NEULASTA®

(pegfilgrastim)

Oncologic Drugs Advisory Committee Pediatric Subcommittee Meeting

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Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

List of Abbreviations

Abbreviation or Term	Definition/Explanation
ANC	absolute neutrophil count
ARDS	adult respiratory distress syndrome
COG	Children's Oncology Group
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
G-CSF	granulocyte colony-stimulating factor
IE	chemotherapy with ifosfamide and etoposide
kD	kilodalton
NCI	National Cancer Institute
PEG	polyethylene glycol
Q2W	every 2 weeks
Q3W	every 3 weeks
rHuG-CSF	recombinant human granulocyte colony-stimulating factor
r-metHuG-CSF	recombinant human methionyl granulocyte colony-stimulating factor (filgrastim)
SC	subcutaneous
US	United States
VAdC	chemotherapy with vincristine, doxorubicin, and cyclophosphamide

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1. Executive Summary

Amgen believes that innovative new therapies for children who have cancer can best be developed in collaboration with cooperative groups, investigators, patients, and regulatory authorities. Amgen is grateful for the opportunity at the Oncologic Drugs Advisory Committee Pediatric Subcommittee Meeting (20 October 2005) to highlight the challenges and issues inherent in the development of pediatric oncology drugs and to contribute ideas to enhance this development. Amgen believes that the study of oncology drugs in children merits special consideration and strongly supports the use of adequate safety and efficacy evaluation in the framework of controlled clinical trials in the pediatric population. Most children receive cancer therapy as participants in clinical research protocols that have become the standard of care in pediatric oncology. The Children's Oncology Group (COG), which has a mission to cure and prevent childhood and adolescent cancer through scientific discovery and compassionate care, is a key partner in the design, conduct, and evaluation of these trials in pediatric hematology and oncology.

Unfortunately, differences in tumor biology and drug pharmacokinetics and pharmacodynamics in children and adults make it difficult to extrapolate clinical drug effects from adults to children. Consequently, there may be potential risks in relying on the pharmacokinetic and safety data gathered from studies of a cancer drug in adults to define the appropriate use of that drug in children. Therefore, it is imperative to evaluate the effectiveness and safety of new cancer drugs in pediatric populations.

Amgen incorporates development plans for pediatric use within the initial clinical development of all new products that could be used in children. Through collaboration with cooperative groups and regulatory agencies, Amgen develops specific protocols to examine the safety and efficacy of these oncology therapies in children of various age groups. Initiating and completing such protocols in a timely manner, however, remains difficult. The issues presented in this document are common in pediatric oncologic drug development and include a limited patient population, competition for eligible patients among studies, issues with study design, and rapid changes in medical practice. Unlike the adult patient population in the United States, most children with cancer are enrolled in clinical studies that are typically run by cooperative groups. Because of the association of specific tumor types with age groups in the pediatric population, a trial with a single tumor type and regimen may not cover all possible age ranges within the

pediatric population. In addition, because differences exist in the metabolism and biologic responses between adults and children, the pharmacokinetic and pharmacodynamic data generated from studies in adults can only be used as a guide for dosing in children. Therefore, dose-finding studies usually are required before initiating efficacy studies in children. Finally, most malignancies in children are considered to be curable, a fact that typically favors participation in a therapeutic clinical trial of a novel chemotherapy treatment rather than a supportive-care trial.

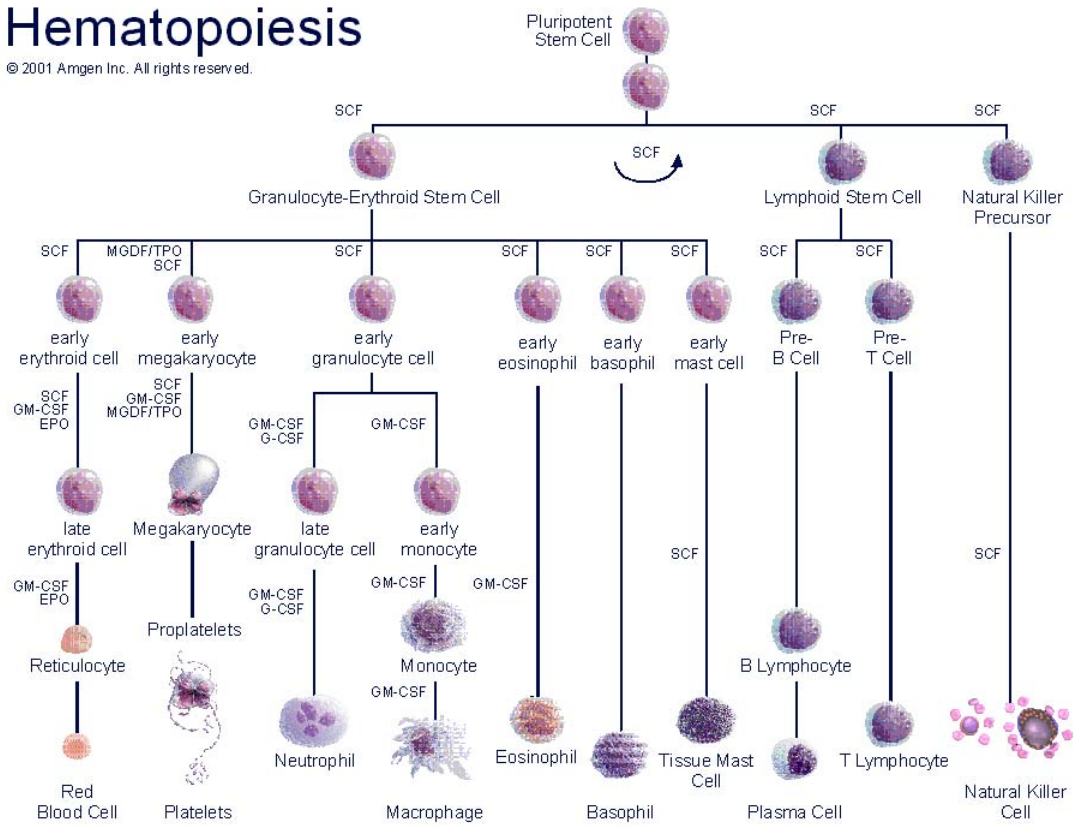
Although the cooperative groups, regulatory agencies, and Amgen work together, improvement is needed in the process of pediatric drug registration. One approach to facilitate the generation of appropriate data for registration would be to have all parties work together concurrently, before initiation of any study, so that the results from the studies will address the various needs of the different groups, and ultimately lead to effective treatments for the pediatric population.

