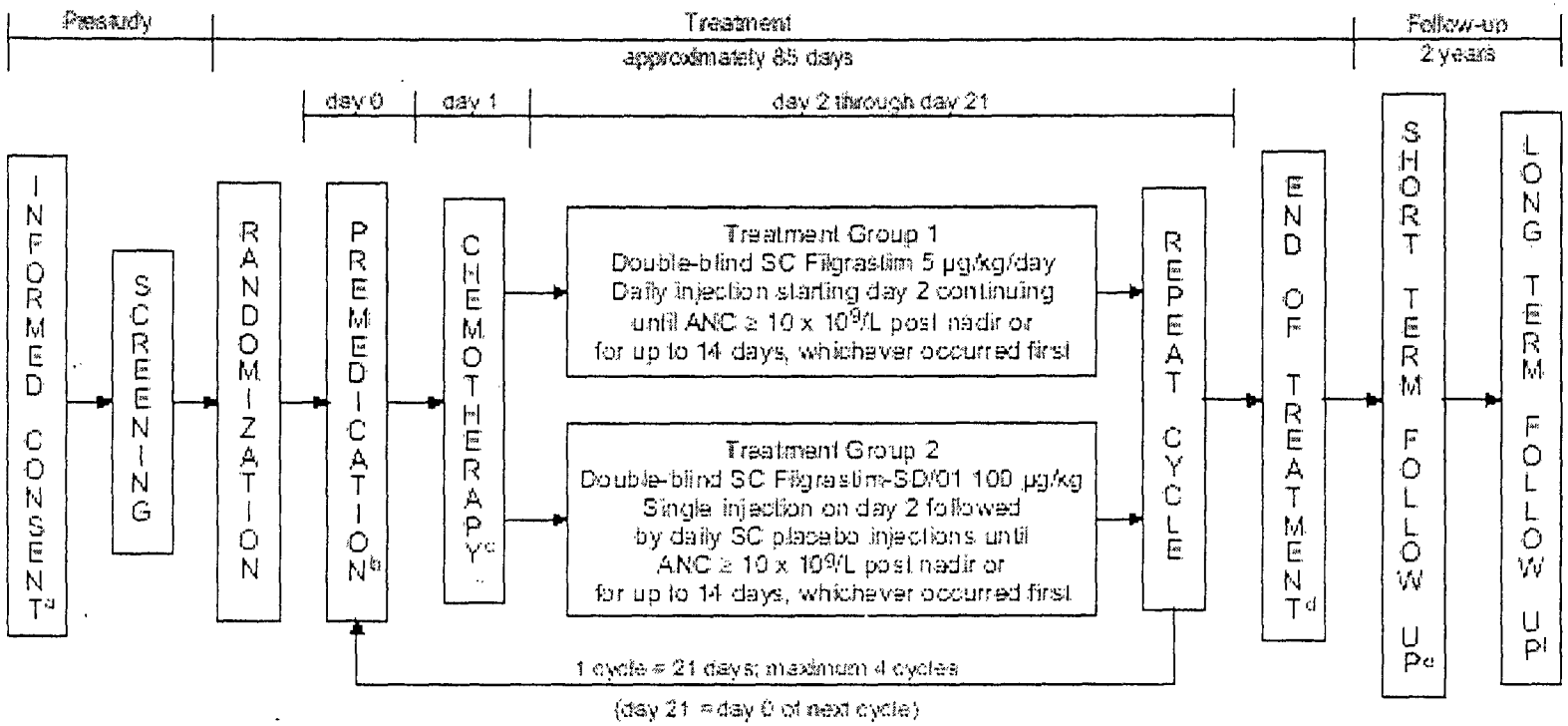
Figure 2: Study 980226 Schema of Study Design



[a] Informed consent was to be obtained before performing any procedures solely for study purposes. Subjects, however, could receive premedication for chemotherapy before randomization.

[b] Subjects were allowed to receive premedications for chemotherapy per suggested guidelines (dexamethasone, 8 mg twice daily, on day 0 and 1 before docetaxel and on day 2) or according to institutional practice. Subjects were to be randomized on or before the day of chemotherapy.

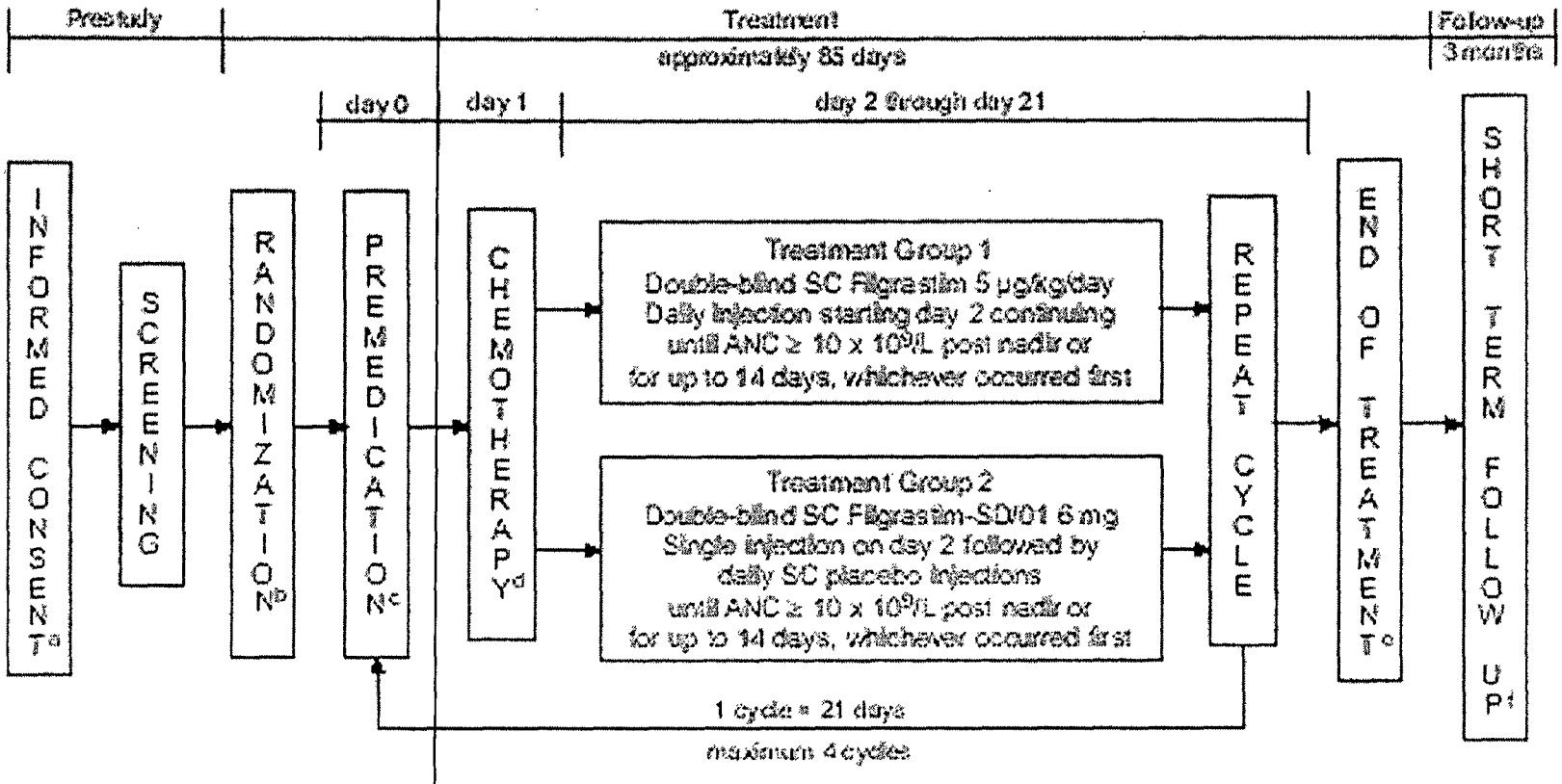
[c] Chemotherapy consisted of ≤ 4 cycles of an intravenous-bolus infusion of doxorubicin (60 mg/m²) followed approximately 1 hour later by a 1-hour intravenous infusion of docetaxel (75 mg/m²).

[d] End-of-treatment evaluations occurred either at the end of cycle 4 or at early termination.

[e] Short-term follow-up visits were scheduled 1 month and 3 months after the end of treatment.

[f] Long-term follow-up visits were scheduled quarterly during the first year after the end of treatment and then twice yearly for 1 additional year.

Figure 3: Study 990749 Schema of Study Design



[a] Informed consent was to be obtained before performing any procedures solely for study purposes.
[b] Subjects were randomized in a 1:1 ratio on the day of or day before chemotherapy.
[c] Subjects were allowed to receive premedications for chemotherapy per suggested guidelines (dexamethasone, 8 mg twice daily, on day 0 and 1 before docetaxel and on day 2) or according to institutional practice.
[d] Chemotherapy consisted of ≤ 4 cycles of an intravenous-bolus of doxorubicin (60 mg/m^2) followed 1 hour later by a 1-hour intravenous infusion of docetaxel (75 mg/m^2).
[e] End-of-treatment evaluations occurred either at the end of cycle 4 or at early termination.
[f] Short-term follow-up visits were scheduled 1 month and 3 months after the end of treatment.

Financial Disclosure

Pursuant to requirements defined in 21 CFR 54, an applicant is required to certify that all investigators and consultants participating in "covered clinical studies" have disclosed any financial arrangements that could influence the study out come.

Investigators in all phase 2 and phase 3 studies were requested to provide information pertaining to the following:

- Any financial arrangement between the sponsor and the individual that could influence the outcome of the study
- Any significant payments of other sorts (for example, grants, honoraria, retainer fees, equipment, etc.) made on or after February 2, 1999
- Any property interest held in the product tested
- Any individual, spousal, or dependent child equity interest exceeding a value of $50,000

The sponsor collected financial disclosure information from February 2, 1999 to a cut off date of December 31, 2000 from 73% of 889 investigators. Of the 27% who did not respond, 91% were subinvestigators. In addition, of the 27% of nonresponders, 56% of those did not enroll any subjects at their site. All but 3% of investigators certified that none of the financial arrangements of concern to FDA existed during the period covering the dates of their participation in the studies.

The sponsor has provided documentation that substantiates their due diligence in pursuing multiple attempts to secure the required information from those investigators who failed to provide financial disclosure.

The sponsor has certified that:

- One PI and 4 subinvestigators (at total 4 centers) held Amgen stock
- One subinvestigator held > $50,000 interest in a publicly traded company
- One subinvestigator reported "Significant Payments, no description"

FDA Conclusion

The distribution of patient accrual was such that no single study site provided a sufficient number of study subjects to allow the introduction of bias by manipulation of results at that site alone. In addition, subset analysis reveals that study results from sites involving investigators who had disclosed significant equity interest were similar to the study results from other study sites and did not significantly alter the efficacy or safety results.

