

ELECTRONIC SUPPLEMENTARY MATERIAL

PF-06881894, a Proposed Biosimilar to Pegfilgrastim, Versus US-Licensed and EU-Approved Pegfilgrastim Reference Products (Neulasta[®]):

Pharmacodynamics, Pharmacokinetics, Immunogenicity, and Safety of Single or Multiple Subcutaneous Doses in Healthy Volunteers

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Online Resource 1 Inclusion/exclusion criteria in the single-dose (C1221001) study

Inclusion criteria	
1	Provided written informed consent approved by an independent ethics committee prior to any study-related activities.
2	Healthy male or female volunteers between 18 and 65 years of age (both inclusive).
3	Body mass index between 19 and 30 kg/m ² , inclusive, and body weight of not <50 kg or >100 kg.
4	Non-smoker (defined as a subject who had not smoked and had not used nicotine-containing products for ≥3 months prior to study drug administration and had a negative urine screen for cotinine) at screening.
5	Female subjects of childbearing potential and male subjects and their partners of childbearing potential, agreed to pregnancy prevention throughout the duration of the study (through the follow-up visit).
6	Willing and able to comply with the requirements of the protocol and available for the planned duration of the study.
Exclusion criteria	
1	Any active systemic or immunologic disease or condition, including but not limited to the following general categories: cardiovascular/pulmonary, hepatorenal, or systemic infection, or lactation.
2	History of, or current, malignancy with the exception of adequately treated squamous or basal cell carcinoma of the skin or cervical carcinoma in situ within 5 years.
3	Any disease or condition that might interfere with the absorption, distribution, metabolism, or excretion of the study drug or would place the subject at increased risk.
4	Hematologic laboratory abnormalities including leukocytosis (defined as total leukocytes >11,000/μL), leukopenia (defined as total leukocytes <4000/μL), neutropenia (defined as ANC <1500/μL), or thrombocytopenia (defined as platelet count of <150,000 /μL).
5	Clinically significant, as judged by the investigator, vital sign, or 12-lead electrocardiogram abnormality.
6	History of biological growth factor exposure, including but not limited to filgrastim and other G-CSFs in the context of treatment, prophylaxis, peripheral blood stem cell mobilization, or previous investigational study setting. This also included exclusion for history of interferon, epoetin, and IVIG exposure.
7	Receipt of live vaccination, or exposure to communicable viral diseases such as varicella, mumps, or measles within the 4 weeks prior to screening.
8	Surgery within the 4 months prior to screening.
9	Use of any prescription medicine (with the exception of contraceptives) within 7 days or ≥5 half-lives, whichever was longer. Use of oral or parenteral anticoagulant or antiplatelet agents and corticosteroids were specifically queried.
10	Administration of a drug by depot injection (with exception of depot contraception) within 30 days prior to randomization or 5 half-lives of that drug, whichever was longer.
11	Use of OTC medications, including aspirin and nonsteroidal anti-inflammatory drugs, or natural preparations (dietary supplement or herbal product) within 7 days or ≥5 half-lives, whichever was longer. Vitamins and calcium were allowed (not to exceed 100% Daily Value).
12	History of drug or alcohol abuse within 2 years prior to randomization, as determined by the investigator, or positive urine drugs of abuse screen at screening. Screening for drugs of abuse minimally included cannabinoids, opiates, barbiturates, amphetamines, cocaine, benzodiazepines, and alcohol.

13	Drug sensitivity, allergic reaction to, or known hypersensitivity/idiosyncratic reaction to <i>Escherichia coli</i> -derived proteins, filgrastim, other G-CSFs, or pegylated agents.
14	History of splenic rupture (or subject who was asplenic), pulmonary infiltrate or pneumonia, sickle cell disease, chronic neutropenia, thrombocytopenia, or vasculitis.
15	Any clinically significant, as determined by the investigator, abnormal laboratory evaluations, including HIVAb, HBsAg, HCVAb, and liver function including ALT and AST <1.5× ULN taken at screening. Negative HIVAb statuses were confirmed at screening and the results were confidentially maintained by the study site.
16	Donated or lost ≥475 mL blood volume (including plasmapheresis) or had a transfusion of any blood product within 3 months prior to screening.
17	Participated in another clinical research study with administration of investigational drug within 30 days prior to randomization.
18	Potentially unable to comply with the requirements of this clinical study, to communicate effectively with study personnel, or was considered by the investigator, for any reason, to be an unsuitable candidate for the study.

