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Original Article

Clinical safety and efficacy of "filgrastim biosimilar 2" in Japanese patients in a post-marketing surveillance study

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ABSTRACT

We conducted a post-marketing surveillance to evaluate the safety and efficacy of TKN732, approved as "filgrastim biosimilar 2", in Japanese patients who developed neutropenia in the course of cancer chemotherapy or hematopoietic stem cell transplantation. A total of 653 patients were registered during the 2-year enrollment period starting from May 2013, and 627 and 614 patients were eligible for safety and efficacy analyses of the G-CSF biosimilar, respectively.

Forty-three adverse drug reactions were reported in 33 patients (5.26%). Back pain was most frequently observed and reported in 20 patients (3.19%), followed by pyrexia (1.28%) and bone pain (0.96%). Risk factors for adverse reactions identified by logistic regression analyses were younger age, presence of past medical history, and lower total dose at the onset of adverse reactions.

Among the 576 cancer patients who developed Grade 2–4 neutropenia after chemotherapy, recovery to Grade 1/0 was reported in 553 patients (96%) following filgrastim biosimilar 2 treatment. The median duration of neutrophil counts below 1500/μL was 5 days. In addition, all 11 patients who underwent hematopoietic stem cell transplantation had good responses to filgrastim biosimilar 2.

In conclusion, this study showed that filgrastim biosimilar 2 has a similar safety profile and comparable effects to the original G-CSF product in the real world clinical setting.

1. Introduction

There have been no large scale studies on biosimilar products of granulocyte-colony stimulating factor (G-CSF) in Japanese patients. TKN732, a biosimilar of filgrastim was approved in Japan in 2013 as "filgrastim biosimilar 2" (F-BS2). The product contains the same active recombinant human G-CSF protein as XM02, which has been extensively used in the EU since 2008 and in the US since 2012.

The original filgrastim was clinically introduced in the US and Japan in 1991 and, since then, its clinical application has expanded to various indications. The recombinant human Met-G-CSF expressed in *E. coli* has comparable effects to natural G-CSF in increasing mature neutrophils by stimulating the growth and differentiation of bone marrow precursor cells. The G-CSF formulation is widely used for neutropenia induced by cancer chemotherapeutic agents and has become an essential supportive care product. In addition, filgrastim is essential for bone marrow and peripheral blood stem cell transplantation (PBSCT), to stimulate the engraftment of hematopoietic stem cells and to mobilize stem cells to the peripheral blood. After the expiration of patents and after the lapse of the exclusivity period of reexamination of the original filgrastim product, several biosimilar products, including F-BS2, have been developed and used due to the associated economic benefit and comparative biological effects and quality.

In the development of F-BS2 overseas, the pharmacokinetics (PK) and pharmacodynamics (PD) profiles were examined in cross-over clinical studies with the original filgrastim [1,2], and three multinational multicenter randomized controlled phase III trials were conducted in breast cancer, lung cancer, and non-Hodgkin lymphoma patients [3–5]. In addition to similar PK and PD profiles, comparability of efficacy and similarity of safety were shown in all 3 comparative studies. Meta-analysis data suggested the same safety and efficacy, irrespective of tumor type and chemotherapeutic regimens employed [6]. Furthermore, the filgrastim biosimilar exhibited

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efficacy in mobilization of hematopoietic stem cells and stimulation of transplanted stem cell growth [7–11]. In the development of TKN732 in Japan, clinical PK and PD studies were conducted in healthy Japanese volunteers [12,13] in accordance with the Guideline on Policies for the Assurance of the Quality, Safety and Efficacy of Biosimilar Products established in 2009, and comparability and similarity with the original G-CSF product was demonstrated, and approval for TKN732 was granted in Japan as F-BS2. Although no racial differences were expected based on the results of previous PK and PD studies, clinical outcomes from Japanese patients were limited. Therefore, Nippon Kayaku and Teva Takeda Pharma conducted a post-marketing surveillance (PMS) in more than 600 Japanese patients treated with F-BS2 in order to analyze the safety and efficacy of the product in the real world clinical setting.