Table 5: Financial Disclosure

Investigators with Reportable Interests and Significant Numbers of Subjects
(n ≥ 10 at Study Site)

Studies Involved: Study 980147 n = 154; Study 980226 n = 310

Name	Study	Site #	Principal Investigator/ Subinvestigator	Nature of Conflict	Number of Subjects at Study Site
			Principal Investigator	1	
			Principal Investigator	1	
			Subinvestigator	1	
			Subinvestigator	1	
			Subinvestigator	1	
			Subinvestigator	2	
			Subinvestigator	1	
			Subinvestigator	3	

Nature of Conflict:

1. Shareholder of Amgen stock
2. Equity interest greater than $50,000 in Amgen
3. Significant Payments, no description

Bioresearch Monitoring Inspection Results

SUMMARY STATEMENT

Bioresearch monitoring inspections were conducted at 3 clinical sites for one of the 2 pivotal trials:

> *Protocol 990749*, "A Blinded, Randomized, Multicenter Study to Evaluate Fixed Dose Single Administration of Pegfilgrastim per Cycle versus Daily Filgrastim as an Adjunct to Chemotherapy in Subjects with High-Risk Stage II or Stage III/IV Breast Cancer"

The results of the bioresearch monitoring inspections of 3 clinical sites in Europe (2 in Spain, 1 in Germany) indicated that the submitted data can be considered reliable and accurate. During the conduct of the trial, the sponsor monitor visited all 3 sites on multiple occasions and performed a 100% audit of case report forms (CRFs) and corresponding study documents. The majority of the deviations observed at the sites were reported by the sponsor in the application submission and the exceptions noted in the bioresearch monitoring inspections were minor in nature. There is no indication that the investigators' conduct of the trial compromised the overall integrity of the trial data.

BACKGROUND

A total of 157 subjects were enrolled under protocol 990749 at 34 sites in Europe, Australia, and the U.S. Inspections of 2 clinical sites in Spain and 1 clinical site in Germany were conducted in support of STN 125031/00 in accordance with FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. A total of 34 subjects were enrolled at the inspected sites representing approximately 22% of the total study enrollment.

Data audits were performed at the following clinical trial sites:

1. Dr. Michael Clemens (Center 18, 16 subjects)
   Trier, Germany
2. Dr. Jose Baselga (Center 22, 10 subjects)
   Barcelona, Spain
3. Dr. Vicente Guillem Porta (Center 24, 8 subjects)
   Valencia, Spain

INSPECTIONAL FINDINGS

All 3 investigators were issued a Form FDA 483 which listed deficiencies noted at the sites other than deviations reported by the sponsor. The following summary was based upon draft inspection reports and the Form FDA 483 observations.

1. **Dr. Michael R. Clemens**

   The inspection at this site revealed minor discrepancies in the ANC values reported on the case tabulations. The sponsor's representative explained that this was due to differences in calculation methods used by the local hospital (local laboratory used primarily for screening tests). In addition, several minor record keeping discrepancies were noted including loss of one randomization code envelope, blood testing results recorded on a CRF for screening procedures that correspond to a sample drawn 5 days after subject 001 was randomized, and a failure to sign and initial laboratory reports or document and explain record discrepancies. Instead of initialing and signing the laboratory reports, Dr. Clemens signed a laboratory data review form that stated laboratory results were reviewed periodically and out of range values were recorded as adverse events if clinically significant.

2. **Dr. Jose Baselga**

   Minor discrepancies were noted in the review of ANC values which the sponsor's representative stated were due to methods used by the local laboratories to calculate the values. This site used local hospital results for subject management purposes whenever central laboratory results were not available.

   Record keeping deficiencies included a failure to sign and date laboratory reports to indicate review by the clinical investigator. Dr. Balcega signed a laboratory data review form stating that he had reviewed laboratory results periodically and that out of range values were recorded as adverse events if considered clinically significant. It was also noted that subject 008 received Primperan as a concomitant medication on 05/03, however, this was not recorded in the CRF as a concomitant medication.

3. Dr Vicente Guillem Porta

Minor discrepancies were noted in the ANC values and the sponsor's representative stated that the discrepancies were due to a difference in calculation method by the local laboratory. This site used local hospital results whenever central laboratory results were not available. It was observed that laboratory reports were not signed and dated indicating the clinical investigator's review, however, a laboratory data review form was signed by Dr. Guillem stating he had reviewed laboratory results periodically and that out of range values were recorded as adverse events if considered significant.

This site was allowed by the sponsor to dispense the study medication to the subjects for self-administration or administration by the local health clinic. Subjects were instructed to keep the study drug refrigerated. There was no monitoring of the actual temperature storage conditions of the study drug. The site did not record the temperatures of the refrigerator where the study drug was kept prior to dispensing it to the subjects.

BIMO ADMINISTRATIVE FOLLOW-UP

Based upon review of the draft inspection reports and the observations listed on the Form FDA 483 issued to each investigator, all 3 inspections have been classified as voluntary action indicated (VAI). Correspondence was issued to each clinical investigator outlining the deviations noted. There is no indication that the investigators' conduct of the trial compromised the overall integrity of the trial data.

Pivotal Trial 980226: Conduct and Results of the Trial

Conduct of the Trial

The study was initiated on August 6, 1999 and the treatment, short-term follow-up phases and 6-month long-term follow-up evaluations were completed on January 25, 2001. The Original BLA submission presented all long-term follow-up data available as of January 30, 2001, and a safety update was submitted September 19, 2001.

Seventy-four centers were initiated, and multiple investigators at 62 centers in the United States and Canada enrolled subjects in this study. This study was conducted in accordance with the principles of the Declaration of Helsinki, the regulations of the United States Food and Drug Administration (FDA) and the International Conference on Harmonisation (ICH) Good Clinical Practice regulations/guidelines. During the course of the trial, no amendments were made to the protocol.

Unless their participation was terminated early, subjects were on study for at least 9 months, including approximately 3 months of active treatment and an additional 6 months for short-term follow-up. A total of 2 years of long-term follow-up after the end of treatment period is in progress.

An external Safety Data Monitoring Committee (SDMC) periodically reviewed the aggregate blinded safety data and unanimously recommended continuing the study at all meetings. The SDMC included 3 voting members and 2 nonvoting members. The voting members included a biostatistician and 2 physicians (including an oncologist) with experience in the use of growth factors. These 3 individuals were not directly involved with the conduct of the study and were not associated with Amgen Inc. Two individuals representing Amgen Inc., but not directly involved with the conduct of the study, served as nonvoting members on the SDMC and were the liaisons between the SDMC and the Clinical Study Management Team (CSMT). The committee was responsible for periodic review of safety data collected during the course of the study, including a review of data from subjects who met prespecified ANC related criteria that may have indicated the development of clinically significant antibodies. Analyses provided to the SDMC were descriptive in nature; inferential testing was neither conducted nor provided to the SDMC; however, the provisions of the SDMC charter allowed the SDMC members to request or to perform ad hoc analyses required to make decisions regarding the safety of the product. After each SDMC meeting, the members made recommendations by letter to the CSMT regarding continuation of the study.

The study protocol, the subject information and written informed consent forms, and any proposed advertising material were reviewed and approved by the institutional review board (IRB) at each participating center in accordance with the principles of FDA regulations 21 CFR 50 and 21 CFR 56, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), or as applicable in local law.

Enrollment and Disposition of Subjects

Three hundred subjects were planned with 150 subjects per treatment group. Sixty-two centers in the US and Canada enrolled 310 subjects (age range: 25 to 87 years) in the study. The first subject enrolled in the study (signed informed consent) on August 6, 1999, and the last subject completed the 6-month follow-up assessment on January 25, 2001. One hundred fifty-four subjects were randomized to receive a single SC injection of Pegfilgrastim 100 µg/kg per chemotherapy cycle, and 156 subjects were randomized to receive daily SC injections of Filgrastim 5 µg/kg/day.

Demographics

The two treatment arms were balanced for:

- Gender
- Age Distribution
- Percentage of Subjects $\geq$ 65 Years
- Racial Distribution
- ECOG Status
- Percentage of Subjects with Prior Radiotherapy
- Percentage of Subjects with Prior Chemotherapy
- Disease Stage

Summary demographic details are provided in the following table

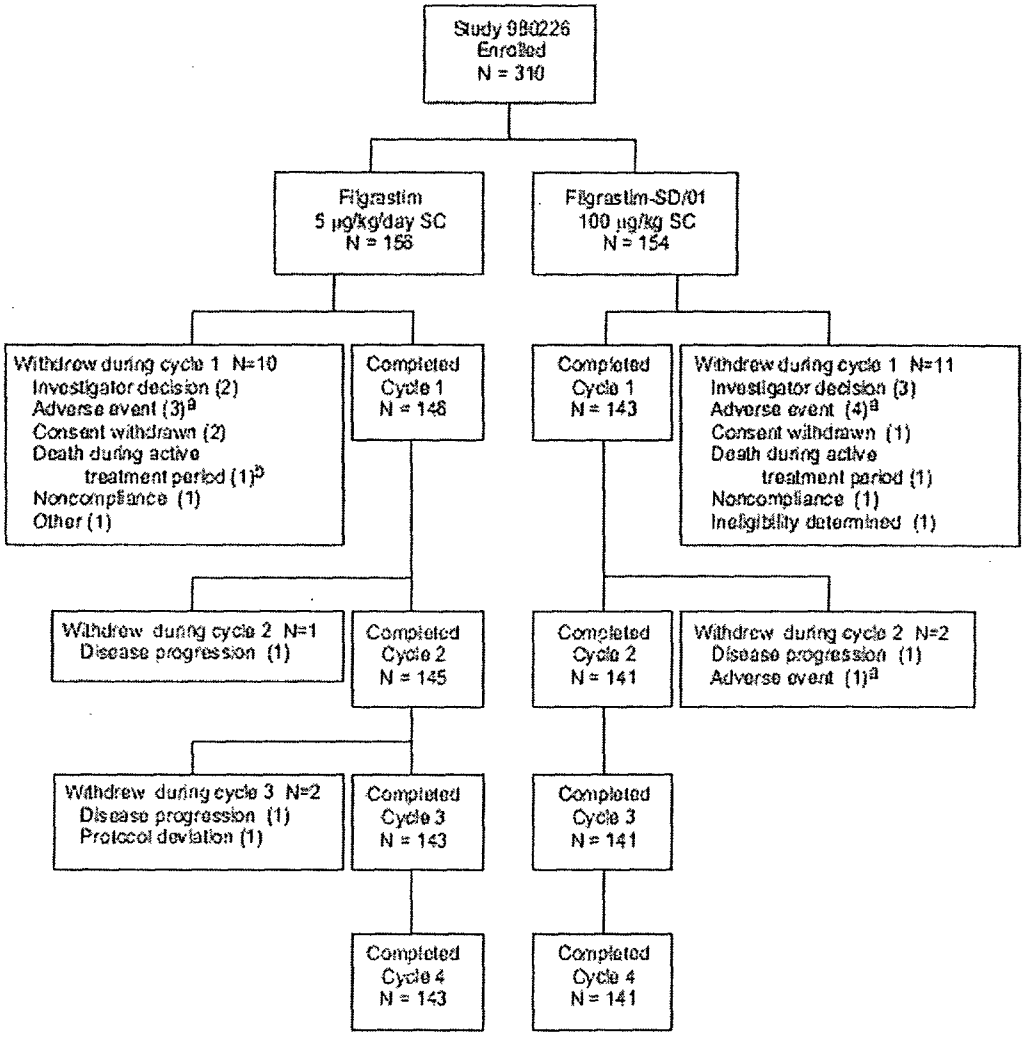
Table 6: Study 980226 Demographic Characteristics

