malignancies; the difference in incidence was primarily due to the higher incidences of skeletal and back pain attributed to Filgrastim

All subjects experienced at least 1 adverse event during the study. The most commonly occurring adverse events were those associated with cytotoxic chemotherapy; these included, in descending order of incidence, nausea, fatigue, alopecia, diarrhea, vomiting, constipation, fever, and anorexia. Other than Alopecia, Skeletal Pain, Stomatitis, and Limb Pain, no adverse event displayed a between-group difference greater than 5%. No adverse effect showed a difference greater than 10% between the all Pegfilgrastim and Filgrastim groups. Adverse events for all Pegfilgrastim doses versus Filgrastim occurring in 5% or more of subjects in either treatment group, in descending order of frequency are summarized in Table 19 below. With the possible exception of skeletal pain, no Pegfilgrastim dose relationship was apparent in any adverse event. The adverse events reported in subjects given a fixed dose of Pegfilgrastim were similar in nature and frequency to those in the per-weight dose groups.

Table 18. Summary of Adverse Events All Cancer

	Filgrastim 5 µg/kg/day	All Pegfilgrastim
Number of Subjects in Subset	331	465
All AEs	331 (100%)	464 (100%)
Severe, life-threatening, or fatal AEs	165 (50%)	228 (49%)
Serious AEs	81 (24%)	110 (24%)
Related AEs	154 (47%)	175 (38%)
Related, severe, life-threatening, or fatal AEs	21 (6%)	17 (4%)
Related, serious AEs	2 (1%)	1 (0%)
Withdrawals due to AEs	22 (7%)	32 (7%)

Events observed in the musculoskeletal body system that are commonly associated with Filgrastim included skeletal pain, myalgia, arthralgia, limb pain, and back pain. As noted above, skeletal pain and back pain occurred less frequently in the Pegfilgrastim group, while limb pain was more frequent. An integrated discussion of all bone pain events is presented in "Events of Special Interest" below.

Table 19: Incidence of Adverse Events Occurring in ≥ 5% of All Patients with Cancer

	Filgrastim 5 µg/kg/day	Pegfilgrastim All Doses
Number of Subjects in Subset	331	465
Number of Subjects Reporting AEs	331 (100%)	464 (100%)
Nausea	237 (72%)	333 (72%)
Fatigue	223 (67%)	326 (70%)
Alopecia	207 (63%)	320 (69%)
Diarrhea	162 (49%)	226 (49%)
Vomiting	147 (44%)	188 (40%)
Constipation	111 (34%)	169 (36%)
Fever	130 (39%)	161 (35%)
Anorexia	90 (27%)	127 (27%)
Pain Skeletal	120 (36%)	124 (27%)
Headache	95 (29%)	116 (25%)
Dyspepsia	77 (23%)	114 (25%)
Taste Perversion	79 (24%)	112 (24%)
Myalgia	73 (22%)	103 (22%)
Insomnia	71 (21%)	98 (21%)
Pain Abdominal	76 (23%)	97 (21%)
Arthralgia	52 (16%)	93 (20%)
Asthenia	70 (21%)	91 (20%)
Edema Peripheral	64 (19%)	82 (18%)
Dizziness	73 (22%)	78 (17%)
Granulocytopenia	64 (19%)	74 (16%)
Stomatitis	32 (10%)	73 (16%)
Mucositis	43 (13%)	68 (15%)
Neutropenic Fever	61 (18%)	68 (15%)
Pain Limb	28 (8%)	67 (14%)
Cough	50 (15%)	65 (14%)
Anemia	64 (19%)	64 (14%)
Pain Back	57 (17%)	60 (13%)
Infection Upper Respiratory	44 (13%)	58 (12%)

	Filgrastim 5 µg/kg/day	Pegfilgrastim All Doses
Dyspnea	52 (16%)	57 (12%)
Paresthesia	32 (10%)	57 (12%)
Sore Throat	45 (14%)	56 (12%)
Pain	24 (7%)	53 (11%)
Depression	35 (11%)	47 (10%)
Rhinitis	25 (8%)	47 (10%)
Sinusitis	23 (7%)	47 (10%)
Pain Oral	26 (8%)	45 (10%)
Anxiety	29 (9%)	44 (9%)
Dehydration	28 (8%)	44 (9%)
Moniliasis Oral	36 (11%)	42 (9%)
Erythema	31 (9%)	40 (9%)
Hot Flushes	27 (8%)	40 (9%)
Rash	34 (10%)	40 (9%)
Hypesthesia	12 (4%)	38 (8%)
Upper Respiratory Tract Congestion	16 (5%)	37 (8%)
Pain Chest (Non-Cardiac)	26 (8%)	36 (8%)
Rigors	22 (7%)	36 (8%)
Epistaxis	39 (12%)	35 (8%)
Lesion Oral	22 (7%)	33 (7%)
Flushing	22 (7%)	32 (7%)
Hemorrhoids	16 (5%)	31 (7%)
Conjunctivitis	18 (5%)	29 (6%)
Vision Abnormal	17 (5%)	29 (6%)
Lacrimation Abnormal	15 (5%)	28 (6%)
Gastroesophageal Reflux	22 (7%)	27 (6%)
Dry Mouth	21 (6%)	26 (6%)
Edema	18 (5%)	24 (5%)
Sweating Increased	21 (6%)	24 (5%)
Cough Dry	19 (6%)	19 (4%)
Hypotension	20 (6%)	19 (4%)
Syncope	17 (5%)	19 (4%)
Herpes Simplex	17 (5%)	18 (4%)

All Adverse Events by Weight

Weight classes were prospectively defined as < 80 kg (n= 529) versus ≥ 80 kg (n= 267). Comparing both within weight class (Pegfilgrastim versus Filgrastim) and between weight classes (low versus high body weight), neither treatment nor body weight appeared to be a determinant in the frequency or type of adverse events reported. For the most commonly reported event in the musculoskeletal body system (skeletal pain), in each weight stratum the incidence was less for Pegfilgrastim than for Filgrastim, consistent with the analysis of the total population. No other discernible trends were seen.

All Adverse Events by Gender

Seventy-one men and 394 women received Pegfilgrastim; there were no meaningful differences between the adverse event rates of men and women. Many of the apparent differences in the incidence of adverse events could be attributed to differences in chemotherapy regimens, since the women (the majority of whom received dose-dense chemotherapy for metastatic breast cancer) as a group underwent more intensive chemotherapy than the men. The incidence of skeletal pain was comparable between men (20%) and women (28%).

All Adverse Events by Age

Incidence rates of the most commonly occurring adverse events tended to be lower in subjects ≥ 65 years of age (n= 145) than in those < 65 years (n=651); this was true for both Filgrastim and Pegfilgrastim. However, within age groups, incidence rates of adverse events were similar between Filgrastim and Pegfilgrastim. One notable difference within this subgroup analysis was that, while in the < 65 year age group the incidence of skeletal pain for Pegfilgrastim was lower than that for Filgrastim (27% versus 39%, respectively) consistent with the entire population, the respective rates for the greater ≥ 65 year age group were similar between treatments (25% versus 23%).

There were 21 subjects 75 years or older (14 receiving Pegfilgrastim and 7 receiving Filgrastim), an insufficient number to allow reliable comparisons.

All Adverse Events by Race

Adverse events were examined within racial groups according to white (n= 671), black (n= 59), and "other" (n= 55). The use of the composite category "other" was necessary due to the small number of non-black minorities in the various studies. Numbers of black and "other" subjects are too small to draw valid conclusions regarding differences in adverse event profile by race.

Severe Adverse Events
Across all Pegfilgrastim dose groups, 49% of subjects experienced an adverse event graded severe or greater (NCI CTC grade 3-4), compared with 50% of Filgrastim subjects. The most common were those events associated with chemotherapy, and included, in descending order of incidence, alopecia, granulocytopenia, fever, nausea, vomiting, fatigue, and diarrhea. No event displayed a between-group difference ≥ 5% and no dose relationship was seen within Pegfilgrastim cohorts.

Deaths
Across all studies in the Integrated Summary of Safety, 14 subjects died within 30 days of receiving study drug administration: 6 subjects randomized to Pegfilgrastim versus 8 subjects randomized to Filgrastim. All deaths were directly related to complications of the cancer or its treatment. One fatal event was considered by the investigator to be at least possibly related to study drug: death due to adult respiratory distress syndrome (ARDS), sepsis, and pneumonia in a 59-year-old woman with breast cancer receiving Filgrastim (Study 990749, Subject 9024001). ARDS is a described complication of Filgrastim administration and is included as a Warning in the Filgrastim product label.

