RESEARCH ARTICLE

Randomized, double-blind study comparing proposed biosimilar LA-EP2006 with reference pegfilgrastim in breast cancer

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Aim: This randomized, double-blind trial compared proposed biosimilar LA-EP2006 with reference pegfilgrastim in women receiving chemotherapy for breast cancer (PROTECT-1). **Patients & methods:** Women (≥18 years) were randomized to receive LA-EP2006 (n = 159) or reference (n = 157) pegfilgrastim (Neulasta®, Amgen) for ≤6 cycles of (neo)-adjuvant TAC chemotherapy. Primary end point was duration of severe neutropenia (DSN) during cycle 1 (number of consecutive days with absolute neutrophil count $<0.5 \times 10^9$/l) with equivalence confirmed if 90% and 95% CIs were within a ±1 day margin. **Results:** For DSN, LA-EP2006 was equivalent to reference (difference: 0.07 days; 90% CI: -0.09–0.23; 95% CI: -0.12–0.26). **Conclusion:** LA-EP2006 and reference pegfilgrastim showed no clinically meaningful differences regarding efficacy and safety in breast cancer patients receiving chemotherapy.

Cancer represents a substantial burden on healthcare systems, with escalating drug costs a major contributory factor [1]. Biosimilars are approved biologics in highly regulated markets that have been proven to be highly similar to a reference product with no meaningful differences in clinical performance. Biosimilars offer the potential to allow increased access to biological treatments [2].

The development of biosimilars follows a step-wise approach including analytical comparison to the reference and iterative process development to achieve a product which is essentially the same as the reference product [3]. The clinical trials in support of this step-wise 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 [4]. The clinical trial reported below 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 long-acting pegylated form, pegfilgrastim, are widely used for the prevention of chemotherapy-induced neutropenia. Biosimilars of filgrastim, based on the reference product Neupogen®, have been licensed in Europe for over 6 years and, in 2015, filgrastim (Zarxio®) became the first biosimilar product approved by the US FDA in the USA [5].

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G-CSF guidelines recommend primary G-CSF prophylaxis for patients at greater than 20% risk for FN, including patients receiving TAC chemotherapy [6,7]. Several studies have suggested that the use of daily filgrastim may be suboptimal, with treatment started later and/or dosed for a shorter duration than recommended [6]. Compared with filgrastim, the pegylation of filgrastim results in reduced renal clearance and greater stability [8]. Pegfilgrastim has comparable efficacy and safety to filgrastim, but its longer serum half-life allows once-per-cycle instead of daily administration [9,10]. The greater convenience of once-per-cycle administration may result in better compliance and improved outcomes with pegfilgrastim compared with filgrastim, including reduced incidence of febrile neutropenia (FN) and a lower risk of hospitalization [11,12]. However, a trend for superiority of pegfilgrastim compared with filgrastim was reported in some analyses [13].

This global, prospective randomized, double-blind, multicenter confirmatory efficacy and safety study, PROTECT-1, was a head-to-head comparison of a proposed biosimilar pegfilgrastim (LA-EP2006) with reference pegfilgrastim (Neulasta®). The study was designed to show equivalence of LA-EP2006 to the reference pegfilgrastim in the reduction of duration of severe neutropenia (DSN) in breast cancer patients receiving myelosuppressive chemotherapy.

Patients & methods

PROTECT-1 enrolled patients with breast cancer receiving (neo)-adjuvant myelosuppressive chemotherapy (EudraCT number 2011-004532-58). The study was conducted in accordance with ICH Guidelines for Good Clinical Practice, the Declaration of Helsinki, and local regulations. The study protocol was approved by Independent Ethics Committees for each center. All patients provided written informed consent.

Adult women (aged ≥18 years) with histologically proven breast cancer who were eligible for either adjuvant or neoadjuvant chemotherapy with docetaxel 75 mg/m², doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m² (TAC regimen) were enrolled. 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] ≥1.5 × 10⁹/l, platelet count ≥100 × 10⁹/l, hemoglobin ≥10 g/dl); normal total bilirubin; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) level ≤2 × upper limit of normal (ULN); liver-derived alkaline phosphatase level ≤3 × ULN; creatinine ≤1.5 × ULN and for women of child-bearing potential, a negative pregnancy test within 7 days before randomization and use of an effective method of birth control. Patients were excluded for reasons including: history of chronic myeloid leukemia or myelodysplastic syndrome; history of sickle cell disease; previous or concurrent malignancies; any significant relevant medical condition and concurrent or prior anti-breast cancer treatment.

