 hours after completing the chemotherapy cycle.

TABLE 1. Demographic and Clinical Characteristics at Baseline

Characteristic	PegFilBS (N = 58)	PegFilOR (N = 62)
Demographic characteristics		
Age, mean (SD), range, years	54.7 (11.6), 34-70	56.9 (9.6), 35-70
Weight, mean (SD), range, kg	71.5 (13.2), 47-100	74.0 (18.2), 42-120
BSA,[a] median (range), m^2	1.74 (1.38-2.11)	1.75 (1.72-2.26)
Breast cancer characteristics		
Stage, % (No.)		
II	31.1 (18)	35.5 (22)
III	34.4 (20)	27.4 (17)
IV	34.5 (20)	37.1 (23)
Metastases,[b] % (No.)		
Bone	20.7 (12)	25.8 (16)
Others	10.3 (6)	11.3 (7)
Prior chemotherapy, % (No.)	19.0 (11)	22.6 (14)
Prior chemotherapy regimens, % (No.)		
None	79.0 (41)	72.5 (37)
One	11.5 (6)	21.6 (11)
Two	3.8 (2)	2.0 (1)
Three	3.8 (2)	3.9 (2)
Four	1.9 (1)	0
Prior radiotherapy, % (No.)		
Adjuvant	19.0 (11)	17.7 (11)
Breast	19.0 (11)	17.7 (11)
Axillary	1.7 (1)	6.5 (4)
Supraclavicular	0	4.8 (3)
For metastases	5.2 (3)	3.2 (2)
Stratification results, % (No.)		
Adjuvant chemotherapy	33.9 (20)	37.1 (23)
Neoadjuvant chemotherapy	32.2 (19)	25.8 (16)
First line—metastatic	27.1 (16)	27.4 (17)
Other lines—metastatic	6.8 (4)	9.7 (6)
Chemotherapy regimen administered[a]		
Taxane plus doxorubicin plus cyclophosphamide	46.6 (27)	42 (26)
Taxane plus carboplatin or doxorubicin or cyclophosphamide	44.8 (26)	56.4 (35)
Taxane plus carboplatin plus antibodies	8.6 (5)	1.6 (1)
Basal leukocytes mean, $10^3/mm^3$	7.20	7.02

Abbreviations: BSA, body surface area; PegFilBS, biosimilar pegfilgrastim; PegFilOR, originator pegfilgrastim; SD, standard deviation.

[a]Five participants excluded because of missing data.

[b]Two participants metastases localization was unknown.

Outcomes and End Points

The primary efficacy end point was the DSN (absolute neutrophil count: $< 500/mm^3$) in the first chemotherapy cycle. To evaluate the primary end point, neutrophil count was measured each day from day 5 to day 9 after chemotherapy, and when the patient developed severe neutropenia (SN) during the first cycle, the same schedule was performed on the following cycle. When the patient did not develop SN on the following cycles, neutrophil count was measured on days 5 and 7. The secondary efficacy end points were the incidences of severe neutropenia that was not associated with fever, grade 3 neutropenia (absolute neutrophils count [ANC]: 500-1,000/mm^3), febrile neutropenia across all cycles (ANC: $< 1{,}000/mm^3$ plus a single temperature of > 38.3°C or a sustained temperature of > 38°C for > 1 hour), infection, requirement for intravenous anti-infection treatment, postchemotherapy hospitalization and duration, neutropenia-related hospitalization and duration, infection-related mortality, and ability to maintain the planned chemotherapy regimen during cycles 2-6 ($\geq 80\%$ of the planned dose and no dose > 3 days late).

The safety end points included the incidences of serious and nonserious adverse drug reactions (ADRs), as well as patient withdrawal because of inability to tolerate the drug (systematically or at the injection site). Immunogenicity was evaluated on the basis of titers of neutralizing antibodies and binding antibodies to PegFilBS and PegFilOR, which were measured using validated surface plasmon resonance technology at baseline and on days 5 and 28 of the last chemotherapy cycle. The immunogenicity tests were performed at a Immunology Department-IDEHU Laboratory (Pharmacy and Biochemist School, Buenos Aires University).

