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ORIGINAL ARTICLE

Incidence of bone pain in patients with breast cancer treated with lipegfilgrastim or pegfilgrastim: an integrated analysis from phase II and III studies

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Abstract
Purpose Lipegfilgrastim is a once-per-cycle, fixed-dose, glycoPEGylated recombinant granulocyte colony-stimulating factor (G-CSF) recently approved in Europe to reduce the duration of chemotherapy-induced neutropenia and incidence of febrile neutropenia in patients with cancer receiving chemotherapy. Bone pain-related (BPR) adverse events are commonly associated with G-CSF therapy. This post hoc analysis examined BPR treatment-emergent adverse events (TEAEs) in two comparative studies of lipegfilgrastim or pegfilgrastim in patients receiving chemotherapy.
Methods A post hoc analysis was conducted using integrated data from two double-blind randomized studies in patients with breast cancer receiving docetaxel and doxorubicin and treated prophylactically with subcutaneous lipegfilgrastim 6 mg or pegfilgrastim 6 mg once per cycle. BPR TEAEs were defined as arthralgia, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, noncardiac chest pain, and pain in extremity. Relationship of BPR TEAEs to study treatment or chemotherapy was also reported by the investigators.
Results The analysis included 306 patients (lipegfilgrastim: $n=151$; pegfilgrastim: $n=155$). The proportion of patients experiencing BPR TEAEs was similar with lipegfilgrastim and pegfilgrastim (25.2 vs 21.9 %, respectively), as was the proportion of patients experiencing BPR treatment-emergent adverse drug reactions (TEADRs) (18.5 vs 16.8 %, respectively). No BPR TEADRs were serious, and none led to discontinuation.
Conclusions Nonsevere BPR TEAEs and TEADRs were observed in patients with breast cancer receiving chemotherapy and G-CSF; rates of BPR events were similar between lipegfilgrastim and pegfilgrastim. The similar BPR safety profile of lipegfilgrastim and pegfilgrastim provides support for use in patients with breast cancer receiving chemotherapy.

Keywords Lipegfilgrastim · Pegfilgrastim · Bone pain · Drug-related side effect · Docetaxel · Doxorubicin

Introduction

Recombinant human granulocyte colony-stimulating factors (G-CSFs) reduce the incidence of neutropenia and febrile neutropenia (FN; absolute neutrophil count (ANC) $<0.5\times10^9$/L with fever) in patients receiving myelosuppressive chemotherapy [1, 2]. Treatment guidelines from the National Comprehensive Cancer Network (NCCN), the European Organization for Research and Treatment of Cancer (EORTC), the American Society of Clinical Oncology (ASCO), and the European Society for Medical Oncology (ESMO) all recommend prophylactic G-CSF therapy for patients receiving chemotherapy whose risk of developing FN is ≥20 % [2–5].

Lipegfilgrastim (Lonquex®; Teva Pharmaceuticals Ltd., Petach Tikva, Israel) is a highly homogenous, once-per-cycle, fixed-dose, glycoPEGylated recombinant human G-CSF (r-metHuG-CSF) developed using highly site-specific glycoPEGylation technology for site-directed PEGylation. Lipegfilgrastim was recently approved in Europe to reduce the duration of neutropenia and incidence of FN in patients with cancer receiving chemotherapy [6]. The noninferiority of

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lipegfilgrastim to pegfilgrastim was demonstrated in a randomized, double-blind, controlled, phase III trial evaluating the efficacy and safety of lipegfilgrastim in 202 chemotherapy-naive patients with breast cancer [7]. The primary efficacy endpoint, duration of severe neutropenia (± standard deviation (SD)) during cycle 1, was comparable between agents at 0.7±0.9 days for lipegfilgrastim and 0.8± 0.9 days for pegfilgrastim (95 % confidence interval (CI) −0.498 %, 0.062 %; P=0.126) [7].