Other Serious Adverse Events
The proportion of subjects experiencing 1 or more serious events was the same between treatment groups (24%). No Pegfilgrastim dose-related trends were present. Serious adverse events that occurred in greater than or equal to 2% of Pegfilgrastim subjects were common complications of chemotherapy including fever, granulocytopenia, dehydration, vomiting, diarrhea, nausea, and sepsis.

Treatment-related Adverse Events
Across all Pegfilgrastim dose groups, 38% of subjects experienced 1 or more adverse events that were considered by the investigator to be at least possibly related to study drug, compared with 47% of those receiving Filgrastim. Except for skeletal pain (21% in those receiving Pegfilgrastim vs. 27% in those receiving Filgrastim), no single treatment-related adverse event displayed a between-group difference greater than or equal to 5%.

One notable pattern was that found in the thoracic tumor analysis set, which consisted of 70 subjects, of whom 26 received Filgrastim and 53 received Pegfilgrastim. In this subset almost twice as many subjects receiving Pegfilgrastim as those receiving Filgrastim experienced a treatment-related adverse event: 28% versus 15%, respectively. The incidence of skeletal pain demonstrated the difference of greatest magnitude contributing to this finding (11% versus 0% for Pegfilgrastim and Filgrastim, respectively), followed by neck

pain (6% versus 0%) and headache (4% versus 0%). This difference was not seen in the breast analysis set or in the hematologic malignancies analysis set, in which there were 40% and 34% incidences of related events for Pegfilgrastim versus 50% and 45% for Filgrastim, respectively. Given the small dataset and lack of reproducibility in other populations, the higher incidence of study drug-related adverse events in Pegfilgrastim versus Filgrastim-treated subjects may be the result of chance alone.

Study Withdrawals due to Adverse Event

A total of 54 subjects experienced a nonfatal adverse event that led to their removal from study: 32 receiving Pegfilgrastim (7%) versus 22 receiving Filgrastim (7%). There was no relationship between dose of Pegfilgrastim and the likelihood of withdrawal due to an adverse event.

Laboratory Variables

Elevations in alkaline phosphatase, LDH, and uric acid were seen, respectively, in 9%, 19% and 8% of subjects receiving Pegfilgrastim, and in 16%, 29%, and 9% of subjects receiving Filgrastim. No Pegfilgrastim dose-related trends were apparent within the All Cancer analysis set. As has been the historical experience with Filgrastim, treatment-related increases in these blood chemistries were transient and asymptomatic.

Key hematology variables that were examined in the All Cancer analysis set included hemoglobin, platelets, and WBC to assess the comparative effect of growth factor on hemoglobin, platelet and leukocyte recovery by end of chemotherapy cycle. No treatment-related differences were noted in hemoglobin recovery at end-of-cycle. At end-of-study, median hemoglobin values in all treatment and dose groups were decreased relative to baseline by between 13% and 16% for Pegfilgrastim and Filgrastim, respectively. No Pegfilgrastim dose relationship was apparent. Summary statistics of platelet counts likewise showed no treatment- or dose-related trends in end of treatment cycle platelet recovery. Median WBC showed a possible Pegfilgrastim dose-related trend in percent change from baseline at end-of-study: -13.7%, -6.8%, and 5.0% for dose levels of 30, 60, and 100 µg/kg, respectively. However, the median Pegfilgrastim value was higher for all doses than that for Filgrastim (-17.7).

Events of Special Interest

Bone Pain

The overall incidence of bone pain in the all Pegfilgrastim and Filgrastim groups were 44% and 50%, respectively, with skeletal pain, back pain, and limb pain most commonly reported. A dose relationship was seen in all bone pain for Pegfilgrastim, with incidence rates of 26%, 41%, and 43% for the 30-, 60-, and 100-µg/kg dose groups, respectively. The rate of bone pain for the 6 mg fixed

dose was 57%, higher than that for the overall Filgrastim group (50%), but less than that for its study-specific Filgrastim control group (64%).

A similar pattern was observed for study drug-related bone pain. As was seen in the all bone pain analysis, a Pegfilgrastim dose relationship was apparent, with incidence rates of 12%, 17%, and 28% for the 30-, 60-, and 100-µg /kg dose groups, respectively. The rate of related bone pain in the 6 mg fixed dose was 37%, compared with the study-specific Filgrastim control of 42%. This higher rate of bone pain in the fixed dose study is difficult to interpret, as this study included only 1 dose level of Pegfilgrastim and hence dose relationship cannot be effectively evaluated.

Overall, treatment-related bone pain occurred in 26% of subjects across all Pegfilgrastim dose groups, compared with 33% for Filgrastim. These rates both compare closely with the rate of 24% of subjects who experienced medullary bone pain in the Filgrastim registration trials.

The incidence of bone pain that was graded severe (NCI CTC grade 3 and 4) ranged from 3% in subjects receiving Pegfilgrastim 30 µg/kg, 60 µg/kg and 6 mg fixed dose to 6% in subjects receiving Filgrastim 5 µg/kg/day and Pegfilgrastim 100 µg/kg. Due to the low occurrence of severe bone pain, dose relationship was difficult to access.

Treatments for pain in general in these cancer subjects included a variety of nonnarcotic and opioid analgesics. The most commonly used pain medications across all subjects (irrespective of specific indication) included, in descending order of incidence, acetaminophen, ibuprofen, hydrocodone, oxycodone, codeine, propoxyphene, aspirin, and morphine. Concomitant medication usage within these 2 drug classes was similar between treatment groups. Nonnarcotic analgesics were used in 74% versus 76% of subjects treated with Pegfilgrastim and Filgrastim, respectively, and opioid analgesics in 44% versus 48% of subjects, respectively. Although all pain medication use was included in this analysis irrespective of specific indication, these findings were consistent with bone pain in the Pegfilgrastim treatment group being similar to that in the Filgrastim group.

Splenic Events

Across all studies, only one subject experienced a splenic event: subject 456004, a 44-year-old white woman with stage IV breast cancer on study 980226 who exhibited mild splenomegaly while receiving cycle 4 of Filgrastim 5 µg/kg/day.

Allergic Reactions

No subject in either treatment group experienced an allergic reaction to study drug.

Respiratory Events
Across all studies, ARDS, respiratory failure, or serious events of hypoxia were reported in 3 subjects. Two cases occurred in study 990749, both of which were reported to be at least possibly related to study drug. Subject 9010001 (Pegfilgrastim 6 mg), a 47-year-old woman with stage IV breast cancer, developed hypoxia, chest pain, and vomiting. She recovered with treatment. Subject 9024001 (Filgrastim 5 μg/kg/day), a 59-year-old woman with stage IV breast cancer and a history of dyspnea, developed bilateral bronchopneumonia and sepsis accompanied by stupor, hypotension, cough, and sinus tachycardia while on study, and died on day 26 of cycle 3. The third, subject 11801002 in study 990118 (Pegfilgrastim 100 μg/kg), was a 68-year-old male with stage IV NHL, who developed hypoxia associated with pulmonary edema on day 4 of cycle 1; he recovered with treatment. This event was reported by the investigator as not related to study drug.

Transfusion requirements
Transfusion usage showed no treatment- or dose-related trends. For the combined Pegfilgrastim group, 14% of subjects required 1 or more RBC transfusion, compared with 19% of subjects receiving Filgrastim. In both the Filgrastim and combined Pegfilgrastim groups, 4% of subjects received 1 or more platelet transfusions

Disease Progression and Survival
Long-term follow-up data, including disease progression and survival status through 6 months post-treatment, were available from study 980226; follow-up will continue through 2 years. Median follow-up as of the safety update submission of September 19, 2001 was 404 days for the Pegfilgrastim group versus 395 days for the Filgrastim group. As of last available follow-up, the rates of subjects who had experienced disease progression were 12% versus 19% for Pegfilgrastim and Filgrastim, respectively; survival rates were 90% in both groups. No statistically significant between-group differences were seen in either time to progression ($p=0.466$) or overall survival ($p= 0.729$). Due to the small number of events, median times to progression and death could not be calculated.

Drug-drug Interactions
No analysis was performed on possible drug interactions with Pegfilgrastim. Since no drug-drug Interactions have been encountered with Filgrastim after over 10 years of clinical experience the applicant felt that none would be expected with Pegfilgrastim.

Serum Antibodies

Background on Methodology

The first assay used in the Pegfilgrastim development program to detect antibodies binding to Pegfilgrastim and/or Filgrastim was a radioimmunoassay (RIA) that used immobilized r-metHuG-CSF and ^{125}I-labeled protein A. [redacted] a broader second-generation assay was developed: an enzyme immunosorbent assay (EIA) that used immobilized r-metHuG-CSF and enzyme-labeled anti-human IgG. [redacted]

The [redacted] was consequently adopted, which allows antibodies present in serum samples that bind to either Pegfilgrastim or Filgrastim to be detected and characterized. Additionally, this method has the ability to detect low-affinity antibodies [redacted] Using the [redacted] assay, seroreactivity previously observed in clinical samples with the RIA and EIA assays was determined to be due to nonspecific reactivity rather than specific antibody.