2. Patients and methods

2.1. Patients

Japanese patients were registered into the PMS of F-BS2 during a 2-year period starting from May 2013, with a target number of 600 patients in order to detect at least one patient reporting adverse reactions at an incidence of 0.5% at a 95% or higher probability. The patients were registered via a central registration system and the surveillance was conducted in accordance with the Good Post-marketing Surveillance Practice Ordinance of the Ministry of Health, Labour and Welfare.

The indications of G-CSF usage for enrolled patients were limited to (1) neutropenia caused by cancer chemotherapy, (2) mobilization of hematopoietic stem cells into peripheral blood for autologous PBSCT, (3) enhancement of engraftment of transplanted hematopoietic stem cells, and (4) neutropenia due to HIV infection.

2.2. Surveillance methods

Besides patient characteristics, the treatment modality of F-BS2, and concomitantly administered medications, information concerning adverse drug reactions (ADRs), including clinical laboratory test data and a description of objective/subjective symptoms were collected.

In addition, if the physician suspected the generation of anti-filgrastim antibodies in a patient, collected blood sample from the patient was to be examined by ELISA and determined neutralizing activity.

Responses to F-BS2 were evaluated by the primary care physician and categorized as effective, ineffective, or not evaluable. Changes in blood cell counts measured at appropriate time points before and after F-BS2 treatment were used for objective analyses.

The observation period lasted until 3 weeks after the last dose of F-BS2, or up to 3 months after the first dose of F-BS2 if the product was used in multiple cycles.

2.3. Evaluation methods

In addition to each physician's assessment of the safety and efficacy, Efficacy and Safety Evaluation Committee meetings were convened to identify evaluable patients and to evaluate the safety and efficacy of F-BS2 objectively. The adverse events reported by physicians were comprehensively re-evaluated by the Committee in terms of causal relationship with administered agents and were graded based on CTCAE (Common Terminology Criteria for Adverse Events) ver. 4.0. Preferred terms and system organ class based on MedDRA/J (Medical Dictionary for Regulatory Activities/Japanese version) ver. 19.0 were used to code ADRs.

In order to evaluate efficacy, changes in neutrophil counts (alternatively, 1/2 of the white blood cell counts if neutrophil counts were not available) during the first treatment cycle of chemotherapy were evaluated and (1) nadir of neutrophil counts, (2) maximum neutrophil counts after F-BS2 administration, and (3) duration of neutrophil counts less than 1500/μL were calculated. The grade of neutropenia was evaluated based on CTCAE as Grade 4: less than 500/μL, Grade 3: 500–1000/μL, Grade 2: 1000–1500/μL, and Grade 1/0: 1500/μL or higher.

2.4. Statistical analysis

To evaluate the risk factors affecting adverse reactions of F-BS2 in cancer patients treated with cancer chemotherapy, Fisher's exact test or a chi-square test was used in the univariate analyses. A logistic regression analysis using a stepwise method was utilized for multivariate analyses.

The time to recovery from neutropenia was expressed as cumulative recovered patient proportion estimated by the Kaplan-Meier method, and the difference in recovery periods between patient subgroups was evaluated by the Generalized Wilcoxon test.

3. Results

3.1. Patients and administration status

A total of 653 patients were registered from 67 institutions, and 643 case report forms were collected. Sixteen patients were excluded from the analyses due to errors in the registration process and safety data reporting, and 627 patients were evaluated in the safety analyses. In these 627 patients, F-BS2 was used in 616 patients for neutropenia associated with cancer chemotherapy, 6 for mobilization of autologous hematopoietic stem cells into peripheral blood, and 5 for the enhancement of engraftment of hematopoietic stem cell transplants. There were no patients with HIV infection registered. The case report forms for 13 cancer patients had insufficient information on blood counts and, therefore, these patients were excluded from the efficacy analysis set (Fig. 1).