One of the most common adverse events associated with the administration of G-CSFs is bone pain. In a report from the Research on Adverse Drug Events and Reports (RADAR) project that reviewed data from several studies in which G-CSF was administered to healthy individuals for peripheral blood stem cell harvesting, bone pain occurred in 52 to 84 % of patients, was transient in nature, and was generally controlled with standard analgesics [8]. In previously conducted randomized trials evaluating pegfilgrastim in patients with breast cancer, bone pain was associated with pegfilgrastim treatment in 25 to 59 % of patients [9–16]. Additionally, of those patients experiencing bone pain, 1 to 24 % reported severe bone pain or required narcotic analgesics [9–16].

A post hoc analysis of a phase II dose-finding trial and a phase III noninferiority trial conducted in patients with breast cancer receiving chemotherapy compared the incidence of bone pain-related (BPR) symptoms in patients treated with lipegfilgrastim or pegfilgrastim.

Methods

Full details of the study designs and patient populations of the two clinical trials have been reported elsewhere [7, 17, 18].

Study design and treatments

This post hoc combined analysis included safety and tolerability data from two clinical studies. Study 1 was a phase II, double-blind, randomized, dose-finding study in which patients were assigned in a 1:1:1:1 fashion to lipegfilgrastim (3, 4.5, or 6 mg administered via subcutaneous (SC) injection) or pegfilgrastim 6 mg SC once per cycle in addition to chemotherapy [17, 18]. Study 2 was a phase III, double-blind, randomized, noninferiority study in which patients received either lipegfilgrastim 6 mg SC or pegfilgrastim 6 mg SC once per cycle in addition to chemotherapy [7]. In both studies, patients received doxorubicin 60 mg/m^2 as an intravenous (IV) bolus and docetaxel 75 mg/m^2 IV infusion administered on day 1 for a total of four 21-day cycles; each study drug was administered on day 2 of each chemotherapy cycle or 24 h after chemotherapy (Fig. 1) [7, 17, 18]. Patients were required to have a recovered ANC of ≥1.5×10^9/L and a platelet count of ≥100×10^9/L to receive full-dose chemotherapy on day 1 of cycles 2, 3, and 4. A delay of up to 14 days was permitted to allow for recovery of a patient's hematologic values [7].

Study population

Eligible adult patients (≥18 years of age) had a diagnosis of stage II, III, or IV breast cancer, were chemotherapy naive, and had an Eastern Cooperative Oncology Group (ECOG) performance status ≤2. Patients were required to have adequate cardiac function (defined as a left ventricular ejection fraction ≥50 %), adequate hepatic function (defined as alanine aminotransferase and aspartate aminotransferase levels <2.5 × upper limit of normal (ULN), alkaline phosphatase level <5 × ULN, and bilirubin level <ULN), and adequate renal function (defined as serum creatinine level <1.5 × ULN). To be eligible for randomization, patients had to have an ANC ≥1.5×10^9/L and a platelet count ≥100×10^9/L at the baseline visit. Key exclusion criteria included a known hypersensitivity to filgrastim or pegfilgrastim or exposure to those agents or other G-CSFs prior to randomization, a prior malignancy within the previous 5 years, radiation therapy within 4 weeks of randomization, or chronic use of oral corticosteroids.

Integrated bone pain analysis

All patients who received at least a single injection of either lipegfilgrastim 6 mg SC or pegfilgrastim 6 mg SC in study 1 or study 2 were included in this analysis. Patients were required to report adverse events spontaneously, and at each visit, investigators asked patients about the occurrence of adverse events. In addition, patients were followed up for 30 days after the last drug administration to evaluate adverse events. Adverse events were classified using the preferred terms from the Medical Dictionary for Regulatory Activities. Investigators assessed each adverse event as serious or nonserious and its intensity as mild (tolerated), moderate (affected normal activities), or severe (severe effects on normal activities, inability to work, or necessity to discontinue treatment). The incidence of BPR treatment-emergent adverse events (TEAEs) was tabulated by treatment group and compared using Fisher's exact test. To ensure that all BPR TEAEs were collected that might have been documented using slightly different terminology, BPR TEAEs were defined as any of the following preferred terms: arthralgia, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, noncardiac chest pain, and pain in extremity.