For the phase 1 and certain phase 2 studies (970144, 970230, 980147, and 980230) only the RIA and EIA were available. The [redacted] assay was used in the later phase 2 and the pivotal studies (990117, 990118, 980226, and 990749). Although the results from all 8 studies are presented below, it should be noted that 3 different screening methodologies are represented. However, the same cell-based bioassay to detect neutralizing antibodies was used throughout.

Antibody Results

Antibody data were presented for 534 subjects who received Pegfilgrastim and 340 subjects who received Filgrastim. One or more samples from 57 subjects tested reactive in the screening assays: 46 who received Pegfilgrastim (9%) and 11 who received Filgrastim (3%). Only 3 of these reactive results (all in subjects receiving Filgrastim) were from the [redacted] assay, the more reliable test. Upon further analysis, seroreactivity originally detected with the RIA and EIA assays in the remaining 54 samples was determined to be due to nonspecific reactivity rather than specific antibody. When the 57 reactive samples were tested in a cell-based immunoassay, no neutralizing antibodies were detected.

Across all Pegfilgrastim dose groups, 5 subjects (2%) had a last available ANC less than 1.0 x 109/L, compared with 6 Filgrastim subjects (2%). Notably, none of those with a low ANC were the same subjects who tested seropositive in the [redacted] assay (see above).

Summary of All Cancer Analysis Set

Seven hundred ninety-six subjects receiving multicycle chemotherapy for a variety of adult malignancies were included in the All Cancer Analysis Set: 331 who received multiple doses of Filgrastim per cycle and 465 who received single doses of Pegfilgrastim per cycle. This population consisted of subjects with stages II, III, or IV breast cancer, lung and other thoracic tumors, NHL, and Hodgkin's disease receiving standard or dose-intense chemotherapy regimens. Cumulative doses of Pegfilgrastim ranged from 1.6 to 70mg.

The most frequently occurring adverse events were those typical of cytotoxic chemotherapy. Bone pain was the major treatment-emergent adverse event associated with Pegfilgrastim. Analysis across all bone pain terms demonstrated a dose-relationship in bone pain with Pegfilgrastim, as has been observed in the historical experience with Filgrastim. Across all Pegfilgrastim dose groups, the incidence rate of study drug-related bone pain was 26%, compared with 33% with Filgrastim. The use of both non-narcotic analgesics and opioid analgesics was similar between treatment groups. Subgroup analyses of adverse events by weight, age, sex, and race revealed no safety trends that were not seen in the entire population. Weight did not appear to be a determinant in the frequency or nature of adverse events, whether Pegfilgrastim was administered as weight-adjusted or a fixed dose. Overall, the nature and frequency of adverse events seen in subjects given a fixed dose of Pegfilgrastim were similar to those seen in subjects dosed with Pegfilgrastim on a weight-adjusted basis and in subjects given Filgrastim.

Transient elevations in alkaline phosphatase, LDH, and uric acid were seen in less than 20% of subjects receiving Pegfilgrastim. These elevations were mild-to-moderate in severity and without clinical sequelae, and no Pegfilgrastim dose relationship was seen in either their incidence or severity. Changes in hematologic variables (WBC, platelets, and hemoglobin) were similar between the two treatment groups. Using the more reliable [redacted] assay, antibodies binding to Pegfilgrastim or Filgrastim were not detected in any subject receiving Pegfilgrastim. No neutralizing antibodies were detected

Other events of special interest, namely, allergic reactions to study drug, splenic enlargement or rupture, and ARDS, were not seen in any subject treated with Pegfilgrastim in the entire clinical program. Within study 980226, for which long-term follow-up data were available, the incidence of disease progression and overall survival showed no between-treatment group differences. Overall, no unexpected safety results were seen in the All Cancer analysis set, with Filgrastim and Pegfilgrastim demonstrating similar safety profiles.

Special Populations

Pediatric Patients
Preliminary results from an ongoing study in pediatric oncology are summarized below. Amgen had been granted a deferral by the FDA for including these data in the initial licensure submission and has agreed to submit final results as a Post-Marketing Commitment.

Because inadequate data are available to determine the safety and efficacy of Pegfilgrastim in children the NEULASTA™ package insert will contain the following statement:

> Under "Precautions, Pediatric Use": "The safety and effectiveness of NEULASTA™ in pediatric patients have not been established."

Because licensure is sought only for a 6 mg. fixed dose pre-filled single use syringe the NEULASTA™ package insert will contain the following statements:

> Under "Precautions, Pediatric Use" and "Dosage and Administration": "The 6 mg fixed dose formulation should not be used in infants, children and smaller adolescents weighing less than 45 kg."

Pediatric Sarcoma Study 990130
Study 990130, entitled "A Study of Single Dose per Cycle Pegfilgrastim as an Adjunct to VAdriaC/IE Chemotherapy in Pediatric Sarcoma Patients" is an ongoing phase 2 study

As of the September 19, 2001 Safety Update, 10 subjects are evaluable for safety. Seven subjects completed all 4 cycles, 1 subject is ongoing, and 2 discontinued. The pattern of adverse events reported to date has been consistent with the chemotherapy regimen or the disease. Most events were mild-to-moderate. Severe adverse events were reported in 2 subjects: nausea/vomiting, neutropenia, and non-cardiac chest pain in 1 subject, and febrile neutropenia and anemia in another subject. Serious adverse events were reported in 8 subjects. In the Pegfilgrastim group, febrile neutropenia, hematemesis, hematuria, and infection were reported. No serious adverse event was reported to be related to study drug. Related adverse events were reported in 2 subjects: back pain and limb pain in 1 subject receiving Pegfilgrastim and generalized pain in 1 subject receiving Filgrastim. No subject withdrew from the study due to adverse events. All subjects achieved adequate post-chemotherapy neutrophil recovery, and no subject had evidence of antibodies to Pegfilgrastim.

Geriatric Patients
Data from 145 subjects over the age of 65 years were summarized in the "All Events by Age" section of the All Cancer Set of the ISS, above. These results include a study of elderly subjects with NHL. No pharmacokinetic testing was performed in this population. Safety data analysis indicated that Pegfilgrastim was well tolerated in these subjects and that the incidence and severity of adverse events in subjects age 65 and older were similar to those younger than 65 years. There are no contraindications to the use of Pegfilgrastim in a geriatric population. The All Cancer analysis set contained an insufficient number subjects 75 years or older to allow reliable comparisons.

Renally-impaired Patients
Amgen has not performed a study of Pegfilgrastim in subjects with renal impairment. Amgen's argument for this decision follows.

Pegfilgrastim consists of a 20-kd PEG molecule covalently bound to the N-terminus of Filgrastim. This pegylation has an effect of increasing the hydrodynamic size of Pegfilgrastim, which would be expected to decrease the glomerular filtration of the drug, and therefore, produce sustained drug levels and sustained pharmacological activity. This is consistent with results shown with other pegylated products (Delgado et al, 1992). Results from a non clinical study in rats showed that the systemic exposure of Pegfilgrastim for sham-operated and bilateral nephrectomized rats was not statistically different, indicating that the kidney plays a minor role in the elimination of Pegfilgrastim.

Nonclinical and clinical PK data show that clearance of Pegfilgrastim is nonlinear with dose, and elimination is by parallel saturable and linear pathways. PK/PD modeling of clinical data indicates that the linear elimination pathway, presumably renal, accounts for only 1% of the total intrinsic clearance at normal ANC.

The saturable clearance pathway is presumably by neutrophil-mediated clearance, which is capacity-limited by saturation of receptor sites. Clinical PK data show a direct relationship between increased ANC and increased clearance of Pegfilgrastim both de novo and in the chemotherapy-induced neutropenia setting, indicating support for the clearance of the drug by neutrophil-mediated clearance.

Although these data suggest that Pegfilgrastim clearance is mainly by a non-renal clearance mechanism and that the effect of diminished renal clearance would not be relevant in patients receiving Pegfilgrastim, at FDA's request Amgen has agreed to conduct a Phase 4 study in subjects with various levels of renal impairment to assess the impact on drug clearance as a Post-Marketing Commitment. FDA requested this commitment because renal clearance, while secondary to neutrophil-mediated clearance, may play a role.

Hepatic Impaired Patients
Amgen has not performed a study of Pegfilgrastim in subjects with hepatic impairment. FDA has not requested a post-marketing study because there appears to be no evidence for hepatic clearance of Pegfilgrastim.

