

## 1. TITLE PAGE

Study Title:	Randomized, Double-blind Study of Peripheral Blood Progenitor Cell (PBPC) Mobilization by Pegfilgrastim or Filgrastim for Autologous Transplantation in Subjects With Hodgkin's or Non-Hodgkin's Lymphoma
Investigational Product:	Pegfilgrastim
Indication:	PBPC mobilization and collection for autologous transplantation
Brief Description:	This was a randomized, double-blind study to assess the CD34 <sup>+</sup> cells/kg yield and the safety of daily subcutaneous injections of filgrastim (10 µg/kg/day) or a single subcutaneous injection of pegfilgrastim (6 or 12 mg) for PBPC mobilization in subjects with Hodgkin's disease or non-Hodgkin's lymphoma. Subjects were randomly assigned in a 1:1:1 ratio to receive daily doses of 10 µg/kg filgrastim, a single dose of 6 mg pegfilgrastim, or a single dose of 12 mg pegfilgrastim.
Study Sponsor:	Amgen Inc., Thousand Oaks, CA USA
Study No:	20020112
IND No:	7110
Study Phase:	2
Study Initiation Date:	01 April 2003 (first subject enrolled)
Study Completion Date:	02 March 2004 (last subject completed study)
Principal Investigators:	This was a multicenter study conducted at 9 centers in the US. Study centers and principal investigators are listed in <a href="#">Appendix 4</a> .
Clinical Study Manager:	Wade Lovelace Amgen Inc. (805) 447-1192 (phone) (805) 480-4978 (fax)
Good Clinical Practice:	This study was conducted in accordance with the principles of the US Food and Drug Administration (FDA) and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. Essential documents will be retained in accordance with ICH GCP.
Report Date:	06 October 2005

## 2. SYNOPSIS

<b>Name of the Sponsor:</b> Amgen Inc. Thousand Oaks, California USA	<b>Name of Finished Product:</b> Neulasta	<b>Name of Active Ingredient:</b> pegfilgrastim
<b>Title of Study:</b> Randomized, Double-blind Study of Peripheral Blood Progenitor Cell (PBPC) Mobilization by Pegfilgrastim or Filgrastim for Autologous Transplantation in Subjects With Hodgkin's or Non-Hodgkin's Lymphoma		
<b>Investigator(s) and Study Center(s):</b> This was a multicenter study conducted at 9 centers in the US. Study centers and principal investigators are listed in <a href="#">Appendix 4</a> .		
<b>Publication(s):</b> None		
<b>Study Period:</b> 01 April 2003 (first subject enrolled) through 02 March 2004 (last subject completed study)	<b>Development Phase:</b> Phase 2	
<b>Introduction and Objectives:</b> The primary objectives were to assess the CD34 <sup>+</sup> cells/kg yield and the safety of 2 fixed, single-dose levels of pegfilgrastim and a by-weight daily dose of filgrastim for PBPC mobilization and collection for autologous transplantation in subjects with Hodgkin's disease or non-Hodgkin's lymphoma. The secondary objectives, as defined in the protocol, were the following: <ul style="list-style-type: none"><li>• to assess CD34<sup>+</sup> dynamics and pharmacokinetics of pegfilgrastim in peripheral blood during the collection phase</li><li>• to evaluate engraftment of PBPC mobilized by pegfilgrastim</li></ul>		
<b>Methodology:</b> Eligible subjects were randomized in a 1:1:1 ratio to receive daily doses of 10 µg/kg filgrastim, a single, fixed dose of 6 mg pegfilgrastim, or a single, fixed dose of 12 mg pegfilgrastim. To maintain the blind, placebo was administered in a manner consistent with the alternative filgrastim and pegfilgrastim dose volumes and schedules. Randomization was stratified according to protocol-specified criteria for the amount of previous cancer therapy received (heavily pretreated versus non-heavily pretreated). The study included a collection phase and a transplant phase. On day 1 of the collection phase, subjects received the first of daily doses of filgrastim (10 µg/kg/day) and placebo or a single dose of pegfilgrastim (6 or 12 mg) and placebo. From day 2 through the last leukapheresis, subjects in the filgrastim group continued receiving daily doses of blinded filgrastim, and subjects in the pegfilgrastim groups received filgrastim-matched placebo. Leukapheresis began on day 5 and continued daily until the maximum target cumulative CD34 <sup>+</sup> yield $\geq 5 \times 10^6$ /kg was met or until a maximum of 5 leukaphereses had been performed, whichever occurred first. Subjects who did not yield the minimum threshold of $\geq 2 \times 10^6$ CD34 <sup>+</sup> cells/kg were withdrawn from the study and did not proceed to transplant.		