The relationship of TEAEs to study treatment was determined by the investigators in each study as probable, possible, unlikely, not classifiable, or not related. For the purposes of this combined analysis, all BPR TEAEs were defined as treatment-emergent adverse drug reactions (TEADRs), except

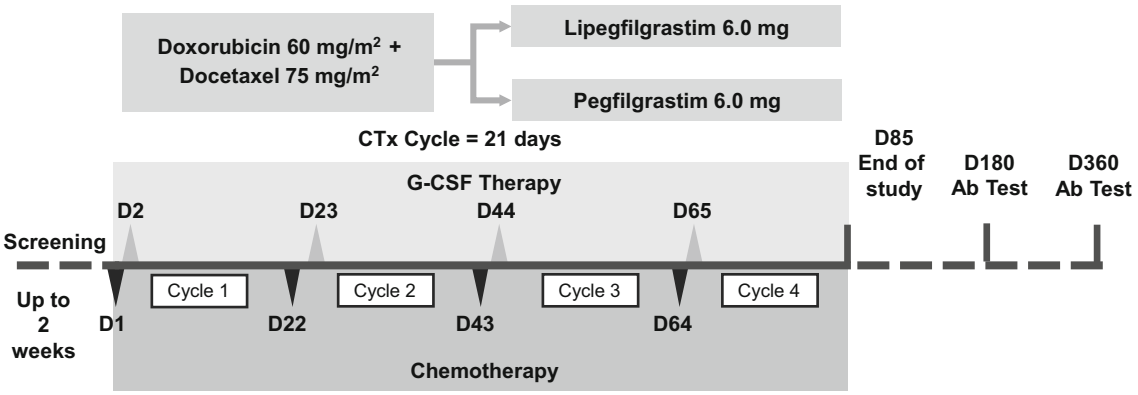

Fig. 1 Study timeline and treatment: studies 1 and 2. Only the 6-mg dose groups were included in the integrated safety analysis

for those specifically assessed by the investigators as "not related" to treatment.

Results

The primary efficacy and safety results of these phase II and III clinical trials have been reported elsewhere [7, 17, 18]. Only the results of the post hoc integrated analysis for the incidence of BPR TEAEs will be presented here.

Patients

The safety population comprised 306 patients from study 1 and study 2, 151 who received lipegfilgrastim 6 mg and 155 who received pegfilgrastim 6 mg following treatment with doxorubicin and docetaxel. All patients in both treatment groups were White, and all but one were female. Patient demographics and baseline clinical characteristics were evenly matched between treatment groups within each study (Table 1). Similarly, there were no notable differences in demographics or baseline clinical characteristics between patients in study 1 and study 2.

Bone pain-related treatment-emergent adverse events

The incidence of BPR TEAEs was similar between groups when examined by each preferred term (Table 2). No serious BPR TEAEs were reported in either group, no deaths related to a BPR TEAE occurred, and no patients in either group discontinued because of a BPR TEAE. One patient (0.7 %) in the lipegfilgrastim group had severe BPR TEAEs (one episode of arthralgia, two episodes of back pain; Table 3). All other BPR TEAEs were mild or moderate in intensity and were either controlled using standard analgesics or required no additional treatment (Table 3). The intensity and frequency of BPR TEAEs were similar across all chemotherapy cycles (Table 4).

Bone pain-related treatment-emergent adverse drug reactions

There was no significant difference between the lipegfilgrastim and pegfilgrastim groups in the percentage of patients with BPR TEADRs (18.5 vs 16.8 %, respectively; P= 0.76) (Table 5). All BPR TEADRs were mild or moderate in intensity. The proportions of patients with BPR TEADRs that were probably or possibly related to treatment were 92.2 % in the lipegfilgrastim group and 86.0 % in the pegfilgrastim group. The proportions of patients with BPR TEADRs that were probably or possibly related to chemotherapy were 70.4 and 64.9 % for the lipegfilgrastim and pegfilgrastim groups, respectively (Table 5).