ALT alanine aminotransferase, *ANC* absolute neutrophil count, *AST* aspartate aminotransferase, *G-CSF* granulocyte-colony stimulating factor, *HBsAg* hepatitis B virus surface antigen, *HCVAb* hepatitis C virus antibody, *HIVAb* human immunodeficiency virus antibody, *IVIg* intravenous immunoglobulin, *OTC* over the counter, *ULN* upper limit of normal

Online Resource 2 Inclusion/exclusion criteria in the multiple-dose (C1221005) study

Inclusion criteria	
1	Evidence of a personally signed and dated informed consent document indicating that the volunteer has been informed of all pertinent aspects of the study.
2	Healthy male or female volunteers between 18 and 65 years of age (both inclusive).
3	Body mass index between 19 and 30 kg/m ² , inclusive, and body weight of not <50 kg or >100 kg.
4	Subjects had abstained from the use of tobacco- or nicotine-containing products for ≥90 days prior to dosing and have a negative urine screen for cotinine at screening.
5	Agreed to abstain from alcohol consumption for ≥48 h prior to Day 1 of dosing in each study phase and has a negative urine screen for alcohol at screening.
6	Female subjects of non-childbearing potential had met at least one of the following criteria: • Achieved postmenopausal status, defined as cessation of regular menses for ≥12 consecutive months with no alternative pathological or physiological cause; status was confirmed by a serum FSH level confirming the postmenopausal state • Had undergone a documented hysterectomy and/or bilateral oophorectomy • Had medically confirmed ovarian failure • All other female subjects (including those with tubal ligations) were considered to be of childbearing potential and agreed to utilize appropriate contraception.
7	Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
Exclusion criteria	
1	Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.
2	Participation in other studies involving an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study drug (whichever was longer) prior to study entry and/or during study participation.
3	Acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may have increased the risk associated with study participation or investigational product administration or may have interfered with the interpretation of study results and, in the judgment of the investigator, made the subject inappropriate for entry into this study.
4	Any active systemic or immunologic disease or condition, including but not limited to the following general categories: cardiovascular/pulmonary, hepatorenal, or systemic infection, or lactation.
5	History of malignancy, including current malignancy, with the exception of adequately treated squamous or basal cell carcinoma of the skin or cervical carcinoma in situ within 5 years.
6	Any disease or condition that might interfere with the absorption, distribution, metabolism, or excretion of the study drug or would place the subject at increased risk.
7	Hematologic laboratory abnormalities at screening or Day -2 including leukocytosis (defined as total leukocytes >11,000/μL), leukopenia (defined as total leukocytes <4000/μL), neutropenia (defined as ANC <1500/μL), or thrombocytopenia (defined as platelet count <150,000/μL).
8	Lacked adequate hepatic reserve at screening or Day -2 as defined by AST and ALT ≥1.5× ULN of the reference lab; lack of renal reserve as defined by serum creatinine of ≥1.2× ULN for reference lab or eGFR of ≤80 mL/min; or had known history of glomerulonephritis.
9	Clinically significant, as judged by the investigator, vital sign, chest X-ray, or 12-lead ECG abnormality.

