

A Comparison of Proposed Biosimilar LA-EP2006 and Reference Pegfilgrastim for the Prevention of Neutropenia in Patients With Early-Stage Breast Cancer Receiving Myelosuppressive Adjuvant or Neoadjuvant Chemotherapy: Pegfilgrastim Randomized Oncology (Supportive Care) Trial to Evaluate Comparative Treatment (PROTECT-2), a Phase III, Randomized, Double-Blind Trial

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Key Words. Granulocyte colony-stimulating factor • Pegfilgrastim • Neutropenia • Biosimilars • Breast cancer

ABSTRACT

Background. Pegfilgrastim is widely used for the prevention of chemotherapy-induced neutropenia. In highly regulated markets, there are currently no approved biosimilars of pegfilgrastim. Pegfilgrastim Randomized Oncology (Supportive Care) Trial to Evaluate Comparative Treatment (PROTECT-2) was a confirmatory efficacy and safety study designed to compare proposed biosimilar LA-EP2006 with reference pegfilgrastim (Neulasta, Amgen) in early-stage breast cancer patients receiving adjuvant or neoadjuvant myelosuppressive chemotherapy.

Methods. A total of 308 patients were randomized to LA-EP2006 or reference pegfilgrastim. Each patient received TAC (intravenous docetaxel 75 mg/m², doxorubicin 50 mg/m², and cyclophosphamide 500 mg/m²) on day 1 of each cycle, for six or more cycles. Pegfilgrastim (LA-EP2006 or reference) was given subcutaneously (6 mg in 0.6 mL) on day 2 of each cycle. The primary endpoint was duration of severe neutropenia (DSN) during cycle 1 (number of consecutive days with an

absolute neutrophil count $<0.5 \times 10^9/L$), with equivalence confirmed if 90% and 95% confidence intervals (CIs) were within a 1-day margin.

Results. Baseline characteristics were well balanced. DSN was equivalent between groups at mean \pm SD 1.36 ± 1.13 (LA-EP2006, $n = 155$) and 1.19 ± 0.98 (reference, $n = 153$) in cycle 1. With a treatment difference (reference minus LA-EP2006) of -0.16 days (90% CI -0.36 to 0.04 ; 95% CI -0.40 to 0.08), LA-EP2006 was equivalent to reference pegfilgrastim. Secondary efficacy parameters were similar between groups during cycle 1 and across cycles. Safety profiles were also similar between groups. No neutralizing antibodies against pegfilgrastim, filgrastim, or polyethylene glycol were detected.

Conclusion. LA-EP2006 and reference pegfilgrastim were therapeutically equivalent and comparable regarding efficacy and safety in the prevention of neutropenia in patients with early-stage breast cancer receiving TAC. *The Oncologist* 2016;21:789–794

Implications for Practice: The granulocyte colony-stimulating factor pegfilgrastim is widely used for the prevention of chemotherapy-induced neutropenia. Biosimilars are biologics with similar quality, safety, and efficacy to a reference product that may increase the affordability of treatment compared with their reference compounds. There are currently no approved biosimilars of pegfilgrastim in highly regulated markets. No previous phase III studies have been performed with LA-EP2006. PROTECT-2 was conducted to confirm the similarity of the proposed biosimilar LA-EP2006 to pegfilgrastim. Biosimilar pegfilgrastim (LA-EP2006) may benefit oncology patients by offering increased access to biological treatments that may improve clinical outcomes. This means that patients could potentially be treated prophylactically with biologics rather than only after complications have occurred.

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INTRODUCTION

Biosimilars are biologics with highly similar quality, safety, and efficacy to a reference product [1]. The development of biosimilars follows a stepwise approach including analytical comparison with the reference and an iterative process to achieve a product that is essentially the same as the reference [2]. Clinical trials in support of this stepwise process are focused on confirming this similarity so that the totality of data reinforce that the biosimilar is essentially the same biological substance as the reference product [3]. The clinical trial reported here was conducted to confirm the similarity of a proposed biosimilar to commercial pegfilgrastim.