Discussion

In this post hoc integrated analysis of two phase II and III studies, the incidence and severity of BPR TEAEs were comparable in patients who received either lipegfilgrastim or pegfilgrastim. Furthermore, BPR TEAEs attributable to study drug or chemotherapy (BPR TEADRs) were comparable between the two treatment groups and were as expected in patients with breast cancer receiving doxorubicin/docetaxel chemotherapy [19, 20]. The incidence of BPR TEAEs in patients receiving either lipegfilgrastim or pegfilgrastim with doxorubicin and docetaxel in this analysis is somewhat lower than the incidence of BPR TEAEs in previous trials of patients with breast cancer receiving pegfilgrastim once per cycle, daily filgrastim, or daily biosimilar filgrastim in combination with doxorubicin and docetaxel [15, 21]. In a phase III study by Kubista et al. of patients who were chemotherapy naive, had received adjuvant therapy, and/or had received one prior regimen of chemotherapy, a retrospective analysis of patient-reported bone pain showed an incidence of 42.1 and 36.7 % in patients receiving either filgrastim 5 μg/kg SC daily or pegfilgrastim 6 mg once per cycle, respectively [15]. In a

Table 1 Demographics and baseline clinical characteristics (intent-to-treat population)

	Study 1		Study 2	
	Lipegfilgrastim 6 mg (n=50)	Pegfilgrastim 6 mg (n=54)	Lipegfilgrastim 6 mg (n=101)	Pegfilgrastim 6 mg (n=101)
Age (years)				
Mean±SD	51.4±9.8	49.5±11.1	49.9±10.1	51.1±9.4
≤64, *n* (%)	45 (90.0)	50 (92.6)	94 (93.1)	94 (93.1)
65 to 74, *n* (%)	5 (10.0)	4 (7.4)	7 (6.9)	7 (6.9)
BSA (m^2)				
Mean±SD	1.8±0.2	1.8±0.2	1.8±0.2	1.8±0.2
Breast cancer stage, *n* (%)				
High-risk stage II	18 (36.0)	22 (40.7)	39 (38.6)	36 (35.6)
Stage III	24 (48.0)	23 (42.6)	48 (47.5)	45 (44.6)
Stage IV	8 (16.0)	9 (16.7)	14 (13.9)	20 (19.8)
Type of CTx, *n* (%)				
Adjuvant therapy	41 (82.0)	43 (79.6)	75 (74.3)	74 (73.3)
Treatment for metastatic disease	9 (18.0)	11 (20.4)	26 (25.7)	27 (26.7)
ECOG performance status, *n* (%)				
0	28 (56.0)	33 (61.1)	45 (44.6)	47 (46.5)
1	21 (42.0)	21 (38.9)	56 (55.4)	54 (53.5)
2	1 (2.0)	0	0	0
Months since first diagnosis				
Mean±SD	2.9±10.2	16.1±50.7	5.3±16.7	6.1±26.6

BSA body surface area, *CTx* chemotherapy, *ECOG* Eastern Cooperative Oncology Group, *SD* standard deviation

phase III study by Waller et al. of patients with breast cancer treated with filgrastim (5 μg/kg SC daily) or biosimilar filgrastim (5 μg/kg SC daily), the incidence of bone pain, myalgia, and arthralgia combined was 32.6 and 47 %, respectively [21].

One reason for the differences in BPR TEAEs reported across different studies may be related to the definitions of BPR adverse events used. In the study reported by Kubista et al. comparing filgrastim 5 μg/kg SC daily with pegfilgrastim 6 mg once per cycle, bone pain adverse events were defined using preferred terms or verbatim terms that were based on the World Health Organization Adverse Reaction Term guidelines for patient-reported adverse events, which included bone/skeletal pain, back, limb, noncardiac sternal, cranial/skull, scapular, sacral, and hip pain [15]. In the study reported by Waller et al., bone pain, myalgia, and arthralgia were reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events [21]. These differences in the definitions of bone pain may affect the incidence of reported bone pain and BPR adverse

Table 2 Number (%) of patients experiencing bone pain-related treatment-emergent adverse events by system organ class and preferred terms: integrated study 1 and study 2 results

Event	Lipegfilgrastim 6 mg (n=151) *n* (%)	Pegfilgrastim 6 mg (n=155) *n* (%)
All	38 (25.2)*[a]	34 (21.9)*[a]
Arthralgia	7 (4.6)	4 (2.6)
Back pain	3 (2.0)	2 (1.3)
Bone pain	24 (15.9)	22 (14.2)
Musculoskeletal chest pain	1 (0.7)	0
Musculoskeletal pain	1 (0.7)	1 (0.6)
Myalgia	16 (10.6)	9 (5.8)
Pain in extremity	0	1 (0.6)