Design

After a screening period of up to 21 days, eligible patients were randomized 1:1 to either proposed biosimilar pegfilgrastim (LA-EP2006, Sandoz GmbH, Kundl, Austria) or Neulasta (Amgen BV, The Netherlands). Randomization was stratified by chemotherapy (adjuvant or neoadjuvant) and region (Europe, Asia or America). TAC chemotherapy was administered intravenously on day 1 of each chemotherapy cycle and given every 3 weeks for up to six cycles. Chemotherapy doses could be reduced by 25% in response to grade 3–4 nonhematological toxicity, grade 4 thrombocytopenia or FN. 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). Patients were followed for a 6-month safety period from the last administration of pegfilgrastim.

• End points

The primary efficacy end point was the mean DSN during cycle 1 of chemotherapy, defined as the number of consecutive days with an ANC <0.5 × 10⁹/l (grade 4 neutropenia). Secondary efficacy parameters were depth of ANC nadir (lowest ANC) and time to ANC recovery (days from ANC nadir until ANC increased to ≥2 × 10⁹/l) during cycle 1, incidence of FN (oral temperature of ≥38.3°C with ANC <0.5 × 10⁹/l) or neutropenic sepsis (FN/NS) by cycle and across all cycles, number of patients with fever (oral temperature ≥38.3°C) for each cycle, number of patients with infections by cycle and across all cycles, and mortality due to infection.

Safety was assessed through the incidence, occurrence and severity of treatment-emergent adverse events (TEAEs), using Common Terminology Criteria for Adverse Events

(CTCAE) version 4.0. According to the study protocol, every FN episode was reported as a serious adverse event (AE). Safety assessments were performed at each visit with safety follow-up visits at 4 weeks and 6 months after the last administration of pegfilgrastim. Immunogenicity of pegfilgrastim was assessed by a validated ELISA for screening and confirmation of binding anti-pegfilgrastim antibodies, and a validated cell-based assay for the detection of neutralizing antibodies (NABs). Immunogenicity was assessed before the first administration of pegfilgrastim (LA-EP2006 or reference), on day 15 of cycle 6, and 4 weeks and 6 months after last administration.

• Statistical analysis

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 standard deviation (SD) of 1.6 days. The primary efficacy end point was analyzed using analysis of covariance (ANCOVA), adjusted for treatment group, region, chemotherapy and baseline ANC count. Equivalence for the difference in the mean DSN was assessed with both two-sided 90% CIs (required by the FDA) and 95% CIs (required by the EMA), with LA-EP2006 considered equivalent to reference pegfilgrastim if CIs were entirely within ±1 day. All secondary efficacy end points and safety parameters were descriptively analyzed. All statistical analyses were performed using SAS (SAS Institute, NC, USA).

The full analysis set (FAS) included all randomized patients who received ≥1 dose of pegfilgrastim with patients analyzed according to randomized treatment allocation. The per-protocol (PP) set included all patients who completed the first cycle without major protocol deviation in cycle 1. The safety analysis (SAF) set included all patients who received ≥1 dose of pegfilgrastim and had ≥1 post-baseline safety assessment.

Results

The study was conducted between June 2012 and February 2014 at 42 study sites. A total of 373 patients were screened, of whom 316 patients were randomized to treatment and included in the FAS set (LA-EP2006, n = 159; reference, n = 157). The PP set included 295 patients (LA-EP2006, n = 146; reference, n = 149). A total of 19 patients discontinued treatment in the LA-EP2006 group compared with seven patients in the reference group. The main reason for this was 'withdrawn consent' (eight vs two patients). Disposition of patients is shown in **Figure 1**. Baseline characteristics of patients were balanced across treatment groups **(Table 1)**.

• Primary efficacy end point

The primary efficacy variable mean (±SD) DSN during cycle 1 was 0.75 ± 0.88 days (median, range: 1, 0–3) with LA-EP2006 and 0.83 ± 0.90 days (median, range: 1, 0–4) with reference pegfilgrastim (FAS). The difference between LA-EP2006 and reference pegfilgrastim was 0.07 days (90% CI: -0.09–0.23; 95% CI: -0.12–0.26). Both the 90% and 95% CIs were within the predefined margin of ±1 day confirming equivalence. Similar results were seen in the PP population (mean DSN: LA-EP2006 0.75 ± 0.88 days, reference 0.79 ± 0.87 days; treatment difference 0.04 days [90% CI: -0.12–0.20; 95% CI: -0.15–0.24]) **(Table 2)**.