The recombinant human granulocyte colony-stimulating factor (G-CSF), filgrastim, and its pegylated form, pegfilgrastim, are widely used for the prevention of chemotherapy-induced neutropenia [4]. Filgrastim undergoes rapid renal clearance and requires daily administration during chemotherapy. Pegfilgrastim is mainly eliminated by neutrophil-mediated clearance, with renal clearance playing only a minor role, resulting in a long serum half-life. Clinical evidence shows that pegfilgrastim has a comparable efficacy and safety profile to filgrastim, but its longer half-life allows once-per-chemotherapy-cycle administration [5, 6], thereby offering greater convenience, which may translate into better patient compliance and improved clinical outcomes [7, 8]. Biosimilars of filgrastim, based on the reference product Neupogen, have been available in Europe since 2009, but in highly regulated markets there are currently no approved biosimilars of pegfilgrastim.

This prospective, randomized, double-blind, multinational multicenter confirmatory efficacy and safety study was a head-to-head comparison of a proposed biosimilar pegfilgrastim, LA-EP2006, with the reference product (Neulasta). The study was designed to show equivalence of LA-EP2006 versus the reference in the reduction of duration of severe neutropenia (DSN) in breast cancer patients receiving myelosuppressive chemotherapy.

PATIENTS AND METHODS

PROTECT-2 enrolled patients with breast cancer receiving neoadjuvant or adjuvant treatment with docetaxel, doxorubicin, and cyclophosphamide (TAC) chemotherapy (EudraCT no. 2012-002039-28).

The study was conducted in accordance with the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, local regulations (including U.S. Code of Federal Regulations Title 21), and the Declaration of Helsinki. The study protocol and all amendments were reviewed by the Independent Ethics Committee for each center. All patients provided written informed consent.

Patients

Women (aged ≥ 18 years) with histologically proven early-stage breast cancer who were eligible for neoadjuvant or adjuvant treatment with TAC chemotherapy (docetaxel 75 mg/m², doxorubicin 50 mg/m², and cyclophosphamide 500 mg/m²) were enrolled. Other key inclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 ; adequate bone marrow function at day 1 of cycle 1 before chemotherapy

(absolute neutrophil count [ANC] $\geq 1.5 \times 10^9/L$, platelet count $\geq 100 \times 10^9/L$, hemoglobin ≥ 10 g/dL); normal total bilirubin; aspartate aminotransferase and alanine aminotransferase levels $\leq 2 \times$ upper limit of normal (ULN); liver-derived alkaline phosphatase level $\leq 3 \times$ ULN; creatinine $\leq 1.5 \times$ ULN; and for women of child-bearing potential, a negative serum pregnancy test within 7 days before randomization and use of a highly effective method of birth control. Key exclusion criteria were history of chronic myeloid leukemia or myelodysplastic syndrome; history or presence of sickle cell disease; previous or concurrent malignancy except noninvasive nonmelanomatous skin cancer, in situ carcinoma of the cervix, or other solid tumor treated curatively and without evidence of recurrence for ≥ 10 years before study entry; any significant serious illness or medical condition; concurrent or prior anticancer treatment (including radiotherapy within 4 weeks of randomization); use of prophylactic antibiotics; prior bone marrow or stem cell transplant; previous therapy with any G-CSF; or infection or positive serology for human immunodeficiency virus (HIV) or hepatitis B or C at screening.

Design

After a screening period of up to 21 days, eligible patients were randomized 1:1 to 6 mg of either LA-EP2006 (Sandoz, Kundl, Austria, <http://www.sandoz.com/>) or reference pegfilgrastim (Neulasta, Amgen, Thousand Oaks, CA, <http://www.amgen.com/>).

