Efficacy and Safety of Balugrastim Compared With Pegfilgrastim in Patients With Breast Cancer Receiving Chemotherapy

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Abstract

Balugrastim is a once-per-cycle fixed-dose recombinant fusion protein composed of human serum albumin and granulocyte colony-stimulating factor (G-CSF), which is being developed to prevent chemotherapy-induced neutropenia. This double-blind randomized phase III trial assessed the efficacy and safety of balugrastim vs. pegfilgrastim in patients with breast cancer. Balugrastim demonstrated noninferiority to pegfilgrastim in reducing the duration of severe neutropenia (DSN) and had a favorable safety profile. Balugrastim is an effective and safe alternative to pegfilgrastim for providing neutrophil support.

Background: Recombinant granulocyte colony-stimulating factors (G-CSFs) reduce the incidence and duration of chemotherapy-induced neutropenia and febrile neutropenia when given as adjunct therapy to patients receiving myelosuppressive chemotherapy. Balugrastim is a long-acting G-CSF composed of a genetic fusion between recombinant human serum albumin and G-CSF. We compared the efficacy and safety of balugrastim and pegfilgrastim, a long-acting pegylated recombinant G-CSF, in patients with breast cancer who were scheduled to receive chemotherapy. **Patients and Methods:** In this double-blind randomized phase III trial, patients with $\geq 1.5 \times 10^9$ neutrophils/L were randomly assigned to subcutaneous injections of balugrastim 40 mg (n = 153) or pegfilgrastim 6 mg (n = 151). The primary efficacy end point was the duration of severe neutropenia (DSN) (days with an absolute neutrophil count [ANC] $< 0.5 \times 10^9$ cells/L) during cycle 1. Efficacy analyses were performed in the per-protocol (PP) population. In a separate open-label single-arm study, newly recruited patients (n = 77) received balugrastim 40 mg and were included in the safety analysis. **Results:** The mean DSN in cycle 1 was 1.1 days in the balugrastim group and 1.0 days in the pegfilgrastim group (95% confidence interval [CI], −0.13-0.37). Two and 4 patients, respectively, had febrile neutropenia during cycle 1. Twenty percent of patients in the balugrastim group and 19% in the pegfilgrastim group had adverse events (AEs) considered to be related to study medication; 3.9% and 4.7% of patients, respectively, experienced serious AEs. **Conclusions:** This study demonstrates the comparable safety and efficacy profile of balugrastim and pegfilgrastim and the noninferiority of balugrastim for reduction in DSN. There were no unexpected safety events.

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Introduction

Neutropenia is a significant dose-limiting toxicity of myelosuppressive chemotherapy.[1] Although neutropenia per se is asymptomatic, it is associated with many clinical sequelae, including increased risk for opportunistic infection, febrile neutropenia, sepsis, and related morbidity and mortality. Severe neutropenia may also delay subsequent cycles of chemotherapy.[1]

In the absence of supportive therapy, the incidence of grade 4 or severe neutropenia (absolute neutrophil count [ANC] $< 0.5 \times 10^9$/L) is almost 100% in patients with breast cancer receiving

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concomitant anthracycline plus taxane-based chemotherapy such as doxorubicin and docetaxel, and the incidence of febrile neutropenia ranges from 23% to 34%.[2] The mean duration of severe neutropenia (DSN) is 3.8 days during the first cycle of treatment for these patients.[3]

Recombinant granulocyte-colony stimulating factor (G-CSF) products have emerged as effective adjunct therapies for reducing the incidence and duration of chemotherapy-induced neutropenia and febrile neutropenia by stimulating neutrophil proliferation and differentiation in patients with cancer. Placebo-controlled clinical studies have shown significant reductions in the incidence of febrile neutropenia in patients treated with recombinant G-CSF products,[4-8] and guidelines recommend that they be used alongside chemotherapy when the risk of febrile neutropenia is 20% or higher.[2]

Filgrastim, the first recombinant human G-CSF (r-metHuG-CSF), was introduced to clinical practice in 1991.[9] However, filgrastim and similar G-CSFs require daily subcutaneous (s.c.) injections throughout the chemotherapy cycle. Attachment of a polyethylene glycol molecule (pegylation) to filgrastim to create pegfilgrastim decreases plasma clearance and extends the drug's half-life in the body, allowing for less frequent dosing.[10] Data from randomized controlled studies demonstrate similar efficacy in patients treated with once-per-cycle pegfilgrastim or twice-daily filgrastim,[7,8] and pegfilgrastim is approved as an adjunct therapy in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs.[11]

Balugrastim is a recombinant protein composed of human serum albumin and human G-CSF, which allows for once-per-cycle administration without pegylation. Data from a phase II/III study demonstrated the noninferiority of balugrastim to pegfilgrastim for reducing DSN in patients with breast cancer who received doxorubicin and docetaxel.[12]

The primary objective of this confirmatory phase III study was to evaluate the efficacy and safety of balugrastim compared with pegfilgrastim in patients with breast cancer who received doxorubicin and docetaxel, as evidenced by DSN in the first cycle of chemotherapy.