• Secondary efficacy end points

No clinically meaningful differences between treatment arms were observed. Mean (±SD) depth of ANC nadir in cycle 1 was $1.10 \pm 1.54 \times 10^9$/l (median, range: 0.56, 0.0–8.6) in the LA-EP2006 group and $0.92 \pm 1.18 \times 10^9$/l (median, range: 0.46, 0.0–6.9) in the reference group, with most cases recorded on day 7. Mean number (±SD) of days to ANC recovery was also similar for patients in the LA-EP2006 and reference groups (1.58 ± 1.05 vs 1.72 ± 1.10; median of 2 days in both groups [LA-EP2006 range: 0.0–4.0; reference range: 0.0–5.0]). Time course of mean ANC was almost superimposable for both groups **(Figure 2)**.

In cycle 1 and across all cycles, fewer patients treated with LA-EP2006 compared with reference pegfilgrastim experienced at least one event of FN/NS (cycle 1: n = 6 [3.8%] vs 11 [7.0%]; all cycles, n = 9 [5.7%] vs 12 [7.6%]). The incidence of fever (cycle 1: n = 9 [5.7%] vs 14 [8.9%]; all cycles, n = 26 [16.4%] vs 26 [16.6%]) and frequency of infections (cycle 1: n = 7 [4.4%] vs 4 [2.5%]; all cycles, n = 22 [13.8%] vs 24 [15.3%]) were similar in both the LA-EP2006 and reference groups. Two patients, both treated with reference pegfilgrastim, died due to infections **(Table 3)**.

• Chemotherapy relative dose intensity

Relative mean (±SD) dose intensity of the chemotherapy was similar between groups across cycles: docetaxel: LA-EP2006, 0.99 ± 0.025, reference: 0.98 ± 0.048; doxorubicin: LA-EP2006,
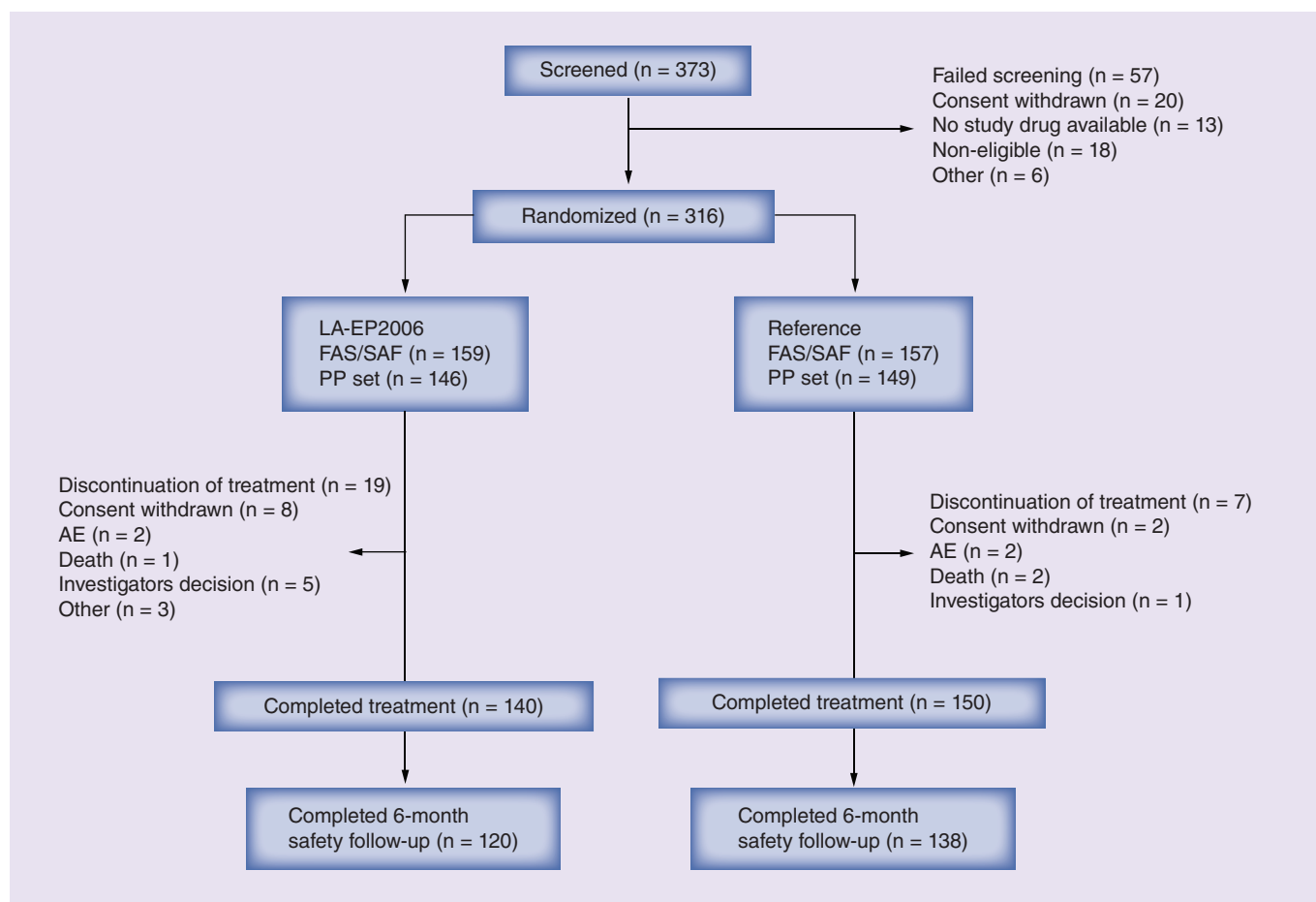
Figure 1. Patient disposition.
AE: Adverse event; FAS: Full analysis set; PP: Per-protocol; SAF: Safety analysis.