10	History of biological growth factor exposure, including but not limited to pegfilgrastim, filgrastim, and other G-CSFs in the context of treatment, prophylaxis, peripheral blood stem cell mobilization, or previous investigational study setting.
11	Receipt of live vaccination, or exposure to communicable viral diseases such as chicken pox, varicella, or measles within the 4 weeks prior to screening.
12	Surgery within the 4 months prior to screening.
13	Use of any prescription medicine (with the exception of contraceptives) within 7 days or ≥ 5 half-lives, whichever was longer. Use of oral or parenteral anticoagulant or antiplatelet agents and corticosteroids was specifically queried.
14	Administration of a drug by depot injection (with exception of depot contraception) within 30 days prior to the initial study drug administration or 5 half-lives of that drug, whichever was longer.
15	Use of OTC medications, including aspirin and NSAIDs, or natural preparations (dietary supplement or herbal product) within 7 days or ≥ 5 half-lives, whichever is longer. Vitamins and calcium supplements were allowed (not to exceed 100% Daily Value).
16	History of drug or alcohol abuse within 2 years prior to randomization, as determined by the investigator or a positive urine screen for drugs of abuse at screening. Screening for drugs of abuse at minimum included cannabinoids, opiates, barbiturates, amphetamines, cocaine, and benzodiazepines.
17	Drug sensitivity, allergic reaction to, or known hypersensitivity/idiosyncratic reaction to <i>Escherichia coli</i> -derived proteins, pegfilgrastim, filgrastim, other G-CSFs or any component of the product or known hypersensitivity to pegylated products. Subjects with the rare heredity problem of fructose intolerance were excluded due to the excipient sorbitol.
18	History of splenic rupture (or subject who was asplenic), pulmonary infiltrate or pneumonia, sickle cell disorders, chronic neutropenia, thrombocytopenia, or vasculitis.
19	Any clinically significant, as determined by the investigator, abnormal laboratory evaluations, including HIVAb, HBVsAg, HBVcAb, HCVAb, and liver function taken at screening. The negative HIVAb status was confirmed at screening, and the results were maintained confidentially by the study site.
20	Blood/plasma donations of approximately 500 mL or more within 60 days prior to dosing, or transfusion of any blood product within 90 days before screening.
21	Pregnant or breastfeeding female subjects, fertile male/female subjects not using ≥ 1 highly effective method of contraception during the study and ≥ 28 days after the last dose of the investigational product.
22	Unwilling or unable to comply with the lifestyle requirements per protocol criteria.

ALT alanine aminotransferase, *ANC* absolute neutrophil count, *AST* aspartate aminotransferase, *ECG* electrocardiogram, *eGFR* estimated glomerular filtration rate, *FSH* follicle-stimulating hormone, *G-CSF* granulocyte-colony stimulating factor, *HBVcAb* hepatitis B virus core antibody, *HBVsAg* hepatitis B virus surface antigen, *HCVAb* hepatitis C virus antibody, *HIVAb* human immunodeficiency virus antibody, *NSAID* nonsteroidal anti-inflammatory drug, *OTC* over the counter, *ULN* upper limit of normal

Online Resource 3 Immunogenicity assays and (a) flow of sample testing

For immunogenicity testing, sensitive bioanalytical methods were utilized with the aim of evaluating treatment-emergent immune responses.

Anti-drug antibody assays

A validated electrochemiluminescence (ECL)-based bridging assay was utilized for the analysis of anti-drug antibodies (ADAs) against pegfilgrastim (PF-068811894 and pegfilgrastim-US and -EU) in human serum. Biotin- and ruthenium-labeled PF-068811894 were used in the ECL method as capture and detection agents. A component of this assay included an assessment for the filgrastim moiety.

Anti-pegfilgrastim antibody assay cut-point determinations

In study C1221001, the confirmatory assay cut-point (CP) factor was based on 51 commercially sourced normal human serum samples. Using a 95% confidence interval (CI) the screening assay CP factor was 1.08, and using a 99.9% CI the confirmatory CP was 21.5% (Fig. a). A 99% CI (guideline recommended) for the confirmatory CP factors in an ~1% false-positive rate (FPR), so the approach adopted was deemed acceptable as the FPR was above the approximate 1%.

In study C1221005, the CP was determined from 50 random Day 1 predose serum samples to attain a target positive rate of 5% and 1% for the screening and confirmatory assays, respectively. The screening CP factor was 1.02 (95% CI) and the confirmatory CP was 15.4% (99.9% CI; considered appropriate given the FPR for Day 1 predose samples was 2.9%).

Anti-PEG assay

A validated and a partially validated (updated parts only) enzyme-linked immunosorbent assay (ELISA) assay were utilized to detect antibodies to the polyethylene glycol (PEG) moiety in studies C1221001 and C1221005, respectively. The CP factors for screening were 1.73 and 2.29 for C1221001 and C1221005, respectively, and the confirmatory CPs were 72.1% and 74.0%.