2. Background Information

Neutropenia is defined as a neutrophil count < 1.5 x 10^9/L (Hutchinson and Boxer, 1991). Neutropenia has several etiologies, including inherent dysfunction of the bone marrow, or it can occur secondary to exogenous substances, such as chemotherapy. Whatever the cause, neutropenia predisposes patients to potentially life-threatening infections (Bodey et al, 1966). The relative risk of infection has been shown to be directly correlated to the severity, rapidity of development, and duration of neutropenia (Bodey et al, 1966). The severity of neutropenia depends on the intensity of the chemotherapy regimen, as well as on host- and disease-related factors. Fever may be the only manifestation of infection because underlying immunosuppression may obscure the other signs and symptoms. Delay in initiating subsequent cycles of chemotherapy or decrease in the dose of chemotherapy, or both, may be required because of severe neutropenia. Such delay may compromise an otherwise effective chemotherapy regimen.

Hematopoietic growth factors are glycoproteins that act on hematopoietic cells by binding to specific cell-surface receptors to stimulate the proliferation, differentiation, commitment, and end-cell functions. Several hematopoietic growth factors have been cloned, and recombinant forms manufactured and approved for marketing. Filgrastim (Neupogen®) is a recombinant human granulocyte colony-stimulating factor (rHuG-CSF) that acts on neutrophil precursors (Figure 1).

Figure 1. Schema of Hematopoiesis, Including Some of the Growth Factors That Influence the Production of Blood Cells



In addition to being indicated as an adjunct to myelosuppressive chemotherapy, filgrastim is indicated:

- as an adjunct to induction or consolidation chemotherapy for acute myeloid leukemia
- to reduce the duration of neutropenia of high-dose chemotherapy in bone marrow or peripheral stem cell transplantation setting
- for the mobilization of peripheral blood stem cells for collection by leukapheresis
- to treat chronic neutropenia, such as congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia

The use of filgrastim reduced the incidence of infections, decreased hospital admissions, and decreased use of intravenous anti-infectives for patients with cancer and improved cancer therapy (Morstyn et al, 1994). Filgrastim transformed the lives of children and adults with severe chronic neutropenia (Dale et al, 1993).

Filgrastim use, however, requires multiple daily injections. It was thought that a product that could be administered less frequently, ideally once per chemotherapy cycle, would be more acceptable to patients, their caregivers, and healthcare providers and that it might allow for more flexible administration. A drug candidate with a similar safety and efficacy profile, but with a longer half-life, was desirable. Pegfilgrastim is a sustained-duration formulation of filgrastim that has been developed by covalent attachment of a polyethylene glycol (PEG) molecule to the filgrastim molecule. Neulasta® (pegfilgrastim) was approved on 31 January 2002 for reduction of the incidence of infection, as manifested by febrile neutropenia, in patients with chemotherapy-induced neutropenia caused by cancer chemotherapy. The recommended adult dosage is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle.

An overview of the clinical development of pegfilgrastim is provided in Section 2.2. Numerous papers have suggested that pegfilgrastim provides the same safety and efficacy benefits as filgrastim (Vogel et al, 2005; Green et al, 2003; Holmes et al, 2002a; Holmes et al, 2002b; Johnston et al, 2000).

2.1 Chemotherapy-induced Neutropenia

2.1.1 Description of Disease Setting

Chemotherapy-induced neutropenia is the most common leukopenia condition in oncology clinical practice and is a major contributing factor to infection, morbidity, mortality, and chemotherapy-dose modifications (Pettengell et al, 1992; Bodey et al, 1966). The severity and duration of the neutropenia are related to the risk of infection (Blackwell and Crawford, 1994).

2.1.2 Description of Currently Available Therapies

Broad-spectrum antibiotics have long been the mainstay of therapy for infections occurring in immunocompromised hosts.

2.2 Clinical Development of Pegfilgrastim for the Treatment of Adult Patients With Chemotherapy-induced Neutropenia

Pegfilgrastim is a sustained-duration formulation of rHuG-CSF that has been developed by covalent attachment of a 20-kilodalton (kD) PEG molecule to the filgrastim molecule (Molineux et al, 1999). PEG modification of proteins sustains the duration of action by reducing renal clearance of the protein and decreasing rates of cellular uptake and

proteolysis (Roberts et al, 2002; Delgado et al, 1992). Data from cellular proliferation, receptor-binding, neutrophil response, and neutrophil function studies suggest that pegfilgrastim has the same mechanism of action as endogenous granulocyte colony-stimulating factor (G-CSF) and filgrastim, namely binding to the G-CSF receptor on myeloid cells that causes the preferential stimulation of neutrophil precursors and the activation of mature neutrophils (Lord et al, 2001; de Haan et al, 2000; Molineux et al, 1999; Jensen-Pippo et al, 1996).

The clinical development of pegfilgrastim was based on the use of filgrastim in clinical research and on significant postmarketing experiences. The clinical development program followed a traditional pathway, with clinical studies in phase 1, 2, and 3 performed with adults. Once safety and efficacy had been demonstrated in phase 2 studies in adults, development was started in pediatric subjects (Section 3).

A phase 1 study in healthy adult volunteers confirmed nonclinical findings that pegfilgrastim has reduced clinical clearance and prolonged persistence in vivo compared with filgrastim (Molineux et al, 1999). Once activity was confirmed in volunteers, phase 2 studies were conducted in adult subjects with thoracic tumors, breast cancer, or lymphoma, or in elderly subjects with non-Hodgkin's lymphoma (Holmes et al, 2002a; Johnston et al, 2000). These studies showed that a single injection of pegfilgrastim was comparable to multiple doses of filgrastim in supporting neutrophil recovery and that the adverse event profile resembled that of filgrastim. The conclusions from the phase 2 studies were confirmed in phase 3 studies with adult subjects (Section 2.2.1).

2.2.1 Summary of Efficacy in Pivotal Studies in Adults

Pegfilgrastim has been evaluated in 3 randomized, double-blind, controlled studies. Two studies (Green et al, 2003; Holmes et al, 2002b) were included in the original license application and a third study (Vogel et al, 2005) was conducted after the initial approval.