Patients received TAC chemotherapy administered intravenously on day 1 of each cycle and every 3 weeks for up to 6 cycles. G-CSF guidelines recommend primary G-CSF prophylaxis for patients at $>20\%$ risk for febrile neutropenia (FN), including patients receiving TAC chemotherapy [9, 10]. Pegfilgrastim (LA-EP2006 or reference) 6 mg in 0.6 mL in prefilled single-use syringes was administered by subcutaneous injection on day 2 of each cycle (≥ 24 hours after end of chemotherapy).

Endpoints

The primary efficacy endpoint was the mean duration of severe (grade 4) neutropenia (DSN) during cycle 1 of chemotherapy, defined as the number of consecutive days in which a patient had an ANC $<0.5 \times 10^9/L$. For DSN, ANC missing value imputation was performed to determine the time point of severe neutropenia but not the replacement of the ANC value itself. ANC was scheduled for day 1 of cycle 1, and then daily until the ANC had recovered to $10 \times 10^9/L$ after nadir or until day 15, whichever occurred first.

Further ANC was scheduled on day 1 of cycles 2–6, before chemotherapy administration and at the end of treatment, including in case of early discontinuation.

Secondary efficacy parameters were depth of ANC nadir (lowest ANC) during cycle 1, time to ANC recovery (days from ANC nadir until ANC increased to $\geq 2 \times 10^9/L$) during cycle 1, number of days of fever (defined as oral body temperature $\geq 38.3^\circ\text{C}$) for each cycle, frequency of infections by cycle and across all cycles (identified by the adverse event documentation page selecting all events coded with system organ class “infections and infestations” as recorded by the investigator), mortality from infection, and number of episodes of febrile neutropenia by cycle and across all cycles. The secondary

efficacy parameter of febrile neutropenia included the serious treatment-emergent adverse events (TEAEs) of FN (defined as oral body temperature of $\geq 38.3^{\circ}\text{C}$ with $\text{ANC} < 0.5 \times 10^9/\text{L}$) and neutropenic sepsis (NS) (referred to as FN/NS). Further ANC was scheduled for each day a patient reported a fever episode, the next day, and every other day thereafter until the ANC reached a value $> 0.5 \times 10^9/\text{L}$. Neutropenic sepsis was identified by adverse event documentation page, selecting all neutropenic sepsis events as recorded by the investigator.

Safety was assessed through the incidence and occurrence of TEAEs by severity according to Common Terminology Criteria for Adverse Events, version 4.0. The safety follow-up visit was performed 4 weeks after the final administration of pegfilgrastim. Immunogenicity of pegfilgrastim, filgrastim, and polyethylene glycol (PEG) was assessed by a validated enzyme-linked immunosorbent assay for screening and confirmation of binding antipegfilgrastim antibodies and a validated cell-based neutralization antibody assay. Immunogenicity assessments were performed before the first administration of pegfilgrastim, on day 15 of cycle 6, and 4 weeks after the final pegfilgrastim administration (at the end-of-study visit).

Statistical Analysis

Equivalence between LA-EP2006 and reference pegfilgrastim was assessed for the primary endpoint based on the full analysis set (FAS), which included all randomized patients who received ≥ 1 dose of pegfilgrastim, with patients analyzed according to allocation at randomization. Because of the different regulatory requirements in the U.S. and Europe, equivalence was assessed using two-sided 90% and 95% confidence intervals (CIs) for the difference in the mean DSN, with LA-EP2006 considered equivalent to reference pegfilgrastim if CIs were within the predefined margin of 1 day. A sample size of 302 patients was considered sufficient to achieve 90% power for testing of equivalence (two one-sided tests) at the 2.5% significance level, assuming no difference in mean DSN between treatments with a common SD of 1.6 days. The primary efficacy endpoint was analyzed using analysis of covariance (ANCOVA), with treatment group, region, chemotherapy, and baseline ANC as factors, with corresponding 90% and 95% CIs based on the residual standard error and adjusted least squares means of the ANCOVA. The robustness of the results was evaluated with a sensitivity analysis performed for the ANCOVA model on the per-protocol (PP) set (all randomized patients who received ≥ 1 dose of pegfilgrastim and completed cycle 1 without major protocol deviations).

