RESEARCH ARTICLE

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Proposed biosimilar pegfilgrastim (LA-EP2006) compared with reference pegfilgrastim in Asian patients with breast cancer: an exploratory comparison from two Phase III trials

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Aim: This is a pooled subgroup analysis of Asian patients enrolled in two Phase III confirmatory studies comparing proposed biosimilar LA-EP2006 with reference pegfilgrastim in women receiving chemotherapy for breast cancer. **Patients & methods:** Women were randomized to LA-EP2006 (n = 90) or reference (n = 84) pegfilgrastim (Neulasta®, Amgen, Inc., CA, USA) for ≤6 cycles of TAC chemotherapy. Primary end point was duration of severe neutropenia during Cycle 1 (number of consecutive days with absolute neutrophil count $<0.5 \times 10^9/l$) with equivalence confirmed if 95% CIs were within a ±1-day margin. **Results:** Mean duration of severe neutropenia (days) in Cycle 1 was 1.36 ± 0.98 (LA-EP2006) versus 1.35 ± 1.06 (reference) (difference 0.01 days; 95% CI: -0.30–0.32, indicating equivalence). **Conclusion:** LA-EP2006 showed similar clinical efficacy and safety compared with reference pegfilgrastim.

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The recombinant human granulocyte colony-stimulating factor (G-CSF), filgrastim, and its long-acting pegylated form, pegfilgrastim, are widely used for reducing the risk of chemotherapy-induced neutropenia. Biosimilars of filgrastim are available in several regions but to date no pegfilgrastim biosimilar has been approved in highly regulated markets including Europe, Japan and the USA.

Guidelines for biosimilar development stipulate that clinical trials are performed in a sensitive patient population using appropriate end points in order to detect any differences between the proposed biosimilar and reference agent [1]. For pegfilgrastim, patients with breast cancer undergoing myelosuppressive chemotherapy are considered a sensitive population to confirm similarity. In this population, any uncertainties about the similarity of a proposed biosimilar can be further investigated. TAC (docetaxel, doxorubicin and cyclophosphamide) is recommended in international treatment guidelines as a standard (neo)-adjuvant chemotherapy regimen in patients with breast cancer and as such is widely used [2,3]. The TAC regimen is myelotoxic, inducing a median duration of severe neutropenia (DSN) of 7 days in breast cancer patients receiving no G-CSF treatment, which is effectively reduced with G-CSF treatment [4,5]. Assessment of DSN in breast cancer patients treated with TAC chemotherapy represents a sensitive setting in which any difference between the reference and proposed biosimilar is likely to be detected.

KEYWORDS

- biosimilars • breast cancer: Asian patients • granulocyte colony-stimulating factor
- neutropenia
- pegfilgrastim

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The incidence of breast cancer in Asian populations is rapidly increasing, in line with economic growth and urban development in several Asian countries [6]. Although the overall incidence of breast cancer in Asia is still lower than in Western countries, the mortality-to-incidence ratio for breast cancer is higher in Asia compared with the USA, showing that patients in Asia are more likely to die from breast cancer than patients in the USA [7]. This highlights a need for appropriate treatment and supportive care in Asian patients with breast cancer. It is also of note that while G-CSF has been extensively studied in other patient populations, there is a lack of recommendations for the use of G-CSF in Asian patients with breast cancer undergoing TAC chemotherapy, and limited data from randomized controlled trials of G-CSF performed in Asian patients, particularly in the breast cancer population [8,9]. According to recent data, the use of anthracycline- and taxane-based chemotherapy regimens is increasing in the Asian population [10]. For example, a nationwide 10-year study on the use of such chemotherapy reported an increase from 14 to 45% in Chinese patients with breast cancer receiving chemotherapy as adjuvant treatment [10].

Two prospective, double-blind, randomized, Phase III trials (PROTECT-1 and -2) showed similar efficacy and safety of proposed biosimilar pegfilgrastim (LA-EP2006) compared with reference pegfilgrastim (Neulasta®, Amgen, Inc.) in patients with breast cancer receiving myelotoxic chemotherapy [11,12]. Here, we present a pooled subgroup analysis of patients of Asian ethnicity enrolled in these trials to broaden the evidence based on G-CSF in Asian patients with breast cancer undergoing TAC chemotherapy.