0.99 ± 0.022, reference: 0.99 ± 0.040; cyclophosphamide: LA-EP2006, 0.99 ± 0.022, reference: 0.99 ± 0.039.

• **Safety**

A total of 88.1 and 82.8% of patients receiving LA-EP2006 or reference pegfilgrastim experienced ≥1 TEAE during the treatment period (i.e., date of onset of or after the first administration of chemotherapy and not later than 30 days after last pegfilgrastim administration) **(Supplementary Figure 1)**. Type and frequency of TEAEs were similar with LA-EP2006 and reference pegfilgrastim, with the most frequent being alopecia (51.6 vs 50.3%), nausea (40.9 vs 37.6%), asthenia (39.6 vs 35.7%), vomiting (21.4 vs 21.7%) and neutropenia (17.0 vs 21.7%). TEAEs in the system organ class musculoskeletal and connective tissue disorders (including bone pain, arthralgia, myalgia, pain in extremity, back pain and neck pain) were reported in 15.1% of

patients in the LA-EP2006 group and 22.9% of patients in the reference group, all of which were grade 1 or 2 in severity. A total of 42 patients (LA-EP2006 11.9%, n = 19; reference 14.6%, n = 23) had TEAEs with suspected relationship to pegfilgrastim. Serious TEAEs reported in ≥2% of patients in either treatment group were FN (LA-EP2006: 5.7%, reference: 7.6%) and neutropenia (1.9 vs 3.8%). Six patients reported TEAEs in the 6-month safety follow-up period (LA-EP2006: 2.5%, reference: 1.3%), none of which were serious.

FN was reported as a serious TEAE with suspected relationship to pegfilgrastim in three patients in the LA-EP2006 group; two of these patients also had neutropenic sepsis. No patient in the reference group had any serious pegfilgrastim-related TEAE. The incidence of serious neutropenic events are reported in **Table 4**.

Six deaths occurred during the study, none of which were suspected to be related to pegfilgrastim.

