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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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Clinical Pharmacology Review of Filgrastim-SD/01

Sponsor: Amgen
Product: Filgrastim-SD/01
Indication: Febrile neutropenia
BLA STN 125031

Filgrastim-SD/01 is a modified form of Filgrastim to which a 20 kd polyethylene glycol group is bound at the N-terminal methionine residue. Filgsrastim-SD/01 retains the basic pharmacological and toxicological properties of Filgrastim, but has a longer duration of action due to its pharmacokinetic properties. By increasing the size and molecular weight of Filgrastim, its renal clearance is decreased and the likelihood of its cellular uptake and subsequent proteolysis is decreased.

Filgrastim-SD/01 and Filgrastim levels in serum were determined using an ELISA [redacted] methodology that does not distinguish between Filgrastim-SD/01, Filgrastim and G-CSF. Microtiter immunoassay plates were coated with a murine monoclonal anti-G-CSF antibody as the capture antibody. A log-log fit was employed to determine levels of analyte in human serum. The lower limit of quantification was [redacted] ng/ml for assays performed prior to April 6, 2000 and [redacted] ng/ml for assays performed after April 6, 2000. Linearity was demonstrated in the range of [redacted] ng/ml for Filgrastim-SD/01 and [redacted] ng/ml for Filgrastim. Human rheumatoid factor positively interacted with the assay, [redacted]

Seroreactivity to Filgrastim-SD/01 was at first measured using a radioimmunoassay (RIA) and subsequently with an isotyping enzyme immunoassay (EIA) to detect IgM antibodies. An immunoassay that was [redacted] was utilized to assess neutralization.

The pharmacokinetics of Filgrastim-SD/01 were determined for each subject using a noncompartmental analysis of the data. Additionally, a compartmental analysis was used to determined the absolute bioavailability after sc dosing.

Filgrastim reached a peak serum concentration 2 to 8 hours after sc administration in human subjects. The clearance and half-life of Filgrastim are dependent on dose and absolute neutrophil count (ANC). Clearance is saturated at high doses. This characteristic is mostly likely due to neutrophil mediated clearance. As the neutrophils have a limited capacity to take-up the biologic product the pharmacokinetics appear as saturable system. After iv or sc dosing the elimination half-life ranges from 2 to 4 hours.

The bioavailability of Filgrastim after sc injection is estimated to be between 60% to 70%. The elimination of Filgrastim is dependent both on renal as well as neutrophil mediated mechanisms.

In healthy subjects and patients with cancer, the pharmacokinetics of Filgrastim-SD/01 were nonlinear and were observed as a decreasing rate of clearance that occurred with increasing dose. In healthy subjects a range of doses between 30 to 300 ug/kg was investigated. The mean time to reach Cmax increased from 9.5 to 30 hours as the dose increased from 30 to 300 ug/kg. Serum clearance decreased with increasing dose as measured by Cmax and AUC. The bioavailability of Filgrastim-SD/01 is estimated to be 4% in healthy subjects; however, due to the nonlinearity across dosage the true bioavailability may be approximately 15%. In patients with nonsmall-cell lung cancer clearance was lower after chemotherapy as compared to clearance measured before chemotherapy. This effect is most likely due to the decrease in ANC. Chemotherapy does not modify Cmax but does prolong the plateau associated with Tmax. In patients with cancer Tmax occurred from 8 to 120 hours postdosing. After repeated administration, levels of Filgrastim-SD/01 were higher in first cycle of chemotherapy as compared to later cycles due to an expansion in the number of neutrophils or their precursors. The elimination of Filgrastim-SD/01 is dependent on neutrophil mediated mechanisms and is relatively independent of renal mechanisms.

Pharmacokinetic parameters varied widely among cancer patients. Patients with higher weights or lower levels of neutrophils exhibited higher systemic levels when dosing was based on a ug/kg approach.

The following studies were reported in the BLA.

Study 970230, Pharmacokinetics and Pharmacodyanmics of Filgrastim-SD/01 in Normal Volunteers. Lot number 11001F7. This was an open-label phase 1 study using a single dose of 30, 60, 100 or 300 ug/kg given sc with N = 8 for each dose (given as divided sc doses to the deltoid area). The volume of injection for each of the divided doses was 1.5 ml. A minimum of 3 men and 3 women were entered into each cohort. As the dose increased the peak serum levels increased in duration indicating a change in its underlying pharmacokinetics. Dose was inverse and nonlinear to clearance in the range of doses studied. Pharmacokinetics were not found to be different between the sexes. Neutrophil levels increased with respect to dose with a counterclockwise hysteresis being observed between doses of Filgrastim-SD/01 and ANC. During the first hour of dosing with Filgrastim-SD/01, a transient decrease in ANC was found that was followed by a rapid increase in ANC similar to that observed with Filgrastim. Filgrastim-SD/01 increased the number of circulating CD34+ cells in a dose dependent manner. As for toxicity, the incidence of bone pain was unrelated to dose and no neutralizaing antibodies were found. Serum Filgrastim-SD/01 levels declined in a similar manner for all doses

when serum levels reached 5 ng/ml. The mean terminal t1/2 ranged between 48 to 62 hours. The pharmacokinetics obtained from this study are summarized below:

Pk parameter	30 ug/kg	60 ug/kg	100 ug/kg	300 ug/kg
Cmax, ng/ml	43 (20)	104 (62)	305 (93)	1066 (359)
Tmax, hr	9.5 (3.5)	12.3 (5.7)	19 (4.1)	30 (9.1)
T1/2, hr	51 (11)	62 (5.8)	50 (12)	46 (10.3)
AUCinf, ng-hr/ml	887 (336)	3164 (2093)	13136 (5774)	66474 (24429)

Table of pharmacokinetic parameters after sc injection of Filgrastim-SD/01. Mean (SD)

Study 980230, Pharmacokinetics and Pharmacodyanmics of Filgrastim-SD/01 After a Single Subcutaneous and Intravenous Injection in Healty Volunteers. This was an open-label randomized study using sc and iv doses of 30 or 60 ug/kg. The effects of Filgrastim-SD/01 were compared to an arm of the study investigating the effect of Filgrastim given as a 5 ug/kg/day dose. Eight individuals were dosed per group. Filgrastim-SD/01 was nonlinear after either iv or sc injection. Serum clearance decreased with increased dose. The absolute bioavailability was estimated to be 15%. Although the systemic exposure to Filgrastim-SD/01 was lower after sc dosing the response in terms of ANC levels were higher than those after iv dosing. The ANC response was 75% higher for the 30 ug/kg dose and 40% higher for the 60 ug/kg dose.

In the Filgrastim-SD/01 groups, 16 of 32 subjects were found to be positive for seroreactivity by RIA and 3 subjects by EIA. Two of the 8 subjects given Filgrastim were positive by EIA.

Study 970144, Pharmacokinetics and Pharmacodyanmics of Filgrastim-SD/01 in Patients With Non-small-cell Lung Cancer or Other Thoracic Tumors Treated With Carboplatin and Paclitaxel. This study was composed of two open-label, dose escalation studies examining the effects of Filgrastim before and after chemotherapy. Part A investigated the effects of a single dose of 30, 100 or 300 ug/kg given sc before chemotherapy. In part A, patients were also randomized to receive sc injections of Filgrastim daily for 5 days or until the ANC reached > or = to 75 X 10-9/L. Part B examined the effects of 30, 60 or 100 ug/kg given sc after chemotherapy. In part B, patients were enrolled from part A as a continuation. Twenty-fours after completion of chemotherapy, patients received their previous dose of Filgrastim-SD/01 or Filgrastim. In part C, patients with NSCLC or other thoracic tumors were given single sc doses of 60 or 100 ug/kg Filgrastim-SD/01 or daily sc injections of 5 ug/kg of Filgrastim until recovery of ANC. Study drug was given 24 hours after chemotherapy and a cycle was repeated every 3 weeks for up to 6 cycles. Part D used patients with NSCLS or other thoracic tumors and were randomized to receive a single sc dose of 30 ug/kg of Filgrastim-SD/01 or daily sc injections of 5 ug/kg of Filgrastim until ANC recovery. Study drug and chemotherapy followed the schedule

according to that indicated in part C. No pharmacokinetic sampling was performed in part D.

When a single injection of Filgrastim-SD/01 was given prior to chemotherapy, Cmax was sustained longer as the dose increased. Both Cmax and AUC increased in a manner more than proportional to dose in these patients.

When a single injection of Filgrastim-SD/01 was given after 1 cycle of chemotherapy, Cmax for each dose group was similar to the pharmacokinetics of patients prior to chemotherapy. After chemotherapy, a prolonged plateau was observed after administration that declined with recovery of the neutrophil count. When daily injections of Filgrastim were given after chemotherapy, serum levels of Filgrastim accumulated until the advent of the ANC nadir. With recovery of ANC levels of Filgrastim declined.

The pharmacokinetics of Filgrastim-SD/01 in patients with NSCLC was nonlinear to dose. Clearance was decreased after chemotherapy due to reductions in levels of neutrophils.