All secondary efficacy endpoints and safety parameters were analyzed descriptively. Safety analyses were performed for the safety analysis set (SAF), including all patients who received ≥ 1 dose of study medication and had ≥ 1 postbaseline safety assessment. All statistical analyses were performed using SAS (SAS Institute, Cary, NC, http://www.sas.com/en_us/home.html).

RESULTS

Baseline Characteristics and Demographics

The study was conducted from March 2012 (first patient, first visit) to December 2013 (last patient, last visit) at 53 study sites in 8 countries (Argentina, Chile, India, Malaysia, Puerto Rico, Russia, Spain, U.S.). A total of 352 patients were screened, of

whom 308 were randomized 1:1 to treatment (LA-EP2006, $n = 155$; reference, $n = 153$). All patients received at least one cycle of chemotherapy and at least one dose of pegfilgrastim. Patient disposition, including reasons for premature withdrawals by treatment arm, is described in Figure 1. A total of 131 (84.5%) patients in the LA-EP2006 treatment group and 123 (80.4%) patients in the reference group received pegfilgrastim during all 6 chemotherapy cycles. Baseline characteristics of patients were similar across treatment groups (Table 1).

Primary Efficacy Endpoint

LA-EP2006 was equivalent to reference pegfilgrastim. The primary efficacy variable of mean \pm SD DSN during cycle 1 was 1.36 ± 1.13 days with LA-EP2006 ($n = 155$) and 1.19 ± 0.98 days with reference pegfilgrastim ($n = 153$) (Table 2). The difference between LA-EP2006 and reference pegfilgrastim was -0.16 days (90% CI -0.36 to 0.04 ; 95% CI -0.40 to 0.08). The 90% and 95% CIs were within the predefined equivalence margin of 1 day. Results in the PP set were comparable to those of the FAS (Table 2).

Secondary Efficacy Endpoints

Secondary endpoints were similar in the two treatment groups (supplemental online Table 1), including depth of ANC nadir, time to ANC recovery, number of fever episodes, number of episodes of FN/NS, number of infections, and mortality from infection. Mean depth of ANC nadir was $0.49 \times 10^9/\text{L}$ (SD 0.72; median 0.24; range 0.0–4.4) and $0.44 \times 10^9/\text{L}$ (SD 0.57; median 0.30; range 0.0–3.8) in patients receiving LA-EP2006 or reference pegfilgrastim, respectively. Mean number (\pm SD) of days to ANC recovery was similar for patients receiving LA-EP2006 (2.11 ± 0.89) and reference pegfilgrastim (2.04 ± 0.95). The percentage of patients with ≥ 1 fever episode across all cycles was comparable in both treatment groups (20.6% and 22.9% for LA-EP2006 or reference pegfilgrastim, respectively). Twelve patients (7.7%) who received LA-EP2006 and 15 patients (9.8%) who received reference pegfilgrastim experienced ≥ 1 FN/NS episode in cycle 1. Across all cycles, FN/NS occurred in 16 (10.3%) and 20 (13.1%) patients, respectively. Overall, the number of infections was low and similar between treatment groups. In Cycle 1, 10 patients (6.5%) treated with LA-EP2006 and 14 patients (9.2%) treated with reference pegfilgrastim experienced infections. No patient died from infection.

Treatment Delivery

In both treatment arms, there were few dose interruptions across all cycles: doxorubicin, 8 (5.2%) vs 17 (11.1%) patients; cyclophosphamide, 9 (5.8%) vs 17 (11.1%); and docetaxel, 17 (11.0%) vs 20 (13.1%) for LA-EP2006 and reference products, respectively. In addition, relative mean (\pm SD) dose intensity of the chemotherapy, defined as delivered chemotherapy dose/planned chemotherapy dose, was similar between groups across cycles: docetaxel, 0.98 ± 0.053 vs. 0.97 ± 0.06 ; doxorubicin, 0.98 ± 0.05 vs. 0.97 ± 0.06 ; and cyclophosphamide, 0.98 ± 0.05 vs. 0.98 ± 0.056 for LA-EP2006 and reference product, respectively.