Methods

• Study design

Women aged ≥ 18 years with histologically proven breast cancer eligible for neoadjuvant or adjuvant chemotherapy treatment with TAC (docetaxel 75 mg/m², doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m²) were enrolled in two trials of similar design (NCT01735175; NCT01516736). These trials have been published previously and the study design has been described in detail [11,12]. Both studies were conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Guidelines for Good Clinical Practice. Participating sites were regularly visited

by field monitors who reviewed site conduct, electronic data and data management processes. Study protocols were reviewed by independent ethics committees for each participating site. Patients provided written informed consent for study participation.

Data from the two studies were combined for this efficacy and safety subanalysis. The clinical cut-off for the pooled analysis was the end of the follow-up period, which occurred 4 weeks after the last pegfilgrastim administration for PROTECT-2 and 6 months after the last pegfilgrastim administration for PROTECT-1.

• Patients

Key inclusion criteria included Eastern Cooperative Oncology Group performance status ≤ 2 and adequate bone marrow function on Day 1 of Cycle 1 before chemotherapy (defined as absolute neutrophil count [ANC] $\geq 1.5 \times 10^9/l$, platelet count $\geq 100 \times 10^9/l$ and hemoglobin ≥ 10 g/dl). Exclusion criteria included history of hematological malignancies, concurrent or prior radiotherapy within 4 weeks of randomization and prior chemotherapy or anticancer treatment for breast cancer, treatment with prophylactic antibiotics and previous therapy with G-CSF.

Eligible patients were randomized 1:1 to receive either LA-EP2006 or reference pegfilgrastim.

Chemotherapy was administered on Day 1 of each cycle and given every 3 weeks for six cycles. Pegfilgrastim (LA-EP2006 or reference) was administered as a 6 mg subcutaneous injection (0.6 ml in prefilled single-use syringes) on Day 2 of each chemotherapy cycle (≥ 24 h after the end of chemotherapy).

Analysis of race subgroups followed the recommendations given in US FDA's Guidance for Industry Collection of Race and Ethnicity Data in clinical trials (2005). Race (white, Asian and other [black or African American and other (Mestizo, Parda and Hispanic)]) was recorded. This pooled subgroup analysis focused on patients of Asian ethnicity.

• End points

The primary efficacy end point was the mean DSN (number of consecutive days with grade 4 neutropenia [ANC $< 0.5 \times 10^9/l$]) during the first chemotherapy cycle. The analyses presented here should be considered exploratory.

Secondary efficacy parameters were depth of ANC nadir and time to ANC recovery (days

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

Parameter	LA-EP2006 n = 90 [†]	Reference pegfilgrastim n = 84 [†]
Age, years:		
– n [‡]	90	84
– Mean (SD)	47.8 (10.42)	47.4 (9.53)
– Median (range)	47.5 (25–69)	47.0 (27–70)
BMI, kg/m ² :		
– n [‡]	90	84
– Mean (SD)	25.0 (5.47)	24.8 (4.52)
– Median (range)	24.6 (14–42)	24.5 (15–38)
Race, n [‡] (%):		
– Asian	90 (100)	84 (100)
Time since initial diagnosis (months):		
– n [‡]	88	80
– Median (range)	1.36 (0.4–62.6)	1.4 (0.5–11.2)
Stage at initial diagnosis, n [‡] (%):		
– I	1 (1.1)	2 (2.4)
– II	46 (51.1)	36 (42.9)
– III	43 (47.8)	45 (53.6)
– IV	0	1 (1.2)
Chemotherapy, n [‡] (%):		
– Neoadjuvant	14 (15.6)	13 (15.5)
– Adjuvant	76 (84.4)	71 (84.5)
Any breast cancer surgical procedure, n [‡] (%)	89 (98.9)	84 (100.0)
Any prior radiotherapy, n [‡] (%)	1 (1.1)	0
ECOG coding at screening, n [‡] (%):		
– 0	57 (63.3)	51 (60.7)
– 1	31 (34.4)	33 (39.3)
– 2	2 (2.2)	0

ECOG: Eastern Cooperative Oncology Group; SD: Standard deviation.
[†]Number of patients in a treatment group or analysis set.
[‡]Number of evaluable patients.

from ANC nadir until ANC increased to $\geq 2 \times 10^9/l$) during Cycle 1, incidence of febrile neutropenia (FN) (oral temperature of $\geq 38.3^\circ\text{C}$ with ANC $< 0.5 \times 10^9/l$) or neutropenic sepsis (FN/NS) by cycle and across all cycles, number of patients with fever (oral temperature $\geq 38.3^\circ\text{C}$) by cycle and across all cycles, number of patients with infections by cycle and across all cycles and mortality due to infection.