The approved dosage and modality of F-BS2 varies depending on the indication, and a different administration route, dosage and treatment period were employed accordingly for the patients in this surveillance. For solid tumors, including malignant lymphomas, subcutaneous injection was mainly used in 591 out of 595 patients, 4 patients were treated intravenously, and the median daily dose and duration was 50 μg/m^2 (range: 38–245 μg/m^2) and 4

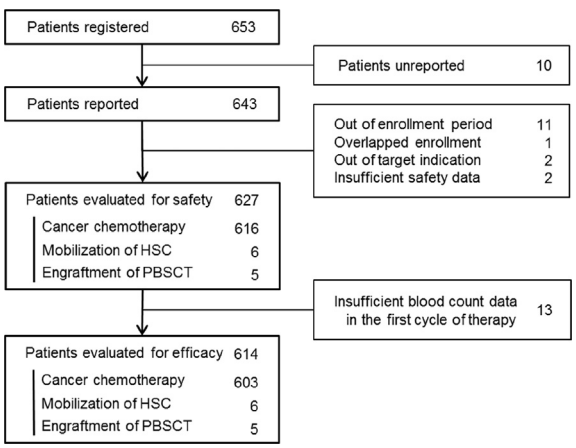

Fig. 1. Breakdown of patients in the Japanese post-marketing surveillance of filgrastim biosimilar 2. HSC: hematopoietic stem cell, PBSCT: peripheral blood stem cell transplants.

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days (range:1–60 days), respectively. For acute leukemia, 18 patients received F-BS2 subcutaneously, 1 received the product intravenously and 2 received a combination of the two. The respective dose and duration was 62 μg/m^2 (42–226 μg/m^2) and 7 days (3–32 days). For stem cell transplantation, 321 μg/m^2 (96–438 μg/m^2) was given subcutaneously for mobilization for 6.5 days (3–9 days), and 300 μg/m^2 (249–320 μg/m^2) was administered intravenously for the engraftment of transplanted stem cells for 11 days (5–59 days). The median to the onset of the F-BS2 treatment from the start of chemotherapy was 12 days, and early administrations initiated within 5 days were in 27 cases (4.3%).

3.2. Safety analysis

3.2.1. Incidence of adverse drug reactions

The profiles of ADRs in 627 evaluable patients are summarized in Table 1. A total of 43 ADRs were reported in 33 patients (5.26%). Back pain appeared in 20 patients (3.19%), followed by bone pain in 6 (0.96%). All of these events were Grade 1 or 2 and resolved within 3 days for most patients. Pyrexia was observed in 8 patients (1.28%) and persisted for 3 days. In addition, 8 types of adverse reactions were reported in 1 or 2 patients, including one patient each of erythema and rash. However, neither was considered to be hypersensitivity to F-BS2, and there were no reports of reductions in efficacy or hypersensitivity reactions suggesting the antigenicity of F-BS2. Therefore, no samples were collected for the detection of blood anti-G-CSF antibodies by ELISA.

There were 2 out of 43 ADRs that were classified as severe. One was acute respiratory distress syndrome (ARDS) reported in a colon cancer patient who received F-BS2 immediately after hospitalization for febrile neutropenia due to FOLFILI therapy. The other was interstitial pneumonia reported in a breast cancer patient who was treated with 4 repetitive cycles of FEC with F-BS2 and was hospitalized due to high fever. Both patients recovered with appropriate treatment and were discharged from the hospital after 15 and 8 days, respectively. Although both patients had received cancer chemotherapy and developed Grade 4 neutropenia with fever, the causal relationship of F-BS2 to these severe adverse reactions could not be denied.

Table 1
Incidence of adverse drug reactions to F-BS2.

