

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125031Orig1s180

Trade Name: Neulasta, injection for subcutaneous use

Generic or Proper Name: pegfilgrastam

Sponsor: Amgen, Inc.

Approval Date: November 13, 2015

Indication: Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).

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APPLICATION NUMBER:

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APPROVAL LETTER



BLA 125031/S-180

**sBLA APPROVAL –
ANIMAL EFFICACY**

Amgen Inc.
Attention: Tai H. Yu, M.S.,
Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-A
Thousand Oaks, CA 91320-1799

Dear Mr. Yu:

Please refer to your Supplemental Biologics License Application (sBLA), dated February 13, 2015, and received on February 13, 2015, submitted under section 351(a) of the Public Health Service Act for Neulasta® (pegfilgrastim).

We acknowledge receipt of your amendments dated August 14, and 17, 2015.

This Prior Approval supplemental biologics application provides for a new indication of use of Neulasta® (pegfilgrastim) for the treatment of adult and pediatric patients at risk of developing myelosuppression after a radiological/nuclear incident.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, under the provisions of 21 CFR 601, Subpart H (Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible), effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and required patient labeling. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced animal efficacy regulations.

SUBPART H APPROVAL REQUIREMENTS

Approvals under 21 CFR Part 601, Subpart H (Approval of Biological Product When Human Efficacy Studies Are Not Ethical or Feasible) are subject to three requirements:

1. *Approval with restrictions to ensure safe use.* This subsection permits the Agency to require postmarketing restrictions as are needed to ensure safe use of the drug product, commensurate with the specific safety concerns presented by the drug product. We have concluded that Neulasta[®] (pegfilgrastim) can be safely used without restrictions on distribution or use.
2. *Information to be provided to patient recipients.* This subsection requires applicants to prepare labeling to be provided to patient recipients for drug products approved under this subpart. We have concluded that FDA approved patient labeling for Neulasta[®] (pegfilgrastim) meets the requirement for this subsection. We remind you that the medication guide must be available with the product to be provided, when possible, prior to administration or dispensing of the drug product for the use approved under this subpart.
3. *Postmarketing Studies.* This subsection requires you to conduct postmarketing studies, such as field studies, to verify and describe the biological product's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical. We remind you of your postmarketing requirement specified in your protocol outline submission dated December 11, 2014, designed to verify and describe Neulasta (pegfilgastrim)'s clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical in accordance with 21 CFR 601.90. This requirement, along with required completion dates, is listed below.

2997-1 Conduct a phase 4 observational study evaluating the efficacy and safety of Neulasta[®] (pegfilgrastim) in the setting of Hematopoietic Syndrome (HS) following acute radiation exposure.

Draft Protocol Submission: 05/30/2016

Final Protocol Submission: 11/30/2016

Study Completion: To be determined should an event occur

Final Report Submission: To be determined should an event occur

Submit final reports to this BLA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirements.**"

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

Under 21 CFR 601.94, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.94, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Frank Lutterodt, Regulatory Project Manager, at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LIBERO L MARZELLA
11/13/2015

**CENTER FOR DRUG EVALUATION AND
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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NEULASTA safely and effectively. See [full prescribing information](#) for NEULASTA.

NEULASTA® (pegfilgrastim) injection, for subcutaneous use
Initial U.S. Approval: 2002

RECENT MAJOR CHANGES

- Indications and Usage (1.2) 11/2015
- Dosage and Administration (2.2, 2.3) 11/2015
- Warnings and Precautions (5.6, 5.7, 5.8) 09/2015
- Dosage and Administration (2.4, 2.5) 12/2014
- Warnings and Precautions (5.4) 12/2014

INDICATIONS AND USAGE

Neulasta is a leukocyte growth factor indicated to

- Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. (1.1)
- Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome). (1.2)

Neulasta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

DOSAGE AND ADMINISTRATION

- Patients with cancer receiving myelosuppressive chemotherapy
 - o 6 mg administered subcutaneously once per chemotherapy cycle. (2.1)
 - o Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy. (2.1)
 - o Use weight based dosing for pediatric patients weighing less than 45 kg; refer to Table 1. (2.3)
- Patients acutely exposed to myelosuppressive doses of radiation
 - o Two doses, 6 mg each, administered subcutaneously one week apart. Administer the first dose as soon as possible after suspected or confirmed exposure to myelosuppressive doses of radiation, and a second dose one week after. (2.2)
 - o Use weight based dosing for pediatric patients weighing less than 45 kg; refer to Table 1. (2.3)

DOSAGE FORMS AND STRENGTHS

- Injection: 6 mg/0.6 mL solution in a single use prefilled syringe for manual use only. (3)

- Injection: 6 mg/0.6 mL solution in a single prefilled syringe co-packaged with the On-body Injector for Neulasta.