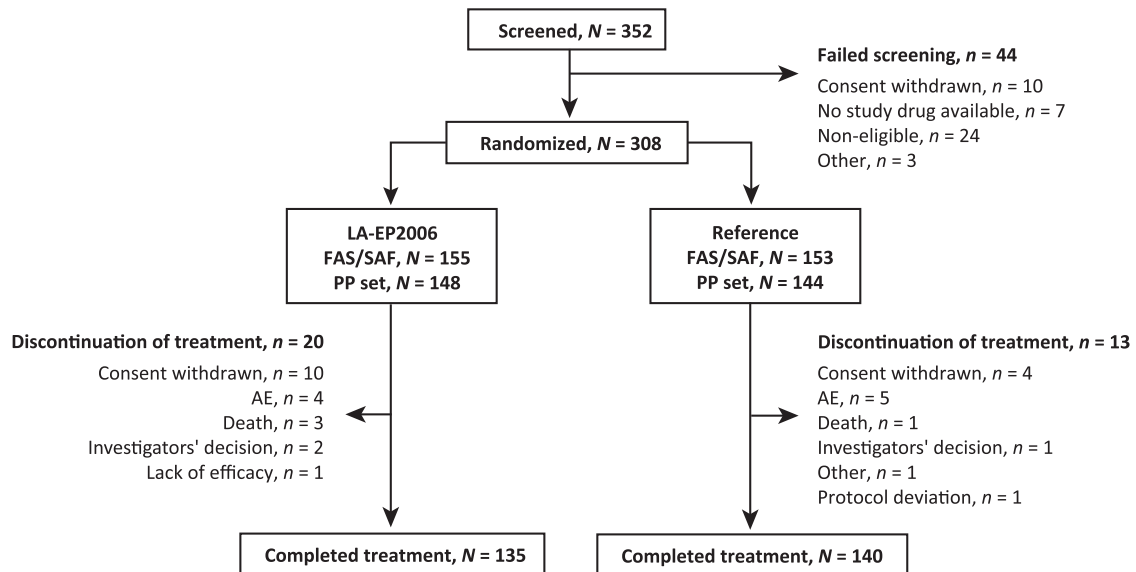


Figure 1. Patient disposition and analysis sets. All patients who discontinued treatment received at least one cycle of chemotherapy and at least one dose of pegfilgrastim. One additional patient in the reference group experienced a treatment-emergent adverse event with the outcome death. This patient was not recorded as having discontinued treatment and therefore is not included as a discontinuation in this figure.

Abbreviations: AE, adverse event; FAS, full analysis set; N, number of patients in a treatment group or analysis set; n, number of patients with an event; PP, per-protocol; SAF, safety analysis set.

Table 1. Patient demographics and baseline characteristics (full analysis/safety set)

Characteristic	LA-EP2006 (N = 155)	Reference (N = 153)
Age, years, mean ± SD	48.8 ± 10.5	49.1 ± 10.07
Race, n		
White	90	93
Asian	62	58
Black	1	2
Other	2	0
BMI, kg/m ² , mean ± SD	26.56 ± 5.771	26.49 ± 5.126
Time since diagnosis, months, median (range)	1.28 (0.2–42.3)	1.28 (0.3–11.2)
Disease stage, n (%)		
I	7 (4.5)	13 (8.5)
II	70 (45.2)	61 (39.9)
III	78 (50.3)	78 (51.0)
IV	0	1 (0.7)
Previous breast cancer surgery, n (%)	154 (99.4)	152 (99.3)
Previous radiotherapy, n (%)	2 (1.3)	1 (0.7)
ECOG performance status, n (%)		
0	117 (75.5)	110 (71.9)
1	36 (23.2)	43 (28.1)
2	2 (1.3)	0
Starting chemotherapy dose, mg, mean ± SD		
Doxorubicin	84.0 ± 10.98	84.9 ± 9.96
Cyclophosphamide	838.8 ± 114.73	849.9 ± 99.44
Docetaxel	126 ± 17.21	127.5 ± 15.28

Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group.