Outline of the post-marketing surveillance	
Number of patients subject to safety analyses	627
Number of patients with ADRs	33
Incidence of ADRs (%)	5.26%
Total number of ADRs	43
Category of ADRs	**Number of patients (%)**
Nervous system disorders	1 (0.16%)
Headache	1 (0.16%)
Respiratory, thoracic and mediastinal disorders	2 (0.32%)
Acute respiratory distress syndrome	1 (0.16%)
Interstitial lung disease	1 (0.16%)
Skin and subcutaneous tissue disorders	2 (0.32%)
Erythema	1 (0.16%)
Rash	1 (0.16%)
Musculoskeletal and connective tissue disorders	23 (3.67%)
Arthralgia	1 (0.16%)
Back pain	20 (3.19%)
Bone pain	6 (0.96%)
General disorders	8 (1.28%)
Pyrexia	8 (1.28%)
Investigations	2 (0.32%)
Alanine aminotransferase increased	2 (0.32%)
Aspartate aminotransferase increased	1 (0.16%)

ADRs: adverse drug reactions, F-BS2: filgrastim biosimilar 2.

3.2.2. Risk factors for adverse reactions

Out of 33 reported patients who experienced adverse reactions, 32 patients were treated with F-BS2 for neutropenia associated with cancer chemotherapy. The remaining patient who experienced back pain was treated with F-BS2 to promote the engraftment of PBSC at higher dose of 249 μg/m^2 for 59 days. Considering the difference in therapeutic purpose and G-CSF dosage, a statistical analysis of the ADRs observed in the 32 patients with neutropenia due to cancer chemotherapy was performed. The incidence of ADRs was analyzed by patient background factors and statistical significances are shown in Table 2. In a total of 616 patients, 254 males and 362 females were registered, and the incidence of ADRs in the groups were 2.8% vs. 6.9%, respectively, with significant differences being observed ($P = 0.022$). The incidence of adverse reactions was significantly higher in younger patients than in older patients in 10-year aggregate increments ($P < 0.001$). No significant differences in the incidence of ADRs by BMI, performance status, inpatient/outpatient status, prior G-CSF treatment experience, allergies, medical history, or complications, including liver dysfunction and renal dysfunction, were observed. The initial daily dose of F-BS2 less than 60 μg/m^2 was used for 540 patients and induced ADRs in 30 patients (5.6%), whereas 1 out of 69 patients who were treated at the higher dose experienced adverse reactions ($P = 0.473$). The incidence of ADRs was inversely proportional to the total dosage at the onset of adverse reactions and a strong significance was observed. This means that the onset of adverse reactions tended to be at the beginning of G-CSF use and, in actuality, 11 patients experienced ADRs after one dose, and 8 patients experienced ADRs after the second injection. The median number of injections of F-BS2 to induce adverse reactions was 2 times (1–23 times), and the rate of development of ADRs after long-term treatment was lower.

Multivariate logistic regression analyses were subsequently performed using 6 factors consisting of gender, age, BMI, inpatient/outpatient status, previous medical history, and total injected dose at the onset of ADRs, of which P values were less than 0.3 in the aforementioned univariate analysis. As shown in Table 3, age, medical history and total injected dose were significant factors associated with all ADRs in 32 patients, with respective odds ratios of 5.4, 0.43, and 5.3, and the other three factors not being significant. Medical history includes disorders commonly seen in the study population like diabetes mellitus and hypertension. Assuming that bone and back pain were similar in nature, these two ADRs were combined in the analysis. The results showed that age and total injected dose were significant, with respective odds ratios of 5.6 and 6.1. For pyrexia, total injected dose was extracted as a significant risk, with an odds ratio of 9.7.

3.3. Efficacy analysis

All but 6 unevaluable patients were judged to be effective by the primary care physicians. In addition, objective analyses were carried out with reported blood cell counts in the case report form. As shown in Fig. 2a, among the 603 cancer patients, 343 patients (56.9%) developed Grade 4 neutropenia with various type of cancer chemotherapy, while 174 patients (28.9%) and 59 patients (9.8%) reported Grade 3 and Grade 2 as the highest grade of neutropenia, respectively. There were 27 patients (4.5%) with neutrophil counts that did not decrease below 1500/μL. For the 553 out of 576 patients (96.0%) with Grade 2–4 neutropenia, the counts recovered to more than 1500/μL (Grade 1/0) after the administration of the G-CSF biosimilar (Fig. 2b). The neutrophil counts for 23 patients (4.0%) did not recover to Grade1/0 within 30 days of observation period after the start of F-BS2. There were 2 patients who had no improvement in neutropenia, while no aggravations were reported in any patients on study. One of them was a patient of acute myeloid

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Table 2
Incidence of ADRs in patients receiving F-BS2 for chemotherapy-induced neutropenia.