Patients and Methods

Study Design

This was a phase III double-blind randomized noninferiority study (clinical trials registration number NCT01126190) conducted by 59 investigators in 5 countries—Bulgaria, Romania, Russia, Serbia, and Ukraine.

The study was conducted in 2 phases: (1) a randomized double-blind active-comparator phase, which was powered to evaluate whether a fixed dose of balugrastim was noninferior to pegfilgrastim in terms of safety and efficacy when given to patients with breast cancer alongside doxorubicin and docetaxel and (2) a further open-label single-arm phase in which additional patients received balugrastim. Patients who were enrolled in the open-label phase were included in the safety analysis.

A limited number of blood samples for the analysis of balugrastim or pegfilgrastim were collected in cycles 1 and 4. Samples were obtained before study drug administration and after administration at 24, 72, and 144 hours after the dose was administered. In addition, a drug-drug interaction substudy was conducted in a subset of patients during the randomized phase of the study. A comparison of the pharmacokinetics (PK) of doxorubicin and its main metabolite doxorubicinol was performed between treatment groups: doxorubicin/doxorubicinol with balugrastim vs. doxorubicin/doxorubicinol with pegfilgrastim. An echocardiographic (ECG) substudy was also conducted to define the ECG changes in intervals and morphologic features caused by balugrastim or pegfilgrastim and to define the relationship of the change in the duration of the QT interval corrected using Fridericia's formula with serum concentration of balugrastim or pegfilgrastim over time.

The institutional review boards or ethics committees of the participating centers approved the protocol, and all patients gave written informed consent before any study-related procedures were performed. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and according to current International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice guidelines. The study was sponsored by Teva Pharmaceuticals, Inc.

Study Participants

Patients with histologically or cytologically confirmed breast cancer who were scheduled to receive doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2 were eligible for the study. Patients must have been 18 years of age or older and had adequate hematologic (ANC $\geq 1.5 \times 10^9$/L; platelets $\geq 100 \times 10^9$/L), hepatic, and renal function (serum creatinine level < 2.0 mg/dL; alanine aminotransferase and aspartate aminotransferase levels $< 1.5 \times$ the upper limit of normal; alkaline phosphatase levels $< 2.5 \times$ the upper limit of normal; and total bilirubin levels within normal limits).

Patients were excluded from participating in the study if they had received 1 or more previous chemotherapy regimens (including adjuvant or neoadjuvant therapy, or both, if given ≤ 12 months before the study chemotherapy), had a previous lifetime cumulative anthracycline dose of > 240 mg/m^2 of doxorubicin (or equivalent), or had received previous chemotherapy, immunotherapy, G-CSF, granulocyte macrophage-colony stimulating factor, erythropoietin, or any investigational agent ≤ 30 days before study commencement.

Treatment Procedures

In the randomized double-blind active-comparator phase of this study, patients were randomized in a 1:1 ratio to receive s.c. injections of balugrastim 40 mg or pegfilgrastim 6 mg. Patients were stratified by weight (< 50 kg, ≥ 50 kg, < 80 kg, or ≥ 80 kg), previous chemotherapy exposure, and regional location. Patients enrolled in the open-label single-arm phase of the study received balugrastim.

All patients were treated with doxorubicin 60 mg/m^2 followed by docetaxel 75 mg/m^2 administered by intravenous infusion on day 1 of a 21-day cycle for up to 4 cycles. For each cycle, patients received single injections of study medication approximately 24 hours ($\pm$ 6 hours) after chemotherapy administration. Subsequent cycles of chemotherapy were started only if a patient had an ANC of $\geq 1.5 \times 10^9$/L and a platelet count of $\geq 100 \times 10^9$/L. A delay of up to 14 days for subsequent cycles of chemotherapy was

acceptable to reach these levels before chemotherapy. A 25% reduction in the dose of both chemotherapies was allowed if grade 3/4 nonhematologic toxicity or grade 4 thrombocytopenia occurred in the previous cycle, or if the patient experienced 2 grade 3/4 infectious episodes. Patients who experienced severe hypersensitivity reactions or nonhematologic toxicities that precluded further cycles of chemotherapy were removed from study treatment. Participants were monitored for adverse events (AEs) and concomitant medications throughout the study.

Patient Populations

For the double-blind phase, the intent-to-treat (ITT) population included all randomized participants. For the open-label cohort, the ITT population included all enrolled participants who satisfied eligibility criteria.