*P=0.590 between groups

[a] Each patient is counted once; patients could have multiple TEAEs

Table 3 Patients experiencing the most severe bone pain-related treatment-emergent adverse events and event intensity

Intensity	Lipegfilgrastim 6 mg (n=151) n (%)	Pegfilgrastim 6 mg (n=155) n (%)
Any	38 (25.2)	34 (21.9)
Mild	30 (19.9)	24 (15.5)
Moderate	7 (4.6)	10 (6.5)
Severe	1 (0.7)[a]	0

[a] The patient experienced one episode of arthralgia during chemotherapy cycle 2 and two episodes of back pain during chemotherapy cycle 4; all were considered not related to study medication by the investigator. The episode of arthralgia was treated with paracetamol for 3 days, and the two episodes of back pain were treated with ketorolac for 3 and 1 days, respectively. The episode of severe bone pain resolved with treatment; the patient was not discontinued from the study

events across studies. In a meta-analysis of five randomized controlled trials comparing daily filgrastim and once-per-cycle pegfilgrastim in patients with breast cancer, non-Hodgkin lymphoma, and Hodgkin lymphoma, the incidence of bone pain was 25 to 45 % with pegfilgrastim and 26 to 50 % with filgrastim [22].

Differences in patient populations and study methodology may also be important factors in the incidence of BPR adverse events reported with G-CSFs. For example, the incidence of bone pain was reported to be as low as 3 % in a retrospective chart review of children treated with myelosuppressive chemotherapy and pegfilgrastim (up to 6 mg) [23] and 1.3 % in a retrospective observational study of patients receiving pegfilgrastim (6 mg or 100 μg/kg SC) in combination with various chemotherapy regimens for breast or lung cancer,

Table 4 Number (%) of patients experiencing bone pain-related treatment-emergent adverse events by cycle and maximal severity

Event	Lipegfilgrastim 6 mg (n=151)				Pegfilgrastim 6 mg (n=155)			
Cycle	1	2	3	4	1	2	3	4
Any								
Mild	20 (13)	15 (10)	13 (9)	13 (9)	11 (7)	15 (10)	13 (8)	15 (10)
Moderate	2 (1)	4 (3)	5 (3)	4 (3)	6 (4)	2 (1)	5 (3)	2 (1)
Severe	0	1 (<1)	0	1 (<1)	0	0	0	0
Arthralgia								
Mild	2 (1)	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)	0	0
Moderate	0	2 (1)	0	2 (1)	2 (1)	1 (<1)	0	0
Severe	0	1 (<1)	0	0	0	0	0	0
Back pain								
Mild	1 (<1)	0	1 (<1)	0	2 (1)	0	0	0
Moderate	1 (<1)	0	1 (<1)	0	0	0	0	0
Severe	0	0	0	1 (<1)	0	0	0	0
Bone pain								
Mild	13 (9)	9 (6)	5 (3)	7 (5)	5 (3)	9 (6)	7 (5)	9 (6)
Moderate	1 (<1)	1 (<1)	4 (3)	2 (1)	4 (3)	1 (<1)	4 (3)	1 (<1)
Severe	0	0	0	0	0	0	0	0
Musculoskeletal chest pain								
Mild	0	1 (<1)	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0
Musculoskeletal pain								
Mild	1 (<1)	0	0	0	0	1 (<1)	1 (<1)	1 (<1)
Moderate	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0
Myalgia								
Mild	5 (3)	8 (5)	7 (5)	6 (4)	5 (3)	4 (3)	5 (3)	5 (3)
Moderate	0	1 (<1)	2 (1)	1 (<1)	0	0	0	0
Severe	0	0	0	0	0	0	0	0
Pain in extremity								
Mild	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	1 (<1)	1 (<1)
Severe	0	0	0	0	0	0	0	0

Patients could have experienced multiple treatment-emergent adverse events

Table 5 Incidence of bone pain-related treatment-emergent adverse drug reactions by probable relation to study drug or chemotherapy: integrated study 1 and study 2 results