CONTRAINDICATIONS

Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as pegfilgrastim or filgrastim. (4)

WARNINGS AND PRECAUTIONS

- Fatal splenic rupture: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture. (5.1)
- Acute respiratory distress syndrome (ARDS): Evaluate patients who develop fever, lung infiltrates, or respiratory distress. Discontinue Neulasta in patients with ARDS. (5.2)
- Serious allergic reactions, including anaphylaxis: Permanently discontinue Neulasta in patients with serious allergic reactions. (5.3)
- The On-body Injector for Neulasta uses acrylic adhesive. For patients who have reactions to acrylic adhesives, use of this product may result in a significant reaction (5.4)
- Fatal sickle cell crises: Have occurred. (5.5)
- Glomerulonephritis: Evaluate and consider dose-reduction or interruption of Neulasta if causality is likely. (5.6)

ADVERSE REACTIONS

Most common adverse reactions ($\geq 5\%$ difference in incidence compared to placebo) are bone pain and pain in extremity. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing Mothers: Caution should be exercised when administered to a nursing woman. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 11/2015

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- 1.2 Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome

2 DOSAGE AND ADMINISTRATION

- 2.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy
- 2.2 Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome
- 2.3 Administration
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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy

Neulasta is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia [see *Clinical Studies (14.1)*].

Neulasta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

1.2 Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome

Neulasta is indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation [see *Dosage and Administration (2.2)* and *Clinical Studies (14.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy

The recommended dosage of Neulasta is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle. For dosing in pediatric patients weighing less than 45 kg, refer to Table 1. Do not administer Neulasta between 14 days before and 24 hours after administration of cytotoxic chemotherapy.

2.2 Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome

The recommended dose of Neulasta is two doses, 6 mg each, administered subcutaneously one week apart. For dosing in pediatric patients weighing less than 45 kg, refer to Table 1. Administer the first dose as soon as possible after suspected or confirmed exposure to radiation levels greater than 2 gray (Gy). Administer the second dose one week after the first dose.

Obtain a baseline complete blood count (CBC). Do not delay administration of Neulasta if a CBC is not readily available. Estimate a patient's absorbed radiation dose (i.e., level of radiation exposure) based on information from public health authorities, biodosimetry if available, or clinical findings such as time to onset of vomiting or lymphocyte depletion kinetics.

2.3 Administration

Neulasta is administered subcutaneously via a single prefilled syringe for manual use or for use with the On-body Injector for Neulasta which is co-packaged with a single prefilled syringe. Use of the On-body Injector for Neulasta has not been studied in pediatric patients.

Pediatric Patients weighing less than 45 kg

The Neulasta prefilled syringe is not designed to allow for direct administration of doses less than 0.6 mL (6 mg). The syringe does not bear graduation marks which are necessary to accurately measure doses of Neulasta less than 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of less than 0.6 mL (6 mg) is not recommended due to the potential for dosing errors. Refer to Table 1.

Table 1. Dosing of Neulasta for pediatric patients weighing less than 45 kg

Body Weight	Neulasta Dose	Volume to Administer
Less than 10 kg*	See below*	See below*
10 - 20 kg	1.5 mg	0.15 mL
21 - 30 kg	2.5 mg	0.25 mL
31 - 44 kg	4 mg	0.40 mL

*For pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of Neulasta.

Visually inspect parenteral drug products (prefilled syringe) for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer Neulasta if discoloration or particulates are observed.

The needle cap on the prefilled syringes contains dry natural rubber (derived from latex); persons with latex allergies should not administer these products.