Efficacy analyses, including the primary efficacy comparison, were performed on the per-protocol (PP) population of the double-blind cohort. The PP population included all data that were obtained from randomized participants before the occurrence of major protocol violations.

Safety analyses were performed on the safety population, which included all participants who received at least 1 dose of study drug.

End Points

The primary efficacy end point was DSN in cycle 1 of chemotherapy in the PP population. Severe neutropenia was defined as grade 4 neutropenia with an ANC $< 0.5 \times 10^9$/L. The DSN was calculated by cycle as the number of days from the first day in which the ANC fell to less than 0.5×10^9/L after chemotherapy until a patient reached an ANC $\geq 0.5 \times 10^9$/L within this cycle.

Secondary efficacy end points that were derived from ANC profiles included the DSN during cycles 2, 3, and 4; time to ANC recovery; ANC nadir; and time to ANC nadir. Additional efficacy end points included the incidence of febrile neutropenia, severe neutropenia, grade 3/4 neutropenia, and various types of infection.

The safety of balugrastim was assessed by evaluation of the type, frequency, and severity of AEs; changes in clinical laboratory test results (hematology and clinical chemistry); immunogenicity; ECG evaluations; physical examinations; and the monitoring of vital signs over time.

Noncompartmental PK parameters for balugrastim and pegfilgrastim were determined from the concentration-time profiles. Maximum observed serum concentration, time of maximum concentration, and partial area under the serum concentration-time curve from time 0 to144 hours were calculated from the PK population. Terminal elimination half-life was calculated when applicable.

Assessments

Patients were monitored for AEs and concomitant medication use throughout the study. Measurements of vital signs—including heart rate, respiratory rate, systolic and diastolic blood pressure, and body temperature—were collected at screening, before and at the end of docetaxel infusion, before drug administration, and at 30 and 60 minutes after administration. Immunogenicity was assessed before each administration of study drug (day 2 of each cycle), at the end of treatment period visit (~30 days after the last dose of study drug), and during the long-term follow-up at 6 months and 1 year after initiation of study treatment.

Blood samples were collected for ANC determination during each chemotherapy cycle $\leq$ 24 hours before chemotherapy, on day 3, daily from days 5 to 9 or until ANC reached $\geq 2.0 \times 10^9$/L after the nadir, and then twice weekly until the next chemotherapy cycle. Serum samples for PK analyses were obtained before administration of study drugs and 24, 72, and 144 hours after dose administration in cycles 1 and 4. All patients were followed over a 1-year period for disease progression and survival. Follow-up was scheduled 30 days after the last dose of study drug and at 6, 9, and 12 months after the start of treatment.

Statistical Analyses

The sample size for this study was based on a noninferiority design and the mean DSN observed in pivotal efficacy studies for pegfilgrastim combined with data from the phase II/III study.[6,7,12]

The primary analysis assessed noninferiority in the PP population with a procedure that provided an overall 1-sided alpha of 0.025. The primary analysis consisted of hypothesis testing and corresponding confidence interval (CI) estimation of the difference in mean DSN in cycle 1 between the balugrastim treatment group and the pegfilgrastim control group, defined as the mean DSN in the balugrastim group minus the mean DSN in the pegfilgrastim group.

Balugrastim was considered noninferior to pegfilgrastim if in cycle 1, the upper limit of the 2-sided 95% CI for the difference in DSN was $<$ 1 day. If noninferiority to within 1 day was established, the upper limit of the CI was compared with margins of $<$ 1 day to establish the smallest treatment difference that could be excluded at a 1-sided alpha of 0.025. This closed testing procedure controlled overall 1-sided alpha at 0.025.

Secondary end points were assessed by descriptive statistics and exploratory analyses. Mean time to ANC recovery (ANC $\geq 1.5 \times 10^9$/L), mean ANC nadir, and mean time to ANC nadir in all cycles were compared between treatment groups using a t test. If the test was deemed significant, 95% CIs for the mean difference between treatment groups were calculated. Mean DSN was estimated and compared between treatment groups at cycles 2 to 4 by 1-way analysis of variance; 95% CI for the difference in mean DSN between treatment groups was also presented. The Fisher exact test was used for testing the differences in incidence of febrile neutropenia, severe neutropenia (ANC $< 0.5 \times 10^9$/L), and grade 3/4 neutropenia between treatment groups. If the test was deemed significant, 95% CIs for relative risk of febrile neutropenia were calculated.