Safety was assessed by the incidence and severity of adverse events (AEs), using Common Terminology Criteria for Adverse Events version 4.0. AEs were recorded at each visit and follow-up visits were scheduled at 4 weeks (PROTECT-1 and -2) and 6 months (PROTECT-1 only) after last study drug administration. Validated assays for detection of anti-rhG-CSF antibodies and neutralizing antibodies were used to assess the immunogenicity of pegfilgrastim before the first pegfilgrastim injection, on Day 15 of

Cycle 6, and 4 weeks (PROTECT-1 and -2) and 6 months (PROTECT-1 only) after the last study drug administration.

• Statistical analysis

DSN during the first chemotherapy cycle was analyzed using analysis of covariance with treatment, chemotherapy as factor/cofactors and baseline ANC counts as covariate to estimate the differences in the adjusted mean DSN with corresponding 95% CI. Equivalence was confirmed if the 95% CIs for the difference in mean DSN between groups were within a predefined margin of ± 1 day. Baseline ANC is defined as the ANC value at Day 1 of Cycle 1.

The full analysis set included all randomized patients who received ≥ 1 dose of pegfilgrastim with patients analyzed according to randomized treatment allocation. The per-protocol set (PPS) included all patients who completed the first

Table 2. Primary efficacy parameter: DSN (duration of severe neutropenia) in Cycle 1 (days) (full analysis set and per protocol set).

Parameter	FAS		PPS	
	LA-EP2006 (n = 90)	Reference (n = 84)	LA-EP2006 (n = 85)	Reference (n = 82)
n	87	84	85	82
Mean ± SD, days	1.36 ± 0.976	1.35 ± 1.058	1.34 ± 0.983	1.34 ± 1.068
Median (range), days	1.00 (0.0–4.0)	1.00 (0.0–4.0)	1.00 (0.0–4.0)	1.00 (0.0–4.0)
Inferential test results of ANCOVA				
Treatment difference:	0.01		0.02	
Reference-LA-EP-2006 (days)	(-0.30, 0.32)		(-0.29, 0.33)	

ANCOVA: Analysis of covariance; FAS: Full analysis set; PPS: Per protocol set; SD: Standard deviation.

cycle without major protocol deviation. The safety analysis set included all patients who received ≥1 dose of pegfilgrastim and had ≥1 postbaseline safety assessment.

Results

A total of 174 Asian patients were randomized (LA-EP2006: n = 90; reference pegfilgrastim: n = 84). All patients were women and baseline demographics were balanced between the treatment groups (Table 1). All patients were based in Asia (India and Malaysia, due to the location of the investigation sites), other than one patient in the LA-EP2006 group and one patient in the reference group, both of whom were based in Europe.

Mean (± standard deviation [SD]) DSN during Cycle 1 was 1.36 ± 0.98 days with LA-EP2006 and 1.35 ± 1.06 days with reference pegfilgrastim (FAS). The difference in DSN between treatment groups was 0.01 days (95% CI: -0.30–0.32), indicating statistical equivalence. Similar results were seen in the PPS population (mean ± SD DSN: LA-EP2006 1.34 ± 0.983 days, reference pegfilgrastim 1.34 ± 1.068 days; treatment difference 0.02 days [95% CI: -0.29–0.33] Table 2).

Secondary efficacy parameters were similar between groups including depth of ANC (×10⁹/l) nadir in Cycle 1, time to ANC recovery in Cycle 1, patients with ≥1 episode of FN/NS, patients with ≥1 episode of fever, patients with ≥1 infection and mortality due to infection (Table 3) for both the FAS and PPS populations. Mean depths of ANC nadir were 0.48 × 10⁹/l (SD: 0.74; median: 0.27; range: 0.0–3.1) and 0.40 × 10⁹/l (SD: 0.44; median: 0.30; range: 0.0–1.91) in patients receiving LA-EP2006 or reference pegfilgrastim, respectively (FAS). Mean number (±SD) of days to ANC recovery was comparable for patients receiving LA-EP2006 (1.76 ± 1.05)