	Filgrastim 5µg/kg/d (N = 156)	Pegfilgrastim 100 µg/kg (N = 154)
Mean Age (SD)	51.8 (11.6) years	50.9 (11.6) years
Age < 65 years	134	131
Age ≥ 65 years	22	23
Sex:	154 Female/ 2 Male	152 Female/ 2 Male
Race/ethnicity:	120 white, 19 black	116 white, 15 black,
	9 Hispanic, 4 Asian	12 Hispanic, 4 Native American
	1 Native American, 3 other	2 Asian, 5 other
ECOG Status		
0	115 (74%)	111 (72%)
1	32 (21%)	40 (26%)
2	6 (4%)	3 (2%)
3	0	0
4	0	0
Radiotherapy		
Yes	16 (10%)	13 (8%)
No	140 (90%)	141 (92%)
Chemotherapy		
Yes	18 (12%)	13 (8%)
No	138 (88%)	141 (92%)
Disease Stage		
II	75 (48%)	87 (56%)
III	41 (26%)	38 (25%)
IV	40 (26%)	29 (19%)

Subject disposition

Subject disposition by cycle during the treatment phase is presented in Figure 4 on the next page.

Figure 4: Study 980226 Subject Disposition



a "Adverse Event" combines withdrawals due to both "Intolerable Adverse Events" and "Intolerable Adverse Events (Consent Withdrawn)."

b Subject 4569001 died before receiving study drug.

Note: numbers in parentheses are numbers of subjects

Treatment Period

Of the 310 randomized subjects, 150 of 156 Filgrastim subjects (96%) received at least one dose of study drug while 151 of the 154 Pegfilgrastim subjects (98%) received at least one dose of study drug. Of the 310 subjects randomized, 284 (92%) subjects completed 4 cycles of chemotherapy and study drug administration.

Short-term Follow-up Period

Two hundred seventy-six of 288 subjects (96%) eligible for short-term follow-up at 1 month (136 Pegfilgrastim and 140 Filgrastim) completed the 1-month follow-up visit. Two hundred eighty-one of 285 subjects (99%) eligible for short-term follow-up at 3 months (141 Pegfilgrastim and 140 Filgrastim) completed the 3-month short-term follow-up visit.

Long-term Follow-up Period

Subjects on study were to be followed for a minimum of 2 years or until death. Of the 310 randomized subjects, 301 received study drug and were therefore eligible for long-term follow-up. The median follow-up duration at the time of the Safety update (September 19, 2001) was 395 days in the Pegfilgrastim group and 404 days in the Filgrastim group, with maximum follow-up of 590 days and 599 days for Pegfilgrastim and Filgrastim subjects, respectively.

Withdrawals

Treatment Period

Numbers of subjects and reasons for withdrawal were similar between Pegfilgrastim and Filgrastim subjects. Twenty-six (13 Pegfilgrastim and 13 Filgrastim: 8% of each treatment group) of 310 subjects did not complete the treatment period. The most frequent reason for discontinuation was an intolerable adverse event (5 Pegfilgrastim and 3 Filgrastim); none of these events were considered by the investigator to be related to study drug. Five subjects (3 Pegfilgrastim and 2 Filgrastim) were withdrawn because of an administrative/investigator decision. Three subjects (1 Pegfilgrastim and 2 Filgrastim) were withdrawn because of disease progression while on study. Three subjects (1 Pegfilgrastim and 2 Filgrastim) withdrew consent. Two subjects (1 Pegfilgrastim and 1 Filgrastim) were withdrawn because of noncompliance. One Pegfilgrastim subject was withdrawn because ineligibility was determined. One Filgrastim subject was withdrawn because of a protocol deviation (refused study drug injection). One Filgrastim subject was withdrawn for other reasons (a docetaxel adverse reaction).

One Filgrastim subject died before receiving study drug, and one Pegfilgrastim subject died during the active treatment phase; neither death was considered by the investigator to be related to study drug. One Filgrastim subject died within 30 days after last dose of study drug of septic shock and myocardial infarction subsequent to withdrawing from the study.

Short-term Follow-up Period
Four Filgrastim subjects died during the short-term follow-up period; no Pegfilgrastim subjects died during this period. Three subjects died of disease progression, and one died of *Pseudomonas* sepsis infection None of these deaths were considered by the investigator to be related to study drug. No other subjects withdrew during this time period.

Long-term Follow-up Period
Eight Pegfilgrastim and 6 Filgrastim subjects subject died of disease progression during the long-term follow-up period to the time of the Safety Update (September 19, 2001). No death was considered by the investigator to be related to study drug. Disease progression was reported in 18 (12%) Pegfilgrastim subjects, and 28 (19%) Filgrastim subjects. No new malignancies other than breast cancer were reported. Seven subjects are of unknown status because they were lost to follow-up.

Efficacy Results

During this review, the completeness of the efficacy data sets was assessed and analysis revealed minimal missing data (<5%). The sponsor's major efficacy analyses were confirmed by FDA reviewers.

In subjects receiving myelosuppressive chemotherapy, a single, SC injection of Pegfilgrastim 100 µg/kg per chemotherapy cycle met the criteria for non-inferiority to daily SC injections of Filgrastim 5 µg/kg/day for all primary and secondary efficacy endpoints in both the pP and mITT populations.

Primary Endpoint
The mean DSN in cycle 1 (pP subset) in the Pegfilgrastim and Filgrastim groups was 1.7 days and 1.6 days, respectively. The difference in the mean DSN was 0.1 days and the upper 97.5% confidence limit was 0.4 days, which was within the 1-day prespecified non-inferiority margin. (See Tables 7 and 8 below) The study, therefore, met the criterion for non-inferiority of Pegfilgrastim compared to Filgrastim.

Table 7: Study 980226 Cycle 1 Duration of Severe Neutropenia

	Filgrastim 5 µg/kg/day	Pegfilgrastim 100 µg/kg
Number of Subjects in Subset	141	146
Number of Subjects Started Cycle	129	131
Number (%) with Severe Neutropenia		
Yes	98 (76%)	100 (76%)
No	30 (23%)	31 (24%)
Unknown	1 (1%)	0 (0%)
Duration of Severe Neutropenia (Days)		
Unknown	1 (1%)	0 (0%)
0	30 (23%)	31 (24%)
1	27 (21%)	33 (25%)
2	46 (36%)	35 (27%)
3	18 (14%)	20 (15%)
4	5 (4%)	7 (5%)
5	2 (2%)	3 (2%)
6	0 (0%)	1 (1%)
Duration of Severe Neutropenia (Days)		
Mean	1.6	1.7
Median	2.0	2.0
SD	1.2	1.4
Q1, Q3	1.0, 2.0	1.0, 2.0
Min, Max	0, 5	0, 7

Table 8: Study 980226 Difference in Mean Duration of Severe Neutropenia, Cycle 1

Difference in Mean Duration of Severe Neutropenia: Pegfilgrastim vs. Filgrastim	
Difference Between Means	0.1
95% Confidence Interval	(-0.2, 0.4)

Secondary Endpoints
The calculated subject incidence of FN in cycle 1 was similar in the Pegfilgrastim and Filgrastim pP analysis subgroups (8% and 10%, respectively). The incidence of FN across all cycles was similar in the Pegfilgrastim and Filgrastim pP analysis subgroups. (Table 9) A claim for statistically significant superiority of Pegfilgrastim over Filgrastim in terms of FN incidence is not warranted for this study since no endpoint multiplicity adjustment was applied to the sponsor's reported confidence interval.

Exploratory analyses revealed no differences between the Pegfilgrastim and Filgrastim groups in DSN by prior chemotherapy exposure, DSN by age, DSN by weight, depth of ANC nadir, and median time to ANC recovery Aspects of these analyses are discussed further in the section "Special Populations". Analysis of DSN in cycles 2 through 4 was consistent with that of cycle 1, indicating that Pegfilgrastim is not less effective than Filgrastim in reducing the DSN in multicycle chemotherapy. (Table 10)

No meaningful differences between the Pegfilgrastim and Filgrastim groups were observed in time to ANC recovery; however, post-nadir ANCs in all cycles were different between treatment groups. Although of no clinical significance, the cycle day 10 to day 14 ANCs in the Filgrastim group were uniformly higher than those of the Pegfilgrastim group (see Figure 5, "Median ANC Profiles in Cycle 1"). This could be attributable to the different modes of administration and clearance of the two drugs. The Pegfilgrastim group received one administration of active drug on cycle day 2, while the Filgrastim group received active drug daily until either ANC greater than or equal to 10×10^9/L after the expected nadir or for up to 14 days, whichever came first. This may have produced a prolonged pharmacodynamic effect in the latter group, as the daily doses of Filgrastim replenished the available pool of growth factor despite a relatively short circulating half-life mediated by renal clearance. In contrast, although Pegfilgrastim posses a longer circulating half-life due to its diminished renal clearance, it is removed by receptor-mediated clearance as the ANC rises, and was not replenished during each cycle.