Subjects who met the minimum CD34<sup>+</sup> yield threshold entered a rest period of 3 to 14 days and then entered the transplant phase, in which subjects received myeloablative conditioning chemotherapy followed by autologous PBPC transplant with the harvested CD34<sup>+</sup> cells. During the transplant phase, all subjects received filgrastim 5 µg/kg/day from the date of transplant until absolute neutrophil count (ANC) recovery (ANC > 5 x 10<sup>9</sup>/L for 3 days or > 10 x 10<sup>9</sup>/L for 1 day). The transplant phase ended with platelet engraftment (defined as platelet count > 20 x 10<sup>9</sup>/L on 2 or more occasions, separated by at least 1 day, in the absence of transfusion). Subjects were followed for 100 days after transplant.

**Number of Subjects Planned:**

The planned sample size was 90 subjects, with 30 subjects in each of 3 treatment groups.

**Number of Subjects Enrolled:**

Because this study was discontinued early, fewer than the planned 90 subjects were enrolled into the study. Forty-one subjects were enrolled into the study, and 40 subjects (98%) received filgrastim or pegfilgrastim (13 subjects in the 10-µg/kg/day filgrastim group, 13 subjects in the 6-mg pegfilgrastim group, and 14 subjects in the 12-mg pegfilgrastim group).

**Sex:** filgrastim: 10 (77%) men, 3 (23%) women; pegfilgrastim 6 mg: 6 (46%) men, 7 (54%) women; pegfilgrastim 12 mg: 11 (73%) men, 4 (27%) women

**Mean (SD) Age:** filgrastim: 45.6 (16.6) years; pegfilgrastim 6 mg: 45.1 (14.9) years; pegfilgrastim 12 mg: 53.5 (9.4) years

**Ethnicity (Race):** filgrastim: 11 (85%) white, 1 (8%) Hispanic, 1 (8%) black; pegfilgrastim 6 mg: 11 (85%) white, 2 (15%) black; pegfilgrastim 12 mg: 12 (80%) white, 2 (13%) Hispanic, 1 (7%) black

**Diagnosis and Main Criteria for Eligibility:**

Subjects who provided informed consent and met the following criteria were eligible for this study:

- diagnosed with Hodgkin's disease or non-Hodgkin's lymphoma of any histologic classification
- 18 years of age or older
- considered a suitable candidate for autologous PBPC transplantation according to institutional guidelines
- ANC ≥ 1.5 x 10<sup>9</sup>/L and platelets ≥ 80 x 10<sup>9</sup>/L

**Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number:**

Pegfilgrastim was administered subcutaneously as a single dose of 6 or 12 mg, supplied in a prefilled syringe containing a clear, colorless, sterile protein solution (10 mg/mL). The buffered solution (pH 4.0) contained 0.35 mg acetate, 30 mg sorbitol, 0.02 mg Tween® 20, and 0.02 mg sodium. The fill lot number of the pegfilgrastim used in this study was 11A011968. The fill lot numbers of pegfilgrastim administered to individual subjects are provided in [Appendix 18](#).

**Duration of Treatment:**

Each subject's participation in the study, including participation in the collection, transplantation, and follow-up phases, was expected to be approximately 16 weeks.

**Reference Therapy, Dose and Mode of Administration, Lot Number:**

Filgrastim was administered subcutaneously at a dose of 10 µg/kg/day, provided in prefilled syringes containing a clear, colorless, sterile protein solution (0.6 mg/mL). The buffered solution (pH 4.0) contained 0.472 mg acetate, 40 mg sorbitol, 0.004% Tween 80, and 0.028 mg sodium. The fill lot number for the filgrastim used in this study was P005215.

Placebo for the filgrastim treatment group was dosed by weight and was supplied in prefilled syringes containing 0.8 mL vehicle for filgrastim. The fill lot number of filgrastim placebo used in this study was 06A016680.