Sample Size Calculation

The original pivotal study that supported the approval of PegFil used a fixed dose of 6 mg, which produced an average grade 4 neutropenia duration of 1.8 days (estimated standard deviation: 2.1 days). On the basis of those results and the width of the 95% CI around the difference in the median times for ANC recovery, a sample size of 120 patients (assuming 10% lost to follow-up) would be needed to provide 80% power with a one-sided α value of .05 to support a preliminary conclusion of noninferiority.[16] Using 60 patients per treatment group, one-half the width of the 95% CI for the difference in the median DSN was estimated to be < 1 day, which was defined as the noninferiority margin.

Statistical Analysis

The statistical analyses were performed using SPSS software (version 16.0, SPSS Inc, Chicago, IL), the Primer of Biostatistics (version 4.02, 1996), and a measurement worksheet for noninferiority studies (Digestive Unit, Hos-

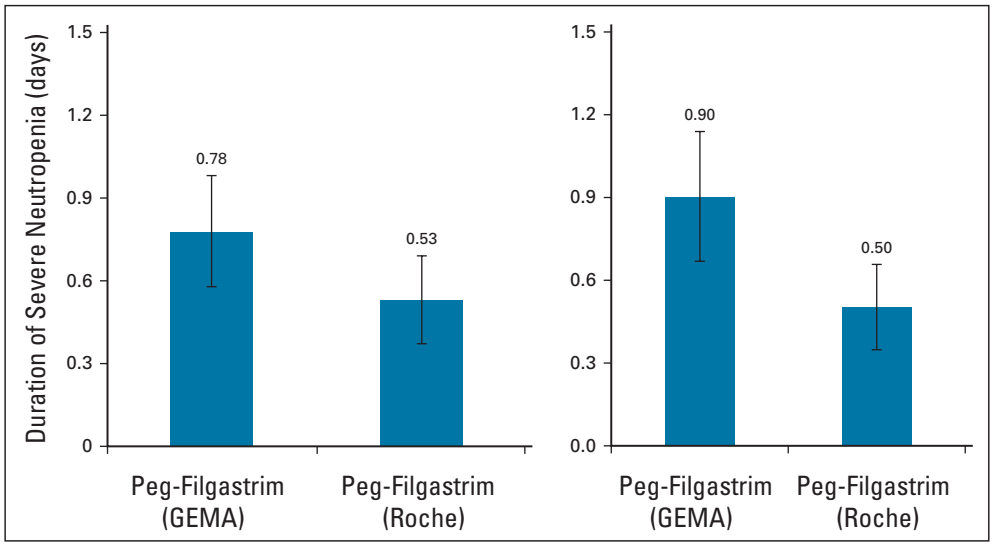

FIG 2. Primary efficacy end point duration of severe neutropenia, per-protocol, and intention-to-treat analysis.

pital Sagunto, Valencia). The primary efficacy analyses were performed using a one-sided test of the difference in means, and the 95% CIs for these estimates were also calculated. The Schuirmann two one-sided test was used for the post hoc equivalence analysis. The null hypotheses of the Schuirmann one-sided double *t* tests indicate that bioinequivalence are rejected with a significance level of .05. The T-test for comparisons of proportions was used for the secondary end point analysis. The last observation carried forward approach was selected for missing data in the intention-to-treat (ITT) analysis. The safety parameters were reported using descriptive statistics. The secondary end points were not adjusted for multiplicity.

RESULTS

Patient Characteristics

The recruitment period started on July 21, 2015, and the last patient visit was enrolled on September 19, 2018. A total of 121 patients were randomly assigned, although one patient was not treated, to receive PegFilBS (58 patients) or PegFilOR (62 patients). Twenty-seven patients discontinued treatment (Fig 1, CONSORT), although discontinuations occurred after completing the first chemotherapy cycle. Thus, the primary end point could be evaluated for 117 patients.