The Holmes and the Green studies were active-controlled studies that used doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2 administered every 21 days for up to 4 cycles for the treatment of metastatic breast cancer. The Green study investigated the utility of a fixed dose of pegfilgrastim, and investigated a weight-adjusted dose. In the absence of growth factor support, similar chemotherapy regimens have been reported to cause a 100% incidence of severe neutropenia (absolute neutrophil count [ANC] < 0.5 x 10^9/L) with a mean duration of 5 to 7 days and a 30% to 40% incidence of febrile neutropenia

(defined as body temperature ≥ 38.2°C and ANC ≥ 0.5 x 10^9/L) (Nabholtz et al, 2001; Misset et al, 1999). Based on the correlation between the duration of severe neutropenia and the incidence of febrile neutropenia found in studies with filgrastim, duration of severe neutropenia was chosen as the primary endpoint in both studies. The efficacy of pegfilgrastim was demonstrated by establishing comparability to filgrastim-treated subjects in terms of the mean number of days of severe neutropenia.

In the Green study, 157 subjects were randomly assigned to receive a single subcutaneous injection of pegfilgrastim 6 mg on day 2 of each chemotherapy cycle or daily subcutaneous injections of filgrastim 5 µg/kg beginning on day 2 of each chemotherapy cycle. In the Holmes study, 310 subjects were randomly assigned to receive a single subcutaneous injection of pegfilgrastim 100 µg on day 2 of each chemotherapy cycle or daily subcutaneous injections of filgrastim 5 µg/kg/day beginning on day 2 of each chemotherapy cycle.

Both studies met the primary objective of demonstrating that the mean number of days of severe neutropenia for subjects treated with pegfilgrastim did not exceed the mean number of days of severe neutropenia for subjects treated with filgrastim by > 1 day in cycle 1 of chemotherapy (Table 1). The rates of febrile neutropenia in the 2 studies were comparable for pegfilgrastim and filgrastim (in the range of 10% to 20%). Other secondary endpoints included days of severe neutropenia in cycles 2 to 4, the depth of the ANC nadir in cycles 1 to 4, and the time to ANC recovery after nadir. In both studies, the results for the secondary endpoints were similar between the 2 treatment groups.

Table 1. Mean Number of Days of Severe Neutropenia in Cycle 1

		Mean days of severe neutropenia		
Study	n	Pegfilgrastim[a]	Filgrastim (5 µg/kg/day)	Difference in means (95% CI)
Green et al, 2003	157	1.8	1.6	0.2 (-0.2, 0.6)
Holmes et al, 2002b	310	1.7	1.6	0.1 (-0.2, 0.4)

[a] Study 1 dose = 6 mg x 1; study 2 dose = 100 µg/kg x 1

The effectiveness of pegfilgrastim in chemotherapy regimens associated with lower incidence of febrile neutropenia was recently assessed in a further phase 3 study (Vogel et al, 2005), which was a randomized, double-blind, placebo-controlled study that used

docetaxel 100 mg/m^2 administered every 21 days for up to 4 cycles for the treatment of metastatic or nonmetastatic breast cancer. In this study, 928 subjects were randomly assigned to receive a single subcutaneous injection of pegfilgrastim 6 mg or placebo on day 2 of each chemotherapy cycle. The Vogel study met the primary objective of demonstrating that the incidence of febrile neutropenia (defined as temperature $\geq$ 38.2°C and ANC $\leq$ 0.5 x 10^9/L) was lower for subjects who received pegfilgrastim compared with subjects who received placebo (1% versus 17%, $p < 0.001$). The incidence of hospitalizations (1% versus 14%) and intravenous anti-infective use (2% versus 10%) for the treatment of febrile neutropenia also were lower for subjects who received pegfilgrastim compared with subjects who received placebo.

2.2.2 Summary of Safety in Adults

2.2.2.1 Safety in Clinical Trials

More than 3800 patients have received at least 1 dose of pegfilgrastim in a clinical study as of 31 January 2005. In general, pegfilgrastim appears to be safe and well tolerated at the doses and schedules tested in patients with cancer. Table 2 summarizes the adverse events occurring in the Vogel study (Vogel et al, 2005; placebo controlled). The most commonly reported adverse events were generally consistent with the underlying cancer diagnosis and its treatment with chemotherapy, with the exception of bone pain, which occurred at a higher incidence in subjects who received pegfilgrastim compared with subjects who received placebo. Bone pain generally was reported to be mild-to-moderate severity. Transient changes in serum enzymes and blood chemistries were not associated with any clinical sequelae.

Table 2. Adverse Events Occurring in ≥ 10%[a] of Subjects in the Placebo-controlled Study

Event	Pegfilgrastim (n = 467)	Placebo (n = 461)
Alopecia	48%	47%
Bone Pain[b]	31%	26%
Diarrhea	29%	28%
Pyrexia (not including febrile neutropenia)	23%	22%
Myalgia	21%	18%
Headache	16%	14%
Arthralgia	16%	13%
Vomiting	13%	11%
Asthenia	13%	11%
Edema peripheral	12%	10%
Constipation	10%	6%

[a] Events occurring in ≥ 10% of subjects who received pegfilgrastim and at a higher incidence compared with subjects who received placebo.

[b] Bone pain is limited to the specified adverse event term “bone pain”.

2.2.2.2 Postmarketing Surveillance

More than 517,000 patients have received at least 1 dose of pegfilgrastim since its commercialization. The pegfilgrastim pharmacovigilance program includes evaluation and follow-up of reported adverse events and ongoing surveillance of safety information from the medical literature. Analyses are performed both at the individual case level as well as at the aggregate population level. Although retrospective, anecdotal, and frequently incomplete, postmarketing reports can provide insights into product impact in a broader patient population than clinical trials, including patients with multiple comorbidities and concomitant medications. Amgen considers that the postmarketing safety surveillance provides an important window on "real world" patient and prescriber experience with pegfilgrastim therapy. When appropriate, Amgen works with Food and Drug Administration (FDA) to ensure that important safety information is added to the package insert to help inform medical practitioners.