Patients Retreated with Pegfilgrastim
Re-exposure Study 990736
Study 990736, entitled "A Study of Retreatment with Pegfilgrastim in Subjects Receiving Myelosuppressive Chemotherapy", is an ongoing, open-label, phase 2, multicenter study enrolling subjects who have received Pegfilgrastim previously and are now receiving further myelosuppressive chemotherapy and Pegfilgrastim. Each subject is treated with a chemotherapeutic regimen specific for their tumor type and prior treatment history. Subjects are treated for up to 4 cycles at 3- to 4-week intervals with Pegfilgrastim 100 µg/kg. Endpoints include ANC response, PK, and safety.

At the time of this review, two subjects were evaluable for safety. The adverse event profile in both subjects was consistent with the disease or the chemotherapy regimen received. Most events were mild to moderate in severity and were considered unrelated to study drug. No subject was seropositive for anti-Pegfilgrastim antibodies and each displayed ANC recovery. Narratives by subject follow.

Subject 603001, a 62-year-old white woman with NSCLC, was previously enrolled in study 970144, receiving Pegfilgrastim 60 µg/kg for 4 cycles. In the retreatment study, this subject completed 2 cycles of docetaxel, was discontinued from treatment due to disease progression, and completed the 3-month follow-up period. Severe adverse events included dehydration, constipation, back pain, abdominal pain, emesis, leg weakness, and deep vein thrombosis. The subject was hospitalized twice for back and abdominal pain secondary to disease progression and once for central line-related deep vein thrombosis.

Subject 614002, a 64-year-old black woman with lung adenocarcinoma, was previously enrolled in the Investigator-held IND study —

— , in which she received Pegfilgrastim 100 µg/kg for 2 cycles. In the retreatment study, the subject received 4 cycles of carboplatin and paclitaxel and is still on study. Severe adverse events included fever and pneumonia, for which she was hospitalized. Moderate general body aches and bilateral leg/foot pain was considered at least possibly related to study drug.

Splenic Rupture
Although no subject receiving Pegfilgrastim experienced splenic rupture, it has been associated with the use of Filgrastim, the parent compound of Pegfilgrastim. The package insert for NEUPOGEN® contains a warning regarding the risk for splenic rupture. Across all studies, only one subject experienced a splenic event: subject 456004, a 44-year-old white woman with stage IV breast cancer on study 980226 who exhibited mild splenomegaly while receiving cycle 4 of Filgrastim 5 µg/kg/day.

Therefore, the following bolded, all capitals warning will be included in the NEULASTA™ Package insert: "**RARE CASES OF SPLENIC RUPTURE HAVE BEEN REPORTED FOLLOWING THE ADMINISTRATION OF THE PARENT COMPOUND OF NEULASTA™, FILGRASTIM, FOR PBPC MOBILIZATION IN BOTH HEALTHY DONORS AND PATIENTS WITH CANCER. SOME OF THESE CASES WERE FATAL. NEULASTA™ HAS NOT BEEN EVALUATED IN THIS SETTING, THEREFORE, NEULASTA™ SHOULD NOT BE USED FOR PBPC MOBILIZATION. PATIENTS RECEIVING NEULASTA™ WHO REPORT LEFT UPPER ABDOMINAL OR SHOULDER TIP PAIN SHOULD BE EVALUATED FOR AN ENLARGED SPLEEN OR SPLENIC RUPTURE.**"

Adult Respiratory Distress Syndrome
Although no subject receiving Pegfilgrastim experienced ARDS, it has been associated with the use of Filgrastim, the parent compound of Pegfilgrastim. The package insert for NEUPOGEN® contains a warning regarding the risk for ARDS. Across all studies, only one subject experienced an event that could be classified as ARDS: subject 9024001, a 59-year-old woman on study 990749 with stage IV breast cancer and a history of dyspnea, who developed bilateral bronchopneumonia and sepsis accompanied by stupor, hypotension, cough, and sinus tachycardia while receiving Filgrastim 5 µg/kg/day, and died on day 26 of cycle 3.

Therefore, the following warning will be included in the NEULASTA™ Package insert: "Adult respiratory distress syndrome (ARDS) has been reported in neutropenic patients with sepsis receiving Filgrastim, the parent compound of NEULASTA™, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Neutropenic patients receiving NEULASTA™ who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, NEULASTA™ should be discontinued and/or withheld until resolution of ARDS and patients should receive appropriate medical management for this condition."

Patients with Sickle Cell Disease
Although no subjects with sickle cell disease were entered into any trial in the Pegfilgrastim Clinical Development Program, severe sickle cell crises have been reported in patients with sickle cell disease who received Filgrastim, the parent compound of Pegfilgrastim, for PBPC mobilization or following chemotherapy. One of these cases was fatal. The package insert for NEUPOGEN® contains a warning regarding the risk associated with the use of NEUPOGEN® in patients with sickle cell disease.

Therefore, the following warning will be included in the NEULASTA™ Package insert: "Severe sickle cell crises have been reported in patients with sickle cell disease (specifically homozygous sickle cell anemia, sickle/hemoglobin C disease, and sickle/β+ thalassemia) who received Filgrastim, the parent compound of pegfilgrastim, for PBPC mobilization or following chemotherapy. One of these cases was fatal. Pegfilgrastim should be used with caution in patients with sickle cell disease, and only after careful consideration of the potential risks and benefits. Patients with sickle cell disease who receive NEULASTA™ should be kept well hydrated and monitored for the occurrence of sickle cell crises. In the event of severe sickle cell crisis supportive care should be administered, and interventions to ameliorate the underlying event, such as therapeutic red blood cell exchange transfusion, should be considered."

Allergic Reactions
Although no subject receiving Pegfilgrastim or Filgrastim experienced an allergic reaction, such events have been associated with the use of Filgrastim, the parent compound of Pegfilgrastim. The package insert for NEUPOGEN® contains a warning regarding the risk for allergic reactions.

Therefore, the following warning will be included in the NEULASTA™ Package insert: "Allergic-type reactions, including anaphylaxis, skin rash and urticaria, occurring on initial or subsequent treatment have been reported with the parent compound of NEULASTA™, Filgrastim. In some cases, symptoms have recurred with rechallenge, suggesting a causal relationship. Allergic-type reactions to NEULASTA™ have not been observed in clinical trials. If a serious allergic reaction or an anaphylactic reaction occurs, appropriate therapy should be administered and further use of NEULASTA™ should be discontinued."

Special Topics

Basis for Non-Inferiority Trial Design

Background

Amgen's licensing strategy for Pegfilgrastim was to demonstrate non-inferiority to the licensed product Filgrastim (NEUPOGEN®) in two phase 3 pivotal trials: one (study 980226) using a weight adjusted dose of Pegfilgrastim and the second (study 990749) using a fixed dose. In preliminary discussions, FDA established the following requirements for the development program: that two trials would be required to establish reproducibility, and that the trials should be conducted in a population receiving chemotherapy regimens that would produce a significant incidence of febrile neutropenia (approximately 40% as outlined in the ASCO guidelines for use of Hematopoietic Growth Factors). In addition, the non-inferiority margin (the amount of the therapeutic effect of Filgrastim which could be lost yet still result in a determination of non-inferiority) would need to be one which would retain a clinically important effect (i.e., clinically important reduction in DSN likely to predict reduction in incidence of febrile neutropenia). Amgen chose to use the combination of doxorubicin 60 mg/m2 and docetaxel 75 mg/m2, and designated a non-inferiority margin of 1 day based on a proposed effect size of 4 days (i.e., that addition of Filgrastim reduces DSN from approximately 6 days to approximately 2 days and that the incidence of febrile neutropenia would increase most rapidly with DSN of ≥4 days). This discussion will examine the validity of these design elements.

Discussion Regarding Febrile Neutropenia Rate

In the background package for the End of Phase 2 meeting (IND — amendment —, March 5, 1999), Amgen provided three references to characterize the relationship between the dose-intense combination regimens of doxorubicin and docetaxel and the incidence of febrile neutropenia (Kennedy, 1997; Dieras, 1997; and Misset et. al, 1998). Data from Nabholtz (personal communication) was also included. Additional abstracts by Dieras (1998) and Di Leo (1998) were presented at the End of Phase 2 meeting (May 13, 1999). A subsequent literature review identified the following additional references: Itoh (2000), Muthalib (2000), Lembersky (2000) and Nabholtz (2001). These references are briefly summarized below.