The median age was 55.8 years, and the average body surface area was 1.71 m^2. All patients were Hispanic, and the two treatment groups had balanced baseline characteristics in terms of age, weight, body surface area, breast cancer stage, number of prior chemotherapy regimens, prior radiotherapy, chemotherapy regimen administered, and leukocyte count (Table 1).

Efficacy

In the per-protocol analysis, 117 patients were evaluated. One patient allocated to PegFilBS who did not receive the allocated intervention and three patients with protocol deviations (two patients recruited violating an inclusion or exclusion criterion and one patient who received PegFilOR instead of receiving PegFilBS) were excluded. Severe neutropenia occurred in 52 of 283 cycles (18.4%) for 27 patients who received PegFilBS and in 48 of 297 cycles (16.2%) for 20 patients who received PegFilOR ($P = .48$). During the first chemotherapy cycle, severe neutropenia

TABLE 2. Efficacy Secondary End Points Results Per Treatment Arm

Secondary End Points Efficacy	PegFilBS (N = 58), No. (%)	PegFilOR (N = 59), No. (%)	Difference, %	*P*
Incidence of severe neutropenia not associated with fever across the cycles	18 (31.0)	24 (40.7)	–9.7	.2741
Grade 3 neutropenia across the cycles	28 (49.3)	20 (33.9)	15.4	.0910
Incidence of febrile neutropenia	2 (3.4)	1 (1.7)	1.7	.5592
Incidence of ANC $< 500/mm^3$ and body temperature of $> 38.3°C$	1 (1.7)	1 (1.7)	0.0	—
Incidence of fever	2 (3.4)	1 (1.7)	1.7	.5592
Incidence of infections	3 (5.2)	1 (1.7)	3.5	.2987
Incidence of postchemotherapy hospitalization	1 (1.7)	2 (3.4)	–1.7	.5603
Mortality because of infection	1 (1.7)	0	1.7	.3145

NOTE. Hypothesis test: t-test for comparisons of proportions.

Abbreviations: ANC, absolute neutrophils count; PegFilBS, biosimilar pegfilgrastim; PegFilOR, originator pegfilgrastim.

TABLE 3. Adverse Drug Reactions Results Per Treatment Arm

ADRs	PegFilBS (N = 58)	PegFilOR (N = 62)
Patients, No. (%)	3 (5.2)	10 (16.1)
Reactions, No.	7	31
Arthralgia		
Patients, No. (%)	0	2 (3.2)
Reactions, No.		2
Asthenia		
Patients, No. (%)	0	1 (1.6)
Reactions, No.		2
Bone pain		
Patients, No. (%)	0	2 (3.2)
Reactions, No.		2
Myalgias		
Patients, No. (%)	2 (3.4)	7 (11.3)
Reactions, No.	6	25
Gastroesophageal reflux disease		
Patients, No. (%)	1 (1.7)	0
Reactions, No.	1	

Abbreviations: ADR, adverse drug reaction; PegFilBS, biosimilar pegfilgrastim; PegFilOR, originator pegfilgrastim.

occurred in 16 patients who received PegFilBS and 11 patients who received PegFilOR. The per protocol analysis revealed that the mean DSN values during the first cycle were 0.78 ± 1.53 days for the PegFilBS group and 0.53 ± 1.25 days for the PegFilOR group (95% CI for the difference, –0.26 to 0.76). The difference was well within the predetermined noninferiority margin of 1 day. Similar results were observed in the ITT population. For the ITT analysis, all the randomly assigned 121 patients were evaluated including one patient allocated to PegFilBS who did not receive the allocated intervention. For this patient, the DSN was estimated as 8 days taking into account the maximum length of SN observed during the study. The mean DSN values were 0.90 ± 1.79 days for the PegFilBS group and 0.50 ± 1.21 days for the PegFilOR group (95% CI for the difference, –0.15 to 0.95; Fig 2). An equivalence analysis was conducted as a sensitivity analysis. For both per-protocol and ITT populations, the Schuirmann two one-sided test showed equivalence. For per-protocol population, the results were first-sided test 1 = –2.915; P = .002 and second-sided test = 4.859; P, .001. For the ITT population, the results were first-sided test 1 = –2.127; P = .018 and second-sided test = 4.964; P, .001, showing equivalence as well.