and reference pegfilgrastim (1.72 ± 1.05 [FAS]). The percentage of patients with ≥1 fever episode in Cycle 1 and across all cycles was similar in both groups (Cycle 1: LA-EP2006, 15.6%; reference, 17.9%; all cycles: LA-EP2006, 32.2%; reference, 34.5% [FAS]). At least one FN/NS episode in Cycle 1 was reported in 15 patients (16.7%) in the LA-EP2006 group and 13 patients (15.5%) in the reference pegfilgrastim group (FAS). Across all cycles, FN/NS occurred in 18 patients (20.0%) and 17 patients (20.2%), respectively (FAS). In Cycle 1, four patients (4.4%) in the LA-EP2006 group and eight patients (9.5%) in the reference pegfilgrastim group experienced infections (FAS). Overall incidence of infections was low and similar between groups.

Treatment-emergent adverse events (TEAEs) were similar across groups in the safety analysis set population (Table 4). TEAEs were reported in 96.7% of the LA-EP2006 group and 97.6% of the reference pegfilgrastim group. TEAEs with a suspected relationship to study drug were reported in 27.8% (n = 25) of patients in the LA-EP2006 group and 21.4% (n = 18) of patients in the reference group. The most frequently reported TEAEs with a suspected relationship to study drug were of the system organ class blood and lymphatic system disorders (LA-EP2006: 13.3%; reference: 7.1%) and musculoskeletal and connective tissue disorders (LA-EP2006: 11.1%; reference: 6.0%; Table 5). One patient in the LA-EP2006 group reported bone pain. Serious TEAEs were reported in 31.1% of patients in the LA-EP2006 group and 32.1% of patients in the reference group. Serious TEAEs considered related to study drug were reported in 5.6% of patients in the LA-EP2006 group and 1.2% of patients in the reference group.

A total of six patients died during the studies, four patients receiving LA-EP2006 and two

receiving reference. Of the four patients in the LA-EP2006 group, one patient died due to pulmonary embolism (reported as cardiac arrest) and three patients died due to cardiorespiratory arrest. Of the three patients dying due to cardiorespiratory arrest, one patient experienced FN as a result of chemotherapy, and deteriorated into respiratory distress, which led to cardiorespiratory arrest; another patient had experienced severe vomiting which, together with poor food intake and antidiabetic medication, may have led to hypoglycemia and cardiorespiratory arrest; and the third patient experienced TEAEs including abdominal pain, dyspnea and thrombocytopenia and a sudden decrease in blood pressure before dying of cardiorespiratory arrest.

In the reference group, one patient died due to disease (breast cancer) progression and the other died due to a lower respiratory tract infection. None of the deaths was considered related to biosimilar or reference pegfilgrastim.

Immunogenicity results were similar across the two studies and no postdose treatment-related binding and neutralizing antibodies against pegfilgrastim, filgrastim or PEG were detected in any patient at any time.

Discussion

This pooled analysis of the PROTECT-1 and -2 studies reports that in Asian patients with breast

cancer undergoing myelotoxic chemotherapy, proposed biosimilar pegfilgrastim showed similar efficacy and safety to reference pegfilgrastim for the prevention of severe neutropenia. These data were in line with those observed in the overall study population [11,12].

Although pegfilgrastim has been widely used in patients with breast cancer undergoing myelosuppressive chemotherapy, there is a paucity of data in Asian patients. The need for well-controlled clinical studies is particularly important given the increasing incidence of breast cancer in Asian patients [6] and evidence that Asian patients may be more likely to die from breast cancer than other populations [7,13,14]. Evidence also suggests that patients are not treated according to international guidelines in some Asian populations [15,16], and there is a shortage of recommendations for use of G-CSF in Asian patients. This is important since recent data has shown an increase in use of myelosuppressive chemotherapy in Chinese patients with breast cancer, from 14 to 45% over a 10-year period [10].

Two previous studies have been performed in Asian breast cancer patients receiving TAC chemotherapy who were treated with pegfilgrastim at equivalent doses to our study. Zhang *et al.* performed a dose-finding study in Chinese patients with early breast cancer receiving TAC [9]. Patients receiving a dose of 100 µg/kg/cycle of

Table 3. Secondary efficacy parameters (full analysis set and per protocol set).