Table 1. Patient demographics and baseline characteristics.		
Characteristic	LA-EP2006 (N = 159)	Reference (N = 157)
Age, years (mean ± SD)	49.9 ± 9.5	50.5 ± 10.9
Race (n):		
– White	129	127
– Asian	28	26
– Other	2	4
BMI (mean ± SD), kg/m^2	27.5 ± 26.8	27.4 ± 26.4
Time since diagnosis, months; median (range)	1.35 (0.1–76.0)	1.38 (0.2–10.9)
Disease stage, n (%):		
– I	4 (2.5)	3 (1.9)
– II	74 (46.5)	73 (46.5)
– III	81 (50.9)	78 (49.7)
– IV	0	3 (1.9)
Previous breast cancer surgery, n (%)	149 (93.7)	146 (93.0)
Previous radiotherapy, n (%)	7 (4.4)	9 (5.7)
ECOG performance status 0/1, n (%)	128 (80.5)/31 (19.5)	123 (78.3)/34 (21.7)
'Other' race patients (n = 6) were of Mestizo or Parda origin. Time of initial diagnosis missing for six patients in LA-EP2006 group and ten patients in reference group. ECOG: Eastern Cooperative Oncology Group; N: Number of patients in a treatment group or analysis set; n: Number of evaluable patients; SD: Standard deviation.		

Four deaths occurred in the LA-EP2006 group and two in the reference group.

No neutralizing antibodies were detected in any patient at any time point during the study. Binding antibodies against pegfilgrastim and polyethylene glycol (PEG) were detected in 20 patients (LA-EP2006, n = 7; reference, n = 13) before treatment (on day 1 of cycle 1) but only one patient (LA-EP2006 arm) was positive for anti-pegfilgrastim/PEG antibodies at the end of treatment and another patient (LA-EP2006 arm, tested positive at day 1, cycle 1) was positive at the end of 6-month follow-up.

Discussion

In this global, prospective, randomized study, LA-EP2006 was shown to be equivalent to reference pegfilgrastim (Neulasta®), with a difference in DSN between treatments of 0.07 days (90% CI: -0.09–0.23; 95% CI: -0.12–0.26). The DSN observed in both groups (0.75 days with LA-EP2006 and 0.83 days with reference) was lower than observed in earlier studies of reference pegfilgrastim (mean DSN of 1.3–1.8 days) [9–10,14] but is consistent with more recent studies which reported mean DSNs of 0.8–0.9 days with pegfilgrastim [15,16]. This was one of two similar studies comparing LA-EP2006 with reference pegfilgrastim in patients with breast cancer (PROTECT-1 and -2). Equivalence to the reference product was also shown in the PROTECT-2 study [17].

There were also no clinically meaningful differences between LA-EP2006 and reference pegfilgrastim in any of the secondary end points. Incidence of FN was consistent with previous

Table 2. Primary efficacy parameter: duration of severe neutropenia in cycle 1 (days; full analysis set and per-protocol).				
DSN	FAS		PP	
	LA-EP2006 (N = 159)	Reference (N = 157)	LA-EP2006 (N = 146)	Reference (N = 149)
n	155†	155†	146	149
Mean ± SD, days	0.75 ± 0.878	0.83 ± 0.898	0.75 ± 0.875	0.79 ± 0.872
Median (range); days	1 (0–3)	1 (0–4)	1 (0–3)	1 (0–3)
Inferential test results of ANCOVA				
Treatment difference: reference LA-EP2006 (days)	0.07 90% CI: -0.09–0.23 95% CI: -0.12–0.26		0.04 90% CI: -0.12–0.20 95% CI: -0.15–0.24	
†Four patients in the LA-EP2006 group and two patients in the reference group had missing ANC data and were excluded (blinded data review meeting). ANCOVA: Analysis of covariance; DSN: Duration of severe neutropenia; FAS: Full analysis set; N: Number of patients in a treatment group or analysis set; n: Number of evaluable patients; PP: Per-protocol set; SD: Standard deviation.				
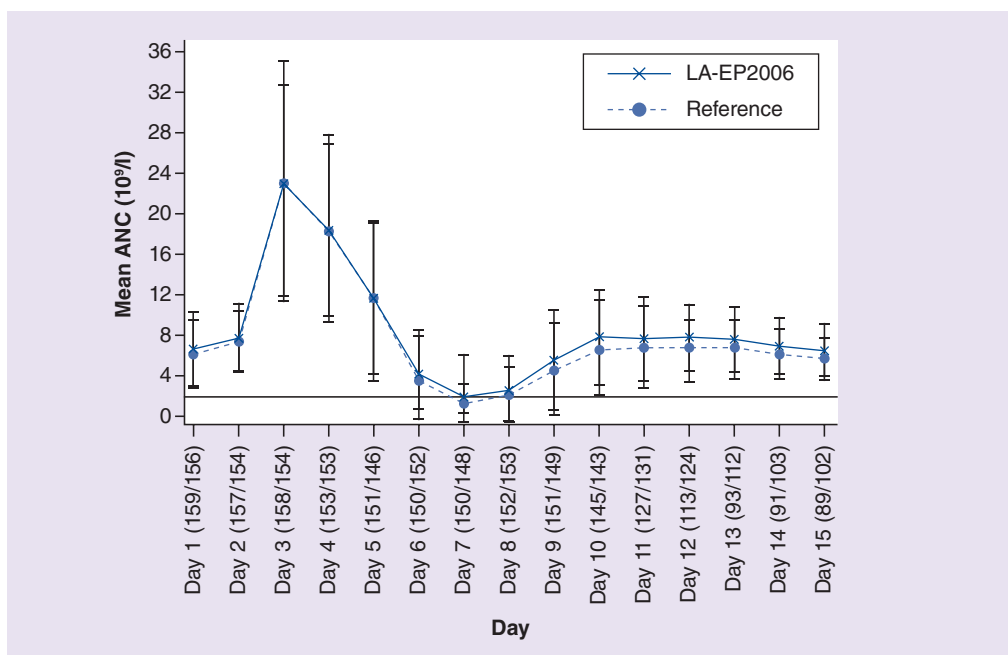
Figure 2. Absolute neutrophil count time course during cycle 1 (mean ± standard devation; full analysis set).
The horizontal line indicates the threshold of $2 \times 10^9/l$ defined for ANC recovery.
ANC: Absolute neutrophil count.