Neutralizing antibody assay (cell-based)

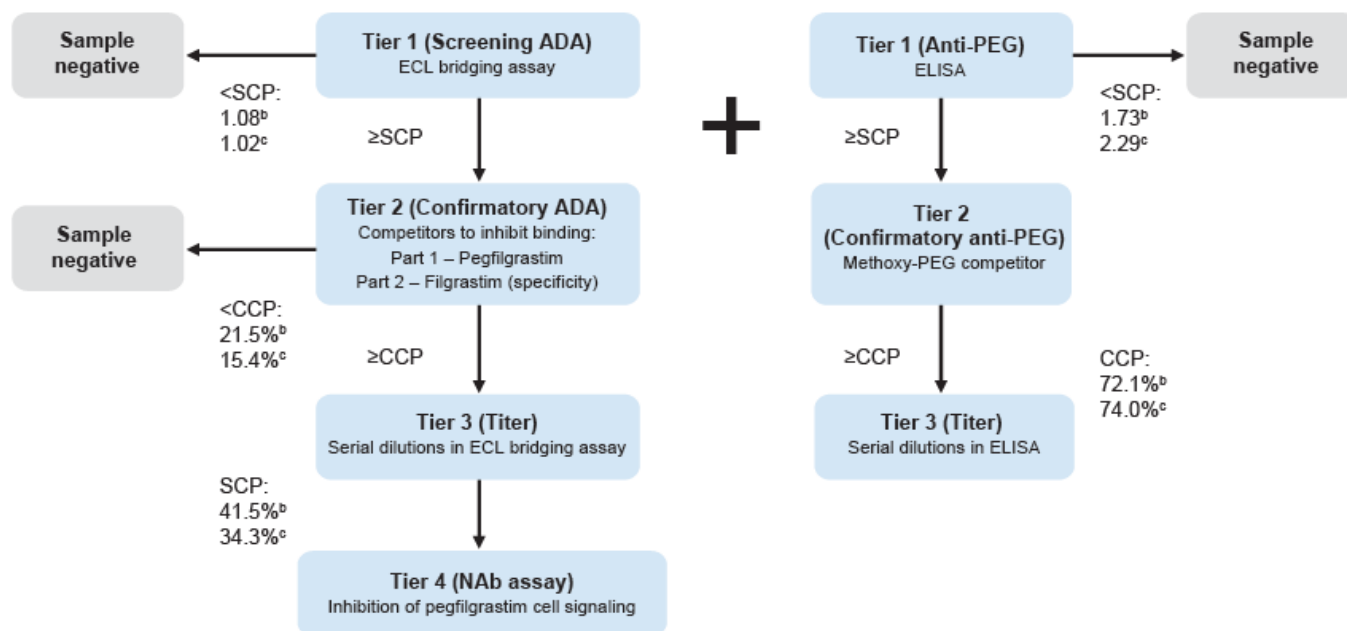
Confirmed anti-pegfilgrastim antibody-positive samples were evaluated for neutralizing antibody (NAb) capability utilizing the engineered GloResponseTMSIE-luc2P stable U937 cells (Promega, Madison, WI; cell line ID: CS185302a). These cells express the firefly luciferase in the presence of granulocyte-colony stimulating factor (G-CSF; filgrastim). NAb inhibits G-CSF-mediated luciferase activity. The luciferase enzyme activity is detected by the addition of ONE-Glo™ reagent (Promega) and assessed by the measurement of luminescence in relative light units (RLU) using the GloMax®-Multi Detection System (Promega). The RLU signal is proportional to the intensity of the G-CSF receptor signaling.

The screening CPs were 41.5% for study C1221001 and 34.3% for study C1221005.

Anti-filgrastim NAb (C1221001)

To determine specificity against filgrastim, the same anti-pegfilgrastim cell-based NAb assay methodology was employed, except that filgrastim was used as the cell-stimulating agent. When cells are stimulated with filgrastim, anti-PEG control antibodies are NAb negative; however, when cells are stimulated with pegfilgrastim, they are NAb positive. The screening CP (% inhibition) for the cell-based NAb method against filgrastim (not shown in figure) was 48.4% for study C1221001.

(a) Flow diagram of the multi-tier immunogenicity sample testing^a



^a Anti-PEG specificity was determined based on a separate ELISA format because this methodology yields the highest sensitivity and specificity to all forms of anti-PEG antibodies tested.

^b Study C1221001.

^c Study C1221005; updated partial validations were obligatorily applied in response to the most recently available FDA regulations. Note: Normal serum predose samples from study C1221005 were used for the anti-PEG ADA ELISA and the cell-based NAb assay methods.