Background factor	Category	No. of patients	No. of patients with ADRs	P value
Total		616	32 (5.2%)	
Gender	Male	254	7 (2.8%)	<0.05[a]
	Female	362	25 (6.9%)	
Age	<45	51	6 (11.8%)	<0.001[a]
	45–55	74	8 (10.8%)	
	55–65	133	10 (7.5%)	
	65–75	218	3 (1.4%)	
	75≤	140	5 (3.6%)	
BMI	<18.5	91	5 (5.5%)	0.269[b]
	18.5–25	386	18 (4.7%)	
	25–30	105	5 (4.8%)	
	30–35	18	2 (11.1%)	
	35–40	5	1 (20.0%)	
Performance status	0	342	17 (5.0%)	0.537[b]
	1	213	13 (6.1%)	
	2	36	1 (2.8%)	
	3	17	0 (0.0%)	
	4	7	1 (14.3%)	
Hospitalization status	Outpatient	266	18 (6.8%)	0.270[b]
	Inpatient	349	14 (4.0%)	
Prior G-CSF experience	No	484	27 (5.6%)	0.361[a]
	Yes	115	4 (3.5%)	
Allergy	No	541	28 (5.2%)	1.000[b]
	Yes	72	3 (4.2%)	
Medical history	No	364	15 (4.1%)	0.120[a]
	Yes	243	17 (7.0%)	
Complications	No	368	21 (5.7%)	0.486[a]
	Yes	248	11 (4.4%)	
Hepatic impairment	No	556	29 (5.2%)	1.000[b]
	Yes	56	3 (5.4%)	
Renal impairment	No	585	31 (5.3%)	1.000[b]
	Yes	26	1 (3.8%)	
Initial daily dose of F-BS2 (μg/m^2/day)	<60	540	30 (5.6%)	0.473[b]
	60–120	58	1 (1.7%)	
	120–250	11	0 (0.0%)	
Total injected dose of F-BS2 at the time of onset of ADRs (μg/m^2)	<60	88	10 (11.4%)	<0.001[b]
	60–120	58	9 (15.5%)	
	120–250	198	8 (4.0%)	
	250–500	139	2 (1.4%)	
	500–1000	93	1 (1.1%)	
	1000≤	33	1 (3.0%)	

[a] chi-square test.
[b] Fisher's exact test.

leukemia whose response to F-BS2 was recorded as 'not evaluable' and the other with prostate cancer was assessed by the primary care physician as 'effective' by being able to maintain the general condition in a good status.

The median duration of Grade 2 neutropenia in all of the patients was 5.0 days (5.0–6.0, 95% confidence intervals). The cumulative numbers of recovered patients (%) are plotted in Fig. 2c according to neutropenia grade associated with cancer chemotherapy. The recovery period for neutrophil counts to more than 1500/μL in half of the patients in each of the three groups was 6.0 days (6.0–7.0, 95% confidence intervals) for Grade 4, 4.0 days (4.0–5.0) for Grade 3, and 4.0 days (2.0–5.0) for Grade 2 neutropenia patients after the start of F-BS2 administration. There were statistical differences between Grade 4 vs. Grade 3, and Grade 4 vs. Grade 2 neutropenia as assessed using the Generalized Wilcoxon test using the Tukey-Kramer adjustment ($P < 0.001$ and < 0.0001).

The recovery periods in relation to patient background factors were investigated and are shown in Supplemental data 1. There were significant differences in recovery times of neutrophil counts between female and male patients (6.0 vs. 4.0, $P < 0.0001$, Generalized Wilcoxon test). This appeared to be caused by the high proportion of women who developed high grades of neutropenia ($P < 0.001$, chi-square test). Similarly, patients who were younger than 65 years took more days to recover (7.0 vs. 4.0, $P < 0.0001$), and this difference was related to the high incidence of severe neutropenia observed in the younger group ($P < 0.01$). There were also differences in recovery time between inpatients and outpatients (4.0 vs. 7.0, $P < 0.001$) and presence or absence of complications (5.0 vs. 6.0, $P < 0.01$).