<u>Discussed in Background Package or Presented for End of Phase 2 Meeting</u>

The Kennedy (1997 ASCO abstract) data containing the results for subjects with solid tumors receiving a dose-intensive docetaxel/doxorubicin regimen without hematopoietic growth factor support was presented. The information presented included rates of febrile neutropenia (defined as grade 4 neutropenia with

unspecified fever level). Eight subjects (20 cycles total) received doxorubicin and docetaxel at 40/60 and 5 subjects (13 cycles total) received 50/60. Of these subjects, 5/8 (63%) and 4/5 (80%) experienced febrile neutropenia.

Dieras (1997 review article), Misset (1998 ASCO abstract) and Misset (1999 publication) reported on a single dose-finding study of doxorubicin and docetaxel in the first line treatment of patients with metastatic breast cancer. The following information has been taken from Misset (1999). Forty-two patients were enrolled in one of six dose groups made up of the following combinations of doxorubicin and docetaxel: 40/50, 40/60, 50/60, 50/75 50/85 and 60/60. For the purpose of documenting the potential febrile neutropenia rate (defined as grade 4 neutropenia, grade 2 fever and IV antibiotic use or hospitalization) for the chemotherapy utilized in studies 980226 and 990749, the following doses are most relevant because they are similar to but do not exceed the dose of 60/75 utilized in studies 980226 and 990749): 50/60, 60/60 and 50/75. The febrile neutropenia rates for these groups were 60% (5/10), 33% (2/6) and 50% (5/10), respectively for an overall rate of 46% (12/26).

The data presented from Nabholtz at the End of Phase 2 meeting was from a personal communication, and Amgen was unable to obtain for submission to the BLA the source data from the company (now — , that sponsored the referenced trial. The data was subsequently reported in preliminary form in an article (Oncologist, 2001) which will be discussed in the following section.

Dieras (1998 abstract) discussed the results for 45 metastatic breast cancer patients treated with doxorubicin and docetaxel (50/75). Thirty-six percent of patients were reported to have experienced febrile neutropenia (no definition provided).

Additional Data from Literature Search Included in the BLA Submission
Di Leo (1998 abstract) reported a trial using doxorubicin and docetaxel in alternating cycles (75/100 over six cycles total) and concurrently (50/75 over four cycles). The rate of febrile neutropenia (no definition provided) for the 29 subjects in the concurrent group was 48%.

Itoh (2000) studied advanced breast cancer patients receiving combination doxorubicin and docetaxel with randomization as to which drug was administered first. For each randomized group, the MTD was established for the combination. For the purpose of this discussion, only the results for the doxorubicin first group will be discussed as this was the sequence used in the Pegfilgrastim pivotal trials. The dose escalation for this sequence resulted in 6 patients receiving doxorubicin and docetaxel 50/60 and 6 receiving doxorubicin and docetaxel 50/70. Febrile neutropenia was reported only for the 50/70 group. In this group, 67% of subjects (4/6) experienced febrile neutropenia (defined as grade 4 neutropenia with temperature >38.0 C). An additional patient in this group received G-CSF for prolonged neutropenia.

Muthalib (2000) studied 18 patients with metastatic breast cancer receiving doxorubicin and docetaxel 50/60 for six cycles. Six subjects experienced febrile neutropenia (as defined as a temperature of at least grade 2 fever and grade 4 neutropenia with i.v. antibiotics or hospitalization). An additional 3 subjects had leukopenia with fever or infection. The febrile neutropenia rate, including leukopenia with fever or infection, was therefore 50% (9/18).

Lembersky (ASCO 2000 abstract) reported on an NSABP phase 2 trial conducted at 14 centers in stage IIIB and stage IV breast cancer subjects. Doxorubicin and docetaxel 60/60 was administered for an average of 5.2 cycles. Of 73 subjects considered eligible for toxicity assessment, 40% (29/73) experienced febrile neutropenia (no definition provided).

Nabholtz (2001) reviewed a number of studies utilizing doxorubicin and docetaxel. In addition to a number of the studies discussed by the authors above, Nabholtz describes data from an additional study (TAX 306). In TAX 306, doxorubicin and docetaxel was used in 213 subjects at a dose of 50/75 for an average of 8 cycles. Febrile neutropenia (defined as grade 4 neutropenia, grade 2 fever and IV antibiotic use or hospitalization) was reported in 33% of subjects. These results correspond to the analyses presented at the End of Phase 2 meeting based upon personal communication from Nabholtz.

Summary

The results for the studies discussed above are presented in the summary table below. The febrile neutropenia rate varies from 33% to 80% with an overall average (weighted by sample size) of 39%. The 95% confidence intervals (normal approximation) around the polled rate are 34% (lower bound) to 43% (upper bound).

Although the doses of doxorubicin and docetaxel and the definitions of febrile neutropenia differ from study to study, on the whole these studies might be expected to somewhat underestimate the underlying rate of febrile neutropenia without growth factor support for the chemotherapy regimen used in pivotal studies 980226 and 990749 for the following reasons:

- The doses of one or more of the agents in the doxorubicin and docetaxel combination were uniformly lower than the 60/75 used in studies 980226 and 990749.

Although some studies had a slightly lower temperature threshold for fever in the case definition of febrile neutropenia than did Amgen's pivotal studies (grade 2 (>38.0 C) vs. ≥38.2 C), several defined febrile neutropenia to include administration of IV antibiotics or hospitalization in addition to the more objective ANC and temperature criteria.

Based on the above data, FDA determined that there are adequate data to support that the doxorubicin and docetaxel regimen used in Pegfilgrastim pivotal studies was sufficiently myelosuppressive to justify the use of primary prophylactic Filgrastim, based on an overall estimated febrile neutropenia rate of approximately 40%.

Table 20: Summary of Referenced Publications

Study	Doxorubicin/ Docetaxel Dose (mg/m^2)	Number of Subjects	Febrile Neutropenia Rate (%)
Kennedy 1997 ASCO Abstract	40/60	8	63
	50/60	5	80
Misset 1999 Annals of Oncology	50/60	10	60
	60/60	6	33
	50/75	10	50
Dieras 1998 ASCO Abstract	50/75	45	36
DiLeo 1998 ASCO Abstract	50/75	29	48
Itoh 2000 Clinical Cancer Research	50/70	6	67
Muthalib 2000 Jpn. J. Cancer Chemother.	50/60	18	50
Lembersky 2000 ASCO Abstract	60/60	73	40
Nabholtz 2001 The Oncologist	50/75	213	33
Overall (95% confidence interval)		423	39 (34 to 43)

Justification of the1 day Non-inferiority Margin Used in Pegfilgrastim Pivotal Studies

The primary endpoint for pivotal studies 980226 and 990749 was the duration of severe neutropenia (DSN: days with ANC < 0.5 x 10^9/L), with a specified non-inferiority margin of one day. This margin was chosen based upon both clinical and statistical grounds, and was felt to represent preservation of 75% to 80% of the treatment effect (shortening of DSN) predicted to be associated with the use of Filgrastim in the proposed dose-dense chemotherapy regimen. The basis for use of DSN as a surrogate for febrile neutropenia (the clinical benefit endpoint of interest) was derived from published data regarding the relationship between DSN and the incidence of febrile neutropenia, the relationship between DSN and incidence of febrile neutropenia associated with the use of dose-intensive regimens of doxorubicin and docetaxel in the absence of growth factor support, and the prior experience with Filgrastim in which reduction febrile neutropenia was correlated with reduction in DSN. The use of a non-inferiority margin of 1 day was discussed and accepted during pre-phase 3 discussions in 1999.

The following is a review of information used to support selection of the 1-day non-inferiority margin. The key points include:

1. ***The published median DSNs in the absence of hematopoietic growth factor support for dose-intensive doxorubicin and docetaxel regimens similar to that proposed for the pivotal studies were 6 to 7 days.***

At the time the phase 3 program for Pegfilgrastim was being developed, 2 studies described the relationship between various doses of doxorubicin and docetaxel and the duration of severe neutropenia (DSN) in the absence of growth factor support. Dieras (1997 review article), Misset (1998 ASCO abstract), and Misset (1999 publication) published reports on the first, a dose-finding study of doxorubicin and docetaxel in the first line treatment of patients with metastatic breast cancer. Forty-two patients were enrolled in one of six dose groups made up of the following combinations of doxorubicin and docetaxel: 40/50, 40/60, 50/60, 50/75, 50/85, and 60/60. The results indicated consistency between dose groups with a median duration of grade 4 neutropenia of at least 5 days. The dose (50/75) closest to that used in the two pivotal trials (60/75) resulted in a median duration of grade 4 neutropenia of 7 days. In a second study reported by Dieras (1998), 45 subjects with metastatic breast cancer were treated with doxorubicin and docetaxel at 50/75 without growth factor support. The median DSN was 6 days with a range of 1-13 days. The predicted median DSN with the proposed dose-intensive regimen in the

absence of growth factor support of 6 to 7 days was similar to that observed in the control arm of Amgen Study 8801, the pivotal study for the approval of NEUPOGEN® (Filgrastim) in the setting of chemotherapy-induced neutropenia. Table 21 shows the relationship between doxorubicin and docetaxel dose and DSN in these 2 studies.