ADA anti-drug antibody, CCP confirmatory cut-point, ECL electrochemiluminescence, ELISA enzyme-linked immunosorbent assay, NAb neutralizing antibody, PEG polyethylene glycol, SCP screening cut-point

Online Resource 4 Subject demographic and baseline characteristics of study populations in single-dose (C1221001) and multiple-dose (C1221005) studies (safety population)

	Single dose (C1221001)						Multiple dose (C1221005)	
	PF-06881894/ Pegfilg-US/ Pegfilg-EU (n=26)	Pegfilg-US/ Pegfilg-EU/ PF-06881894 (n=25)	Pegfilg-EU/ PF-06881894/ Pegfilg-US (n=25)	Pegfilg-US/ PF-06881894/ Pegfilg-EU (n=26)	PF-06881894/ Pegfilg-EU/ Pegfilg-US (n=25)	Pegfilg-EU/ Pegfilg-US /PF-06881894 (n=26)	PF-06881894 (n=210)	Pegfilg-US (n=210)
Age, years ^a								
Mean (SD)	34.0 (14.2)	27.7 (10.2)	30.3 (12.5)	27.3 (10.9)	29.2 (8.7)	33.5 (16.3)	37.2 (11.7)	36.1 (11.3)
Range (min–max)	19.0–64.0	19.0–64.0	19.0–63.0	18.0–64.0	21.0–51.0	18.0–65.0	18–65	18–64
Female, <i>n</i> (%)	14 (53.8)	14 (56.0)	9 (36.0)	12 (46.2)	10 (40.0)	13 (50.0)	126 (60.0)	111 (52.9)
Race, <i>n</i> (%)								
American Indian /Alaskan Native	0	0	0	0	0	0	2 (1.0)	1 (0.5)
Asian	2 (7.7)	2 (8.0)	1 (4.0)	0	2 (8.0)	1 (3.8)	2 (1.0)	5 (2.4)
Black/African American	1 (3.8)	0	0	0	2 (8.0)	1 (3.8)	54 (25.7)	62 (29.5)
Native Hawaiian/ Other Pacific Islander	1 (3.8)	0	0	0	0	0	1 (0.5)	1 (0.5)
White	21 (80.8)	21 (84.0)	21 (84.0)	24 (92.3)	21 (84.0)	24 (92.3)	150 (71.4)	141 (67.1)
Other/Multiracial ethnicity, <i>n</i> (%)	1 (3.8)	2 (8.0)	3 (12.0)	2 (7.7)	0	0	1 (0.5)	0
Hispanic/Latino	3 (11.5)	1 (4.0)	4 (16.0)	3 (11.5)	1 (4.0)	0	131 (62.4)	127 (60.5)
Mean weight, kg (SD)	72.4 (12.5)	70.0 (11.1)	75.7 (13.9)	71.8 (12.6)	74.2 (10.5)	73.5 (12.8)	72.8 (11.6)	72.1 (10.7)

^a In the single-dose study, age was the integer value of (date of consent–date of birth)/365.25 in years.

max maximum, *min* minimum, *n* number of subjects meeting prespecified criteria, *pegfilg-EU* pegfilgrastim sourced from the European Union (reference product), *pegfilg-US* pegfilgrastim sourced from the United States (reference product), *PF-06881894* proposed biosimilar of pegfilgrastim (test product), *SD* standard deviation

Online Resource 5 Exploratory immunogenicity results for subjects with >1 anti-pegfilgrastim antibody sample who were NAb negative

Subject (S) #: (treatment sequence)	Visit		Parameters assessed				
			Anti-pegfilg Ab confirmed ^a	Anti-pegfilg Ab titer	Anti-filgrastim Ab specificity	Anti-PEG Ab confirmed ^b	Anti-PEG Ab titer
S1: ^c (Pegfilg-US→PF-06881894→Pegfilg-EU)	Period 1	Day 1	—	N/A	—	—	N/A
		Day 13	+	80	—	+	3200 (peak)
		Follow-up	—	N/A	—		3200
	Period 2	Day 1	+	40	+	+	3200
		Day 13	—	N/A	N/A		waned
		Follow-up					
	Period 3	Day 1	—	N/A	N/A	+	waned
		Day 13					400
		Follow-up					800
S2: ^c (Pegfilg-EU→PF-06881894→Pegfilg-US)	Period 1	Day 1	—	N/A	N/A	—	N/A
		Day 13	+	20	+	+	400 (peak)
		Follow-up			—		waned
	Period 2	Day 1	+	<cutoff	—	+	waned
		Day 13		20	+		
		Follow-up					
	Period 3	Day 1	+	20	+	+	waned
		Day 13				—	N/A
		Follow-up					
S3: ^c (PF-06881894→Pegfilg-EU→Pegfilg-US)	Period 1	Day 1	—	N/A	N/A	—	—
		Day 13				+	100 (peak)
		Follow-up					waned
	Period 2	Day 1	+	160	—	+	waned
		Day 13	—	N/A	N/A	—	N/A
		Follow-up					
	Period 3	Day 1	+	80	—	—	N/A
		Day 13					
		Follow-up					

^a Determined using unlabeled pegfilgrastim as the competitive ligand in the confirmatory antibody assay.