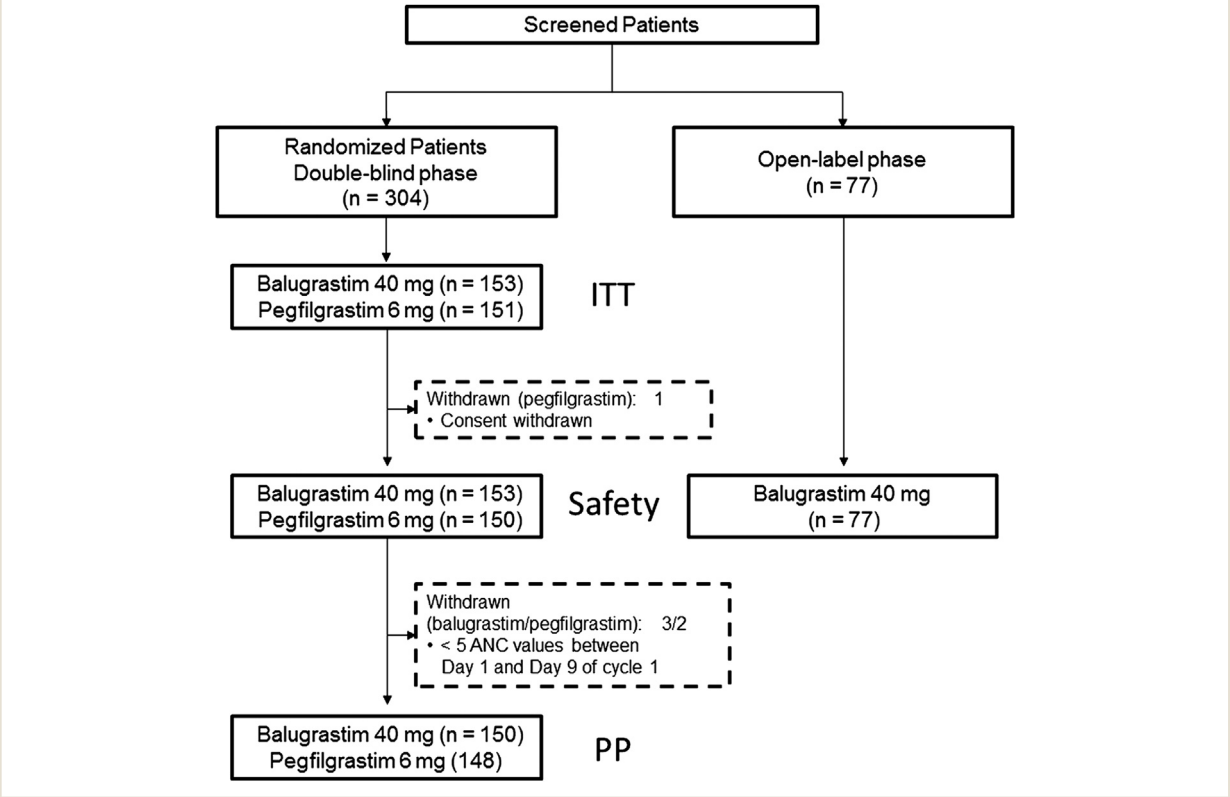
Results

Patients

Between July 2010 and May 2011, 304 patients with breast cancer were enrolled and treated in the double-blind phase of the study, and 77 additional patients were enrolled and treated in the open-label phase.

All patients randomized in the double-blind phase of the study received at least 1 dose of study medication (153 received balugrastim and 151 received pegfilgrastim) and were evaluable for efficacy analysis (ITT population) (Fig. 1). One participant who was randomized to pegfilgrastim received chemotherapy but withdrew

Figure 1 Patient Disposition



Abbreviations: ANC = absolute neutrophil count; ITT = intent to treat; PP = per protocol.

consent before being treated with the study drug. As a result, 150 patients were evaluable for safety analysis (safety population in Fig. 1). Six patients had protocol violations and were excluded from the PP population; therefore, 298 patients (150 receiving balugrastim and 148 receiving pegfilgrastim) were eligible for efficacy analysis of the primary end point. Twenty-one patients (15 [9.8%] treated with balugrastim and 6 [4.0%] treated with pegfilgrastim) did not complete the study. The most frequent reasons for early discontinuation were withdrawal of patient consent (5 receiving balugrastim, 2 receiving pegfilgrastim), treatment failure/disease progression (4 receiving balugrastim), failure to return/lost to follow-up (3 receiving balugrastim, 1 receiving pegfilgrastim), and AEs (2 receiving balugrastim, 1 receiving pegfilgrastim).

Of the 77 patients enrolled in the open-label safety cohort, 11 patients did not complete the study. The most frequent reasons for early discontinuation were withdrawal of consent (6 patients) and AEs (4 patients).