studies of reference pegfilgrastim [9–10,14]. The numbers of patients with episodes of fever or with infections were similar in both groups.

Both treatments were well tolerated with a safety profile as expected for patients with breast cancer receiving TAC chemotherapy [9–10,14]. Pegfilgrastim-related TEAEs were similar in both groups and consistent with the known safety profile of pegfilgrastim. The incidence of TEAEs in the system organ class 'musculoskeletal and connective tissue disorders' (15.1% in patients receiving LA-EP2006 and 22.9% in patients receiving reference) in this study was slightly lower than in previously randomized double-blind studies with pegfilgrastim which have reported bone pain in the range 25–37% with pegfilgrastim [9–10,18].

Although fewer patients experienced FN in the LA-EP2006 group (nine vs 12 patients in the reference group across all cycles), more episodes in the LA-EP2006 group were considered to be pegfilgrastim-related (three patients, two of whom also had neutropenic sepsis versus no patients in the reference group).

None of the six deaths occurring during the study were suspected to be related to pegfilgrastim. In the LA-EP2006 arm, one patient experienced FN as a result of chemotherapy, and deteriorated into respiratory distress leading to cardiorespiratory arrest. Another patient in the LA-EP2006 arm died due to cardiorespiratory arrest. This patient had experienced severe vomiting which, together with poor food intake (over several days) and antidiabetic treatment, may have caused hypoglycemia and cardiorespiratory arrest. The third patient in the LA-EP2006 arm died due to cardiac arrest. A further patient in the LA-EP2006 arm died due to disease progression during the 6-month safety follow-up. Two patients in the reference pegfilgrastim group died, both due to infectious disease.

Immunogenicity can be a concern for any biological product and may occur in response to even seemingly small product-related differences, for example, structural alterations or impurities [19]. No neutralizing anti-pegfilgrastim antibodies were detected in the study, including at the end of the 6-month safety follow-up, indicating that LA-EP2006 had no increased immunogenic potential compared with reference pegfilgrastim. This would be expected given the low immunogenic potential of pegfilgrastim and the immunocompromised status of patients receiving myelosuppressive chemotherapy. Binding antibodies against PEG were detected in 20 patients before treatment. The common use of PEGylated

Table 3. Secondary efficacy parameters (full analysis set).

Secondary efficacy parameter	LA-EP2006 (N = 159)	Reference (N = 157)
Depth of ANC nadir (×10^9/l) in cycle 1, mean ± SD	1.102 ± 1.5398	0.921 ± 1.1771
Time to ANC recovery in cycle 1, mean ± SD (median)	1.58 ± 1.053 (2.0)	1.72 ± 1.100 (2.0)
Patients with ≥1 episode of FN/NS, n (%)[†]:		
– Cycle 1	6 (3.8)	11 (7.0)
– All cycles	9 (5.7)	12 (7.6)
Patients with ≥1 episode of fever, n (%)[†]:		
– Cycle 1	9 (5.7)	14 (8.9)
– All cycles	26 (16.4)	26 (16.6)
Patients with ≥1 infection, n (%)[†]:		
– Cycle 1	7 (4.4)	4 (2.5)
– All cycles	22 (13.8)	24 (15.3)
Mortality due to infection, n (%)	0	2 (1.3)