At the time of approval, the warnings section of the pegfilgrastim package insert contained information about events observed in the postmarketing surveillance of filgrastim. Since approval, as the experience with pegfilgrastim has increased, the warnings section has been updated to include information regarding splenic rupture,

allergic reactions, and sickle cell disease, based on a small number of events reported with pegfilgrastim use:

- Rare cases of splenic rupture have been reported after administration of pegfilgrastim.
- Adult respiratory distress syndrome (ARDS) has been reported in neutropenic patients with sepsis who were receiving filgrastim, the parent compound of pegfilgrastim, which has been postulated to be secondary to an influx of neutrophils to sites of inflammation in lungs.
- Allergic reactions to pegfilgrastim, including anaphylaxis, skin rash, and urticaria, have been reported in postmarketing experience.
- Severe sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell disease.

2.2.3 Study Design Issues Encountered in Pegfilgrastim Registration Studies

The design of studies to support licensure of pegfilgrastim necessarily includes hospital or clinic visits solely for study procedures. For example, extensive sampling for measurement of ANC (ie, blood draws) is needed to assess neutrophil response, which is then included in the statistical analysis. Potential study subjects may opt to receive commercially available filgrastim (even with multiple injections) to avoid the extra time and medical procedures of a clinical study.

2.2.4 Conclusions

Chemotherapy-induced neutropenia continues to be a major dose-limiting toxicity of myelosuppressive chemotherapy. Growth factors, such as pegfilgrastim, have been used as adjunctive treatment for chemotherapy and have been shown to decrease the incidence of febrile neutropenia, infectious complications, and hospitalizations and reduce the use of intravenous anti-infectives. A clear understanding of the native G-CSF molecule and an ability to use pegylation to extend half-life facilitated the development of pegfilgrastim in chemotherapy-induced neutropenia. Potential benefits of the longer acting pegfilgrastim molecule include fewer injections, increased patient compliance, and decreased burden on healthcare providers.

3. Description of Amgen-sponsored Pegfilgrastim Development Program for the Treatment of Chemotherapy-induced Neutropenia in Pediatric Subjects

3.1 Regulatory History

Amgen initiated discussions with the FDA regarding the appropriate study design to evaluate the use of pegfilgrastim in the pediatric population once the efficacy, safety, and tolerability had been established in adults. Discussions regarding the final study design took place in 1999 and 2000, during the completion of the registration studies in adults. On 31 January 2002, Neulasta received marketing approval with a postmarketing commitment to submit results from an ongoing study to evaluate the pharmacokinetics, safety, and efficacy of pegfilgrastim in pediatric subjects. The pediatric study to meet the postmarketing commitment is a phase 2 trial of pediatric subjects with Ewing's sarcoma (Amgen Study 990130), where pegfilgrastim is used as an adjunct to VAdC/IE (chemotherapy with vincristine, doxorubicin, and cyclophosphamide, and ifosfamide and etoposide) to reduce the duration of chemotherapy-induced severe (grade 4) neutropenia.

In a letter dated 20 September 2004, the FDA notified Amgen that the Pediatric Research Equity Act (PREA) was enacted 3 December 2003. Therefore, submission of data from this pediatric study under CFR 601.27 was deferred until 15 April 2007, and development of a pediatric dosage form deferred until 15 January 2008.

3.2 Summary of Study Sites for Pediatric Study With Pegfilgrastim

This study is a multicenter study consisting of sites in the United States and Australia. Since the start of the study, 50 sites have been contacted to participate, with 18 sites agreeing to participate and 7 sites currently open to enrollment.

3.3 Patient Population for Pediatric Study With Pegfilgrastim

The patient population for this study includes children aged 0 to 21 years enrolled in 3 age strata (0 to 5 years, 6 to 11 years, and 12 to 21 years). A minimum of 42 children are expected to complete the study.

Subjects are eligible for inclusion in the study if they meet the following key inclusion criteria:

- Confirmed to have sarcoma, including primitive peripheral neuroectodermal tumors
- Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

- Have adequate renal, liver, cardiac, and hematology functions

Subjects are not eligible for inclusion in the study if they have any of the following key exclusion criteria:

- Bone marrow involvement or evidence of hematologic malignancy, myelodysplasia, or other malignancies
- Previous radiotherapy or chemotherapy or surgery within 2 weeks of enrollment
- Treatment with antibiotics or anti-infectives within 72 hours before randomization, treatment with cytokines within 2 weeks of start of chemotherapy, treatment with filgrastim within 1 week of start of chemotherapy, or treatment with corticosteroids or lithium within 1 week of study entry

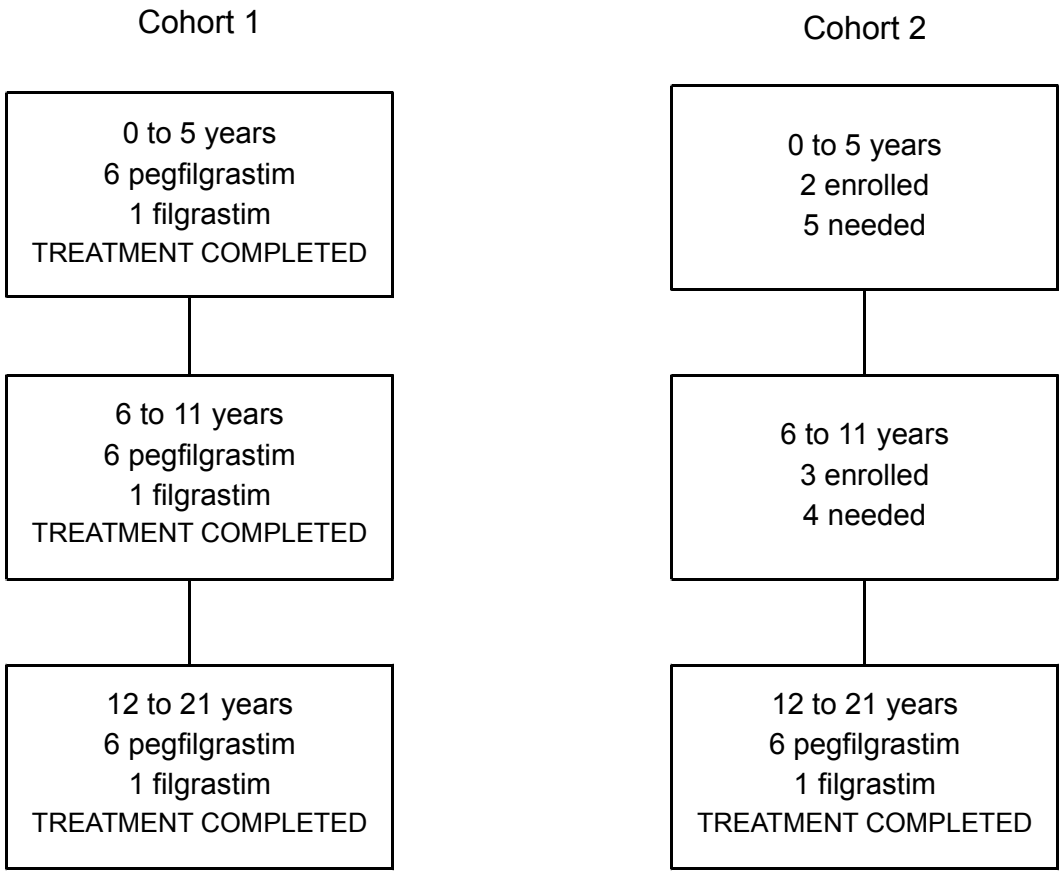
3.4 Study Endpoint for Pediatric Study With Pegfilgrastim