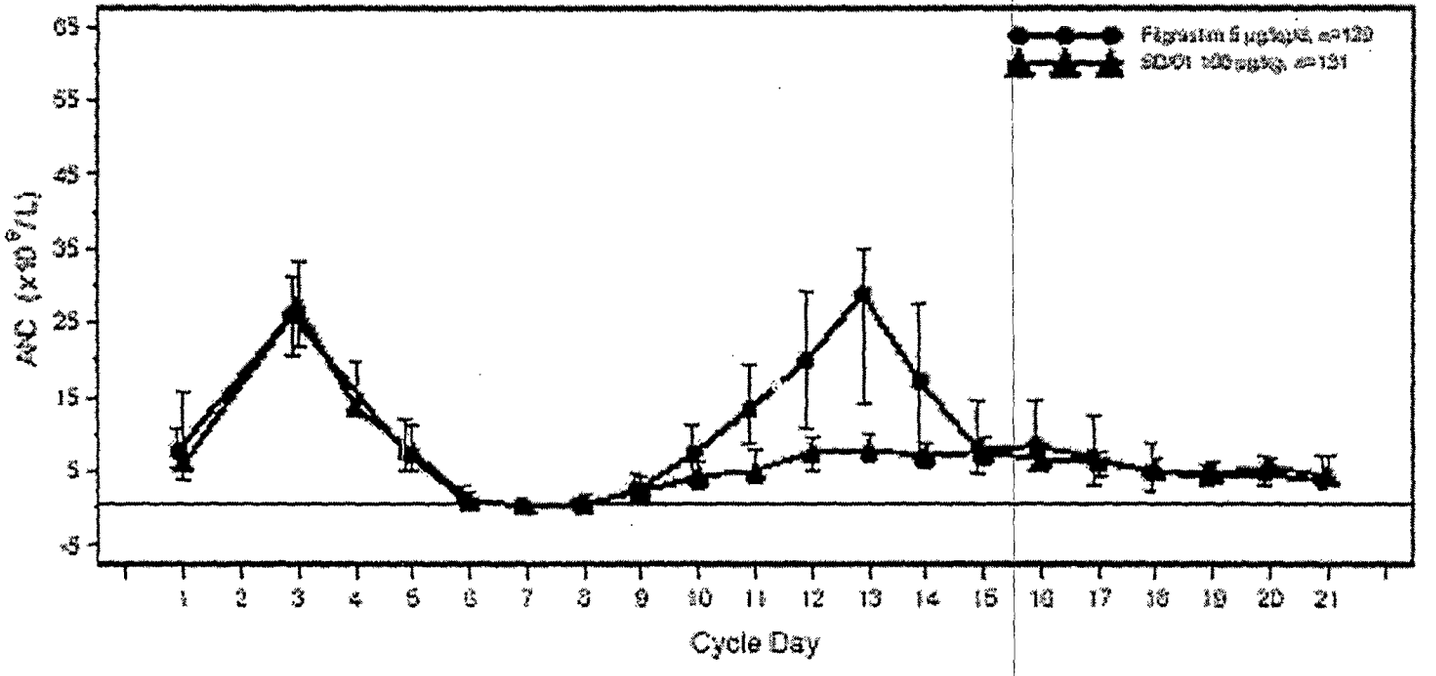
Table 9: Study 980226 Incidence of FN cycles 1-4

	Cycle 1		Cycle 2		Cycle 3		Cycle 4	
	Filgrastim 5 µg/kg/day	Pegfilgrastim 100 µg/kg	Filgrastim 5 µg/kg/day	Pegfilgrastim 100 µg/kg	Filgrastim 5 µg/kg/day	Pegfilgrastim 100 µg/kg	Filgrastim 5 µg/kg/day	Pegfilgrastim 100 µg/kg
Number of Subjects Started Cycle	129	131	133	134	126	131	125	129
Number (%) FN Yes	13 (10%)	11 (8%)	2 (2%)	1 (1%)	4 (3%)	0 (0%)	3 (2%)	3 (2%)
Number (%) FN No	115 (89%)	120 (92%)	131 (98%)	133(98%)	122 (97%)	131 (100%)	122 (98%)	126 (98%)
Difference Between % Filgrastim FN and % Pegfilgrastim FN	-1.68		-0.76		-3.17		-0.07	
95% Confidence Interval	(-8.75, 5.39)		(-3.30, 1.78)		(-6.25, -0.10)		(-3.83, 3.68)	

Table 10: Study 980226 Duration of Severe Neutropenia cycles 2-4

	Cycle 2		Cycle 3		Cycle 4	
	Filgrastim 5 µg/kg/day	Pegfilgrastim fixed 6 mg	Filgrastim 5 µg/kg/day	Pegfilgrastim fixed 6 mg	Filgrastim 5 µg/kg/day	Pegfilgrastim fixed 6 mg
Number of Subjects Started Cycle	133	134	126	131	125	129
Number (%) with SN	74 (56%)	58 (43%)	73 (58%)	47 (36%)	66 (53%)	53 (41%)
Mean DSN	1.0	0.7	1.0	0.6	1.1	0.8
Difference Between Mean DSN: Pegfilgrastim vs. Filgrastim	-0.3		-0.4		-0.3	
95% Confidence Interval	(-0.57, -0.12)		(-0.66, -0.19)		(-0.61, -0.01)	

Figure 5: Study 980226 Median ANC Profiles in Cycle 1
(note:SD/01 was investigational designation for Pegfilgrastim)



Horizontal reference line at ANC = 0.5 x 10^9/L
Bars indicate interquartile range.

PK Results
A single injection of Pegfilgrastim was shown to produce sustained serum concentrations relative to Filgrastim. The PK results for Pegfilgrastim were consistent with a neutrophil-mediated clearance mechanism: serum cytokine concentrations were higher in subjects who had longer DSN and lower ANC at nadir.

Safety Results
Pegfilgrastim was well tolerated in this population with breast cancer. All subjects reported adverse events; however, most were attributable to complications arising from myelosuppressive chemotherapy or the primary disease. Sixteen subjects (7 Pegfilgrastim and 9 Filgrastim) died during the study; all deaths were attributable to disease progression or chemotherapy-related toxicity. Ten subjects (6 Pegfilgrastim and 4 Filgrastim) withdrew because of adverse events; 6 adverse events were attributable to chemotherapy, 3 to disease progression, and 1 to a syncopal episode.

Serious adverse events were reported in 19% of Pegfilgrastim subjects and in 20% of Filgrastim subjects; none were considered by the investigator to be related or possibly related to study drug. Severe, life-threatening, or fatal adverse events were reported in 41% of Pegfilgrastim subjects and in 39% of Filgrastim subjects; 5% of subjects in each treatment group reported severe, life-threatening, or fatal adverse events that were considered by the investigator to be possibly related to study drug.

The per patient incidence of bone pain was 41% in Pegfilgrastim subjects and 46% in Filgrastim subjects. Most bone pain adverse events were considered by the investigator to be mild to moderate in severity. The utilization of opiate and non-opiate analgesia is discussed in the Integrated Summary of Safety under "Events of Special Interest"

No differences were observed in hemoglobin and platelets between treatment groups and the overall pattern of anemia and thrombocytopenia reflected those that might be anticipated in subjects receiving myelosuppressive chemotherapy.

Transient, mild changes in liver enzymes were observed; these changes were not associated with any reported clinical sequelae. None of these changes could be directly linked by frequency of occurrence to treatment with Pegfilgrastim or Filgrastim.

No neutralizing antibodies to Pegfilgrastim or Filgrastim were detected in any serum sample collected during the treatment or follow-up periods. All subjects exhibited an ANC less than 1.0 x 10^9/L after the expected nadir as of their last observed ANC with the exception of 2 subjects who either withdrew from study or died before ANC recovery.

Time to disease progression and subject survival status was similar between treatment groups.

Conclusion

Results from this study in subjects receiving multiple cycles of myelosuppressive chemotherapy demonstrate that once-per-cycle SC injection of Pegfilgrastim 100 µg/kg met the prespecified criteria for non-inferiority to daily injections of Filgrastim 5 µg/kg/day in reduction of the duration of SN. The effect on DSN was similar irrespective of weight, extent of prior chemotherapy exposure, or age. Administration of a 100 µg/kg weight-adjusted dose of Pegfilgrastim yielded a toxicity profile similar to that observed with daily injections of Filgrastim 5 µg/kg/day.

APPEARS THIS WAY
ON ORIGINAL

Pivotal Trial 990749: Conduct and Results of the Trial

Conduct of the Trial

The study was initiated on November 18, 1999 and the treatment and follow-up phases were completed on November 7, 2000. The BLA submission presented all follow-up data available as of January 24, 2001

Thirty-seven centers were initiated, and multiple investigators at 34 centers in Europe, Australia, and the United States enrolled subjects in this study. This study was conducted in accordance with the principles of the Declaration of Helsinki, the regulations of the United States Food and Drug Administration (FDA) and the International Conference on Harmonisation (ICH) Good Clinical Practice regulations/guidelines. During the course of the trial, one amendment was made to the protocol on February 9, 2000 to enable US centers to participate in the study, and to add an extra randomization stratification variable (US centers versus centers in Europe or Australia) to enable balanced representation of US subjects in both treatment groups.

Unless their participation was terminated early, subjects were on study for at least 6 months. This included approximately 3 months of active treatment and an additional 3 months for short-term follow-up.

An external Safety Data Monitoring Committee (SDMC) periodically reviewed the aggregate blinded safety data and unanimously recommended continuing the study at all meetings. The SDMC included 3 voting members and 2 nonvoting members. The voting members included a biostatistician and 2 physicians (including an oncologist) with experience in the use of growth factors. These 3 individuals were not directly involved with the conduct of the study and were not associated with Amgen Inc. Two individuals representing Amgen Inc., but not directly involved with the conduct of the study, served as nonvoting members on the SDMC and were the liaisons between the SDMC and the Clinical Study Management Team (CSMT). The committee was responsible for periodic review of safety data collected during the course of the study, including a review of data from subjects who met prespecified ANC related criteria that may have indicated the development of clinically significant antibodies. Analyses provided to the SDMC were descriptive in nature; inferential testing was neither conducted nor provided to the SDMC; however, the provisions of the SDMC charter allowed the SDMC members to request or to perform ad hoc analyses required to make decisions regarding the safety of the product. After each SDMC meeting, the members made recommendations by letter to the CSMT regarding continuation of the study.

The study protocol, protocol amendment, subject diary, subject information and written informed consent forms were reviewed and approved by the institutional review board (IRB) at each participating center in accordance with the principles

of FDA regulations 21 CFR 50 and 21 CFR 56, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), or as applicable in local law.

Enrollment and Disposition of Subjects

One hundred-fifty subjects were planned with 75 subjects per treatment group. Thirty-four centers in the US and Canada enrolled 157 subjects (age range: 30 to 75 years) in the study. The first subject enrolled in the study (signed informed consent) on November 18 1999, and the last subject completed the follow-up assessment on November 7, 1999. Eighty subjects were randomized to receive a single SC injection of 6 mg of Pegfilgrastim per chemotherapy cycle, and 77 subjects were randomized to receive daily SC injections of Filgrastim 5 μg/kg/day.