Mean ages of patients in the double-blind phase of the study were 51.5 (standard deviation [SD], 10.28) years and 50.8 (SD, 9.65) years for the balugrastim and pegfilgrastim groups, respectively. The 2 groups were balanced for other demographic factors and disease status at baseline (Table 1). All patients were white women. No clinically relevant differences between the groups were noted for the density and intensity of chemotherapy. The majority of patients in both the double-blind and open-label phases of this study completed all 4 treatment cycles (97.9%, 93.3%, and 88.3% for the balugrastim double-blind, pegfilgrastim, and balugrastim open-label groups, respectively).

Of the 381 patients enrolled in the open-label and double-blind phases of this study, 348 (211 who received balugrastim and 137 who received pegfilgrastim) supplied at least 1 serum sample and were included in PK analyses.

Primary Efficacy End Point

DSN in cycle 1 was comparable between treatment groups, with a mean of 1.0 day in the pegfilgrastim group and 1.1 days in the balugrastim group (95% 2-sided CI, −0.13-0.37 days). Because the upper limit of the CI was 0.37, noninferiority of balugrastim to pegfilgrastim in terms of mean cycle 1 DSN was demonstrated within a margin of 0.37 at a 1-sided alpha of 0.025. Analyses of the ITT and PP populations were consistent and supported the same conclusion—that balugrastim is noninferior to pegfilgrastim for reducing DSN in patients treated with doxorubicin and docetaxel (Table 2).

Secondary Efficacy End Points

In the double-blind phase of this study, the incidence of severe neutropenia in the PP population was 58.0% among balugrastim-treated patients and 58.8% among pegfilgrastim-treated patients during the first cycle of treatment. In cycles 2 to 4, the incidence of

Table 1 Demographic and Baseline Characteristics[a]

Parameter	Pegfilgrastim 6 mg Double Blind	Balugrastim 40 mg		
		Double Blind	Open Label	All
N	151[b]	153[c]	77	230
Age, years (mean ± SD)	50.8 (9.65)	51.5 (10.28)	52.2 (10.22)	51.8 (10.24)
Height, cm (mean ± SD)	162.1 (6.31)	162.3 (6.85)	162.2 (6.75)	162.3 (6.80)
Weight, kg (mean ± SD)	70.3 (14.43)	71.8 (13.17)	73.5 (13.64)	72.4 (13.32)
BSA, m^2 (mean ± SD)	1.8 (0.19)	1.8 (0.17)	1.8 (0.18)	1.8 (0.18)
BMI, kg/m^2 (mean ± SD)	26.8 (5.62)	27.3 (4.97)	28.0 (5.17)	27.5 (5.04)
Time Since Histologic Diagnosis, years (mean ± SD)	0.7 (1.72)	1.1 (3.33)	0.8 (1.68)	1.0 (2.88)
Metastatic Disease, n (%)	35 (23.2)	42 (27.5)	28 (36.4)	70 (30.4)
ECOG Status, n (%)				
0	99 (65.6)	99 (64.7)	51 (66.2)	150 (65.2)
1	52 (34.4)	54 (35.3)	22 (28.6)	76 (33.0)
2	0 (0)	0 (0)	4 (5.2)	4 (1.7)
Location of Metastasis, n (%)				
Liver	10 (6.6)	11 (7.2)	4 (5.2)	15 (6.5)
Lung	10 (6.6)	14 (9.2)	10 (13.0)	24 (10.4)
Bone	12 (7.9)	19 (12.4)	11 (14.3)	30 (13.0)
Brain	0 (0)	1 (0.7)	0 (0.0)	1 (0.4)
Distant lymph nodes	14 (9.3)	10 (6.5)	11 (14.3)	21 (9.1)
Other	12 (7.9)	18 (11.8)	3 (3.9)	21 (9.1)

Abbreviations: ANC = absolute neutrophil count; BMI = body mass index; BSA = body surface area; ECOG = Eastern Cooperative Oncology Group; SD = standard deviation.
[a]Patient demographic data were identical between the intent-to-treat (ITT) and per-protocol (PP) populations.
[b]Three patients were excluded from the PP population: 2 patients had < 5 ANC values between day 1 and day 9 of cycle 1; 1 patient withdrew consent.
[c]Three patients were excluded from the PP population because < 5 ANC values were obtained between day 1 and day 9 of cycle 1.

severe neutropenia was comparable in both treatment groups (≤ 22.6% in the ITT and PP populations), and the mean DSN was ≤ 0.4 days.

In cycle 1, the mean ANC nadir in the PP population was 0.8×10^9/L in both the balugrastim and pegfilgrastim groups. Mean time to nadir and recovery were 6.8 and 2.0 days, respectively, in the balugrastim group and 6.7 and 2.1 days, respectively, in the pegfilgrastim group (Table 3).