Table 21: Duration of Grade 4 Neutropenia (DSN)
Doxorubicin/Docetaxel without Hematopoietic Growth Factor Support

Study	Doxorubicin/Docetaxel (mg/m^2)	Number of Subjects	Median DSN (Range)
Dieras (1997) Misset (1998) Misset (1999)	40/60	8	5 (2-11)
	50/60	10	5 (2-13)
	50/75	10	7 (1-13)
	60/60	6	6 (3-12)
Dieras (1998)	50/75	45	6 (1-13)

2. ***The predicted treatment effect of Filgrastim (the shortening of the DSN with the use of Filgrastim) with the proposed dose-intensive doxorubicin and docetaxel regimen was estimated at approximately 4 days.***

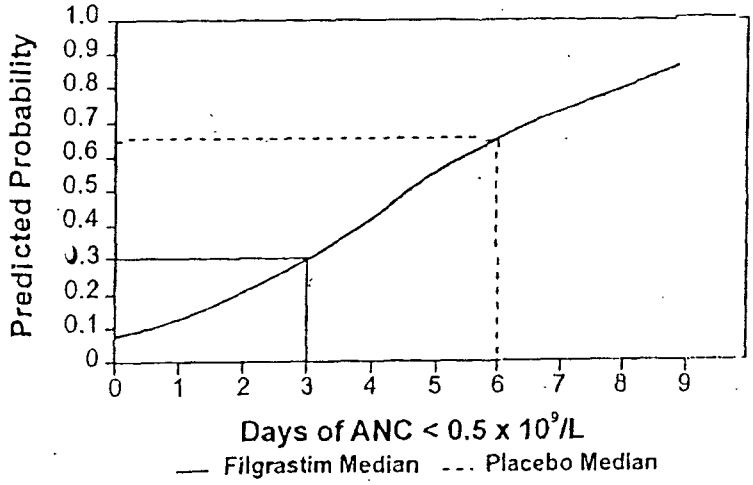
Because at the time of the design of these studies only limited data were available for patients with breast cancer treated with dose-intensive doxorubicin and docetaxel regimens with concurrent hematopoietic growth factor support, the predicted treatment effect of Filgrastim (the shortening of the DSN of the proposed dose-intensive regimen with the use of Filgrastim) could only be estimated. Based on Filgrastim study 8801, a reduction in median DSN of approximately 3.5 to 5

days would be expected with the use of growth factor support. During the planning of study 990147, the results of Amgen's phase 2 pilot study 980147 "A Randomized Study of Single Administration Pegfilgrastim or Daily Filgrastim as an Adjunct to Chemotherapy in Patients with High-risk Stage II or Stage III/IV Breast Cancer" were available. In this study, subjects in the control arm received the proposed dose-intensive doxorubicin and docetaxel regimen (60/75) with concomitant Filgrastim 5 µg/kg/day. The cycle 1 mean and median DSNs in this group were 2.2 days and 2.0 days, respectively, each with a standard deviation of 1.4 days. Using these data, the predicted treatment effect of Filgrastim with the proposed dose-intensive regimen could be estimated at approximately 4 days.

3. ***Demonstration of a difference of less than 1 day between the mean DSNs of subjects receiving Pegfilgrastim and Filgrastim during cycle 1 treatment with the proposed dose-intensive regimen would indicate that less than 25% of the treatment effect of Filgrastim was lost with the use of Pegfilgrastim. In addition, based on the literature (including Filgrastim licensing study 8801), a 1-day difference in DSN would be anticipated to result in approximately a 10% difference in febrile neutropenia. This was felt to be a meaningful and practical difference to exclude when comparing Pegfilgrastim to Filgrastim.***

The relationship between duration of neutropenia and incidence of febrile neutropenia was characterized in Amgen study 8801, the pivotal phase 3 trial of Filgrastim versus placebo in subjects undergoing chemotherapy for small-cell lung cancer (Blackwell and Crawford, 1994). In that trial, the median duration of grade 4 neutropenia in chemotherapy cycle 1 was 6 days for placebo subjects (n = 94) compared with 3 days for Filgrastim subjects (n = 86). Corresponding rates of febrile neutropenia (temperature $\geq$ 38.2 C with ANC $< 0.5 \times 10^9$/L) were 57% and 28%, respectively ($p < 0.001$). In a logistic regression analysis using both treatment groups, each day of grade 4 neutropenia was associated with an approximately 10% increase in the rate of febrile neutropenia. Figure 17 shows a plot of the predicted probability of developing febrile neutropenia versus duration of grade 4 neutropenia in chemotherapy cycle 1 of study 8801. A similar relationship was seen in subsequent cycles. These results in subjects with small-cell lung cancer are very similar to those reported by Bodey (1966) using data from subjects with acute leukemia.

Figure .17: Predicted Probability of FN from Study 8801



Adapted from Blackwell and Crawford, 1994

Based on the above data, FDA concludes that a 1-day non-inferiority margin was satisfactory to determine whether the beneficial effect of Filgrastim with the proposed dose-intensive doxorubicin and docetaxel regimen would be adequately preserved with the use of Pegfilgrastim.

APPEARS THIS WAY
ON ORIGINAL

Immunogenicity

Summary

- Three different assays were used for detection of binding antibodies against either Filgrastim or Pegfilgrastim: a radioimmunoassay (RIA), an enzyme-linked immunosorbant assay (EIA), and the — assay.

- Forty-six of the 534 subjects who received Pegfilgrastim were found to be seropositive to Filgrastim (32 subjects in the RIA assay, 2 subjects in the EIR assay, and 12 subjects in both RIA and EIA assays).

- Data obtained from competition assays with Pegfilgrastim or Filgrastim or by using the ' — demonstrated that seroreactivity observed with the RIA and EIA assays was due to nonspecific reactivity rather than specific antibody

- No subject was found to have evidence of neutralizing antibodies.

Assays for Detection of Serum Antibodies

The assays used to detect the presence of antibodies capable of binding to Pegfilgrastim and/or Filgrastim were changed during the course of the Pegfilgrastim development program. The first immunoassay used to detect antibodies binding to Pegfilgrastim or Filgrastim was a radioimmunoassay (RIA) that utilized immobilized r-metHuG-CSF (Filgrastim), followed by addition of serum samples, followed by ^{125}I-labeled protein A.

Therefore, a broader second-generation assay was developed : an enzyme-linked immunosorbant assay (EIA) that utilizied immobilized Filgrastim followed by serum sample addition, and enzyme-labeled anti-human IgG.

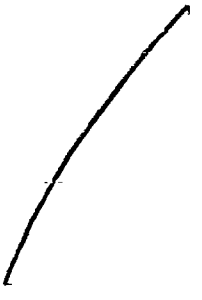
The — was adopted to overcome these limitations. The — represents state-of-the-art antibody detection and characterization methodology. With this new assay platform, any antibodies present in serum samples that can bind to either Pegfilgrastim or Filgrastim can be reliably detected. The major advantages gained by implementing this new assay — were the ability to detect antibodies specific to Pegfilgrastim that do not bind to Filgrastim, and the ability to detect low-affinity antibodies —

— In addition to detecting an immune response of a serum sample to between 1 and 4 different immobilized ligands, this system can be used to further characterize any immune response that is generated. The isotype(s), relative concentration, and relative affinity of the antibodies can be determined directly. The assay uses —

— A significant advantage of this detection system is that low affinity antibodies can be detected. There are immunoassay techniques that demonstrate better sensitivity than the —, however, these assays lack the ability to demonstrate specificity to the same degree possible with this new platform.

Throughout the Pegfilgrastim development program, one cell-based bioassay was used to test serum samples reactive in the above screening assays for neutralizing antibodies. This — Assay was an — that tests for the effect of antibodies to Pegfilgrastim or Filgrastim in human serum on the proliferation of — cells, a — cell line that responds to Pegfilgrastim, Filgrastim, and murine IL-3 (mIL-3) in a dose dependent manner.

Validation of assays



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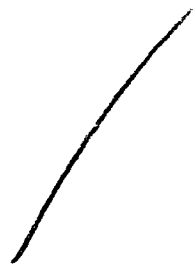

Results

For the phase 1 and certain phase 2 studies (970144, 970230, 980147, and 980230) only the RIA and EIA were available. The — assay was used in the later phase 2 and the pivotal studies (990117, 990118, 980226, and 990749). Although the Integrated Summary of Safety presents results from all 8 studies, it should be noted that 3 different screening methodologies are represented. However, the same cell-based bioassay to detect neutralizing antibodies was used throughout. Table 23 summarizes the incidence of antibodies detected in subjects receiving Pegfilgrastim or Filgrastim.