Secondary efficacy parameter	FAS		PPS	
	LA-EP2006 (n = 90) [†]	Reference (n = 84) [†]	LA-EP2006 (n = 85) [†]	Reference (n = 82) [†]
Depth of ANC (×10 ⁹ /l) nadir in Cycle 1, mean ± SD	0.482 ± 0.7445	0.399 ± 0.4336	0.407 ± 0.5207	0.403 ± 0.4370
Time to ANC recovery in Cycle 1 (days), mean ± SD (median)	2.00 ± 0.876 (2.0)	2.21 ± 0.919 (2.0)	2.04 ± 0.833 (2.0)	2.20 ± 0.909 (2.0)
Patients with ≥1 episode of FN/NS, n [‡] (%) [§] :				
Cycle 1	15 (16.7)	13 (15.5)	14 (16.5)	13 (15.9)
All cycles	18 (20.0)	17 (20.2)	17 (20.0)	17 (20.7)
Patients with ≥1 episode of fever, n [‡] (%) [§] :				
Cycle 1	14 (15.6)	15 (17.9)	14 (16.5)	15 (18.3)
All cycles	29 (32.2)	29 (34.5)	29 (34.1)	28 (34.1)
Patients with ≥1 infection, n [‡] (%) [§] :				
Cycle 1	4 (4.4)	8 (9.5)	4 (4.7)	8 (9.8)
All cycles	17 (18.9)	16 (19.0)	16 (18.8)	15 (18.3)
Mortality due to infection, n [‡] (%) [§]	0	1 (1.2)	0	1 (1.2)

[†]Number of patients in a treatment group or analysis set.

[‡]Number of patients with at least one episode.

[§]Patients with >1 episode are counted only once. All patients with FN/NS also experienced ≥1 fever episode.

ANC: Absolute neutrophil count; ANC nadir: Lowest ANC (×10⁹/l); FAS: Full analysis set; FN/NS: Febrile neutropenia/neutropenic sepsis; PPS: Per protocol set; SD: Standard deviation; Time to ANC recovery: Time in days from ANC nadir until ANC had increased to ≥2 × 10⁹/l.

Table 4. Adverse events (safety analysis set).

Number (%) of patients with at least one event	LA-EP2006 (n = 90) [†]	Reference pegfilgrastim (n = 84) [†]
TEAE, n (%) [‡]	87 (96.7)	82 (97.6)
Study drug-related TEAE	25 (27.8)	18 (21.4)
Chemotherapy-related AE	85 (94.4)	81 (96.4)
Serious TEAE	28 (31.1)	27 (32.1)
Study drug related serious TEAE	5 (5.6)	1 (1.2)
Chemotherapy-related serious AE	25 (27.8)	26 (31.0)
TEAE leading to study drug discontinuation	4 (4.4)	3 (3.6)
Study drug related TEAE leading to discontinuation	0	0
TEAE leading to death	4 (4.4)	2 (2.4)

[†]Number of patients in a treatment group or analysis set
[‡]Number of patients with at least one episode
AE: Adverse event; TEAE: Treatment-emergent adverse event.

pegfilgrastim had a mean (SD) duration of grade 3+ neutropenia of 1.53 (1.16) days. This is similar to the mean ± SD DSN reported in our study (LA-EP2006: 1.36 ± 0.98; reference: 1.35 ± 1.06 days) at an equivalent dose of pegfilgrastim (6 mg). A dose-finding study performed in Japanese patients with early stage chemotherapy undergoing TAC chemotherapy also reported a similar DSN of 1.4 ± 0.7 days with a dose of 6 mg pegfilgrastim [8].

Safety results were generally similar between the LA-EP2006 and reference groups (Table 5). The difference in serious TEAEs considered related to study drug was generally due to a numerical higher frequency of FN recorded as serious TEAEs in the LA-EP2006 group. Despite this, no TEAEs considered related to study drug led to drug discontinuation in either group. The reasons for these differences between groups are unclear given that this is a subgroup analysis so the relatively small patient numbers makes it difficult to draw conclusions.