2.4 Special Healthcare Provider Instructions for the On-body Injector for Neulasta

A healthcare provider must fill the On-body Injector with Neulasta using the prefilled syringe and then apply the On-body Injector for Neulasta to the patient's skin (abdomen or back of arm). The back of the arm may only be used if there is a caregiver available to monitor the status of the On-body Injector for Neulasta. Approximately 27 hours after the On-body Injector for Neulasta is applied to the patient's skin, Neulasta will be delivered over approximately 45 minutes. A healthcare provider may initiate administration with the On-body Injector for Neulasta on the same day as the administration of cytotoxic chemotherapy, as long as the On-body Injector for Neulasta delivers Neulasta no less than 24 hours after administration of cytotoxic chemotherapy.

The prefilled syringe co-packaged in Neulasta Onpro™ kit must only be used with the On-body Injector for Neulasta. The prefilled syringe contains additional solution to compensate for liquid loss during delivery through the On-body Injector for Neulasta. If the prefilled syringe co-packaged in Neulasta Onpro kit is used for manual subcutaneous injection, the patient will receive an overdose. If the single use prefilled syringe for manual use is used with the On-body Injector for Neulasta, the patient may receive less than the recommended dose.

Do not use the On-body Injector for Neulasta to deliver any other drug product except the Neulasta prefilled syringe co-packaged with the On-body Injector for Neulasta.

The On-body Injector for Neulasta should be applied to intact, non-irritated skin on the arm or abdomen.

A missed dose could occur due to an On-body Injector for Neulasta failure or leakage. If the patient misses a dose, a new dose should be administered by single prefilled syringe for manual use, as soon as possible after detection.

Refer to the Healthcare Provider Instructions for Use for the On-body Injector for Neulasta for full administration information.

2.5 Advice to Give to Patients Regarding Administration via the On-body Injector for Neulasta

Advise patients to avoid activities such as traveling, driving, or operating heavy machinery during hours 26-29 following application of the On-body Injector for Neulasta (this includes the 45-minute delivery period plus an hour post-delivery). Patients should have a caregiver nearby for the first use.

Refer the patient to the dose delivery information written on the Patient Instructions for Use. Provide training to patients to ensure they understand when the dose delivery of Neulasta will begin and how to monitor the On-body Injector for Neulasta for completed delivery. Ensure patients understand how to identify signs of malfunction of On-body Injector for Neulasta— [see *Warnings and Precautions (5.3)* and *Patient Counseling Information (17)*].

3 DOSAGE FORMS AND STRENGTHS

- Injection: 6 mg/0.6 mL solution in a single-use prefilled syringe for manual use only.
- Injection: 6 mg/0.6 mL solution in a single-use prefilled syringe co-packaged with the On-body Injector for Neulasta (Neulasta Onpro kit).

4 CONTRAINDICATIONS

Do not administer Neulasta to patients with a history of serious allergic reactions to pegfilgrastim or filgrastim.

5 WARNINGS AND PRECAUTIONS

5.1 Splenic Rupture

Splenic rupture, including fatal cases, can occur following the administration of Neulasta. Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving Neulasta.

5.2 Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) can occur in patients receiving Neulasta. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving Neulasta, for ARDS. Discontinue Neulasta in patients with ARDS.

5.3 Serious Allergic Reactions

Serious allergic reactions, including anaphylaxis, can occur in patients receiving Neulasta. The majority of reported events occurred upon initial exposure. Allergic reactions, including anaphylaxis, can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue Neulasta in patients with serious allergic reactions. Do not administer Neulasta to patients with a history of serious allergic reactions to pegfilgrastim or filgrastim.

5.4 Allergies to Acrylics

The On-body Injector for Neulasta uses acrylic adhesive. For patients who have reactions to acrylic adhesives, use of this product may result in a significant reaction.

5.5 Use in Patients with Sickle Cell Disorders

Severe sickle cell crises can occur in patients with sickle cell disorders receiving Neulasta. Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving filgrastim, the parent compound of pegfilgrastim.

5.6 Glomerulonephritis

Glomerulonephritis has occurred in patients receiving Neulasta. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis

resolved after dose reduction or discontinuation of Neulasta. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose-reduction or interruption of Neulasta.

5.7 Leukocytosis

White blood cell (WBC) counts of $100 \times 10^9/L$ or greater have been observed in patients receiving pegfilgrastim. Monitoring of complete blood count (CBC) during pegfilgrastim therapy is recommended.