Placebo for the pegfilgrastim treatment groups was given as a fixed volume corresponding to 6- or 12-mg doses and was supplied in prefilled syringes containing 0.6 mL vehicle for pegfilgrastim. The fill lot number of the pegfilgrastim placebo used in this study was 06A012070.

The fill lot numbers of filgrastim, filgrastim placebo, and pegfilgrastim placebo administered in individual subjects are listed in [Appendix 18](#).

**Efficacy Endpoints:**

**Primary Efficacy Endpoint**

- subject mean CD34<sup>+</sup> cells/kg yield (the total yield for a subject divided by the number of leukaphereses that the subject needed to collect the total yield)

**Secondary Efficacy Endpoints**

- cumulative subject mean CD34<sup>+</sup> cells/kg yield through each leukapheresis (calculated for each day of leukapheresis as the total yield of CD34<sup>+</sup> cells collected through each leukapheresis, divided by the number of leukaphereses required to harvest those cells [ie, a rolling average])
- CD34<sup>+</sup> cells/kg yield in each leukapheresis
- number of leukaphereses to reach  $\geq 5 \times 10^6$  CD34<sup>+</sup> cells/kg
- number and proportion of subjects who yield  $\geq 2 \times 10^6$  CD34<sup>+</sup> cells/kg
- number and proportion of subjects who yield  $\geq 5 \times 10^6$  CD34<sup>+</sup> cells/kg
- time to neutrophil recovery of ANC  $\geq 0.5 \times 10^9/L$  and ANC  $\geq 1.0 \times 10^9/L$
- time to platelet engraftment of  $\geq 20 \times 10^9/L$  and  $\geq 50 \times 10^9/L$  (independent of platelet transfusions)

**Pharmacokinetic Endpoint**

- pharmacokinetic profile of pegfilgrastim during mobilization and collection

**Safety Endpoints**

- incidence of adverse events
- antibody assessments
- changes in spleen size from baseline (as measured by ultrasound)

**Statistical Methods:**

Subjects were stratified according to the type and amount of previous chemotherapy received (ie, heavily pretreated or non-heavily pretreated). Descriptive statistics were provided for all endpoints for each treatment group. Comparative statistics were provided for descriptive purposes only because the power to show differences among groups was low.

The subject mean CD34<sup>+</sup> yield over each leukapheresis, cumulative subject mean CD34<sup>+</sup> cells/kg yield through each leukapheresis, and changes in spleen size from

baseline were summarized by reporting mean, median, standard deviation (SD), first and third quartiles (Q1, Q3), and minimum and maximum values. Exact 2-sided 95% confidence intervals (CIs) for the ratio in yields between each pegfilgrastim group and the filgrastim group also were provided for certain variables. The number of leukaphereses required to yield  $\geq 5 \times 10^6$  CD34<sup>+</sup> cells/kg was tabulated for each treatment group, and the difference in the median number of leukaphereses among the 3 treatment groups was reported with 95% CIs. The number and proportion of subjects who reached the minimum and maximum cell yields ( $\geq 2 \times 10^6$  CD34<sup>+</sup> cells/kg and  $\geq 5 \times 10^6$  CD34<sup>+</sup> cells/kg) in each treatment group was summarized, and the odds ratio between the filgrastim and pegfilgrastim groups and 2-sided 95% CIs were reported. The number and proportion of subjects who achieved ANC recovery and platelet engraftment was summarized by treatment group for each stratum, and Kaplan-Meier estimates were provided for time-to-engraftment data.

The pharmacokinetic parameters of pegfilgrastim were estimated using noncompartmental analysis and were summarized by treatment group. Safety parameters, including the incidence of adverse events, changes in laboratory measurements, and antibody assessments, were summarized by treatment group and by study phase.

#### **Summary:**

##### **Subject Disposition:**

Forty-one subjects were randomized into this study, and 40 subjects (98%) received 1 or more doses of filgrastim or pegfilgrastim and were evaluated for efficacy, safety, and pharmacokinetics. Thirty-eight subjects (93%) completed the collection phase (ie, received 1 or more leukaphereses). Fifteen subjects (37%) (7 [54%] filgrastim, 4 [31%] pegfilgrastim 6 mg, 4 [27%] pegfilgrastim 12 mg) met the minimum threshold CD34<sup>+</sup> yield of  $\geq 2 \times 10^6$  cells/kg and proceeded to the transplant phase. Of the subjects who proceeded to transplant, 11 subjects (27%) (5 [39%] filgrastim, 4 [31%] pegfilgrastim 6 mg, and 2 [13%] pegfilgrastim 12 mg) completed the study. This study was discontinued early due to futility (ie,  $< 50\%$  of subjects yielded  $\geq 2 \times 10^6$  CD34<sup>+</sup> cells/kg, the minimum yield necessary to proceed to transplant), per the protocol-specified early-stopping guidelines.