The primary objective of this study is to determine the appropriate dose of pegfilgrastim in the pediatric population. Descriptive analyses to characterize the response profiles for the selected dose will be conducted for the study endpoints of duration of severe (grade 4) neutropenia in chemotherapy cycles 1 and 3, rates of febrile neutropenia, and time to ANC recovery > 0.5 x 10^9/L in cycles 1 and 3. Other endpoints include the pharmacokinetic profile of pegfilgrastim in chemotherapy cycles 1 and 3 and the incidence of adverse events across all cycles of chemotherapy.

3.5 Treatment Schema for Pediatric Study With Pegfilgrastim

The study has 2 parts. Part 1 assessed the safety of a dose of 100 μg/kg and is complete. In part 1, 3 subjects received pegfilgrastim. The safety profile after the 3 subjects were treated was deemed to be sufficiently safe to continue the study. Part 2 will enroll at least 42 subjects into 2 cohorts (21 subjects per cohort) of 3 age strata (0 to 5 years, 6 to 11 years, and 12 to 21 years). In each age stratum, 6 subjects will be randomly assigned to receive pegfilgrastim, and 1 subject will be randomly assigned to receive filgrastim (Figure 2).

Figure 2. Study 990130 Part 2 Study Status[a]



[a] Thirty-eight subjects have enrolled in the study as of 19 August 2005 (5 subjects were replaced per protocol). The pegfilgrastim dose has been 100 μg/kg. Additional cohorts (consisting of 1 or more age strata) may be added per protocol should the data indicate that the dose needs to be modified.

After written informed consent is obtained, subjects will be randomly assigned to treatment with pegfilgrastim or filgrastim. Before the start of all cycles, subjects will have a physical examination. Blood will be drawn for hematology and chemistry panels, and determination of the presence of antibodies to pegfilgrastim or filgrastim.

On day 1, cycles 1 and 3, chemotherapy (vincristine, doxorubicin, and cyclophosphamide) will be administered over a 48-hour period. Approximately 24 hours after completion of chemotherapy, study subjects will receive either a single dose of pegfilgrastim 100 μg/kg or filgrastim 5 μg/kg/day until ANC $\geq$ 10 x 10^9/L or until 24 hours before the next chemotherapy cycle. On day 1, cycles 2 and 4, chemotherapy (etoposide, ifosfamide, and mesna) will be administered over 5 days. Approximately 24 hours after completion of chemotherapy, study subjects will receive either a single

dose of pegfilgrastim 100 μg/kg or filgrastim 5 μg/kg/day until ANC ≥ 10 x 10^9/L or until 24 hours before the next chemotherapy cycle. Subjects can have a maximum of 4 cycles of chemotherapy while on study. Continued chemotherapy can be done off study at the discretion of the investigator, but pegfilgrastim or filgrastim will not be provided by Amgen for these additional cycles.

Blood will be drawn for pharmacokinetic samples and complete blood cell counts in cycles 1 and 3 at prespecified timepoints for the first 48 hours after injection of pegfilgrastim or after the first injection of filgrastim and then daily until 2 consecutive ANC > 0.5 x 10^9/L. Body temperature will be measured twice daily and whenever subjects appear to be feverish.

Approximately 1 and 3 months from the day-21 visit of the last on-study chemotherapy cycle, a follow-up appointment will be scheduled. Adverse events deemed serious and related to study drug will be collected, and blood will be drawn for hematology panels and determination of the presence of antibodies to pegfilgrastim or filgrastim.

The study schema is given in Appendix A and the dose escalation schema is given in Appendix B.

3.6 Efficacy and Safety Monitoring for Pediatric Study With Pegfilgrastim

Subjects are monitored continuously for adverse events.

When an age stratum (n = 7) in a cohort has been completely enrolled, the safety monitoring committee (comprising Amgen clinical scientists and statisticians) will review the data and determine whether the dose should be escalated or remain the same, and then decide whether to permit continued enrollment within the next cohort of that same age stratum. If dose escalation is required, the doses of pegfilgrastim will be 150, 225, and 300 μg/kg. If dose decrease is required, the dose of pegfilgrastim will be decreased to 60 μg/kg.

3.7 Statistical Analyses for Pediatric Study With Pegfilgrastim

In addition to the analyses required to establish the dose (ie, dose finding), ANC values will be analyzed using descriptive statistics by treatment group and cycle. It is anticipated that the age groups will be combined for these analyses. Noncompartmental pharmacokinetic parameters will be estimated based on individual serum concentration

data. Rates of all adverse events will be tabulated by body system, preferred term, and severity.

Descriptive statistics will be used to summarize the duration of severe (grade 4) neutropenia by treatment group and cycle, combining the 3 age strata. When 2 or more cohorts of subjects are enrolled at the same dose of pegfilgrastim, data from subjects from the corresponding treatment groups will be combined for analyses. The pegfilgrastim and filgrastim groups will be compared using a 2-sided 95% confidence interval for the difference in duration of severe neutropenia in cycle 1 for both treatments. The incidence of all adverse events (all, severe, serious, and related) will be summarized by cycle, treatment group, age stratum, body system, and preferred term.