Musculoskeletal AEs including bone pain are a well-known adverse event associated with G-CSF treatment. In the current study, musculoskeletal and connective tissue disorders were reported in 11.1% of patients receiving LA-EP2006 and 6% of patients receiving reference pegfilgrastim. In line with the overall findings from the PROTECT studies, these are lower incidences than in other studies of pegfilgrastim in patients receiving myelosuppressive chemotherapy with regimens other than TAC (range: 25–38%) [17]. Musculoskeletal pain was reported in two patients (4.65%) in the Zhang study [9]; and one patient (3.4%) in the Masuda study reported bone pain [8]. Thus, musculoskeletal/bone pain was reported at a similar level in our studies and in these previous studies of Asian patients with breast cancer treated

with TAC chemotherapy. However, there are limitations to comparing results of different studies due to variations in how musculoskeletal/bone pain was reported, how TEAEs were recorded, study design and patient populations. Differences in patient populations are particularly important when considering results between Asian countries where there are different ethnicities, lifestyle factors, healthcare systems and socioeconomic variations [6]. Accordingly, there are significant disparities both between and within Asian countries for breast cancer incidence and mortality [6]. All but two of the patients in our study were based in India and Malaysia and as such represent two different patient populations, which in turn will differ to the Chinese and Japanese patients in the Zhang and Masuda studies. Evidence regarding breast cancer risk, prevalence and mortality from other continents suggests that Asian women in Western countries may be exposed to lifestyle factors that influence breast cancer incidence [18], and have differences in prevalence and mortality compared with other ethnic groups [7,13,14,19,20].

A survey of oncologists across ten Asian countries highlighted variability in practice patterns in G-CSF use across Asia and identified an unmet need in defining prophylaxis and patient selection criteria in the Asian population [21]. The results presented here contribute to the evidence base regarding use of G-CSF prophylaxis in Asian patients undergoing myelosuppressive chemotherapy. Our results were similar to the findings from the overall study population that included patients from 12 countries across North and Latin America, Europe and Asia [11,12]. This highlights that any clinical guidelines developed for Asian patients should be in line with international recommendations.

Future perspective

Cancer presents a considerable burden on health-care systems and a rationale for the development of biosimilars is the potential to increase access to biological treatments with the aim of improving

clinical outcomes. Different Asian countries have different resources, facilities and healthcare systems, which means there is a great variation in how the burden of cancer is managed between countries [22]. The need to develop successful

Table 5. Treatment-emergent adverse events with a suspected relationship to study drug (safety analysis set population).

System organ class and preferred term	LA-EP2006 (n [†] = 90), n [‡] (%)	Reference pegfilgrastim (n [†] = 84), n [‡] (%)
Total number of patients with TEAEs with suspected relationship to study drug	25 (27.8)	18 (21.4)
Blood and lymphatic system disorders:	12 (13.3)	6 (7.1)
– Leukocytosis	6 (6.7)	5 (6.0)
– Neutrophilia	6 (6.7)	5 (6.0)
– Febrile neutropenia	5 (5.6)	0
– Anemia	2 (2.2)	0
– Neutropenia	1 (1.1)	1 (1.2)
– Thrombocytopenia	2 (2.2)	0
– Leukopenia	1 (1.1)	0
Musculoskeletal and connective tissue disorders:	10 (11.1)	5 (6.0)
– Pain in extremity	9 (10.0)	4 (4.8)
– Back pain	2 (2.2)	1 (1.2)
– Bone pain	1 (1.1)	0
General disorders and administration site conditions:	5 (5.6)	7 (8.3)
– Pain	3 (3.3)	3 (3.6)
– Pyrexia	2 (2.2)	1 (1.2)
– Asthenia	0	2 (2.4)
– Injection site pain	0	1 (1.2)
– Peripheral edema	1 (1.1)	0
Gastrointestinal disorders:	3 (3.3)	4 (4.8)
– Nausea	2 (2.2)	2 (2.4)
– Diarrhea	0	3 (3.6)
– Vomiting	1 (1.1)	2 (2.4)
– Constipation	1 (1.1)	0
– Dental discomfort	0	1 (1.2)
– Toothache	0	1 (1.2)
Infections and infestations:	2 (2.2)	2 (2.4)
– Neutropenic sepsis	2 (2.2)	1 (1.2)
– Folliculitis	0	1 (1.2)
Nervous system disorders:	0	2 (2.4)
– Ageusia	0	1 (1.2)
– Headache	0	1 (1.2)
– Paraesthesia	0	1 (1.2)
Respiratory, thoracic and mediastinal disorders:	0	2 (2.4)
– Cough	0	1 (1.2)
– Pneumothorax	0	1 (1.2)
Metabolism and nutrition disorders:	0	1 (1.2)
– Decreased appetite	0	1 (1.2)
Skin and subcutaneous tissue disorders:	1 (1.1)	0
– Rash	1 (1.1)	0

[†]Number of patients in a treatment group or analysis set.