Febrile neutropenia was observed in 12 patients (1.9%); however, all 12 patients were successfully treated with F-BS2 and antibiotics, and none developed serious infections.

As shown in Table 4, the mobilization of hematopoietic stem cells and recovery from PBSCT were successfully achieved by using a higher dose of F-BS2, although the number of patients was small. The harvest of hematopoietic stem cells from peripheral blood was performed in all 6 patients within 5.0 days from the start of F-BS2 administration, and the engraftment of transplanted stem cells was confirmed in all 5 patients based on the recovery of neutrophil counts to 500/μL within 10.0 days after F-BS2 administration, which was 11.0 days after transplantation.

4. Discussion

This is the first clinical investigation conducted on the safety and efficacy of the G-CSF biosimilar, F-BS2, in Japanese clinical practice. Overall, the incidence of ADRs in the analysis set of 627 patients was 5.26%, which primarily included bone pain, back pain, and pyrexia. These three adverse reactions were all Grade 1–2 and recovered in a short period of time. In the previously reported global Phase III studies [3–5], in which Japanese patients did not participate, the same adverse reactions were also mainly observed. The total incidence of adverse reactions was as high as 24.8% in these trials. The difference in incidence of ADRs is commonly seen due to practical differences in clinical trial and daily medical use. The same was true for the incidence of reported ADRs for the original filgrastim product used for chemotherapy-induced neutropenia, wherein 17.1% was reported in clinical studies and 7.2% in PMS. The higher incidence in the global Phase III may also be due to difference in the dosage of G-CSF. The approved dose in Japan for neutropenia in solid tumor patients is 50 μg/m^2, and indeed the median dosage in this surveillance was 50 μg/m^2, whereas the usual dosage in EU/US is 5 μg/kg, which is 4–5 times higher than that for Japanese patients.

One patient each reported ARDS and interstitial pneumonia as serious adverse reactions in this study. The events were also reported with the original filgrastim and other G-CSF products [14,15]. However, both patients received cancer chemotherapy that induced Grade 4 neutropenia and experienced fever due to concurrent infections before the administration of F-BS2. Therefore, clear determination that the F-BS2 was the only cause for these severe pulmonary events could not be made.

In the assessment of the relationship between the incidence of ADRs and patient background, a multivariate analysis was performed and three factors, i.e. age, medical history, and total dose at the onset of ADRs, were found to be significant. The rate of side effects was higher in patients with medical history (7.0% vs. 4.1%, $P = 0.120$), although reported medical history varied and no disease type could not be specified due to low frequency. In general,

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Table 3
Multivariate logistic analysis of incidence of ADRs with F-BS2 used for chemotherapy-induced neutropenia based on patient background factors.

Patient factor	Category	n	All ADR events			Bone pain + Back pain			Pyrexia		
			ADR ratio	Odds ratio (95% CI)	P value	ADR ratio	Odds ratio (95% CI)	P value	ADR ratio	Odds ratio (95% CI)	P value
Gender	Male	254	7 (2.8%)			4 (1.6%)			1 (0.4%)		
	Female	362	25 (6.9%)			18 (5.0%)			7 (1.9%)		
Age	<65	258	24 (9.3%)	5.4	<0.001	17 (6.6%)	5.6	<0.01	6 (2.3%)		
	65≤	358	8 (2.2%)	(2.2–13.0)		5 (1.4%)	(1.8–17.1)		2 (0.6%)		
BMI	<25	477	23 (4.8%)			15 (3.1%)			5 (1.0%)		
	25≤	128	8 (6.3%)			6 (4.7%)			3 (2.3%)		
Hospitalization status	Outpatient	266	18 (6.8%)			13 (4.9%)			7 (2.6%)		
	Inpatient	349	14 (4.0%)			9 (2.6%)			1 (0.3%)		
Medical history	No	364	15 (4.1%)	0.43	<0.05	10 (2.7%)			5 (1.4%)		
	Yes	243	17 (7.0%)	(0.20–0.94)		12 (4.9%)			3 (1.2%)		
Total injected dose of F-BS2 at the time of onset of ADRs (μg/m^2)	<120	146	19 (13.0%)	5.3	<0.001	14 (9.6%)	6.1	<0.001	6 (4.1%)	9.7	<0.01
	120≤	463	12 (2.6%)	(2.5–11.4)		7 (1.5%)	(2.4–15.7)		2 (0.4%)	(1.9–48.6)	