3.8 Study Status of Pediatric Study With Pegfilgrastim

Part 1 of the study has been completed, and a dose of 100 μg/kg was deemed sufficiently safe to allow part 2 of the study to begin.

Part 2 of the study is ongoing. The first cohort of the 3 age strata has been completed (n = 21). All subjects who received pegfilgrastim at a dose of 100 μg/kg achieved ANC recovery (defined as ANC $\geq 0.5 \times 10^9$/L) by day 21 of cycle 1. Enrollment into the second cohort at a dose of 100 μg/kg is ongoing.

3.9 Summary and Conclusions From Pediatric Study With Pegfilgrastim

This study is on-going, but accrual to the younger age strata (ie, 0 to 5 years and 6 to 11 years) has been slower than in the 12-to-21-year age stratum due to the limited population of study subjects with Ewing's sarcoma.

Preliminary data are available from Amgen Study 990130, based upon the findings of an Amgen safety monitoring committee that has reviewed preliminary safety, pharmacokinetic, antibody, and ANC data. In cohort 1, all subjects achieved neutrophil recovery during cycle 1 and no severe or life-threatening adverse events reported by the investigators are being related to study drug.

Amgen is aware of other studies in pediatric patients that are being conducted by the National Cancer Institute (NCI) using pegfilgrastim and other cooperative group studies in the pediatric population using filgrastim (Table 3).

Table 3. Other Pediatric Trials in Ewing's Sarcoma

Sponsor	Age Range	Chemotherapy	Supportive Agents	Issues	Enrollment
COG (AEW50031)		Q2W vs Q3W alternating vincristine, doxorubicin, cyclophosphamide and ifosfamide and etoposide	Filgrastim 5 μg/kg/day SC starting 24 to 36 hours after chemotherapy; continued until ANC ≥ 7.5 x 10^9/L or 7 days	Study was in development at the same time the Amgen study was open for enrollment	First subject enrolled May 2001 Last subject enrolled Aug 2005 Total enrollment = 587 154 COG sites (130 in US) participated Based on data from 545 subjects, 51% ≤ 12 years of age; 6% ≤ 6 years of age
NCI (20000124)	≤ 25 years; 5/29 subjects ≤ 11 years	Vincristine, doxorubicin, cyclophosphamide alternating with ifosfamide and etoposide	Filgrastim 5 μg/kg/day SC starting 24 to 36 hours after day 2 dose of cyclophosphamide and continued until ANC ≥ 10 x 10^9/L vs pegfilgrastim 100 μg/kg 24 to 36 hours after day 2 dose of cyclophosphamide	Study was proposed at same time Amgen study was being developed	First subject enrolled Dec 2000 As of Aug 2005, 30/34 subjects enrolled Based on data to date, 17% ≤ 11 years of age; 7% < 6 years of age
Wendelin et al, 2005	6 subjects aged 10 to 15 years	Vincristine, ifosfamide, doxorubicin, etoposide followed by either vincristine, actinomycin D, and ifosfamide (1 cycle) and vincristine, actinomycin D, and cyclophosphamide (7 cycles) or vincristine, actinomycin D, and ifosfamide alone (8 cycles)	Single dose of pegfilgrastim 100 μg/kg alternating with filgrastim 10 μg/kg/day until ANC ≥ 1 x 10^9/L	No pharmacokinetic studies incorporated.	Six subjects enrolled; study completed and published

ANC = absolute neutrophil count; COG = Cancer Oncology Group; NCI = National Cancer Institute; Q2W = every 2 weeks; Q3W every 3 weeks; SC = subcutaneous; US = United States

Results shared by the NCI study suggest that pegfilgrastim has been well tolerated. Pharmacokinetic data from 27 subjects have been analyzed.

4. Pediatric Experience With Filgrastim

Filgrastim has a long history of use in pediatric patients, particularly in the settings of chemotherapy-induced neutropenia and severe chronic neutropenia. Because of the similar adverse event profile of filgrastim and pegfilgrastim seen in adult patients and, to date, an adverse event profile predicted in the on-going pediatric studies, the safety data available for the use of filgrastim in the pediatric setting may be relevant in assessing how much data should be collected in on-going studies for pegfilgrastim.

5. Issues in Conducting Pediatric Trials

Studies in children with cancer are formidable for a variety of reasons, including:

- Limited patient population (ie, the pediatric oncology population represents 1% of the total oncology population)[1] and, consequently, a greater proportion of the patient population needs to be enrolled in registrational studies in the pediatric setting compared with the adult setting.
- Most children with cancer in the United States are treated on clinical study protocols (Sateren et al, 2002). Cooperative groups that specialize in clinical studies for children have successfully evaluated and developed innovative treatments in the pediatric oncology population, and they enroll most of the children in such clinical studies. Access to children eligible to participate in clinical trials is limited, particularly for a supportive care product such as pegfilgrastim, because patients usually are enrolled in cancer treatment studies that may have life-saving effects with the new treatment.
- Limited hospital centers are available to support studies in children, and children with cancer are treated most frequently at specialized pediatric oncology centers.
- Study design issues required for scientific rigor, such as intensive monitoring and blood sampling, make study feasibility challenging.
- The data needed to be useful to multiple interested parties vary, making a single study difficult to implement. Multiple studies further reduce the pool of available patients.

In addition, specific to the development of pegfilgrastim:

- The choice of tumor and the age strata: This study has a stratum of 0 to 5 years and Ewing's sarcoma is a rare tumor in this age group (NCI Web site).

[1] US estimated prevalence counts were estimated by applying US population to SEER 9 limited duration prevalence proportions. Populations from January 2000 were based on the average of the July 1999 and July 2000 populations estimates from the US Bureau of Census.

- This study was initiated in a similar timeframe to a COG study with similar inclusion criteria that evaluated the effect of a different chemotherapy regimen in children with Ewing's sarcoma.
- The protocol-specific requirement for daily pharmacokinetic and blood counts for a period of up to 4 cycles prevents children returning home, as early as would be possible.
- Parents who are willing to allow their child to have repeated injections of filgrastim are unlikely to enroll in a comparator study because filgrastim is readily available, approved for pediatric use, and well known to pediatric oncologists.

6. Summary and Conclusions

Although the cooperative groups, regulatory agencies, and Amgen are working together, improvement is needed in the process of pediatric drug registration. One approach to facilitate the generation of appropriate data for registration would be to have all parties work together concurrently, before initiation of any study, so that the results from the studies will address the various needs of the different groups.