Safety

Safety profiles were similar in the two treatment groups (Fig. 2). TEAEs were reported in 96.1% of patients receiving LA-EP2006 and 95.4% of patients receiving reference pegfilgrastim. The

incidence of pegfilgrastim-related TEAEs over all cycles was 33.5% in the LA-EP2006 group and 28.1% in the reference group. The most frequently reported TEAEs with suspected relationship to pegfilgrastim were observed in the musculoskeletal and

Table 2. Duration of severe neutropenia in days in cycle 1 (full analysis and per-protocol set)

DSN (days)	FAS set		PP set	
	LA-EP2006, N = 155	Reference, N = 153	LA-EP2006, N = 148	Reference, N = 144
<i>n</i>	151 ^a	149 ^a	148	144
Primary efficacy parameter (DSN in cycle 1)				
Mean ± SD	1.36 ± 1.133	1.19 ± 0.984	1.34 ± 1.141	1.19 ± 0.991
Median (minimum–maximum)	1.00 (0.0–6.0)	1.00 (0.0–4.0)	1.00 (0.0–6.0)	1.00 (0.0–4.0)
Treatment difference (reference minus LA-EP2006) ^b				
90% CI	−0.16		−0.15	
95% CI	−0.36 to 0.04		−0.35 to 0.06	
95% CI	−0.40 to 0.08		−0.39 to 0.10	

^aAbsolute nutrient count profiles were not available for four patients in the LA-EP2006 group and four patients in the reference group.

^bInferential test results of analysis of covariance.

Abbreviations: CI, confidence interval; DSN, duration of severe neutropenia; FAS, full analysis set; PP, per-protocol.

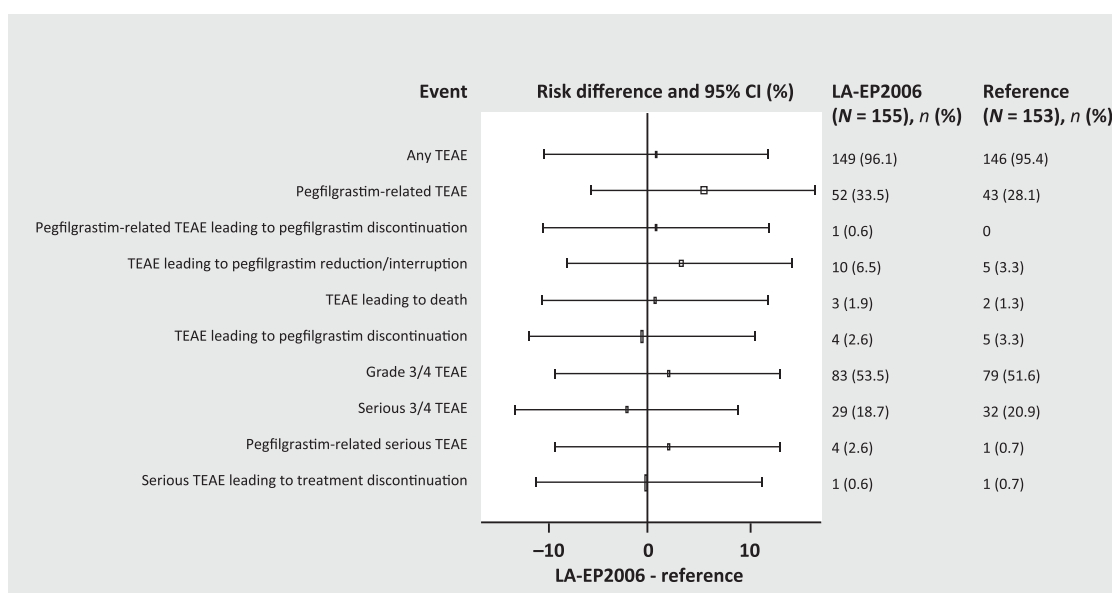


Figure 2. Overview of adverse event incidence. Graph shows patients, *n* (%), with TEAEs and serious events (safety set). Abbreviations: CI, confidence interval; TEAE, treatment-emergent adverse event.