CI: confidence intervals.

younger patients with some previous medical history were susceptible to adverse reactions during the early period of G-CSF administration, signifying a need for careful attention. With regard to bone pain including back pain, age was also a significant factor, and this finding agreed with results reported for not only filgrastim but also pegylated-filgrastim, a long-acting form of G-CSF [16,17]. Bone pain is thought to be caused by the expansion of the bone marrow due to the differentiation of hematopoietic progenitor cells and proliferation of granulocytes stimulated by G-CSF in the bone marrow [18], and the higher incidence of bone pain in younger patients may be due to age-related differences in bone marrow cellularity and structure [17].

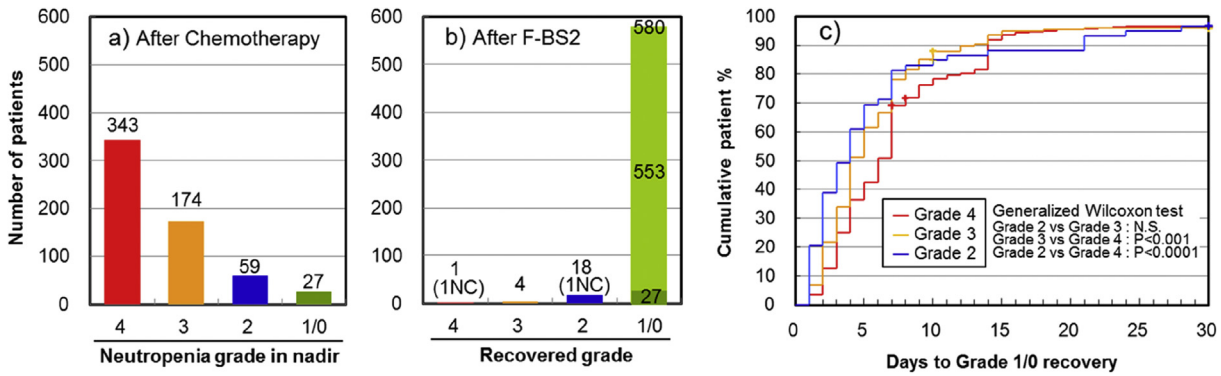

Fig. 2. Effect of F-BS2 on recovery of neutropenia induced by cancer chemotherapy. a) Incidence of neutropenia induced by cancer chemotherapy. b). Incidence of recovery of neutropenia with F-BS2. (NC: No change) c). Accumulation of patients with neutrophil counts that recovered to more than 1500/μL after the start of F-BS2 administration. (+: censored case).

Table 4
Effect of F-BS2 on hematopoietic stem cell transplantation.

	(A) Mobilization of hematopoietic stem cells into peripheral	(B) Engraftment of transplanted peripheral blood stem cells
Male:Female	4:2 (n = 6)	2:3 (n = 5)
Age	60.0 (47–74)	60.0 (50–66)
Initial daily dose (μg/m^2)	321 (96–438)	300 (249–320)
Treatment days (day)	6.5 (3–9)	11.0 (5–59)
Total dose (μg/m^2)	1842 (800–3600)	3300 (1500–14691)
Adverse drug reaction	0/6 (0%)	1/5 (20%)
Nadir of neutrophil counts (/μL)	45 (2–2693)	1 (0–50)
Maximum neutrophil count (/μL)	20430 (3450–45013)	4687 (4473–31388)
Days to reach the maximum counts	5.5 (2–8)	11.0 (4–25)
Duration of neutrophil <1500/μL	8.0 (5–13)	12.0 (4–25)
Number of harvests	2.0 (1–3)	–
Days harvesting stem cells	5.0 (0–8)	–
Days until confirmation of engraftment	–	10.0 (4–21)[a]

[a] The number of days are counted from the first day of F-BS2 treatment (=day0). The number of days until confirmation of engraftment from the time of transplantation was 11.0 (9–26) days.