Demographics

The two treatment arms were balanced for:

- Location (US vs. Non-US)
- Age Distribution
- Percentage of Subjects ≥ 65 Years
- Racial Distribution
- ECOG Status
- Percentage of Subjects with Prior Radiotherapy
- Percentage of Subjects with Prior Chemotherapy
- Disease Stage
- Distribution of Weight

Summary demographic details are provided in the following table (Table 11)

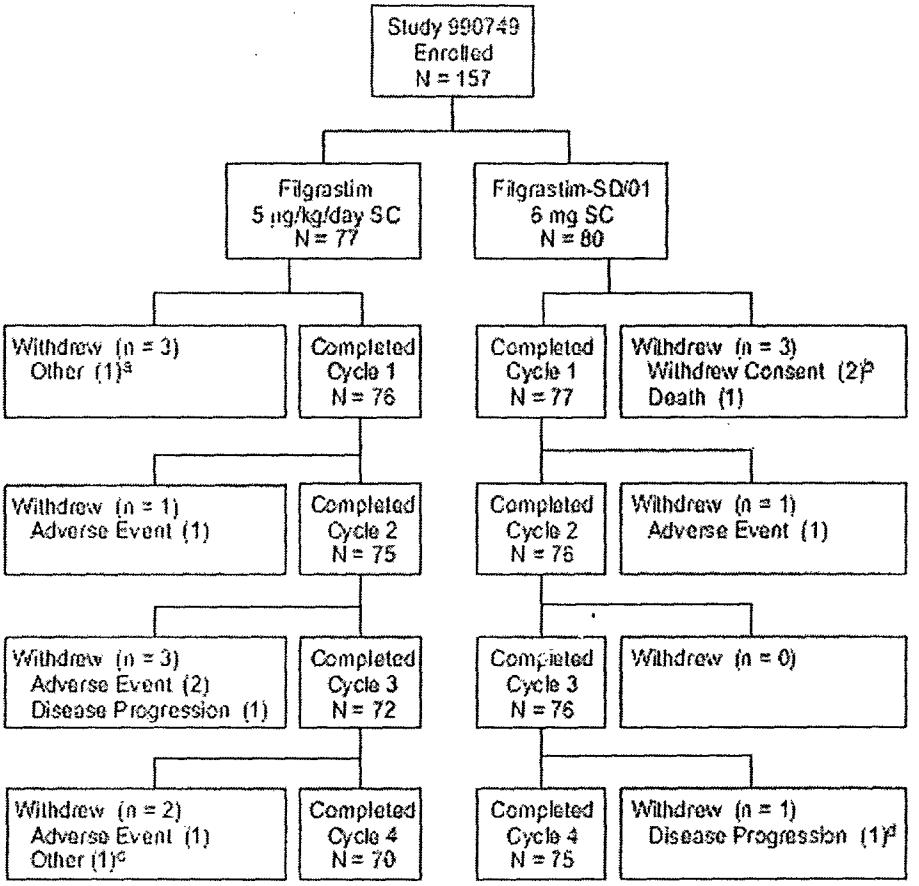
Table 11: Study 990749 Demographic Characteristics

	Filgrastim 5µg/kg/d (N = 77)	Pegfilgrastim 6 mg (N = 80)
Location		
US	10	12
Non-US	67	68
Mean Age (SD)	52.6 (11.5) years	51.9 (9.1) years
< 65 years	66	75
≥ 65 years	11	5
Sex:	76 Female/ 1 Male	80 Female/ 0 Male
Race/ethnicity:	75 white, 1 black	77 white, 1 black,
	1 Hispanic,	0 Hispanic
ECOG Status		
0	56 (73%)	60 (75%)
1	18 (23%)	18 (23%)
2	3 (4%)	2 (3%)
3	0	0
4	0	0
Radiotherapy		
Yes	17 (22%)	23 (29%)
No	60 (78%)	57 (71%)
Chemotherapy		
Yes	23 (30%)	23 (29%)
No	54 (70%)	57 (71%)
Disease Stage		
II	24 (31%)	20 (25%)
III	21 (27%)	21 (26%)
IV	32 (42%)	39 (49%)
Weight (kg)		
< 50	1 (1%)	1 (1%)
50-79	55 (71%)	56 (70%)
≥ 80	21 (27%)	23 (29%)

Subject disposition

Subject disposition during the treatment phase is presented in Figure 6.

Figure 6: Study 990749 Subject Disposition



[a] Subject withdrew consent for further CBC draws, but agreed to continued study drug administration for that cycle.
[b] Two subjects withdrew consent before study chemotherapy.
[c] Subject was withdrawn for surgical treatment.
[d] Subject was withdrawn after cycle 4 chemotherapy, but before cycle 4 study drug administration.

Treatment and Follow-up Period

Of the 157 randomized subjects, 155 (99%) received at least one dose of study drug. One hundred and forty-five (92%) of the randomized subjects completed the treatment phase of the study (cycles 1 through 4). One hundred and forty-six (92%) subjects completed the 3-month follow-up.

Withdrawals

Treatment Period

Numbers of subjects withdrawn and reasons for withdrawal were similar between Pegfilgrastim and Filgrastim subjects. Twelve of the 157 randomized subjects (8%) were withdrawn before completion of 4 cycles of chemotherapy (5 [6%] Pegfilgrastim subjects and 7 [9%] Filgrastim subjects). Two of the 80 Pegfilgrastim subjects (3%) withdrew consent to participate in the study before receiving cycle 1 chemotherapy and study drug. One of the 80 Pegfilgrastim subjects (1%) and 4 of the 77 Filgrastim subjects (5%) were withdrawn because of intolerable adverse events. One subject (1%) from each group was withdrawn because of disease progression and 1 Pegfilgrastim subject (1%) died while in the study treatment phase.

Follow-up Period

One (1%) Pegfilgrastim and 3 (4%) Filgrastim subjects died during the follow-up period. Additionally, 2 (3%) Filgrastim subjects withdrew consent, and 2 (3%) Filgrastim subjects were lost to follow-up.

Efficacy Results

During this review, the completeness of the efficacy data sets was assessed and analysis revealed minimal missing data (<5%). The sponsor's major efficacy analyses were confirmed by FDA reviewers.

In subjects receiving myelosuppressive chemotherapy, a single, SC injection of 6 mg Pegfilgrastim per chemotherapy cycle met the criteria for non-inferiority to daily SC injections of Filgrastim 5 µg/kg/day for all primary and secondary efficacy endpoints in both the pP and mITT populations.

Primary Endpoint

The mean DSN in cycle 1 (pP subset) in the Pegfilgrastim and Filgrastim groups was 1.8 days and 1.6 days, respectively. The difference in the mean DSN was 0.2 days and the upper 97.5% confidence limit was 0.6 days, which was within the 1-day prespecified non-inferiority margin. (See Cycle 1 DSN: Table 10 and 11) The study, therefore, met the prespecified study criterion for non-inferiority of Pegfilgrastim compared to Filgrastim.

Table 12: Study 990749 Cycle 1 Duration of Severe Neutropenia

	Filgrastim 5 µg/kg/day	Pegfilgrastim Fixed 6 mg
Number of Subjects in Subset	62	68
Number of Subjects Started Cycle	62	68
Number (%) with Severe Neutropenia		
Yes	52 (84%)	56 (82%)
No	10 (16%)	12 (18%)
Duration of Severe Neutropenia (Days)		
0	10 (16%)	12 (18%)
1	20 (32%)	19 (28%)
2	20 (32%)	23 (34%)
3	11 (18%)	6 (9%)
4	0 (0%)	5 (7%)
5	1 (2%)	1 (1%)
6	0 (0%)	2 (3%)
Duration of Severe Neutropenia (Days)		
Mean	1.6	1.8
Median	2.0	2.0
SD	1.1	1.4
Q1, Q3	1.0, 2.0	1.0, 2.0
Min, Max	0, 5	0, 6

Table 13: Study 990749 Difference in Mean Duration of Severe Neutropenia, Cycle 1

Difference in Mean Duration of Severe Neutropenia: Pegfilgrastim vs. Filgrastim	
Difference Between Means	0.2
95% Confidence Interval	(-0.2, 0.6)

Secondary Endpoints
The calculated subject incidence of FN in cycle 1 was similar in the Pegfilgrastim and Filgrastim pP analysis subgroups (10% and 15%, respectively). The incidence of FN across all cycles was similar in the Pegfilgrastim and Filgrastim pP analysis subgroups. (Table 14)

Exploratory analyses revealed no differences between the Pegfilgrastim and Filgrastim groups in the DSN as a function of extent of chemotherapy exposure, age, weight, depth of ANC nadir, and median time to ANC recovery. Aspects of these analyses are discussed further in the section "Special Populations". Analysis of DSN in cycles 2 through 4 was consistent with that of cycle 1, indicating that Pegfilgrastim is not less effective than Filgrastim in reducing the DSN in multicycle chemotherapy. (Table 15)

As was found in study 980226, no meaningful differences between the Pegfilgrastim and Filgrastim groups were observed in time to ANC recovery; however, post-nadir ANCs in all cycles were different between treatment groups. Although of no clinical significance, the cycle day 10 to day 14 ANCs in the Filgrastim group were uniformly higher than those of the Pegfilgrastim group (see Figure 7, "Median ANC Profiles in Cycle 1"). This could be attributable to the different modes of administration and clearance of the two drugs. The Pegfilgrastim group received one administration of active drug on cycle day 2, while the Filgrastim group received active drug daily until either ANC greater than or equal to 10×10^9/L after the expected nadir or for up to 14 days, whichever came first. This may have produced a prolonged pharmacodynamic effect in the latter group, as the daily doses of Filgrastim replenished the available pool of growth factor despite a relatively short circulating half-life mediated by renal clearance. In contrast, although Pegfilgrastim posses a longer circulating half-life due to its diminished renal clearance, it is removed by receptor-mediated clearance as the ANC rises, and was not replenished during each cycle.