##### **Efficacy:**

In general, small sample sizes precluded meaningful interpretation of efficacy analyses. Results for the primary efficacy endpoint (subject mean CD34<sup>+</sup> cells/kg yield) showed that CD34<sup>+</sup> cells/kg yields through mobilization by cytokines alone (ie, filgrastim or pegfilgrastim) were lower in the pegfilgrastim groups than the prespecified minimum for continuation of the study (ie,  $< 50\%$  of subjects in the pegfilgrastim groups yielded  $\geq 2 \times 10^6$  CD34<sup>+</sup> cells/kg), resulting in early discontinuation of the study.

All subjects who proceeded to transplant achieved ANC recovery to  $\geq 0.5 \times 10^9$ /L and  $\geq 1.0 \times 10^9$ /L during the study. All subjects achieved platelet engraftment to  $\geq 20 \times 10^9$ /L, and 13 subjects (87%) achieved platelet engraftment to  $\geq 50 \times 10^9$ /L. Times to ANC and platelet engraftment were as expected.

**Safety:**

Filgrastim (10 µg/kg/day) and pegfilgrastim (single, fixed dose of 6 or 12 mg) were well tolerated in this study. The safety profile of pegfilgrastim was similar to filgrastim and was consistent with the known effects of pegfilgrastim. No dose-response effect was noted for the overall incidence or type of adverse events in the 6- and 12-mg pegfilgrastim groups.

During the collection phase, bone pain was the most common treatment-related adverse event (3 subjects [23%] filgrastim, 3 subjects [23%] pegfilgrastim 6 mg, and 3 subjects [21%] pegfilgrastim 12 mg); this incidence rate is consistent with the product literature. Two withdrawals due to adverse events, both in the 12-mg pegfilgrastim group, occurred during the collection phase; neither event was considered by the investigator to be related to pegfilgrastim. One death occurred during the follow-up period in a subject in the 12-mg pegfilgrastim group who had completed CD34<sup>+</sup> cell collection but did not proceed to transplant because of insufficient CD34<sup>+</sup> yield. This death was attributed to neutropenic sepsis, occurred approximately 6 weeks after the subject received a single dose of pegfilgrastim (with no subsequent filgrastim), and was not considered by the investigator to be related to pegfilgrastim.

During the transplant phase, only treatment-related and/or serious adverse events were to be reported. Because all subjects received only open-label filgrastim during the transplant phase, treatment-related adverse events during this phase are related to open-label use of filgrastim. Three subjects (20%) had 1 or more adverse events reported as related to filgrastim; of these, 2 adverse events (tonic convulsions and typhlitis) were serious; these adverse events occurred in a subject who had concurrent posterior leukoencephalopathy. No deaths or withdrawals due to adverse events occurred during the transplant phase.

Spleen volumes increased from baseline during the collection phase. By the end of collection phase, however, spleen sizes had returned to near-baseline volumes in all treatment groups except the 12-mg pegfilgrastim group. No adverse events associated with the spleen were reported.

No subjects tested positive for anti-filgrastim or anti-pegfilgrastim antibodies at the end of the study. Hematology and chemistry laboratory results revealed no trends indicative of treatment-related toxicities.

**Pharmacokinetics:**

Because of saturation of the neutrophil-mediated clearance at higher pegfilgrastim concentrations, exposure to pegfilgrastim increased proportionally more than the dose. As the dose increased 2-fold from 6 to 12 mg, median C<sub>max</sub> value increased 4-fold from 106 to 428 ng/mL, and the median AUC<sub>0-∞</sub> increased 4.9-fold from 3830 to 18,800 ng·hr/mL. The pegfilgrastim profiles for the 6- and 12-mg groups declined almost in parallel, with a median terminal half-life value ranging from 27.6 to 28.8 hours.