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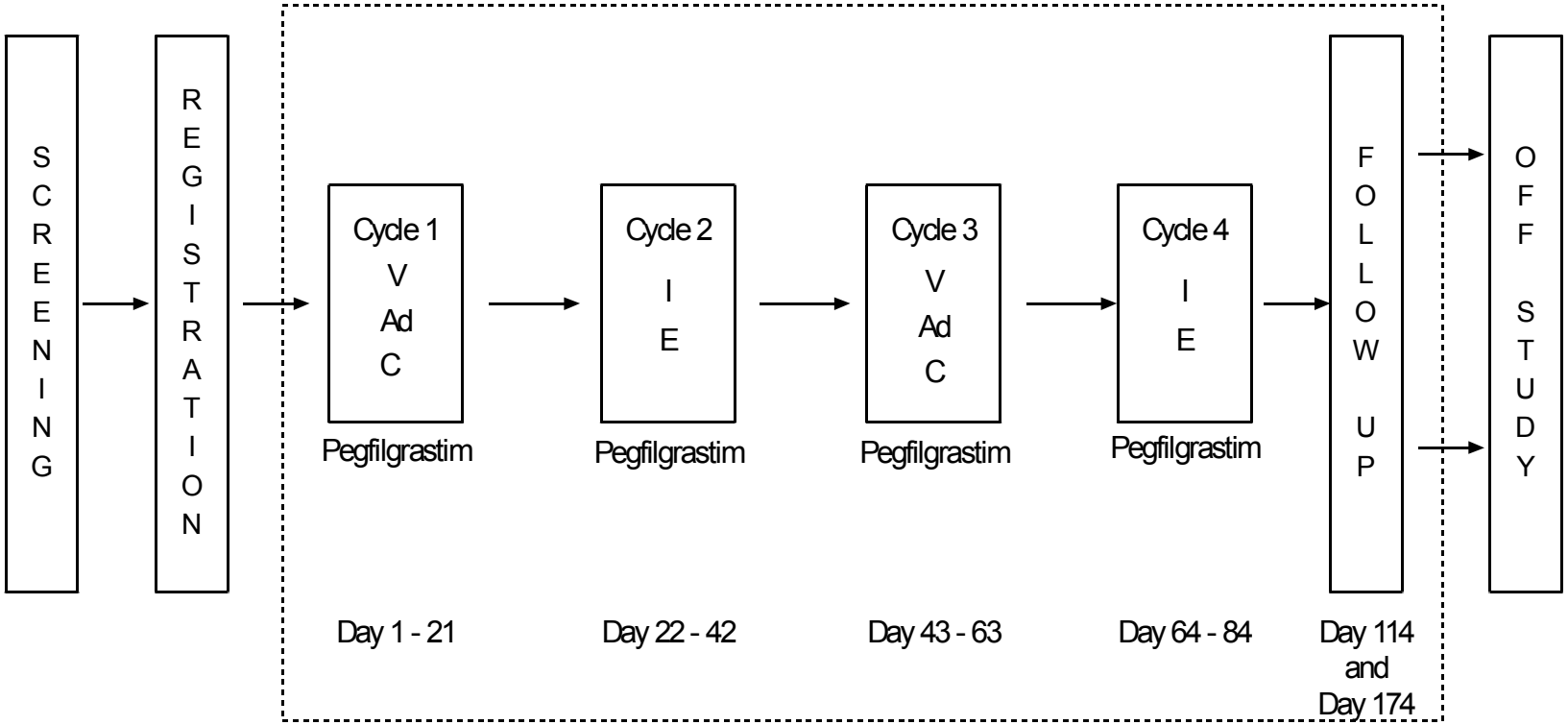
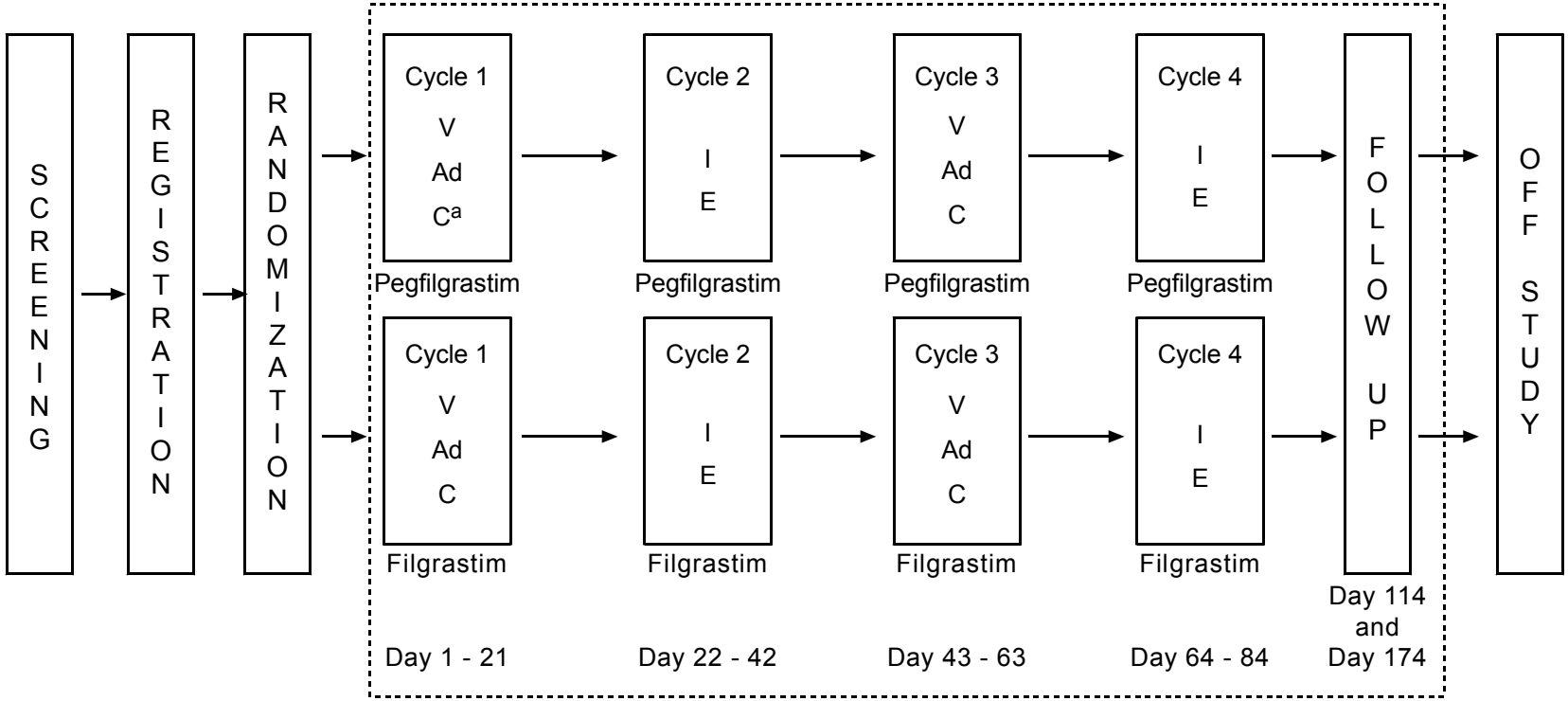
Appendix A. Study Schemas