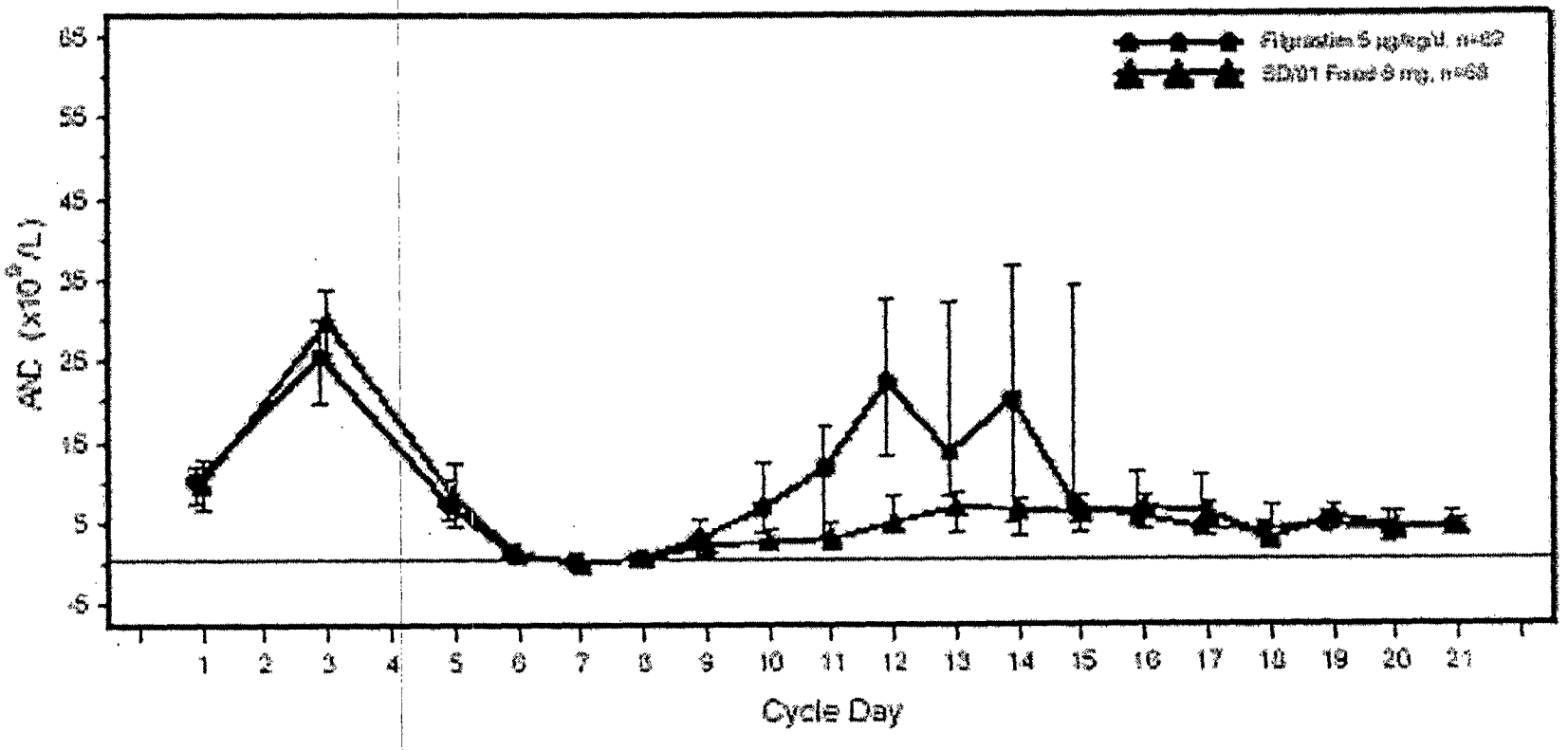
Table 14: Study 990749 Incidence of FN cycles 1-4

	Cycle 1		Cycle 2		Cycle 3		Cycle 4	
	Filgrastim 5 µg/kg/day	Pegfilgrastim fixed 6 mg	Filgrastim 5 µg/kg/day	Pegfilgrastim fixed 6 mg	Filgrastim 5 µg/kg/day	Pegfilgrastim fixed 6 mg	Filgrastim 5 µg/kg/day	Pegfilgrastim fixed 6 mg
Number of Subjects Started Cycle	62	68	62	66	59	69	58	68
Number (%) FN Yes	9 (15%)	7 (10%)	1 (2%)	1 (2%)	2 (3%)	1 (1%)	1 (2%)	2 (3%)
Number (%) FN No	53 (85%)	61 (90%)	61 (98%)	65(98%)	57 (97%)	68 (99%)	57 (98%)	66 (97%)
Difference Between % Filgrastim FN and % Pegfilgrastim FN	-4.2		-0.1		-1.9		1.2	
95% Confidence Interval	(-15.7, 7.25)		(-4.44, 4.25)		(-7.40, 3.52)		(-4.06, 6.50)	

Table 15: Study 990749 Duration of Severe Neutropenia cycles 2-4

	Cycle 2		Cycle 3		Cycle 4	
	Filgrastim 5 µg/kg/day	Pegfilgrastim fixed 6 mg	Filgrastim 5 µg/kg/day	Pegfilgrastim fixed 6 mg	Filgrastim 5 µg/kg/day	Pegfilgrastim fixed 6 mg
Number of Subjects Started Cycle	62	66	59	69	58	68
Number (%) with SN	62 (100%)	66 (100%)	59 (100%)	69 (100%)	58 (100%)	68 (100%)
Mean DSN	0.9	1.0	0.9	1.1	0.9	0.9
Difference Between Mean DSN: Pegfilgrastim vs. Filgrastim	0.1		0.2		0	
95% Confidence Interval	(-0.24, 0.49)		(-0.18, 0.57)		(-0.39, 0.45)	

Figure 7: Study 990749 Median ANC Profiles in Cycle 1
(note:SD/01 was investigational designation for Pegfilgrastim)

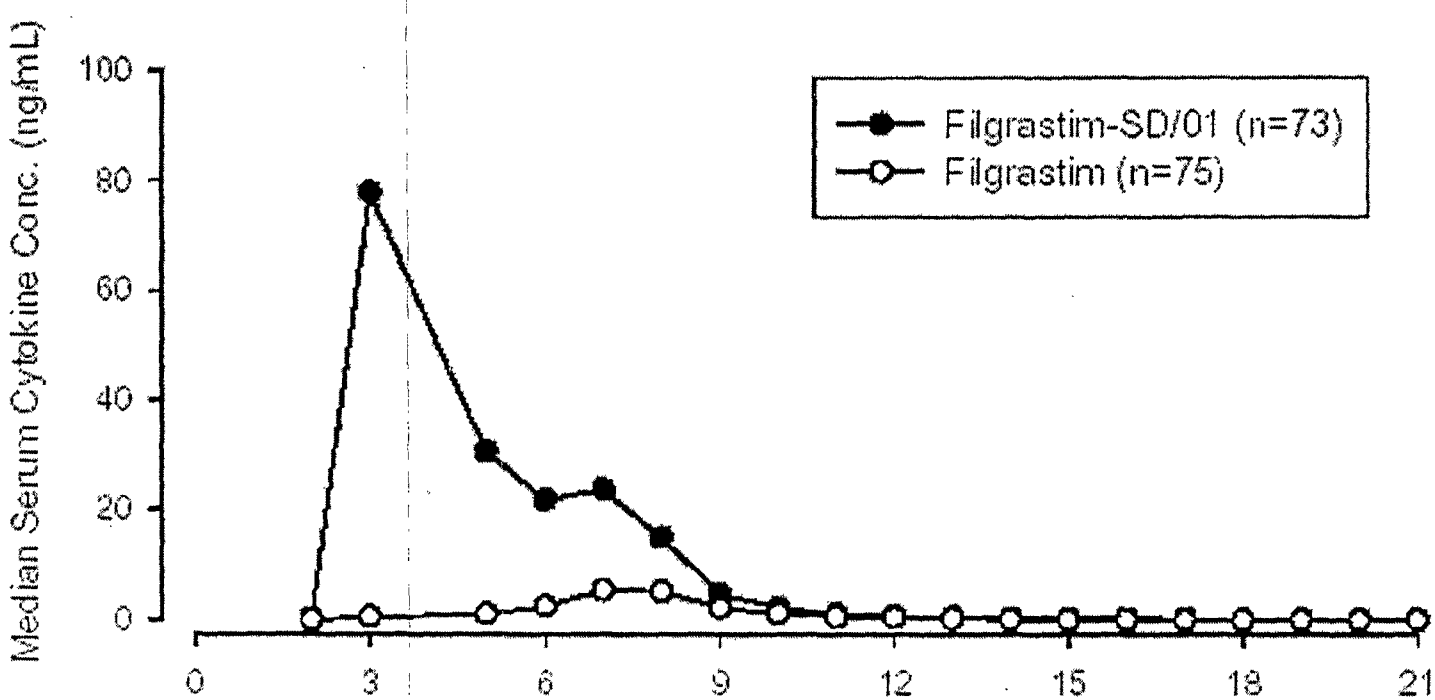


Horizontal reference line at ANC = 0.5 x 10^9/L
Bars indicate interquartile range.

PK Results

A single injection of Pegfilgrastim was shown to produce sustained serum concentrations for approximately 8 days. (Figure 8) The PK results for Pegfilgrastim were consistent with a neutrophil-mediated clearance mechanism: serum cytokine concentrations were higher in subjects who had longer DSN and lower ANC at nadir.

Figure 8: Study 990749 Median Cytokine Concentration-time Profile in Cycle 1
(note: Filgrastim SD/01 was investigational designation for Pegfilgrastim)



Safety Results

Fixed-dose Pegfilgrastim was well tolerated in this subject population. All subjects reported adverse events; however, most adverse events were not considered by the investigator to be related to study drug and were consistent with the underlying disease or the myelosuppressive chemotherapy. The incidence and type of events reported were similar across the subject weight range. Two subjects died during the treatment period or within 30 days of study drug administration (1 in each group). One subject treated with Filgrastim (Subject 9024001) died from acute respiratory distress syndrome (ARDS), bronchopneumonia, and sepsis considered possibly related to study drug. Three additional subjects died during the follow-up period of causes unrelated to study drug.

Eighteen per cent of Pegfilgrastim subjects and 28% of Filgrastim subjects reported serious adverse events. Three serious adverse events (1 Pegfilgrastim subject [hypoxia] and 2 Filgrastim subjects [ARDS and pneumonitis]) were considered by the investigator to be related to study drug.

The per patient incidence of bone pain was 57% in Pegfilgrastim subjects and 64% in Filgrastim subjects; most events were considered by the investigator to be mild to moderate in severity. Study drug-related bone pain was reported in 37% Pegfilgrastim subjects and 42% Filgrastim subjects No differences were observed in the per patient incidence of bone pain in the analyses of Pegfilgrastim adverse events by subject weight quartiles. The utilization of opiate and non-opiate analgesia is discussed in the Integrated Summary of Safety under "Events of Special Interest"

No differences were observed in hemoglobin and platelets between treatment groups and the overall pattern of anemia and thrombocytopenia reflected those that might be anticipated in subjects receiving myelosuppressive chemotherapy.

Transient, mild changes in liver enzymes were observed; these changes were not associated with any reported clinical sequelae.

No antibodies to Pegfilgrastim or Filgrastim were detected in any serum sample collected during the treatment or follow-up periods. All subjects exhibited an ANC greater than or equal to 1 x 10^9/L by the end of their final study chemotherapy cycle. Other than 1 Pegfilgrastim and 3 Filgrastim subjects who received additional post-study chemotherapy, all subjects reported an ANC greater than or equal to 1 x 10^9/L at their final 3-month follow-up observation.