5.8 Capillary Leak Syndrome

Capillary leak syndrome has been reported after G-CSF administration, including Neulasta, and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

5.9 Potential for Tumor Growth Stimulatory Effects on Malignant Cells

The granulocyte-colony stimulating factor (G-CSF) receptor through which pegfilgrastim and filgrastim act has been found on tumor cell lines. The possibility that pegfilgrastim acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which pegfilgrastim is not approved, cannot be excluded.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Splenic Rupture [See Warnings and Precautions (5.1)]
- Acute Respiratory Distress Syndrome [See Warnings and Precautions (5.2)]
- Serious Allergic Reactions [See Warnings and Precautions (5.3)]
- Allergies to Acrylics [See Warnings and Precautions (5.4)]
- Use in Patients with Sickle Cell Disorders [See Warnings and Precautions (5.5)]
- Glomerulonephritis [See Warnings and Precautions (5.6)]
- Leukocytosis [See Warnings and Precautions (5.7)]
- Capillary Leak Syndrome [See Warnings and Precautions (5.8)]
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells [See Warnings and Precautions (5.9)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Neulasta clinical trials safety data are based upon 932 patients receiving Neulasta in seven randomized clinical trials. The population was 21 to 88 years of age and 92% female. The ethnicity was 75% Caucasian, 18% Hispanic, 5% Black, and 1% Asian. Patients with breast (n = 823), lung and thoracic tumors (n = 53) and lymphoma (n = 56) received Neulasta after nonmyeloablative cytotoxic chemotherapy. Most patients received a single 100 mcg/kg (n = 259) or a single 6 mg (n = 546) dose per chemotherapy cycle over 4 cycles.

The following adverse reaction data in Table 2 are from a randomized, double-blind, placebo-controlled study in patients with metastatic or non-metastatic breast cancer receiving docetaxel 100 mg/m² every 21 days (Study 3). A total of 928 patients were randomized to receive either 6 mg Neulasta (n = 467) or placebo (n = 461). The patients

were 21 to 88 years of age and 99% female. The ethnicity was 66% Caucasian, 31% Hispanic, 2% Black, and <1% Asian, Native American or other.

The most common adverse reactions occurring in $\geq 5\%$ of patients and with a between-group difference of $\geq 5\%$ higher in the pegfilgrastim arm in placebo controlled clinical trials are bone pain and pain in extremity.

Table 2. Adverse Reactions with $\geq 5\%$ Higher Incidence in Neulasta Patients Compared to Placebo in (Study 3)

System Organ Class Preferred Term	Placebo (N= 461)	Neulasta 6 mg SC on Day 2 (N= 467)
Musculoskeletal and connective tissue disorders		
Bone pain	26%	31%
Pain in extremity	4%	9%

Leukocytosis

In clinical studies, leukocytosis (WBC counts $> 100 \times 10^9/L$) was observed in less than 1% of 932 patients with non-myeloid malignancies receiving Neulasta. No complications attributable to leukocytosis were reported in clinical studies.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Binding antibodies to pegfilgrastim were detected using a BIAcore assay. The approximate limit of detection for this assay is 500 ng/mL. Pre-existing binding antibodies were detected in approximately 6% (51/849) of patients with metastatic breast cancer. Four of 521 pegfilgrastim-treated subjects who were negative at baseline developed binding antibodies to pegfilgrastim following treatment. None of these 4 patients had evidence of neutralizing antibodies detected using a cell-based bioassay.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Neulasta with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Neulasta. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Splenic rupture and splenomegaly (enlarged spleen) [see Warnings and Precautions (5.1)]
- Acute respiratory distress syndrome (ARDS) [see Warnings and Precautions (5.2)]
- Allergic reactions/hypersensitivity, including anaphylaxis, skin rash, and urticaria, generalized erythema and flushing [see Warnings and Precautions (5.3)]
- Sick cell crisis [see Warnings and Precautions (5.5)]
- Glomerulonephritis [see Warnings and Precautions (5.6)]
- Leukocytosis [see Warnings and Precautions (5.7)]