^b Determined using unlabeled filgrastim as the competitive ligand in the confirmatory antibody assay.

^c PD/PK parameters approximated the median values for the primary analysis and safety population and there was no evidence of immunogenicity-associated adverse events or loss of response resulting from the presence of anti-pegfilgrastim or anti-PEG antibodies.

— negative, **+** positive, *Ab* antibody, *anti-PEG* anti-polyethylene glycol, *anti-pegfilg* anti-pegfilgrastim, *Follow-up* equivalent to Day 30, *NAb* neutralizing antibody, *N/A* not available, *PD* pharmacodynamic, *pegfilg-EU* pegfilgrastim sourced from the European Union (reference product), *pegfilg-US* pegfilgrastim sourced from the United States (reference product), *PF-06881894* proposed biosimilar of pegfilgrastim (test product), *PK* pharmacokinetic

Online Resource 6 Exploratory immunogenicity test results for subjects who tested positive for NAb in the C1221001 study (safety analysis set^a)

Subject (S) #: (treatment sequence)	Visit		Parameters assessed						
			Anti-pegfilg Ab confirmed ^d	Anti-pegfilg Ab titer	Anti-filgrastim Ab specificity ^e	Anti-PEG Ab confirmed	Anti-PEG Ab titer	NAb	NAb titer
S4: ^b PF- 06881894→ Pegfilg-EU→ Pegfilg-US	Period 1	Day 1	—	N/A	N/A	+	N/A	—	N/A
		Day 13	+	320	—		3200	+	8 ^g
		Follow-up		80			3200	—	N/A
	Period 2	Day 1	+	40	—	+	3200	—	N/A
		Day 13		20			N/A		
		Follow-up							
	Period 3	Day 1	+	<20	—	+	N/A	—	N/A
		Day 13		20					
		Follow-up	—	N/A	N/A		Waned to 400	—	
S5: ^c (PF- 06881894→ Pegfilg-US→ Pegfilg-EU)	Period 1	Day 1	—	N/A	N/A	—	N/A	—	N/A
		Day 13	+	40	—	+	6400	+	4 ^g
		Follow-up		< cutoff			Slightly decreased	—	N/A
	Period 2	Day 1	—	N/A	N/A	+	N/A	—	N/A
		Day 13							
		Follow-up							
	Period 3	Day 1	—	N/A	N/A	+	N/A	—	N/A
		Day 13							
		Follow-up					1600		

^a Safety analysis set comprised 153 subjects who received at least one dose of the study drug.

^b Subject #4 is a 39-year-old White male with ongoing folliculitis who was not taking any concomitant medications.

^c Subject #5 is a 21-year-old White male with no ongoing medical history whose concomitant medications consisted of paracetamol for back pain, pseudoephedrine for rhinorrhea, aloe vera for sunburn, and naproxen for musculoskeletal pain.

^d Determined using unlabeled pegfilgrastim as the competitive ligand in the confirmatory antibody assay.

^e Determined using unlabeled filgrastim as the competitive ligand in the confirmatory antibody assay.

^f PD and PK responses to treatment were adversely affected for Subject #5, most notably in Period 2 and to a lesser extent in Period 3 (Online Resource 7). The antibody response was potentially correlated to study drug-related adverse events for this subject; an injection-site urticarial rash (first observed in Period 1,