Conclusion

Results from this study in subjects receiving multiple cycles of myelosuppressive chemotherapy demonstrate that once-per-cycle SC administration of a fixed 6-mg dose of Pegfilgrastim met the prespecified criteria for non-inferiority to daily injections of Filgrastim 5 µg/kg/day in reduction of the duration of SN. The effect on DSN was similar irrespective of weight, extent of prior chemotherapy exposure, or age. Administration of a fixed 6-mg dose of Pegfilgrastim yielded a toxicity profile similar to that observed with daily injections of Filgrastim 5 µg/kg/day.

APPEARS THIS WAY
ON ORIGINAL

Integrated Summary of Safety

STATISTICAL APPROACHES

General Principles

At the time of BLA submission, eight Pegfilgrastim clinical trials had completed active treatment and observation, with the last treatment database locking on 2 November 2000. Available follow-up data through 7 February 2001 were included where applicable. The results from these 8 trials comprise the data in the Integrated Summary of Safety. Available follow-up data through 7 February 2001 were included where applicable. Three additional studies ongoing at the time of submission are not included in the integrated analysis: the pediatric sarcoma study 990130, the re-exposure study 990736, and the [redacted] study [redacted]. Interim data from study 99130 and study 990736 are presented under "Special Populations".

The following analysis sets were defined:

- healthy volunteers
- patients with thoracic tumors
- patients with breast cancer
- patients with solid tumors (thoracic and breast)
- patients with hematologic malignancies
- patients with all cancer

Data from individual studies were pooled as appropriate (e.g., healthy volunteer studies, breast cancer studies, solid tumor studies), and finally data from all studies in patients with cancer were pooled, as illustrated in Figure 5-1 on the following page. The purpose of pooling data was to increase the precision of the estimates of the incidence of adverse events and changes in laboratory values.

The following were analyzed and presented:

For all subjects

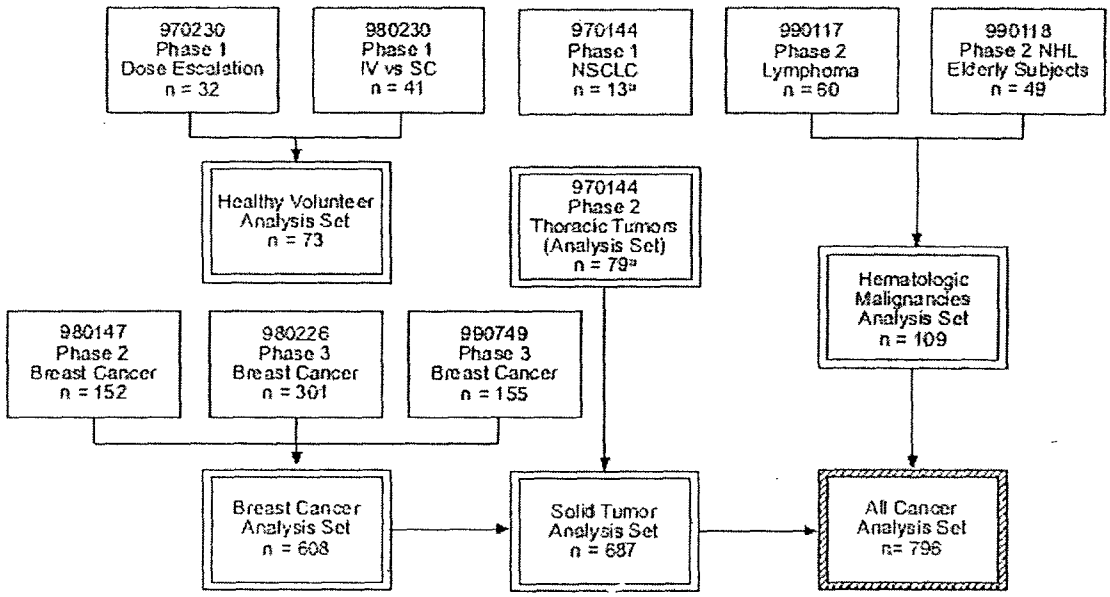
- subject characteristics and disposition
- study drug exposure and chemotherapy dosing
- clinical adverse events: all, treatment-related, severe, and serious adverse events leading to study withdrawal
- key laboratory variables: alkaline phosphatase, LDH, uric acid, white blood cells (WBC), hemoglobin, and platelets
- development of antibodies to Filgrastim or Pegfilgrastim
- adverse events of special interest (bone pain, splenomegaly, allergic reactions, and respiratory events)

For subjects receiving concurrent chemotherapy

- disease progression and survival
- use of transfusions

Exploratory subset safety analyses were conducted for patients with cancer according to weight (< 80 and ≥80 kg), age (<65 and ≥65 years), gender, and race.

Figure 9: Components of Integrated Summary of Safety



n = number of subjects evaluable for safety.

a Thoracic tumor analysis set includes only subjects participating in the multicycle phase of the study (phase 2)

Statistical Methods

Data sets for the integrated safety analysis were created by concatenating the appropriate case report tabulations from each of the individual studies. This process was performed only after data base finalization and lock. Data from all subjects who received 1 or more doses of study drug were included in the analyses; subjects randomized to Filgrastim who subsequently received 1 or more doses of Pegfilgrastim were included in the latter treatment group. Analyses were primarily descriptive. Tabulations were presented by treatment group. Categorical variables were summarized by the frequency and percentage in each category. For continuous variables, the mean, median, standard deviation, interquartile range, and range were provided. Time to disease progression and survival in study 980226 were evaluated for treatment group differences using a Cox model adjusting for subject age, disease stage, number of cycles of chemotherapy, and prior radiotherapy.

Laboratory variables of special interest included the blood chemistries alkaline phosphatase, LDH, and uric acid, which are cited in the Filgrastim product labeling as showing transient increases that were temporally related to treatment. Additionally, the hematology variables WBC, platelets, and hemoglobin were presented. All laboratory variables were presented as summary statistics and

shift tables. For each variable, the largest shift occurring during the study was tabulated by treatment group. Grade shifts were based on the toxicity grades in the World Health Organization (WHO) toxicity grading scale. Summary statistics included baseline, study minimum or maximum as appropriate, end-of-study value, and percent change from baseline to end-of-study. For each of these variables, mean, median, standard deviation, interquartile range, and range were presented by treatment group.

For the integrated analysis of bone pain, per patient incidence was derived by examining the reported adverse events (verbatim and preferred terms) for bone areas that are primary bone marrow-bearing sites. Included in the subject incidence rates of bone pain were bone/skeletal, back, limb, noncardiac sternal, cranial/skull, scapular, sacral, and hip pain as specific items. Although the hip is a joint, it was included because of its large marrow mass. Most other joint-related events were excluded (e.g., shoulder, neck, jaw, hand, knee, elbow, and foot), as were the nonspecific verbatim terms of flank pain (coded to back pain) and axillary pain (coded to limb pain). Terms included in the analysis of respiratory events were ARDS, respiratory failure, and serious events of hypoxia.

Terms referring to clinically significant splenic events were splenomegaly, left upper quadrant abdominal pain, palpable spleen, spleen disorder, enlarged spleen, and spleen pain; inclusion of the term in the analysis involved a clinical assessment of the verbatim term. Inclusion in the special category of allergic-type reactions required involvement of 2 or more body systems, unless the investigator described the event as an allergic or anaphylactoid reaction or anaphylaxis. Terms included urticaria, rash, flushing, edema (facial, circumoral, periorbital, and tongue), wheezing, stridor, dyspnea, bronchospasm, throat tightness, tachycardia, and hypotension.

RESULTS

Healthy Volunteers Analysis Set

A total of 73 healthy volunteer subjects participated in the two phase 1 studies 970230 and 980230. All 73 subjects were evaluable for the safety analyses.

Subject Disposition and Characteristics

Seventy-two of the 73 healthy subjects (99%) completed study participation successfully. Slightly more subjects receiving Pegfilgrastim were women than men, while most of those receiving Filgrastim were men. Median age across groups was 25 years, with an overall range of 18 to 45. Most subjects were white, with other represented ethnic groups including Hispanic, black, and Native American.

Extent of Study Drug Exposure

Eight subjects received multiple SC injections of Filgrastim 5 µg/kg/day for 7 to 10 days for a median cumulative dose of 3.49 mg. Sixty-five subjects received a

single injection of Pegfilgrastim at 30, 60, 100, or 300 µg/kg given SC or IV. Median doses for the 30-, 60-, 100-, and 300-µg/kg dose groups were 1.92, 4.19, 5.80, and 20.37 mg, respectively; individual doses ranged as high as 23.34 mg.

All Adverse Events

An overall summary of adverse event incidence by category is shown in Table 16 for combined Pegfilgrastim dose groups (n = 65) versus Filgrastim (n = 8). The 2 treatment groups showed no apparent differences with regard to overall incidence of all, severe[1], serious[2], or related events.

Table 16. Summary of Adverse Events Healthy Volunteers

	Filgrastim 5 µg/kg/day	All Pegfilgrastim
Number of Subjects in Subset	8	65
All AEs	7 (88%)	60 (92%)
Severe, life-threatening, or fatal AEs	0 (0%)	2 (3%)
Serious AEs	0 (0%)	0 (0%)
Related AEs	7 (88%)	59 (91%)
Related, severe, life-threatening, or fatal AEs	0 (0%)	2 (3%)
Related, serious AEs	0 (0%)	0 (0%)
Withdrawals due to AEs	0 (0%)	1 (2%)

Overall, 92% of subjects receiving Pegfilgrastim and 88% of subjects receiving Filgrastim experienced 1 or more adverse events. Evaluation of data revealed no evidence of a dose response in any clinical adverse event. Adverse events for all Pegfilgrastim doses versus Filgrastim occurring in more than 5% of subjects in either treatment group, in descending order of frequency are summarized in Table 17 below. The musculoskeletal category was the most frequently represented body system. Events of the highest frequency in the combined Pegfilgrastim group were headache (65%), back pain (54%), arthralgia (25%), myalgia (17%), and nausea (14%).