The pharmacokinetics obtained from this study are summarized below:

Pharmacokinetic endpoint	Filgrastim-SD/01, 30 ug/kg, N = 3	Filgrastim-SD/01, 100 ug/kg, N = 3	Filgrastim-SD/01, 300 ug/kg, N =4	Filgrastim, 5 ug/kg/day, N = 3
*T1/2, hr	8	24	48	4
*Cl/F, ml/hr/kg	64	18	6	30
**T1/2, hr	30	25	13	3
**Cl/F, ml/hr/kg	41	14	2	39

Table of pharmacokinetic endpoints from part A before chemotherapy (*) and part B after chemotherapy (**). Medians.

Study 980147, A Randomized Study of Single Administration Filgrastim-SD/01 or Daily Filgrastim as an Adjunct to Chemotherapy in Patients with High Risk Stage II or Stage III/IV Breast Cancer. Lots 11003E8 and 11004C9 of Filgrastim-SD/01.
This was a double-blind study followed by an open-label extension that investigated the effects of Filgrastim-SD/01 (30, 60 or 100 ug/kg sc) or Filgrastim (5 ug/kg/day) in different groups of subjects (N = 19 to 62 individuals per group) with up to 4 cycles of chemotherapy. Patients were treated with doxorubicin/docetaxel as chemotherapy. On day 1 of each cycle of chemotherapy, patients were given an iv bolus dose of doxorubicin (60 mg/m2) followed 1 hour later by an 1-hour infusion of docetaxel (75 mg/m2). On day 2 of each chemotherapy cycle, patient were given either Filgrastim or Filgrastim-SD/01. The primary purpose of the study was to assess the duration of severe

neutropenia in cycle 1 after chemotherapy. Clearance of Filgrastim-SD/01 was inverse and nonlinear to dose with increasing rates of clearance with successive cycles of chemotherapy. Levels of Filgrastim-SD/01 were higher in patients with higher body weights and inversely proportional to the degree of neutropenia.

After sc dosing of Filgrastim-SD/01, Tmax occurred at approximately 26 hours. Levels of Filgrastim-SD/01 were typically sustained until a nadir occurred in ANC. As ANC began to recover, Filgrastim-SD/01 levels declined rapidly. The median Filgrastim-SD/01 levels in cycle 3 were lower than those in cycle 1. As doses of Filgrastim-SD/01 were increased from 30 to 100 ug/kg, the median value for clearance decreased from 26.4 to 6.7 ml/hr/kg. Among the factors that influenced the variability of Filgrastim-SD/01 pharmacokinetics, body weight was found to have the strongest influence on AUC. This relationship became more evident when patients with severe neutropenia (ANC $<0.5 \times 10^9$) were excluded from the analysis. The pharmacokinetics are summarized below:

Pk endpoints	30 ug/kg, N = 18	60 ug/kg, N = 59	100 ug/kg, N = 44
T1/2, hr	46 (20 – 67)	48 (19 – 116)	48 (23 – 88)
Cl/F, ml/hr/kg	26 (7 – 69)	16 (1 – 135)	7 (2 – 131)

Table of Pharmacokinetic endpoints for Filgrastim-SD/01 for cycle 1 of chemotherapy. Median (range)

Study 990117, A Randomized, Multicenter, Open-label Study of Single Dose Filgrastim-SD/01 Versus Daily Filgrastim Following ESHAP Chemotherapy for Non-Hodgkin's Lymphoma. This was an open-label, randomized study of 100 ug/kg of Filgrastim-SD/01 given sc to 33 patients in up to 4 cycles of chemotherapy or daily sc injections of 5 ug/kg/day of Filgrastim for 12 days or until a post-nadir ANC was greater than or equal to 10×10^9/L whichever occurred first. Filgrastim-SD/01 was injected on day 6 which was 1 day after completion of chemotherapy. Another arm of the study examined the effects of 5 ug/kg/day of Filgrastim given sc in 33 subjects. Filgrastim-SD/01 yielded a longer duration of action. Clearance of Filgrastim-SD/01 was directly proportional to ANC. The median Cmax occurred 33 hours after sc administration with sustained levels persisting until the nadir of the ANC. With recovery of ANC, Filgrastim-SD/01 levels declined. The persistence of Filgrastim-SD/01 levels were proportional to nadirs in ANC as those patients with severe neutropenia sustained longer and higher levels. No relationship was found between AUC and body weight, height, age, body surface area, and creatinine clearance. The pharmacokinetics are summarized below.

Pk endpoints	Median (Q1, Q3)
Tmax, hr	33 (19, 51)
T1/2, hr	25 (19, 29)
AUC0-∞, ng-hr/ml	9401 (5973, 23013)
CL, ml/hr/kg	11 (4, 17)

Table of Pharmacokinetics after a 100 ug/kg dose of Filgrastim-SD/01 for 21 of 33 evaluable patients.