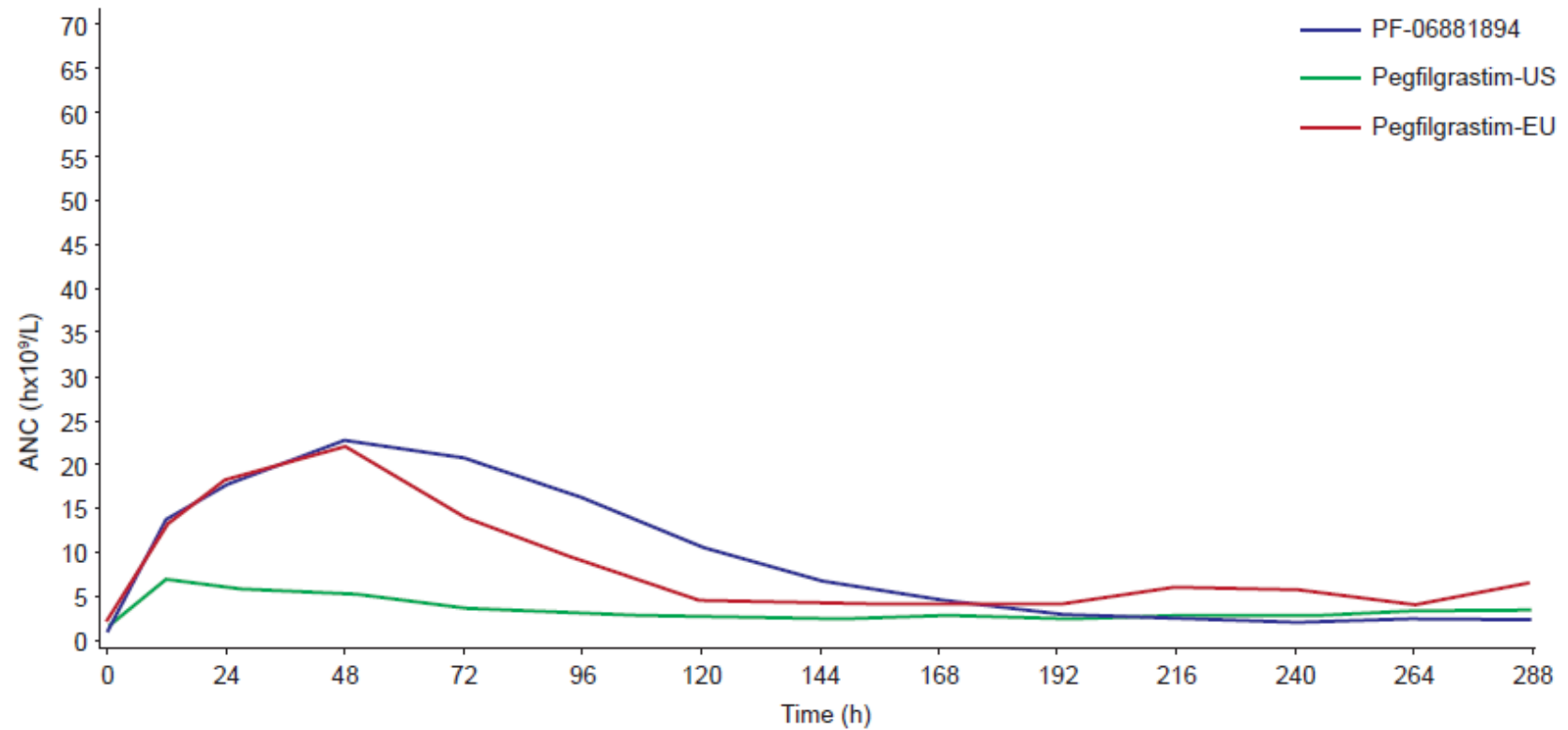
Day 11) of moderate severity and continuous in nature was reported as lasting ~3 weeks, and a second drug-related, continuous, urticarial rash (observed in Period 2, Day 2) of mild severity lasting 4 days was also reported.

^g Samples were further tested for NAb specificity using filgrastim in place of pegfilgrastim as the stimulating agent and were found to be negative, confirming they were specific to PEG and not specific to filgrastim.