In cycles 2 to 4 for both treatment groups in the PP population, the ANC nadir was slightly higher and occurred slightly later than in cycle 1. Time to ANC recovery was also slightly shorter than in cycle 1. In each of the 4 cycles, values for each secondary end point were comparable between treatment groups and consistent between the PP and ITT populations. For the PP and ITT populations, the incidence of grade 3/4 neutropenia during cycle 1 was 75.3% and 75.2%, respectively, among balugrastim-treated patients and 76.4% and 75.3%, respectively, among pegfilgrastim-treated patients. Mean duration of grade 3/4 neutropenia during cycle 1 was 1.6 days in the balugrastim group and 1.7 days in the pegfilgrastim group for both populations. For cycles 2 to 4, the incidence of grade

Table 2 Incidence and Duration of Severe Neutropenia and Incidence of Febrile Neutropenia in Cycle 1 (Double-Blind Phase)

Parameter	Pegfilgrastim 6 mg	Balugrastim 40 mg	*P* Value (95% CI)
PP Population			
N	148	150	–
Incidence of severe neutropenia, n (%)	87 (58.8)	87 (58.0)	.907 (−11.98-10.41)
Mean DSN, d (SD)	1.0 (1.08)	1.1 (1.13)	(−0.13-0.37)
Incidence of febrile neutropenia, n (%)	4 (2.7)	2 (1.3)	.446
ITT Population			
N	150	153	–
Incidence of severe neutropenia, n (%)	87 (58.0)	89 (58.2)	1.000 (−10.94-11.28)
Mean DSN, d (SD)	1.0 (1.08)	1.1 (1.14)	(−0.11-0.38)
Incidence of febrile neutropenia, n (%)	4 (2.6)	2 (1.3)	.446 (0.09-2.65)

Abbreviations: CI = confidence interval; DSN = duration of severe neutropenia; ITT = intent to treat; PP = per protocol; SD = standard deviation.

Table 3 Absolute Neutrophil Count Nadir, Time to Absolute Neutrophil Count Nadir, and Time to Recovery in Cycle 1 (Per-Protocol Population)

Parameter	Double Blind			Balugrastim 40 mg	
	Pegfilgrastim 6 mg	Balugrastim 40 mg	*P* value (95% CI)[b]	Open Label	All
N[a]	148	150	—	77	227
ANC nadir × 10^9/L, mean (SD)	0.8 (1.04)	0.8 (1.17)	.763 (−0.21-0.29)	0.8 (1.01)	0.8 (1.12)
Time to ANC nadir, d, mean (SD)	6.7 (3.33)	6.8 (2.90)	.963 (−0.69-0.73)	6.5 (2.32)	6.7 (2.71)
Time to ANC recovery (≥1.5 × 10^9/L), d, mean (SD)	2.1 (0.96)	2.0 (0.94)	.259 (−0.37-0.10)	1.9 (0.88)	1.9 (0.92)

Abbreviations: ANC = absolute neutrophil count; CI = confidence interval; SD = standard deviation.
[a]Patient numbers for time to ANC recovery are as follows: pegfilgrastim 6 mg double blind, n = 125; balugrastim 40 mg double blind, n = 123; balugrastim 40 mg open label, n = 64; balugrastim 40 mg all, n = 187.
[b]Balugrastim (double-blind) vs. pegfilgrastim.

3/4 neutropenia was comparable in the PP and ITT populations for both treatment groups. The incidence was < 50%, with a mean duration of < 1 day in both treatment groups.

Within the PP population, febrile neutropenia was observed in 2 (1.3%) patients in the balugrastim group and 4 (2.7%) patients in the pegfilgrastim group during cycle 1 of treatment (Table 2) and was not observed in either treatment group during cycles 2 to 4.

Safety

Overall, the type and incidence of treatment-emergent adverse events (TEAEs) was consistent with the underlying medical condition of the study population and administration of myelosuppressive chemotherapy (Table 4).

More than 90% of patients in each treatment group experienced at least 1 TEAE. Most TEAEs (eg, alopecia, nausea, asthenia, diarrhea, and bone pain) were attributable to myelosuppressive chemotherapy or the primary disease and occurred in similar percentages of patients in each group during the study. In the double-blind phase, 19.6% and 18.7% of patients in the balugrastim and pegfilgrastim groups, respectively, had TEAEs related to the study drug (Table 5).The most frequently reported TEAEs considered to be related to the study drug were bone pain and related symptoms (11.8% balugrastim double-blind phase; 10.7% pegfilgrastim; 18.2% balugrastim open-label phase). Bone pain—related symptoms are expected with G-CSF treatment and were well managed using standard analgesics, requiring no additional treatment. None of the bone pain—related TEAEs led to discontinuation of study participation.