	Lipegfilgrastim 6 mg (n=151)	Pegfilgrastim 6 mg (n=155)
All patients with BPR TEAEs, n (%)	38 (25.2)*	34 (21.9)*
Total number of BPR TEAEs	91	76
All patients with BPR TEADRs, n (%)	28 (18.5)**	26 (16.8)**
Total number of BPR TEADRs (% of total TEAEs)	64 (70.3)	57 (75.0)
Related to study drug[a]		
Probably related (% of total BPR TEADRs)	26 (40.6)	14 (24.6)
Possibly related (% of total BPR TEADRs)	33 (51.6)	35 (61.4)
Related to CTx[a]		
Probably related (% of total BPR TEADRs)	28 (43.8)	18 (31.6)
Possibly related (% of total BPR TEADRs)	17 (26.6)	19 (33.3)

All BPR TEAEs were defined as treatment-emergent adverse drug reactions, except for those specifically assessed by the investigators as "not related" to treatment

BPR bone pain-related, *CTx* chemotherapy, *TEAEs* treatment-emergent adverse events, *TEADR* treatment-emergent adverse drug reaction

[a] An event could be counted in both categories, related to both study drug and chemotherapy

*P=0.59 between treatment groups

**P=0.76 between treatment groups

non-Hodgkin lymphoma, Hodgkin lymphoma, and multiple myeloma [24]. However, the retrospective nature of both studies likely demonstrates the underreporting of bone pain and other adverse events in settings that are not prospective trials.

Bone pain is a known adverse event associated with G-CSF therapy. The incidence of bone pain in patients receiving chemotherapy alone compared with those receiving chemotherapy plus a G-CSF was reported in a systematic review and meta-analysis of 17 clinical trials in which patients with a variety of tumor types received pegfilgrastim, filgrastim, or lenograstim at various doses and durations [25]. Among 3029 patients in the 14 trials that reported bone or musculoskeletal pain as an adverse event, it was reported in 10.4 % of patients in the control group and 19.6 % of patients in the G-CSF-treated group. These data are comparable with the incidence of BPR TEAEs deemed by the investigators to be related to G-CSF treatment in the post hoc integrated analysis reported here.

One complication of reporting BPR TEAEs is the confounding effects of the chemotherapy administered. The incidence of BPR TEAEs related to lipegfilgrastim alone is difficult to determine, as the incidence is also dependent upon the chemotherapy regimen. For example, in a recent study of lipegfilgrastim in 373 patients with lung cancer receiving cisplatin and etoposide, the incidence of BPR symptoms was 6.4 % in the placebo group and 8.5 % in the lipegfilgrastim group [26]. This incidence is lower than in the current trial, in which lipegfilgrastim was administered in patients receiving doxorubicin/docetaxel. In the current analysis, it was interesting to note that the percentage of BPR TEAEs assessed as probably or possibly related to chemotherapy was 70.4 and 64.9 % for the lipegfilgrastim and pegfilgrastim groups, respectively, compared with 92.2 and 86.0 %, respectively, being assessed as related to study drug.

Potential limitations of the analysis reported here include that it was done as a post hoc analysis of integrated data from two clinical studies in which BPR events were not a primary endpoint. However, both studies were similar in design, both patient populations were similar, and patients in each study received the same doses and schedules of doxorubicin and docetaxel and the same doses and treatment schedules of lipegfilgrastim and pegfilgrastim. Another potential limitation is the possibility that individual adverse events could have been missed or counted more than once because BPR TEAEs were defined as a set of preferred terms.

In conclusion, lipegfilgrastim and pegfilgrastim are both long-acting G-CSFs that can be given once per chemotherapy cycle to minimize the duration of neutropenia and incidence of FN. In this post hoc analysis, there was no significant difference in the incidence of BPR TEAEs in patients with breast cancer treated with doxorubicin and docetaxel receiving either lipegfilgrastim or pegfilgrastim, and the incidence and severity of treatment-related symptoms of bone pain were low and comparable between lipegfilgrastim and pegfilgrastim.

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Conflict of interest I.M. Bondarenko is a stock shareholder of Merckle GmbH. P. Bias is an employee of Teva Ratiopharm. A. Buchner is an employee and stock shareholder of Merckle GmbH.

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