Study 990118, An Open-label, Randomized, Parallel, Dose-Ranging Study of Single Administration Filgrastim-SD01 Versus Daily Filgrastim as an Adjunct to Chemotherapy in Elderly Subjects With Non-Hodgkin's Lymphoma. This study was an open-label, randomized dose ranging study that investigated the effects of Filgrastim at 60 or 100 ug/kg or Filgrastim at 5 ug/kg/day in up to 6 cycles of chemotherapy in 13 or 14 subjects per dose group. Filgrastim-SD/01 demonstrated longer durations of action. Levels of Filgrastim-SD/01 were higher in patients with more severe neutropenia and levels of Filgrastim-SD/01 declined more rapidly with recovery of neutrophil levels. Pharmacokinetic parameters were not estimated in this study.

Study 980226, A Blinded, Randomized, Multicenter Study to Evaluate Single Administration Filgrastim-SD/01 per Cycle Versus Daily Filgrastim as an Adjunct to Chemotherapy in Subjects With High Risk Stage II or Stage III/IV Breast Cancer. This was a phase 3 study in patients given up to 4 cycles of chemotherapy and either 100 ug/kg sc of Filgrastim-SD/01 or 5 ug/kg/day sc of Filgrastim in 154 to 158 subjects. Levels of cytokine decreased with increased cycles of chemotherapy probably due to increasingly higher levels of neutrophils in each cycle. Decreases in neutrophils were correlated with increased levels of cytokine. Serum levels of Filgrastim-SD-01 were independent of creatinine clearance whereas serum Filgrastim levels increased with decreased creatinine clearance.

Study 990749, A Blinded, Randomized, Multicenter Study to Evaluate Fixed Dose Single Administration Filgrastim-SD/01 per Cycle Versus Daily Filgrastim as an Adjunct to Chemotherapy in Subjects With High-risk Stage II and Stage III/IV Breast Cancer. This was a phase 3 study of patients given up to 4 cycles of chemotherapy and either 6 mg of Filgrastim-SD/01 sc or 5 ug/kg/day of Filgrastim sc in 80 or 77 patients. Levels of Filgrastim-SD/01 were sustained longer than those of Filgrastim after sc injection. Increased levels of neutrophils increased the rate of clearance of the cytokines.

A summary of the pharmacokinetic findings are listed below in the table.

Study	Population	Drug	Cmax, ng/ml	Tmax, h	T1/2, h	Cl, ml/h/kg
970144	NSCLC	F	17 (8.4)	6 (1.5)	3.4 (2.6)	38 (17)
970144	NSCLC	FS	121 (67)	46 (17)	35 (5)	17 (10)
980147	Breast Ca	FS	178 (102)	37 (23)	47 (13)	13 (20)
990117	NHL, HL	FS	140 (110)	48 (40)	25 (11)	16 (24)
990749	Breast Ca	FS*	123 (113)	39 (35)	42 (14)	21 (19)

Table of pharmacokinetic endpoints in patients given sc 100 ug/kg or 6mg (*) Filgrastim-SD/01 (FS) or 5 ug/kg Filgrastim (F). Mean (SD)

Study 980230. Pharmacokinetics and Pharmacodynamics of Filgrastim-SD/01 after a Single Subcutaneous and Intravenous Injection in Healthy Volunteers. Lot Filgrastim-

SD/01 11003E8. This was an open-label, randomized study in which 40 healthy volunteers were given a single IV or IV dose of 30 ug/kg or 60 ug/kg of Filgrastim-SD/01 or daily SC injections of 5 ug/kg of Filgrastim from day 1 to day 10 or until ANC was ≥ 75 X 10E9/L, whichever came first. Eight subjects were assigned to each group. Serum samples were collected up to 14 days after dosing and serum samples were analyzed by an ELISA. Seroreactivity was assessed using a RIA, EIA and — immunassay. The pharmacokinetics of Filgrastim-SD/01 were nonlinear after both IV and SC dosing. Clearance appeared to decrease with increasing doses of Filgrastim-SD/01. The absolute bioavailability of Filgrastim-SD/01 was 15%. Three subjects demonstrated a significant immune response to Filgrastim without an apparent change in pharmacokinetics or pharmacodynamics. The pharmacokinetics are summarized below.

Pk endpoints	Filgrastim	Filgrastim-SD/01			
	5 ug/kg/day	30 ug/kg/day, SC	30 ug/kg/day, IV	60 ug/kg/day, SC	60 ug/kg/day, IV
T1/2, hr	4 (1)	79 (50)	28 (8)	52 (18)	37 (20)
AUC0-∞, ng-hr/ml	145 (32)	709 (372)	16697 (2789)	1755 (575)	43487 (10386)
CL, ml/hr/kg	36 (8)	53 (27)	2	38 (13)	1

Table of pharmacokinetic values for healthy volunteers. Mean (SD)

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