[1] NCI Common Toxicity Grade 3, 4, or 5

[2] Per 21 CFR 312.32: event resulting in death, permanent disability, hospitalization or prolongation of hospitalization, are life-threatening, or require medical/surgical intervention to avoid more serious outcomes

Table 17: : Incidence of Adverse Events in Healthy Volunteers Occurring in ≥ 5%

	Filgrastim	Pegfilgrastim				
	5 µg/kg/day	30 µg/kg SC or IV	60 µg/kg SC or IV	100 µg/kg SC	300 µg/kg SC	All
Number of Subjects in Subset	8	24	25	8	8	65
Number of Subjects Reporting AEs	7 (88%)	23 (96%)	21 (84%)	8 (100%)	8 (100%)	60 (92%)
Headache	5 (63%)	15 (63%)	14 (56%)	5 (63%)	8 (100%)	42 (65%)
Pain Back	6 (75%)	16 (67%)	14 (56%)	3 (38%)	2 (25%)	35 (54%)
Arthralgia	2 (25%)	6 (25%)	5 (20%)	2 (25%)	3 (38%)	16 (25%)
Myalgia	1 (13%)	2 (8%)	3 (12%)	4 (50%)	2 (25%)	11 (17%)
Nausea	0 (0%)	4 (17%)	2 (8%)	0 (0%)	3 (38%)	9 (14%)
Sore Throat	1 (13%)	1 (4%)	3 (12%)	1 (13%)	3 (38%)	8 (12%)
Pain Musculo-Skeletal	0 (0%)	3 (13%)	0 (0%)	1 (13%)	1 (13%)	5 (8%)
Pain Chest (Non-Cardiac)	0 (0%)	1 (4%)	1 (4%)	2 (25%)	0 (0%)	4 (6%)
Vasovagal Episode	0 (0%)	3 (13%)	1 (4%)	0 (0%)	0 (0%)	4 (6%)
Pain Neck	1 (13%)	0 (0%)	2 (8%)	0 (0%)	0 (0%)	2 (3%)
Pain Abdominal	2 (25%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (2%)
Palpitation	1 (13%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Rhinitis	1 (13%)	0 (0%)	0 (0%)	0 (0%)	1 (13%)	1 (2%)
Anorexia	1 (13%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Infection Upper Respiratory	1 (13%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nervousness	1 (13%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

N (%) = Number and percentage of subjects reporting any adverse event in the preferred term

The healthy volunteer studies utilized two routes of administration: SC and IV. Overall, no route-related trends in adverse events were apparent. Intravenous administration is not being pursued as a route of administration for licensure of Pegfilgrastim.

Severe and Serious Adverse Events and Deaths
Two adverse events graded as severe or higher per NCI CTC v.2 scale occurred: arthralgia in a subject receiving Pegfilgrastim 60 µg/kg and headache in a subject receiving Pegfilgrastim 300 µg/kg. Both events were considered to be at least possibly related to study drug. The overall incidence rate of severe adverse events in the combined Pegfilgrastim groups was 3%, (0% in Filgrastim). No serious adverse events occurred in the healthy volunteer studies.

Study Withdrawals due to Adverse Event
One of the 73 subjects was removed due to an adverse event. Subject 30103 on study 980230, who was receiving an IV infusion of Pegfilgrastim 30 µg/kg, experienced a syncopal episode; moderate in severity from which the subject recovered without sequelae

Laboratory Variables
Blood chemistries of special interest included alkaline phosphatase, LDH, and uric acid. Median peak alkaline phosphatase for Pegfilgrastim appeared to be dose proportional, with values of 100, 123, 142, and 211 U/L for the 30-, 60-, 100-, and 300-µg/kg groups, respectively . Only 1 elevation, in the 300 µg/kg cohort, was grade 2; all others were grade 1. The incidence of grade 1 or greater elevations in alkaline phosphatase also suggested dose proportionality: 21%, 32%, 63%, and 88% for the 4 Pegfilgrastim dose levels, respectively. End-of-study values, although for the most part within normal limits, were also elevated in a dose-proportional manner with changes of 13%, 15%, 64%, and 73% above baseline, respectively.

Patterns of change for LDH were similar to those for alkaline phosphatase. Median peak LDH for Pegfilgrastim appeared to be dose proportional, with values of 170, 196, 248, and 349 U/L for the 30-, 60-, 100-, and 300-µg/kg groups, respectively. No elevation was greater than grade 1. The incidence of grade 1 elevations in LDH also suggested dose proportionality: 0%, 0%, 38%, and 63% for the 4 Pegfilgrastim dose levels, respectively. End-of-study values, although all within normal limits, were also affected in a dose-proportional manner with changes of -3%, -6%, 2%, and 4% from baseline, respectively.

Increases in uric acid were seen during the study, although the pattern was less consistent than that with alkaline phosphatase and LDH. All treatment groups displayed increases in uric acid that returned to within normal limits by end-of-study. Median increases did not appear to be dose proportional. Median peak value and median percent change from baseline were higher in the Filgrastim group.

Transient decreases in WBC of grade 1 or greater were seen in 25% and 13% of subjects receiving Pegfilgrastim and Filgrastim, respectively. These generally occurred within 1 to 2 hours after drug administration and possibly represent neutrophil margination, or adhesion to endothelial cells. Decreases in median platelet count were seen in all treatment groups, with some indication of a dose relationship. Median platelet nadirs were 192, 154, 167, and 107 x 10^9/L for the respective Pegfilgrastim dose groups. Most subjects remained within normal limits, with the exception of 5 subjects receiving Pegfilgrastim whose platelet counts decreased to between 85 and 100 x 10^9/L. Modest decreases in hemoglobin between baseline and end-of-study were seen in all treatment groups and did not appear to be dose related and may in part be explained by repetitive blood draws required in these pharmacokinetic studies.

Summary of Healthy Volunteer Analysis Set
Sixty-five subjects received a single dose of Pegfilgrastim in the healthy volunteer phase 1 program; doses of Pegfilgrastim ranged from 0.2 to 23mg (30 to 300 μg/kg). Most subjects (92% receiving Pegfilgrastim) experienced at least 1 adverse event. Headache, back pain, and other events in the musculoskeletal body system were the most frequent. No unexpected clinical findings compared to the known safety profile of Filgrastim were seen. Furthermore, no Pegfilgrastim dose relationship was detected among the clinical adverse events.

Mild-to-moderate increases in alkaline phosphatase, LDH, and uric acid were seen; for the former 2 analytes, these appeared dose-related. The increases were reversible and were not associated with any clinical sequelae.

Overall, Pegfilgrastim was shown to be well-tolerated at doses ranging from 30 to 300 μg/kg with a safety profile similar to that of Filgrastim.

Thoracic Tumors Analysis Set
The thoracic tumor analysis set was derived from a subset of the subjects who were treated in study 970144, of whom 26 received Filgrastim and 53 received Pegfilgrastim. The thoracic tumor analysis subset set comprises data from the subjects who received study drug postchemotherapy for up to 6 cycles in the phase 2 portion of this open-label study (Parts C and D).

All safety data within the thoracic tumor analysis set were examined separately before integration in the all cancer analysis set. Trends unique to the thoracic tumor analysis set are discussed in later sections.

Breast Cancer Analysis Set

The breast cancer analysis set was derived from the subjects who were treated in the phase 2 study 980147 and the 2 pivotal studies 980226 (weight-dose study) and 990749 (fixed-dose study). Of the 621 total subjects who were randomized into the studies, 608 (98%) received study drug and were included in the safety subset: 252 who received Filgrastim and 356 who received Pegfilgrastim. Overall, 92% of subjects completed the study as planned. Reasons for discontinuation of study treatment were qualitatively and quantitatively similar between groups.

Most subjects were women (99%) and white (83%); median age was 51 years across all treatment and dose groups (range: 23-83). Median weight and baseline ANC were comparable between treatment groups. Chemotherapy and study drug exposure were comparable between treatment groups.

Safety data from the breast cancer analysis set were examined separately before integration in the all cancer analysis set. There were no trends that differed from the results discussed under the all cancer analysis set.

Solid Tumor Analysis Set

The solid tumor analysis set is a composite of the thoracic tumor and the breast cancer analysis sets. Six hundred eighty-seven subjects are represented in this set: 278 who received Filgrastim and 409 who received Pegfilgrastim. Most subjects (92%) were women due to the overriding contribution of the 3 breast cancer studies. Median age across all studies and dose groups was 52 years (range: 23-83). Most subjects were white (83%), with the remainder consisting primarily of black (8%) and Hispanic (4%). Median weight and baseline ANC were comparable between treatment groups.

Safety data from the solid tumor analysis set were examined separately before integration in the all cancer analysis set, and there were no trends that differed from the results discussed under that set. The most commonly occurring adverse events were those characteristic of the side effects of chemotherapy (alopecia, nausea, fatigue, diarrhea, vomiting, constipation, fever, and anorexia). These occurred at a similar frequency between treatment groups. Adverse events considered to be at least possibly related to study drug consisted predominantly of musculoskeletal symptoms. Overall, no unexpected safety results were seen, with Filgrastim and Pegfilgrastim demonstrating similar safety profiles.

Hematologic Malignancies Analysis Set

The hematologic malignancies analysis set was derived from the subjects who were treated in the open-label phase 2 trial of NHL and Hodgkin disease (study 990117) and the open-label phase 2 trial of NHL conducted in elderly (age ≥ 60) subjects (study 990118). The 109 subjects in this analysis set received study drug (53, Filgrastim and 56, Pegfilgrastim) in conjunction with multicycle chemotherapy. Cumulative doses of Pegfilgrastim ranged from 5 to 63 mg.

Safety data from the hematologic malignancies analysis set were examined separately before integration in the all cancer analysis set, and there were no trends that differed from the results discussed under that set. The most commonly occurring adverse events were those characteristic of the side effects of chemotherapy which occurred at a similar frequency between treatment groups. Adverse events considered to be at least possibly related to study drug consisted predominantly of musculoskeletal symptoms. Overall, no unexpected safety results were seen, with Filgrastim and Pegfilgrastim demonstrating similar safety profiles.

All Cancer Analysis Set

Subject Characteristics

The all cancer analysis set contains data from 796 subjects who received either Filgrastim (331 subjects) or Pegfilgrastim (465 subjects). It comprises the solid tumor analysis set and the hematologic malignancies analysis set. Malignancies represented in this population were breast cancer, non-small cell lung cancer (NSCLC) and other thoracic tumors, NHL, and Hodgkin's disease. Most subjects (86%) were women with an overall median age of 53 years.

Extent of Study Drug Exposure

Median number of Filgrastim doses was 40 (range: 1-82), while that for Pegfilgrastim was 4 (range: 1-6). Pegfilgrastim dose levels delivered in these studies were 30, 60, and 100 µg/kg, and 6 mg, for which the median cumulative doses of Pegfilgrastim were 11, 16, 28, and 24 mg, respectively, with an overall range of 1.6 to 70 mg.

All Adverse Events

An overall summary of adverse event incidence by severity, seriousness and attribution to study drug for the All Cancer analysis set is given in Table 18 below for Pegfilgrastim and Filgrastim. Incidence rates of adverse events in each category were similar between treatment groups with the exception of investigator identified study drug-related events, which were lower in the Pegfilgrastim group compared with Filgrastim (38% versus 47%, respectively). This was reported in both subjects with breast cancer and with hematologic