- Capillary leak syndrome [see *Warnings and Precautions (5.8)*]
- Injection site reactions
- Sweet's syndrome, (acute febrile neutrophilic dermatosis), cutaneous vasculitis

7 DRUG INTERACTIONS

No formal drug interaction studies between Neulasta and other drugs have been performed. Increased hematopoietic activity of the bone marrow in response to growth factor therapy may result in transiently positive bone-imaging changes. Consider these findings when interpreting bone-imaging results.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Pegfilgrastim was embryotoxic and increased pregnancy loss in pregnant rabbits that received cumulative doses approximately 4 times the recommended human dose (based on body surface area). Signs of maternal toxicity occurred at these doses. Neulasta should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

In animal reproduction studies, when pregnant rabbits received pegfilgrastim at cumulative doses approximately 4 times the recommended human dose (based on body surface area), increased embryoletality and spontaneous abortions occurred. Signs of maternal toxicity (reductions in body weight gain/food consumption) and decreased fetal weights occurred at maternal doses approximately equivalent to the recommended human dose (based on body surface area). There were no structural anomalies observed in rabbit offspring at any dose tested. No evidence of reproductive/developmental toxicity occurred in the offspring of pregnant rats that received cumulative doses of pegfilgrastim approximately 10 times the recommended human dose (based on body surface area) [see *Nonclinical Toxicology (13.3)*].

8.3 Nursing Mothers

It is not known whether pegfilgrastim is secreted in human milk. Other recombinant G-CSF products are poorly secreted in breast milk and G-CSF is not orally absorbed by neonates. Caution should be exercised when administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of Neulasta have been established in pediatric patients. No overall differences in safety were identified between adult and pediatric patients based on postmarketing surveillance and review of the scientific literature.

Use of Neulasta in pediatric patients for chemotherapy-induced neutropenia is based on adequate and well controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients with sarcoma [see *Clinical Pharmacology (12.3)* and *Clinical Studies (14.1)*].

The use of Neulasta to increase survival in pediatric patients acutely exposed to myelosuppressive doses of radiation is based on efficacy studies conducted in animals and clinical data supporting the use of Neulasta in patients with cancer receiving myelosuppressive chemotherapy. Efficacy studies of Neulasta could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Results from population modeling and simulation indicate that two doses of Neulasta (Table 1), administered one week apart provide pediatric patients with exposures comparable to that in adults receiving two 6 mg doses one week apart [see *Dosage and Administration (2.3)*, *Clinical Pharmacology (12.3)* and *Clinical Studies (14.2)*].

8.5 Geriatric Use

Of the 932 patients with cancer who received Neulasta in clinical studies, 139 (15%) were aged 65 and over, and 18 (2%) were aged 75 and over. No overall differences in safety or effectiveness were observed between patients aged 65 and older and younger patients.

8.6 Renal Impairment

Renal dysfunction had no effect on the pharmacokinetics of pegfilgrastim. Therefore, pegfilgrastim dose adjustment in patients with renal dysfunction is not necessary [see *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

The maximum amount of Neulasta that can be safely administered in single or multiple doses has not been determined. Single subcutaneous doses of 300 mcg/kg have been administered to 8 healthy volunteers and 3 patients with non-small cell lung cancer without serious adverse effects. These patients experienced a mean maximum absolute neutrophil count (ANC) of $55 \times 10^9/L$, with a corresponding mean maximum WBC of $67 \times 10^9/L$. The absolute maximum ANC observed was $96 \times 10^9/L$ with a corresponding absolute maximum WBC observed of $120 \times 10^9/L$. The duration of leukocytosis ranged from 6 to 13 days. The effectiveness of leukapheresis in the management of symptomatic individuals with Neulasta-induced leukocytosis has not been studied.

11 DESCRIPTION

Neulasta (pegfilgrastim) is a covalent conjugate of recombinant methionyl human G-CSF (filgrastim) and monomethoxypolyethylene glycol. Filgrastim is a water-soluble 175 amino acid protein with a molecular weight of approximately 19 kilodaltons (kD). Filgrastim is obtained from the bacterial fermentation of a strain of *E coli* transformed with a genetically engineered plasmid containing the human G-CSF gene. To produce pegfilgrastim, a 20 kD monomethoxypolyethylene glycol molecule is covalently bound to the N-terminal methionyl residue of filgrastim. The average molecular weight of pegfilgrastim is approximately 39 kD.