Table 22: Incidence of Antibodies to Filgrastim and Pegfilgrastim

	Filgrastim 5 µg/kg/day	Pegfilgrastim All doses
Number of subjects screened	340	534
Subjects with non-reactive samples	329	488
Subjects with ≥ 1 confirmed reactive samples	11/340 (3%)	46/534 (9%)
RIA and/or EIA*	8/61 (13%)	46/251 (18%)
—	3/279 (1%)	0/283 (0%)
Reactive samples subjected to cell-based immunoassay for neutralizing antibodies	11	46
Detected neutralizing antibodies	0 (0%)	0 (0%)

*Determined to be due to non-specific reactivity, not specific antibody.

Sera of 534 subjects who received Pegfilgrastim were screened for antibodies. Of those, 251 were screened against Filgrastim in the RIA and EIA assays. A total of 46 of these subjects were found seropositive to Filgrastim (32 patients in the RIA assay, 2 patients in the EIA assay and 12 patients in both RIA and EIA assays). The 46 sera reactive in the RIA and/or EIA were not verified to be positive due to human anti Filgrastim antibody. These 46 sera were tested for neutralizing antibodies in the bioassay against Pegfilgrastim and Filgrastim and all were negative against both drugs. Additional sera from 283 patients who received Pegfilgrastim were screened for antibodies against Pegfilgrastim and Filgrastim in the — assay. All sera were negative. The 3 sera from patients who received Filgrastim which were positive in the — when assayed with Filgrastim were negative when assayed with Pegfilgrastim.

Across all Pegfilgrastim dose groups, 5 subjects (2%) had a last available ANC less than 1.0 x 10^9/L, compared with 6 Filgrastim subjects (2%). None of those with a low ANC were the same subjects who tested seropositive in the — assay (see above).

In summary, 3 different assays were used in the screening process for detection of binding antibodies against either Filgrastim or Pegfilgrastim: the EIA assay (the most sensitive assay with a detection level of — the — assay (detection level —, followed by the RIA (detection level — — — assay it is possible to detect binding antibodies against Pegfilgrastim. The specificity of the binding antibodies which were detected in sera from 46 patients (using the RIA and/or EIA) was not confirmed by competition with Pegfilgrastim or Filgrastim. All 46 sera were negative in the neutralizing bioassay (detection level — for Filgrastim and — for Pegfilgrastim). Data obtained using the — confirmed that the seroreactivity observed with the RIA and EIA assays was due to nonspecific reactivity rather than specific antibody.

Although all the assays used to detect antibodies in these investigations have been properly validated, the incidence of antibody development in patients receiving Pegfilgrastim has not been adequately determined. The specific — assay used in these investigations was relatively insensitive, and may not have detected very low levels of antibody. In many studies, the time interval between post treatment and blood drawn for antibody screening is unclear. This time interval is important for the following reasons: 1) The patients are treated with chemotherapy, which can delay immune responses, and 2) Pegfilgrastim, which has a lower renal clearance than Filgrastim, if present in the serum when blood is drawn, can bind to antibodies and mask their presence in the screening assays. At FDA's request Amgen has agreed to develop and validate a more sensitive — based assay, and to confirm the antibody findings in a large number of patients receiving Pegfilgrastim as a Post-Marketing Commitment.

POSTMARKETING COMMITMENTS

Amgen has submitted written commitments to provide additional information on ongoing studies and to conduct post-marketing studies as described in their letters of January 24 and 27, 2002, and as outlined below:

1) To develop and fully validate a — assay with a sensitivity of — or better for detection of anti-Pegfilgrastim antibodies in human serum by July 2002.

   a) Amgen will use — from — for testing the sensitivity of the — assay.

   b) Amgen will use multiple human serum samples that previously tested antibody-positive to Filgrastim or Pegfilgrastim as part of the — assay validation.

   c) If Amgen is unable to achieve a sensitivity of at least — using the — assay by July 2002, the company commits to meet with the Agency to discuss a schedule to develop and validate an ELISA to detect anti-Filgrastim and anti-Pegfilgrastim antibodies with a sensitivity of at least — —

   d) Amgen will obtain serum samples from 500 individual patients enrolled in the Phase 3 protocol #20010144 entitled "A Double-blind, Placebo-Controlled, Multicenter, Randomized Study Evaluating the Prophylactic Use of Pegfilgrastim on the Incidence of Febrile Neutropenia in Subjects with Advanced Breast Cancer Treated with Single Agent Doxetaxel", who have received Pegfilgrastim. Sampling times should take into account the time required to mount an antibody response and ongoing chemotherapy. These samples will be analyzed with the new, validated immunogenicity assay.

2) To obtain data to support the proposed — resin re-use of the — column used in the purification of Pegfilgrastim bulk. Validation studies were initiated in January 2002, will be completed by June 2003, and validation data will be submitted to FDA by December 2003.

3) To submit results from an ongoing study to evaluate the pharmacokinetics (PK), safety and efficacy of Pegfilgrastim in pediatric patients. The protocol for study 990130 entitled "A Single Dose Per Cycle Pegfilgrastim as an Adjunct to VadriaC/IE Chemotherapy in Pediatric Sarcoma Patients" was submitted to BB-IND on August 9, 1999 and the study was initiated in April 2000. Patient accrual will be completed by December 2004, the study completed (last patient exited) by September 2005, and the final clinical study report, with revised labeling if applicable, will be submitted to FDA by February 2006.

   Upon completion of the study and prior to finalization of the study report, Amgen commits to discuss with the Agency the appropriateness of an

— , to make Pegfilgrastim —
— and approval of an indication for pediatric use.

4) To develop a pediatric dosage form based upon the data obtained from the pediatric study 990130 described in item 3. Formulation development will be completed by March 2006, six-month stability studies will be completed by September 2006, and a supplement with revised labeling will be submitted to FDA by November 2006.

5) To submit data from an ongoing study to assess the PK and safety of retreatment with Pegfilgrastim. A retreatment study, SD/01 990736, entitled "A Study of Retreatment with Pegfilgrastim in Subjects Receiving Myelosuppressive Chemotherapy" was submitted to BB-IND — on August 19, 1999 and the study was initiated in February 2000. An amendment to modify eligibility criteria will be submitted by April 2002, patient accrual will be completed by June 2004, the study completed (last patient exited) by October 2004, and a clinical study report, with revised labeling if applicable, submitted to FDA by May 2005.

6) To conduct a surveillance study of patients with sickle cell disease who received treatment with Pegfilgrastim or Filgrastim. This study will be designed to capture demographics and safety data to evaluate the safety profile of these cytokines in this patient population. A protocol will be submitted to FDA by September 2002, the study initiated by December 2002, and data submitted to FDA annually for five years, or until such time as Amgen, Incorporated, the FDA, and an expert panel composed of recognized experts in the field of hemoglobinopathies reach consensus that adequate data has been accrued to assess the safety of Pegfilgrastim or Filgrastim in patients with sickle cell disease.

7) To evaluate the PK of Pegfilgrastim in patients with renal impairment. Amgen, Incorporated will conduct an open-label, single-dose PK study of 6.0 mg subcutaneous Pegfilgrastim. The protocol will be submitted by April 2002, the study initiated by May 2002, patient accrual completed by November 2002, the study completed (last patient exited) by November 2002, and the final clinical study report, with revised labeling if applicable, will be submitted to FDA by August 2003.

Clinical Reviewer's Recommendation

Approval is recommended for pegfilgrastim in a 6 mg. fixed-dose formulation for the following indication with agreed upon labeling and Post Marketing Commitments:

"NEULASTA™ is indicated to decrease the incidence of infection, as manifested by febrile neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia."