All patients with FN/NS also experienced ≥1 fever episode.
[†]Patients with >1 episode are counted only once.
ANC: Absolute neutrophil count; ANC nadir: Lowest ANC (10^9/l) in cycle 1; FAS: Full analysis set; FN/NS: Febrile neutropenia/neutropenic sepsis; N: Number of patients in a treatment group or analysis set; n: Number of patients with at least one episode; SD: Standard deviation; Time to ANC recovery: Time in days from ANC nadir until ANC had increased to ≥2 × 10^9/l.

products in cosmetics may have resulted in pre-existing anti-PEG antibodies and could explain the higher incidence of positive anti-pegfilgrastim antibodies on day 1 of cycle 1. As with other biological drugs, ongoing post-authorization surveillance after marketing authorization of biosimilar products is required to confirm the lack of an immunogenic response.

Future perspective

Cancer represents a substantial burden on healthcare systems. Development of oncology biosimilars such as biosimilar pegfilgrastim could benefit patients by increasing access to biologic agents which has the potential to improve clinical outcomes. An example of this was shown at two hospitals, one in Germany and another in the UK, where the decision to switch from using reference filgrastim to Zarzio® contributed to a shift in treatment practice from secondary prophylaxis to increased primary prophylaxis [20]. This experience suggests that availability of LA-EP2006 may allow preventative treatment of patients, rather than just after they have experienced neutropenic complications. MONITOR-GCSF was an international, multicenter observational study of cancer patients treated with myelosuppressive chemotherapy and receiving prophylaxis with biosimilar filgrastim (Zarzio) [21]. The study showed that in real-world use, clinical and safety outcomes of prophylaxis with biosimilar filgrastim are similar to historical data for reference filgrastim and highlighted the need to improve primary prophylaxis in patients with cancer who are at risk of FN. Biosimilars such as LA-EP2006 may become widely accepted and used, facilitating access to such supportive care treatment for patients.

Table 4. Incidence of serious neutropenic events by category and preferred term (safety analysis set).

Severe neutropenic event	LA-EP2006 (N = 159), n (%)	Reference (N = 157), n (%)
Patients with ≥1 serious neutropenic event		
Febrile neutropenia	9 (5.7)	12 (7.6)
Neutropenia	3 (1.9)	6 (3.8)
Neutropenic sepsis	2 (1.3)	0
Leukopenia	0	1 (0.6)
Patients with ≥1 serious neutropenic event with suspected relationship to pegfilgrastim		
Febrile neutropenia	3 (1.9)	0
Neutropenic sepsis	2 (1.3)	0

A patient may have been counted in more than one preferred term. Serious treatment-emergent adverse events are presented by system organ class and preferred term in descending order of total frequency.
N: Number of patients in a treatment group or analysis; n: Number of patients with at least one event; SAF: Safety analysis.

Conclusion

LA-EP2006 was equivalent to reference pegfilgrastim in efficacy and safety in the prevention of neutropenia in patients with breast cancer receiving TAC chemotherapy.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: http://www.futuremedicine.com/doi/full/10.2217/fon-2016-0016.

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For a full list of the PROTECT-1 trial investigators, please see the **Supplementary Information**.

Disclosure

The study number (EudraCT no.) is 2011-004532-58.

Financial & competing interests disclosure

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.

Open access

EXECUTIVE SUMMARY

Background

- Pegfilgrastim is widely used for the prevention of chemotherapy-induced neutropenia.
- Biosimilars offer the potential to increase access to biological treatments.

Results

- In women with breast cancer receiving TAC chemotherapy, LA-EP2006 was equivalent to reference pegfilgrastim in terms of duration of severe neutropenia in cycle 1.
- Treatment-emergent adverse events were similar across groups and no anti-pegfilgrastim neutralizing antibodies were detected.

Discussion

- LA-EP2006 met the primary end point, demonstrating equivalence to the reference.
- LA-EP2006 and reference pegfilgrastim are similar with no clinically meaningful differences regarding efficacy and safety in breast cancer patients receiving (neo)-adjuvant chemotherapy.

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