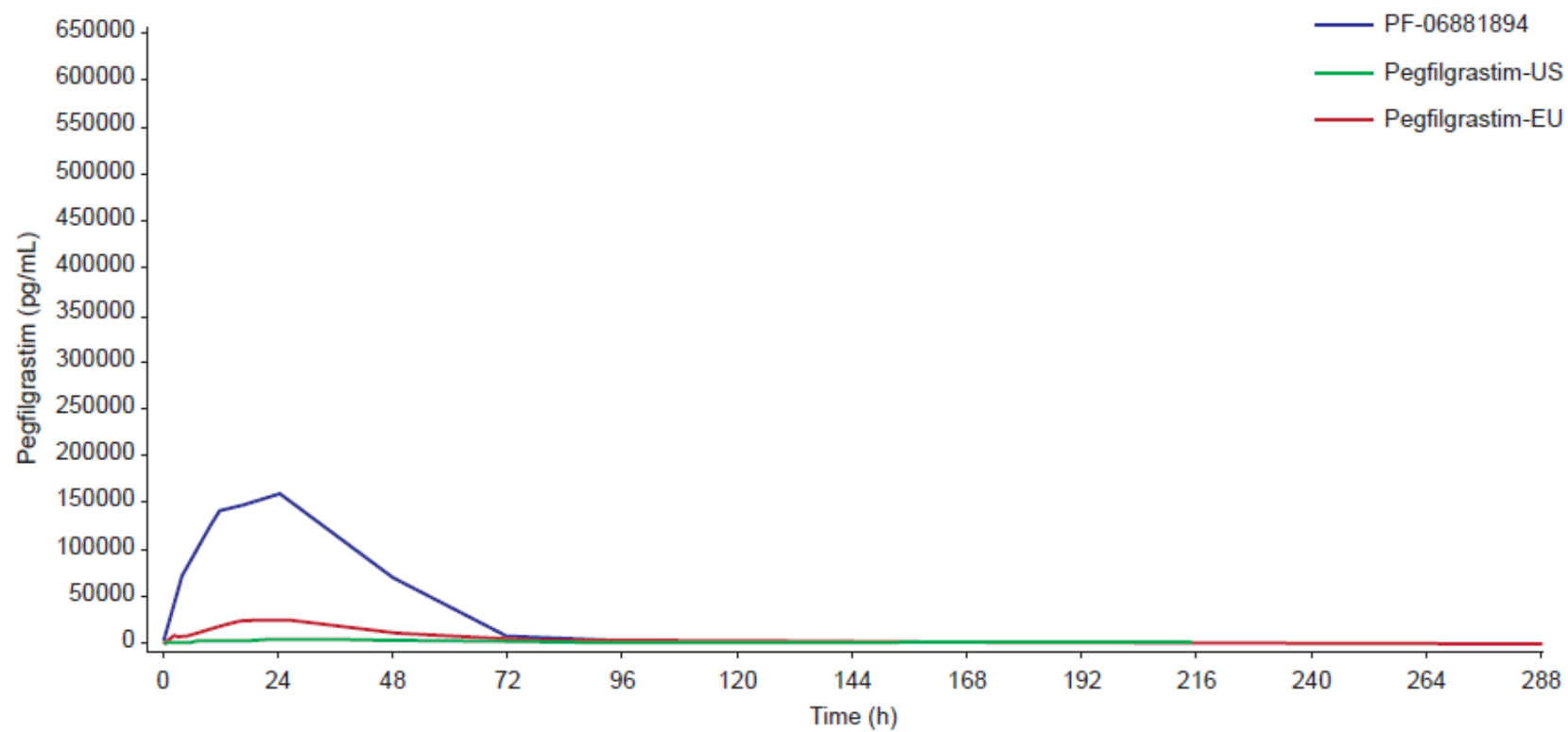
— negative, **+** positive, *Ab* antibody, *anti-PEG* anti-polyethylene glycol, *anti-pegfilg* anti-pegfilgrastim, *n* number of subjects meeting prespecified criteria, *N/A* not available, *NAb* neutralizing antibody, *PD* pharmacodynamic, *pegfilg-EU* pegfilgrastim sourced from the European Union (reference product), *pegfilg-US* pegfilgrastim sourced from the United States (reference product), *PF-06881894* proposed biosimilar of pegfilgrastim (test product), *PK* pharmacokinetic

Online Resource 7 Loss of response for the subject who received PF-06881894→Pegfilgrastim-US→Pegfilgrastim-EU (Study C1221001) and was anti-PEG antibody positive throughout the study, except at baseline, and NAb positive on Day 13, Period 1 based on (a) pharmacodynamic and (b) pharmacokinetic results

(a)



(b)



ANC absolute neutrophil count, *anti-PEG* anti-polyethylene glycol, *NAb* neutralizing antibody, *pegfilgrastim-EU* pegfilgrastim sourced from the European Union (reference product), *pegfilgrastim-US* pegfilgrastim sourced from the United States (reference product), *PF-06881894* proposed biosimilar of pegfilgrastim (test product)