The incidence of serious adverse events (SAEs) was similar for the double-blind treatment groups (3.9% balugrastim; 4.7% pegfilgrastim). None of the SAEs were considered to be related to the study drug; however, SAEs were considered to be related to chemotherapy for 4 (2.6%) patients receiving balugrastim and 4 (2.7%) patients receiving pegfilgrastim in the double-blind phase and 4 (5.2%) patients receiving balugrastim in the open-label phase.

The incidence of TEAEs leading to discontinuation was slightly higher in the balugrastim group (2.6%) than in the pegfilgrastim group (0.7%). However, the investigators considered all AEs leading to discontinuation in both phases of the study to be unrelated to the study drug or chemotherapy.

During cycle 1, 5 patients in the balugrastim group and 3 patients in the pegfilgrastim group had infections, most of which were bacterial. During each cycle, the incidence of infections was low and comparable between treatment groups.

Mean leukocyte counts and ANC levels increased substantially from baseline to day 3 or day 4 and then decreased through day 7

Table 4 Treatment-Emergent Adverse Events with Incidence > 10% (Safety Population)

Adverse Event	Pegfilgrastim 6 mg Double Blind n (%)	Balugrastim 40 mg		
		Double Blind n (%)	Open Label n (%)	All N (%)
N	150	153	77	230
Alopecia	114 (76.0)	124 (81.0)	60 (77.9)	184 (80.0)
Nausea	62 (41.3)	56 (36.6)	26 (33.8)	82 (35.7)
Asthenia	33 (22.0)	42 (27.5)	22 (28.6)	64 (27.8)
Neutropenia	40 (26.7)	45 (29.4)	16 (20.8)	61 (26.5)
Leukopenia	22 (14.7)	26 (17.0)	19 (24.7)	45 (19.6)
Decreased Appetite	20 (13.3)	24 (15.7)	10 (13.0)	34 (14.8)
Bone Pain	16 (10.7)	18 (11.8)	14 (18.2)	32 (13.9)
Diarrhea	17 (11.3)	22 (14.4)	8 (10.4)	30 (13.0)
Headache	16 (10.7)	20 (13.1)	7 (9.1)	27 (11.7)
Thrombocytopenia	10 (6.7)	23 (15.0)	2 (2.6)	25 (10.9)

Table 5 Summary of Treatment-Emergent Adverse Events (Safety Population)

Adverse Event	Pegfilgrastim 6 mg Double Blind N (%)	Balugrastim 40 mg		
		Double Blind N (%)	Open Label N (%)	All N (%)
N	150	153	77	230
≥1 TEAE	140 (93.3)	140 (91.5)	72 (93.5)	212 (92.2)
≥1 TEAE Related to Study Drug[a]	28 (18.7)	30 (19.6)	12 (15.6)	42 (18.3)
≥1 TEAE Related to Chemotherapy[b]	138 (92.0)	140 (91.5)	72 (93.5)	212 (92.2)
≥1 Serious TEAE	7 (4.7)	6 (3.9)	6 (7.8)	12 (5.2)
≥1 Grade 3/4 TEAE	54 (36.0)	69 (45.1)	33 (42.9)	102 (44.3)
Discontinued Because of TEAEs	1 (0.7)	4 (2.6)	4 (5.2)	8 (3.5)

Abbreviation: TEAE = treatment-emergent adverse event.
[a]TEAEs the investigator considered as having a reasonable possibility of a causal relationship to study drug.
[b]TEAEs the investigator considered having a reasonable possibility of a causal relationship to chemotherapy.

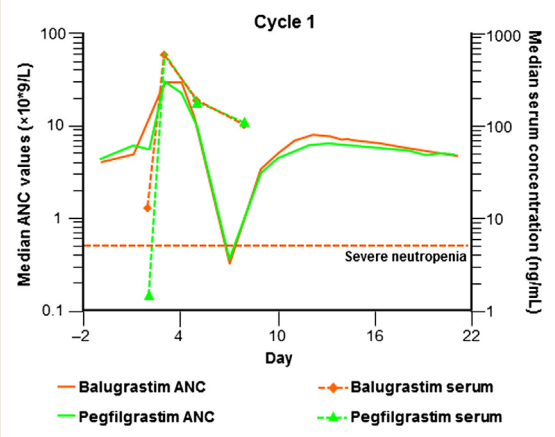
before beginning to return to baseline. This pattern was consistent with a mean time to ANC nadir of 6.7 days in both double-blind treatment groups. Changes from baseline in other leukocyte subpopulations generally were small, and the pattern of changes was similar across treatment cycles. The hematocrit and hemoglobin profiles were similar among treatment groups in all 4 treatment cycles.

No clinically relevant changes in vital signs were observed. Approximately half of all patients in each treatment group had a nonclinically significant abnormality in ECG readings at baseline. Only 1 patient in the balugrastim double-blind group had a clinically significant abnormality. Heart rate and other ECG intervals were similar among treatment groups.