[‡]Number of patients with at least one episode.

TEAE: Treatment-emergent adverse event.

treatment and prevention strategies in countries with limited resources is urgent and biosimilars could help provide a means to release funding for other treatments, as well as increasing access to supportive care. However, it should be considered that some Asian countries have extreme shortages of treatment facilities (e.g., Nepal, with a population of 25 million people has just five specialized cancer hospitals) [22]. Use of biosimilars in such environments can only benefit relatively few patients in the absence of adequate treatment facilities.

Conclusion

In conclusion, in Asian patients with breast cancer receiving cytotoxic chemotherapy, LA-EP2006 showed similar clinical efficacy and safety compared with reference pegfilgrastim. These data were similar to those observed in the overall study population, and with those observed with other studies in Asian populations. Our findings with proposed biosimilar pegfilgrastim are relevant to Asian patients since the majority of Asia's 48 countries are low- and middle-income populations [6], and biosimilars offer the potential to increase access to biological treatments where funding for healthcare may be limited.

Financial & competing interests disclosure

N Harbeck has provided advisory or consulting services to Amgen and Hexal AG. K Blackwell has provided advisory or consulting services to Sandoz GmbH, Kundl, Austria. R Nakov and A Krendyukov are employees of Hexal AG (a Sandoz company), Holzkirchen, Germany, and Y Li is an employee of Sandoz, Inc., Princeton, NJ, USA. This work was supported by Sandoz GmbH, Kundl, Austria and Sandoz Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved. Study numbers (EudraCT register numbers): 2011-004532-58, 2012-002039-28.

SUMMARY POINTS

- There is a need for appropriate treatment and supportive care in Asian patients with breast cancer.
- There are limited data from randomized controlled trials of granulocyte colony-stimulating factor performed in Asian patients with breast cancer.
- In Asian patients with breast cancer receiving myelosuppressive chemotherapy, LA-EP2006 was equivalent to reference pegfilgrastim in terms of duration of severe neutropenia in Cycle 1.
- Similar safety profiles were reported in patients receiving LA-EP2006 and in those receiving reference pegfilgrastim.
- No antipegfilgrastim neutralizing antibodies were detected.
- Data were similar to the overall population of the PROTECT study and in line with those reported in Asian patients with breast cancer receiving an equivalent dose of granulocyte colony-stimulating factor.

References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest

- European Medicines Agency European public assessment reports.
www.ema.europa.eu/ema/index.jsp
- NCCN Clinical Practice Guidelines in Oncology. Breast Cancer version 3.2015.
www.nccn.org/professionals/
- Senkus E, Kyriakides S, Ohno S *et al.* Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 26(Suppl. 5), v8–v30 (2015).
- Nabholtz JM, Mackey JR, Smylie M *et al.* Phase II study of docetaxel, doxorubicin, and cyclophosphamide as first-line chemotherapy for metastatic breast cancer. *J. Clin. Oncol.* 19, 314–321 (2001).
- Kaufman PA, Paroly W, Rinaldi D *et al.* Randomized, double-blind, Phase II study evaluating the safety of same vs next day administration of pegfilgrastim with docetaxel, doxorubicin and cyclophosphamide (TAC) in women with breast cancer. *Breast Cancer Res. Treat.* 88, S59 (2004).
- Fan L, Goss PE, Strasser-Weippl K. Current status and future projections of breast cancer in Asia. *Breast Care (Basel)* 10(6), 372–378 (2015).
- Current review of breast cancer epidemiology and care in Asian countries.
- Bridges JF, Anderson BO, Buzaid AC *et al.* Identifying important breast cancer control