connective tissue disorders system organ class that included bone pain, myalgia, pain in extremity, arthralgia, and back pain. These were reported by 25 patients (16.1%) in the LA-EP2006 group and 21 patients (13.7%) in the reference group. Serious TEAEs considered to be related to pegfilgrastim were reported in 2.6% of patients in the LA-EP2006 group and 0.7% of patients in the reference group. Five deaths occurred during the study, none of which were suspected to be pegfilgrastim related. Three patients in the LA-EP2006 group died. One patient died of hepatic necrosis, with a suspected relationship to chemotherapy; one patient died of pulmonary embolism (reported as cardiac arrest); and one patient died of cardiorespiratory arrest. Two patients in the reference group died. One died of disease (breast cancer) progression, and one committed suicide. No treatment-related binding and neutralizing antibodies against pegfilgrastim, filgrastim, or PEG were detected postdose in any patient at any time during the study.

DISCUSSION

In this prospective, randomized, controlled study, LA-EP2006 was equivalent to the reference pegfilgrastim with regard to

DSN. DSN in cycle 1 was also consistent with other studies of pegfilgrastim in which mean DSN in the first cycle ranged from 1.3 to 1.8 days [11–13]. These previous studies did not include cyclophosphamide or dose adaptations in the chemotherapy regimen. Our results with LA-EP2006 therefore support consistency in duration of DSN across studies with different regimens, including TAC, which has an increased risk of neutropenia compared with other combination chemotherapy treatments [14]. Given the equivalence between the two arms with regard to primary and secondary endpoints and the known clinical benefits of G-CSF, these results can be applied to many chemotherapy regimens that result in high rates of febrile neutropenia, independent of tumor type. The secondary efficacy endpoints were also similar between LA-EP2006 and reference pegfilgrastim. The incidence of FN/NS in cycle 1 was less than 10% (7.7% and 9.8% for LA-EP2006 and reference), which is comparable to that observed in other studies with reference pegfilgrastim (7.0%–9.1%) [11–13]. In the present study, depth of ANC nadir and time to ANC recovery of LA-EP2006 versus reference pegfilgrastim were nearly identical (supplemental online Fig. 1).

The safety profile was comparable between treatment groups and as expected for patients with breast cancer receiving TAC chemotherapy, with the most common TEAEs being alopecia, neutropenia, nausea, asthenia, vomiting, and diarrhea. Pegfilgrastim-related AEs with LA-EP2006 were similar to those in the reference group and consistent with the known safety profile of the G-CSF class [11–13]. The most common pegfilgrastim-related TEAEs were recorded in the musculoskeletal and connective tissue disorders system organ class (16.1% in the LA-EP2006 group vs 13.7% in the reference group). The reported incidence of musculoskeletal/bone pain was lower than in other studies of pegfilgrastim in patients undergoing myelosuppressive chemotherapy regimens other than TAC (range 25%–38%) [15]. However, there may be some limitations in comparing across different clinical trials because of differences in reporting of musculoskeletal/bone pain, recording of adverse events, patient populations, chemotherapy regimens, and clinical settings.

No treatment-related binding and neutralizing antibodies against pegfilgrastim, filgrastim, or PEG were detected during the study, which confirmed the low immunogenic potential of LA-EP2006. These findings are consistent with previous studies of pegfilgrastim in which no neutralizing antibodies were detected [11–13] and the 6 years of clinical experience with the biosimilar filgrastim EP2006, which includes the same filgrastim protein as in LA-EP2006.

CONCLUSION

This study shows that LA-EP2006 and reference pegfilgrastim are therapeutically equivalent and similar regarding efficacy and safety in the prevention of neutropenia in patients with breast cancer receiving TAC chemotherapy.

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