Pharmacokinetics and Pharmacodynamics

Mean balugrastim and pegfilgrastim serum concentrations were, in general, greater in cycle 1 than in cycle 4. For patients who had definable elimination-phase profiles, the mean terminal half-lives were 38.69 hours and 32.64 hours for balugrastim in cycle 1 and cycle 4, respectively, and 41.70 hours and 46.09 hours for pegfilgrastim in cycle 1 and cycle 4, respectively. The mean maximum observed serum concentration for balugrastim 40 mg was 847 ng/mL in cycle 1 and 648 ng/mL in cycle 4. Median T_{max} values for balugrastim were 23.0 hours in cycle 1 and 22.8 hours in cycle 4. Balugrastim mean area under the curve from time 0 to 144 hours (coefficient of variance %) was 59,236 hours × ng/mL (109.1%) for cycle 1 and 31,654 hours × ng/mL (110.0%) for cycle 4. When the effects of balugrastim and pegfilgrastim on ANC were plotted over time, there were no differences in terms of pharmacodynamics (Fig. 2).

Figure 2 Median Absolute Neutrophil Count (ANC) and Concentration-Time Profiles for Balugrastim 40 mg and Pegfilgrastim 6 mg in Cycle 1



Discussion

Randomized trials have demonstrated the benefit of recombinant G-CSF products when used prophylactically for chemotherapy-induced neutropenia, and pegfilgrastim is approved as an adjunct therapy in patients with nonmyeloid malignancies who are receiving myelosuppressive anticancer drugs.[4,5,11] Balugrastim is a long-acting G-CSF being developed for once-per-cycle s.c. administration to provide a safe and effective alternative to pegfilgrastim and filgrastim to decrease the incidence of infection as manifested by febrile neutropenia.

This study demonstrated that a single fixed-dose injection of 40 mg balugrastim was as safe and effective as pegfilgrastim for decreasing DSN in patients with breast cancer who were receiving myelosuppressive chemotherapy, confirming findings from a phase II/III study of balugrastim in patients with breast cancer.[12] In addition, balugrastim demonstrated comparable efficacy to pegfilgrastim based on additional clinical parameters, including ANC nadir, time to ANC nadir, time to ANC recovery, incidence and duration of severe neutropenia, and incidence of febrile neutropenia.

The incidence of all TEAEs, SAEs, and TEAEs considered by the investigators to be related to study drug were comparable for balugrastim and pegfilgrastim, and there were no unexpected safety findings. The results of this study support the conclusion that balugrastim is well tolerated when administered to patients with breast cancer who are receiving myelosuppressive chemotherapy, and the safety profile is similar for balugrastim and pegfilgrastim.

Conclusion

This study demonstrates that balugrastim 40 mg is noninferior to pegfilgrastim 6 mg for reducing DSN in patients with breast cancer who are receiving a first cycle of doxorubicin and docetaxel. Balugrastim is a safe and effective alternative to pegfilgrastim and filgrastim for reducing the incidence of infection as manifested by febrile neutropenia in patients with nonmyeloid malignancies who are receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia.

Clinical Practice Points

- Neutropenia is a significant dose-limiting toxicity of myelosuppressive chemotherapy and is associated with increased risk for opportunistic infection, febrile neutropenia, sepsis, morbidity, and mortality.
- Balugrastim is a once-per-cycle, fixed-dose recombinant fusion protein composed of human serum albumin and G-CSF, which is in development for prevention of severe neutropenia in patients with cancer.
- Placebo-controlled clinical studies have shown significant reductions in the incidence of febrile neutropenia in patients treated with recombinant G-CSF products, and guidelines recommend that they be used alongside chemotherapy when the risk of febrile neutropenia is 20% or higher.
- In this double-blind randomized phase III trial, balugrastim 40 mg demonstrated noninferiority to pegfilgrastim 6 mg for reducing the DSN in patients with breast cancer during the first cycle of myelosuppressive chemotherapy and had a favorable safety and tolerability profile.
- Balugrastim demonstrated efficacy comparable to that of pegfilgrastim based on additional clinical parameters, including ANC nadir, time to ANC nadir, time to ANC recovery, incidence and duration of severe neutropenia, and incidence of febrile neutropenia.
- The incidence of all TEAEs, SAEs, and TEAEs considered to be related to study drug were comparable for balugrastim and pegfilgrastim, and there were no unexpected safety findings.
- Balugrastim is a safe and effective alternative to pegfilgrastim and filgrastim for reducing the incidence of infection as manifested by febrile neutropenia in patients with nonmyeloid malignancies who are receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia.

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Disclosure

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