- strategies in Asia, Latin America and the Middle East/North Africa. *BMC Health Serv. Res.* 11, 227 (2011).
- 8 Masuda N, Tokuda Y, Nakamura S, Shimazaki R, Ito Y, Tamura K. Dose response of pegfilgrastim in Japanese breast cancer patients receiving six cycles of docetaxel, doxorubicin, and cyclophosphamide therapy: a randomized controlled trial. *Support. Care Cancer* 23(10), 2891–2898 (2015).
 - **Study performed in Asian breast cancer patients receiving TAC chemotherapy who were treated with pegfilgrastim at an equivalent dose to the current study.**
 - 9 Zhang W, Jiang Z, Wang L, Li C, Xia J. An open-label, randomized, multicenter dose-finding study of once-per-cycle pegfilgrastim versus daily filgrastim in Chinese breast cancer patients receiving TAC chemotherapy. *Med. Oncol.* 32(5), 147 (2015).
 - **Study performed in Asian breast cancer patients receiving TAC chemotherapy who were treated with pegfilgrastim at an equivalent dose to the current study.**
 - 10 Li Q, Zhang P, Yang Z *et al.* A nation-wide multicenter 10-year (1999–2008) retrospective study of chemotherapy in Chinese breast cancer patients. Presented at: *ESMO Asia 2016 Conference*, Singapore, Republic of Singapore, 16–19 December 2016.
 - **Recent data showing an increase in use of myelosuppressive chemotherapy in Chinese patients with breast cancer.**
 - 11 Blackwell K, Donskih R, Jones CM *et al.* 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. *Oncologist* 21(7), 789–794 (2016).
 - **Results from PROTECT-2, one of the two pivotal registration trials with similar protocols performed for biosimilar pegfilgrastim LA-EP2006.**
 - 12 Harbeck N, Lipatov O, Frolova M *et al.* Randomized, double-blind study comparing proposed biosimilar LA-EP2006 with reference pegfilgrastim in breast cancer. *Future Oncol.* 12(11), 1359–1367 (2016).
 - **Results from PROTECT-1, one of the two pivotal registration trials with similar protocols performed for biosimilar pegfilgrastim LA-EP2006.**
 - 13 Maringe C, Li R, Mangtani P, Coleman MP, Rachet B. Cancer survival differences between South Asians and non-South Asians of England in 1986–2004, accounting for age at diagnosis and deprivation. *Br. J. Cancer* 113(1), 173–181 (2015).
 - 14 Berger S, Huang CC, Rubin CL. The role of community education in increasing knowledge of breast health and cancer: findings from the Asian Breast Cancer Project in Boston, Massachusetts. *J. Cancer Educ.* 32(1), 16–23 (2015).
 - 15 Yuan XM, Wang N, Ouyang T *et al.* Current status of diagnosis and treatment of primary breast cancer in Beijing, 2008. *Chin. J. Cancer Res.* 23, 38–42 (2011).
 - 16 Wang SL, Li YX, Zhang BN *et al.* Epidemiologic study of radiotherapy use in China in patients with breast cancer between 1999 and 2008. *Clin. Breast Cancer* 13, 47–52 (2013).
 - 17 Lambertini M, del Mastro L, Bellodi A *et al.* The five “Ws” for bone pain due to the administration of granulocyte-colony stimulating factors (G-CSFs). *Crit. Rev. Oncol. Hematol.* 89, 112–128 (2014).
 - 18 Ziegler RG, Hoover RN, Pike MC *et al.* Migration patterns and breast cancer risk in Asian-American women. *J. Natl Cancer Inst.* 85(22), 1819–1827 (1993).
 - 19 Licqurish S, Phillipson L, Chiang P, Walker J, Walter F, Emery J. Cancer beliefs in ethnic minority populations: a review and meta-synthesis of qualitative studies. *Eur. J. Cancer Care (Engl.)* (2016). <http://onlinelibrary.wiley.com/doi/10.1111/>
 - 20 Shirley MH, Barnes I, Sayeed S, Finlayson A, Ali R. Incidence of breast and gynaecological cancers by ethnic group in England, 2001–2007: a descriptive study. *BMC Cancer* 14, 979 (2014).
 - 21 Mishra D *et al.* 383P. Survey for patterns of G-CSF use among cancer patients receiving chemotherapy in Asia. *Ann. Oncol.* 26(Suppl. 9), ix115–ix116 (2015).
 - 22 Yoo KY. Cancer prevention in the Asia Pacific region. *Asian Pac. J. Cancer Prev.* 11(4), 839–844 (2010).