Secondary Efficacy End Points

No significant intergroup differences were observed for all the secondary efficacy end points (Table 2).

Safety

Serious AEs. Three patients who received PegFilBS experienced four serious AEs (SAEs), which were febrile neutropenia with pneumonia, followed by death and myocardial infarction, followed by death, vomiting, and dehydration requiring hospitalization. Five patients who received PegFilOR experienced seven SAEs, which were headaches requiring hospitalization (one event), vomiting (one event), and dehydration requiring hospitalization, followed by severe pneumonia (one event), gallstones requiring hospitalization and surgery (one event), febrile neutropenia (two events), dehydration requiring hospitalization (one event), and death due to unknown causes (one event). None of the SAEs were related to the study drug, and most of them were related to the effects of chemotherapy in older patients. In all instances, the study drugs were discontinued because of interruptions in the patient's chemotherapy treatment.

Adverse drug reactions. Three patients who received PegFilBS experienced seven ADRs while 10 patients who received PegFilOR experienced 31 ADRs. The most common ADR was myalgia, and other ADRs included arthralgia, asthenia, bone pain, and gastroesophageal reflux disease. Only one patient who received PegFilBS reported mild pain at the injection site during the fifth treatment cycle (Table 3).

Immunogenicity. Negative results regarding immunogenicity were observed for all 101 patients who underwent testing on day 28 after the last dose of PegFilBS or PegFilOR.

DISCUSSION

Two filgrastim biosimilars have been developed, studied, and approved in Latin America. However, to the best of our knowledge, this is the first clinical trial to evaluate a PegFilBS that was developed in this region.[17,18] The PegFilBS developed by GEMA BIOTECH S.A.U. is the first to be approved in Latin America for preventing febrile neutropenia in patients who are receiving myelosuppressive chemotherapy. Since 2011, Argentina has enacted specific local regulations regarding the use of biosimilars, which can require comparability exercises and nonclinical data, with or without clinical data, depending on the specific product.[19]

This noninferiority trial revealed that, during the first chemotherapy cycle, the mean DSN value was noninferior for patients who received PegFilBS (*v* PegFilOR) during treatment for stage 2-4 breast cancer. The noninferiority margin for DSN was defined as 1 day, which is similar to the margin used in other PegFilBS trials that aimed to support regulatory approval from the European Medical Association.[20,21] Although regulatory authorities recommend equivalence trials, noninferiority trials may be performed if they have been previously justified.[22,23] This is because the biosimilar product may actually provide a superior result or an increase in ADRs, although this is not probable for pegfilgrastim. Our results revealed similar safety profiles for PegFilBS and PegFilOR, with only expected AEs and SAEs, and no newly discovered AEs.

Furthermore, the immunogenicity results seem to indicate that PegFilBS was not associated with an increased likelihood of developing neutralizing antibodies and/or binding antibodies (*v* PegFilOR).

These findings, especially regarding safety, may be limited by the small sample size, although this did not seem to affect the efficacy of PegFilBS. In addition, we only enrolled Argentinian women, although it is important to note that the Argentinian population includes a mixture of European immigrants, Native Americans, and individuals of mixed descent. Furthermore, our study population is slightly different than in other Latin American countries; however, we are not aware of any data that indicate filgrastim/pegfilgrastim provides variable therapeutic effects or AEs in different ethnic populations.

In conclusion, this trial revealed that, relative to PegFilOR, PegFilBS (Peg-Neutropine) was associated with noninferior efficacy and safety outcomes in women who were receiving myelosuppressive chemotherapy for stage 2-4 breast cancer. These results suggest that third-world countries are capable of developing and marketing biosimilar products, which may help dramatically increase the currently limited access to biological drugs among our patients, especially relative to patients in more developed parts of the world.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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