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Considering the absence of suspected events of antigenicity, such as hypersensitivity reactions or reductions in efficacy, the antigenicity of the filgrastim biosimilar is considered very low, similar to the original filgrastim product. All of the primary physicians reported that F-BS2 was effective in controlling neutropenia, and an improvement in grade of neutropenia was confirmed in 96% of cancer patients in the first cycle of chemotherapy. There were 5 patients who still had Grade 4 or 3 neutropenia even after F-BS2 treatment; however, all of these patients were leukemia patients. With regard to the usage of G-CSF in leukemia patients, there was a report that exhibited the recovery period of neutrophil counts to 500/μL and 1000/μL with filgrastim after the induction chemotherapy was 20 days (28 days for control group) and 22 days (34 days for control group), respectively [19]. We conducted post hoc analyses with available data in 19 leukemia patients in this PMS using the similar parameter in the report, and found almost the same median recovery time of 20 days (to 500/μL) and 23 days (to 1000/μL) with F-BS2 (Supplemental data 2a). Furthermore, another clinical study in lung cancer patients showed that the duration of neutrophil counts below 1000/μL was 2.7 ± 3.3 days (9.8 ± 4.2 days for control group) [20], whereas the similarly re-analyzed value in 81 lung cancer patients in this PMS was 3.7 ± 2.4 days (Supplemental data 2b). Although comparisons with these early clinical trials are not simple, the recovery periods with F-BS2 estimated using the similar efficacy parameter are surprisingly close to those in the filgrastim-treated group and were much shorter than the control group in published data, suggesting that the filgrastim biosimilar has efficacy equivalent to the original filgrastim product.

The recovery time was demonstrated to be slower in females and younger patients (Supplemental data 1). This may be due to the high proportion of more severe neutropenia in these patients, since the number of days required for recovery was shown to increase depending on the severity of neutropenia (Fig. 2c). It should be noted that almost all patients with leukemia and breast cancer developed Grade 3 and 4 neutropenia, and consequently the recovery time from neutropenia tended to be longer (Supplemental data 3). It appears that patients with leukemia and breast cancer are younger than patients with other diseases and these patients received a higher intensity of chemotherapy.

There are of course, inherent limitations to make a clear-cut analysis and draw a definitive conclusion in PMS data such as less information on patients and drug administration, and sparsely collected data due to fewer fixed reporting items and time points. However, the real-world information in a large-scale survey involving over 600 patients must be quite useful when F-BS2 is planned to use in clinical practice. In summary, the safety profile of F-BS2 is similar to reports from overseas Phase III studies [3–5] and the original filgrastim product. There were no new unknown ADRs reported, and the 2 possibly drug-related severe events reported were reversible. No suspicious findings of antibody production were observed in this PMS. The efficacy of F-BS2 was confirmed based on the improvement in grade of neutropenia and duration of neutropenia associated with cancer chemotherapy. In addition, the effectiveness of treatment for the mobilization of hematopoietic stem cells and the engraftment of PBSCT were demonstrated in all treated patients. Thus, F-BS2 is shown to be a useful biosimilar product in clinical practice in Japan.

Conflicts of interest

K.T. received advisory fees from Nippon Kayaku Co., Ltd., and Teva Takeda Pharma Ltd.

ICMJE statement

All authors meet the ICMJE Statement. The authors substantially contributed to design of analysis and interpretation of data for the work, and drafted and revised the manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jiac.2017.12.011.

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