Figure A 1. Part 1 - Study Design and Treatment Schema



Each chemotherapy cycle is 21 days in length.
Follow-up visits are approximately 1 and 3 months from day 21 of last on-study chemotherapy cycle.
Off-study chemotherapy is given at the discretion of the investigator. Filgrastim and pegfilgrastim will not be supplied by Amgen for these off-study cycles.
IE = chemotherapy ifosfamide and etoposide; VAdC = chemotherapy with vincristine, doxorubicin, and cyclophosphamide

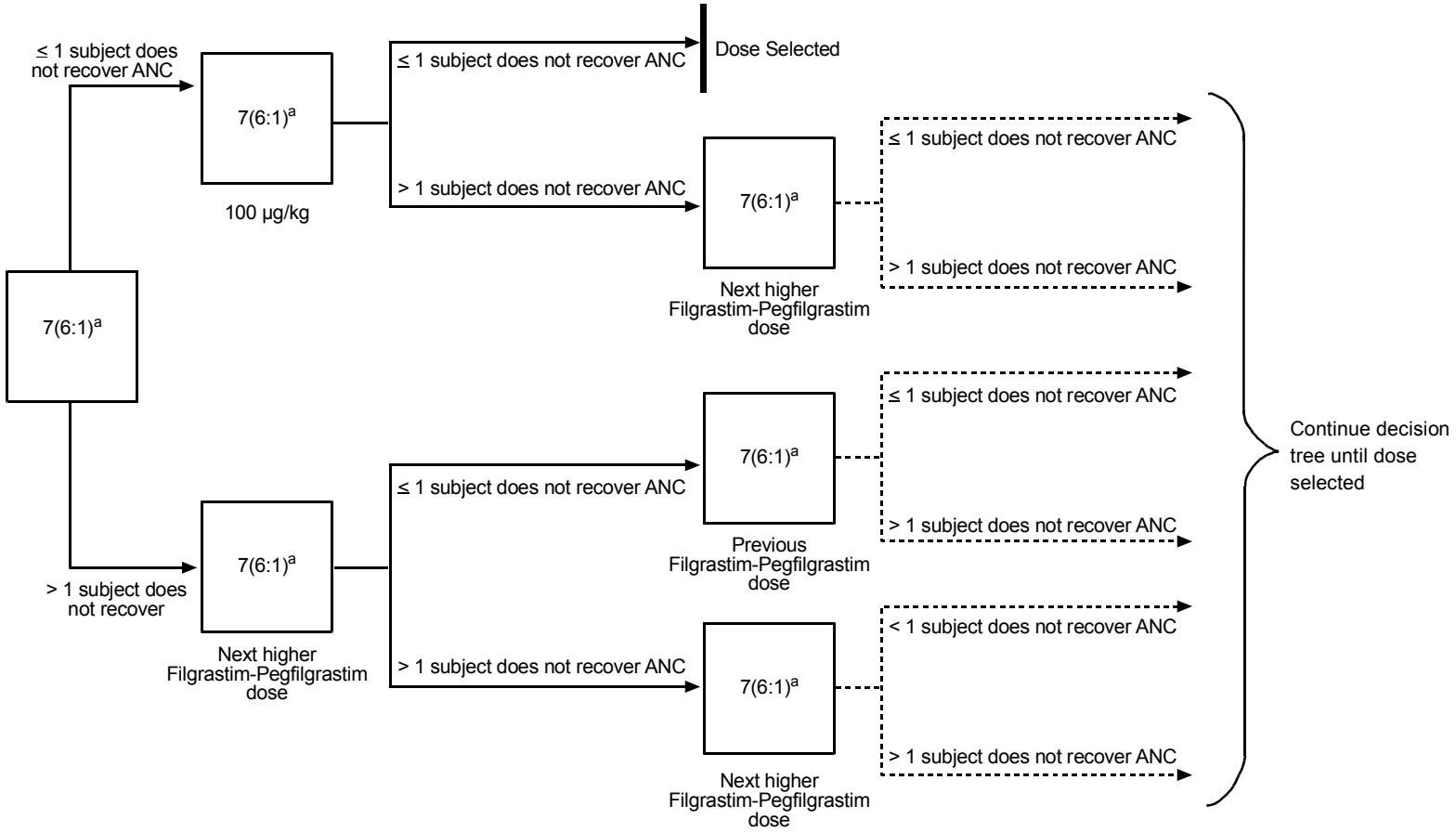
Figure A 2. Part 2 - Study Design and Treatment Schema



[a] Pegfilgrastim dose escalation decision will be based on cycle 1.
Each chemotherapy cycle is 21 days in length.
Follow-up visits are approximately 1 and 3 months from day 21 of last on-study chemotherapy cycle.
Off-study chemotherapy is given at the discretion of the investigator. Filgrastim and pegfilgrastim will not be supplied by Amgen for these off-study cycles.
IE = chemotherapy ifosfamide and etoposide; VAdC = chemotherapy with vincristine, doxorubicin, and cyclophosphamide

Appendix B. Pegfilgrastim Dose-escalation Schema

Figure B 1. Pegfilgrastim Dose-escalation Schema



[a] Seven subjects will be studied in each age stratum (6 pegfilgrastim and 1 filgrastim)
ANC = absolute neutrophil count