/S/ 1/31/02

Joseph E. Gootenberg, MD Date
Clinical Reviewer

Concurrence:

/S/ 1-31-2002

Patricia Keegan, MD Date
Director, DTBOP

Appendices

Review Team Membership

Reviewer	Division	Responsibility
Pluznik, Dov, Chairperson	DTP	Product
Gootenberg, Joseph E., Co-Chair	DCTDA	Clinical
Beaucage, Serge	DTP	Product
Gnecco, Clare	DB	Biostatistics
Serabian, Mercedes	DCTDA	Toxicology
Green, Martin	DCTDA	Pharmacology
Amin, Pankaj	DMPQ	Facilities
Hasemann, Patricia	DIS	Bioresearch Monitoring
Crim, James	DARP	Administrative/Regulatory
Giuliani, Susan	DARP	Administrative/Regulatory

Abbreviations and Definitions of Terms

Abbreviation	Definition or Term
AE	Adverse event
ALT	Alanine transaminase; also known as SGPT, serum glutamic pyruvic transaminase
ANC	Absolute neutrophil count
ANC recovery	ANC observed or imputed to be $\geq 2 \times 10^9$/L after the chemotherapy-induced nadir
AST	Aspartate transaminase; also known as SGOT, serum glutamic oxaloacetic transaminase
CBC	Complete blood count including white blood cell count with differential, platelet count, red blood cell count, hemoglobin, and hematocrit
CLcr	Creatinine clearance
cpm	Counts per minute
CRF	Case report form
CRO	Contract research organization
CSMT	Clinical Study Management Team
%C.V.	Coefficient of variation
DSMC	Data Safety Monitoring Committee
DSN	Duration of severe neutropenia; number of days on which ANC was observed or imputed to be $< 0.5 \times 10^9$/L
ECOG	Eastern Cooperative Oncology Group

Abbreviation	Definition or Term
EIA	Enzyme-linked immunosorbent assay
FDA	United States Food and Drug Administration
Filgrastim-SD/01	Pegfilgrastim; polyethylene glycol covalently bound to Filgrastim (PEG-r-metHuG-CSF)
FN	Febrile neutropenia; for efficacy, FN is defined as ANC < 0.5 x 10^9/L and oral, or its equivalent, temperature ≥ 38.2°C on the same day in a cycle.
G-CSF	Granulocyte colony-stimulating factor
Ig	Immunoglobulin: IgG, IgM, and IgA.
IRB	Institutional Review Board
kd	Kilodalton
LDH	Lactate dehydrogenase
mITT	Modified intent-to-treat
mmHg	Millimeters of mercury
MUGA	Multigated (radionucleotide) angiogram
nadir	Minimum recorded ANC per cycle of chemotherapy
NCI CTC	National Cancer Institute Common Toxicity Criteria, version 2
OD	Optical density
PD	Pharmacodynamics
PEG	Polyethylene glycol
PI	Principal Investigator

Abbreviation	Definition or Term
PK	Pharmacokinetics
pP	Per-protocol
r-metHuG-CSF	Recombinant-methionyl human granulocyte colony-stimulating factor (Filgrastim, NEUPOGEN.)
RBC	Red blood cell
RU	Response units
SD	Standard deviation
SDMC	Safety Data Monitoring Committee
SD/01	Pegfilgrastim; polyethylene glycol covalently bound to Filgrastim (PEG-r-metHuG-CSF)
SE	Standard error
SN	Severe neutropenia; defined as observed or imputed ANC< 0.5×10^9/L
Time to ANC Recovery	Time from study day 1 to first day in which the observed or imputed ANC $\geq 2 \times 10^9$/L, after the expected chemotherapy-induced neutrophil nadir
ULN	Upper limit of normal
WBC	White blood cell

References Cited

Amgen Inc. Study No. 91134. A multicenter double blind placebo-controlled randomized phase 3 trial of Filgrastim as an adjunct to chemotherapy for acute myeloid leukemia. *1996;* Ref Type: Report.

Allen RC, Mireles MA, Welch W, Hunt T, Lockbaum P, Schwab G. Phase I study comparing daily Filgrastim and single dose sustained-duration Filgrastim (SD/01) in normal volunteers: Effects on neutrophil respiratory burst activities. *Blood* 1999;94:172b.

Beuzeboc P, Dieras V, Misset JL, et al. A phase 1 study of taxotere (T) doxorubicin (A) and rhuGCSF (Lenograstim) as 1st line chemotherapy (CT) in metastatic breast cancer (MBC). *Proc Am Soc Clin Oncol.* 1998;17:205a. Abstract.

Blackwell S, Crawford J. Filgrastim (r-metHuG-CSF) in the chemotherapy setting. In: Morstyn G, Dexter TM, eds . *Filgrastim (r-metHuG-CSF) in Clinical Practice.* 1994:103-116.

Bodey GP, Buckley M, Sathf YS, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med* 1966;64:328-340.

Crawford J, Ozer H, Stoller R, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. *N Engl J Med* 1991;325:164-170.

Costa SD, von Minckwitz G, Eiermann W, et al. Phase II trial of dose-intensified preoperative chemotherapy with doxorubicin/docetaxel in operable breast cancer. *Proc Am Soc Clin Oncol.* 1998;17:134a. Abstract.

Delgado C, Francis GE, Fisher D. The uses and properties of PEG-linked proteins. *Critical Reviews in Therapeutic Drug Carrier Systems* 1992;9:249-304.

Dieras V, Chevallier B, Kerbrat P. A multicenter phase II study of docetaxel 75 mg/m2 as first line chemotherapy for patients with advanced breast cancer. *Cancer* 1996;74:650-656.

Dieras V. Review of docetaxel/doxorubicin combination in metastatic breast cancer. *Oncology* 1997;11:31-33.

Dieras V, Barthier S, Beuzeboc P, et al. Phase II study of taxotere in combination with doxorubiin as 1st line chemotherapy of metastatic breast cancer. 21st *San Antonio Breast Cancer Symposium.* 1998;50:262. Abstract.

Di Leo A, Crown J, Nogaret LM, et al. Doxorubicin (A) followed by docetaxel (T) versus doxorubicin + docetaxel (AT) in the adjuvant treatment of breast cancer. *Parallel Session.* 1998:116.

Dorr VJ, Standiford S. A pilot study of Taxotere and Adriamycin combined with surgery and radiation in locally advanced breast cancer. *San Antonio Breast Cancer Symposium.* 1998. Abstract.

Dresel V, Tulusan AH, Costa SD, et al. Dose-intensified preoperative chemotherapy with doxorubicin/doxetaxel in operable breast cancer: a phase II trial. *San Antonio Breast Cancer Symposium.* 1998;327. Abstract.

Itoh K, Sasaki Y, Fujii H, et al. Study of dose escalation and sequence switching of administration of docetaxel and doxorubicin in advanced breast cancer. *Clinical Cancer Research.* 2000;6:4082-4090

Kennedy MJ, Elza K, Donehower R. Phase I and pharmacologic (pk) study of docetaxel and doxorubicin in patients with solid tumors: dose limiting toxicity at the first dose level. *Proceedings of ASCO.* 1997:16:240A. Abstract 845.

Lembersky BC, Anderson S, Smith R, et al. Phase II trial of doxorubicin and docetaxel for locally advanced and metastatic breast cancer: Preliminary results from NASABP BP-57. *Proceedings of ASCO.* 2000;19:403 Abstract 403

Limentani SA, Erban JK, Sprague KA, et al. Phase II study of doxorubicin and docetaxel as neoadjuvant therapy for women with stage IIB or III breast cancer. *Proc Am Soc Clin Oncol.* 2000;19:131a. Abstract.

Misset JL, Dieras V, Gruia G, et al. Dose-finding study of docetaxel and doxorubicin in first-line treatment of patients with metastatic breast cancer. *Annals Of Oncology* 1999;10:553-560.1999

Misset JL, Dieras V, Bozec L, et al. Long term follow up of the phase I/II study of docetaxel and doxorubicin as a first line chemotherapy in metastatic breast cancer. *Proceedings of ASCO.* 1998;17:613. Abstract.

Muthalib A, Darwis I, Pryogo N, et al. Preliminary results of a multicenter phase II trial of docetaxel in combination with doxorubicin as first line chemotherapy in Indonesian patients with advanced or metastatic breast cancer. *Jpn J Cancer Chemother.* 2000;276:498-504.

Nabholtz JM, Riva A. Taxane/anthracycline combnations: setting a new standard in breast cancer. *The Oncologist.* 2001;6:5-12.

Ravdin PM, Burris HA, Cook G. Phase II trial of docetaxel in advanced anthracycline resistant or anthracenedione resistant breast cancer. *J Clin Oncol* 1995;13:2879-2885.

Trillet--Lenoir V, Green J, Manegold C, et al. Recombinant granulocyte colony stimulating factor reduces the infectious complications of cytotoxic chemotherapy. *Eur J Cancer* 1993;29 A:319-324.

Trudeau ME, Eisenhauer EA, Higgins BP. Docetaxel in patients with metastatic breast cancer: a phase II study of the national cancer institute of Canada clinical trials group. *J Clin Oncol* 1996;14:422-428.

Valero V, Holmes FA, Walters RS. Phase II trial of docetaxel: a new, highly effective antineoplastic agent in the management of patients with anthracycline resistant metastatic breast cancer. *J Clin Oncol* 1995;13:2886-2894.

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