Neulasta is provided in two presentations:

- Neulasta for manual subcutaneous injection is supplied in 0.6 mL prefilled syringes. The prefilled syringe does not bear graduation marks and is designed to deliver the entire contents of the syringe (6 mg/0.6 mL).
- On-body Injector for Neulasta is supplied with a prefilled syringe containing 0.64 mL of Neulasta in solution that delivers 0.6 mL of Neulasta in solution when used with the On-body Injector for Neulasta. The syringe does not bear graduation marks and is only to be used with the On-body Injector for Neulasta.

The delivered 0.6 mL dose from either the prefilled syringe for manual subcutaneous injection or the On-body Injector for Neulasta contains 6 mg pegfilgrastim (based on protein weight) in a sterile, clear, colorless, preservative-free solution (pH 4.0) containing acetate (0.35 mg), polysorbate 20 (0.02 mg), sodium (0.02 mg), and sorbitol (30 mg) in Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pegfilgrastim is a colony-stimulating factor that acts on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end cell functional activation.

12.2 Pharmacodynamics

Animal data and clinical data in humans suggest a correlation between pegfilgrastim exposure and the duration of severe neutropenia as a predictor of efficacy. Selection of the dosing regimen of Neulasta is based on reducing the duration of severe neutropenia.

12.3 Pharmacokinetics

The pharmacokinetics of pegfilgrastim was studied in 379 patients with cancer. The pharmacokinetics of pegfilgrastim was nonlinear and clearance decreased with increases in dose. Neutrophil receptor binding is an important component of the clearance of pegfilgrastim, and serum clearance is directly related to the number of neutrophils. In addition to numbers of neutrophils, body weight appeared to be a factor. Patients with higher body weights experienced higher systemic exposure to pegfilgrastim after receiving a dose normalized for body weight. A large variability in the pharmacokinetics of pegfilgrastim was observed. The half-life of Neulasta ranged from 15 to 80 hours after subcutaneous injection. In healthy volunteers, the pharmacokinetics of pegfilgrastim were comparable when delivered subcutaneously via a manual prefilled syringe versus via the On-body Injector for Neulasta.

Specific Populations

No gender-related differences were observed in the pharmacokinetics of pegfilgrastim, and no differences were observed in the pharmacokinetics of geriatric patients (≥ 65 years of age) compared with younger patients (< 65 years of age) [see *Use in Specific Populations* (8.5)].

Renal Impairment

In a study of 30 subjects with varying degrees of renal dysfunction, including end stage renal disease, renal dysfunction had no effect on the pharmacokinetics of pegfilgrastim [see *Use in Specific Populations* (8.6)].

Pediatric Patients with Cancer Receiving Myelosuppressive Chemotherapy

The pharmacokinetics and safety of pegfilgrastim were studied in 37 pediatric patients with sarcoma in Study 4 [see *Clinical Studies* 14.1]. The mean ($\pm$ standard deviation [SD]) systemic exposure ($AUC_{0-\infty}$) of Neulasta after subcutaneous administration at 100 mcg/kg was 47.9 (± 22.5) mcg·hr/mL in the youngest age group (0 to 5 years, $n = 11$), 22.0 (± 13.1) mcg·hr/mL in the (6 to 11 years age group ($n = 10$), and 29.3 (± 23.2) mcg·hr/mL in the 12 to 21 years age group ($n = 13$). The terminal elimination half-lives of the corresponding age groups were 30.1 (± 38.2) hours, 20.2 (± 11.3) hours, and 21.2 (± 16.0) hours, respectively.

Patients Acutely Exposed to Myelosuppressive Doses of Radiation

The pharmacokinetics of pegfilgrastim is not available in patients acutely exposed to myelosuppressive doses of radiation. Based on limited pharmacokinetic data in irradiated non-human primates, the area under the concentration-time curve (AUC), reflecting the exposure to pegfilgrastim in non-human primates following a 300 mcg/kg dose of Neulasta, appears to be greater than in humans receiving a 6 mg dose. Results from population modeling and simulation indicate that two 6 mg doses of Neulasta administered one week apart in adults result in clinically relevant effects on duration of grade 3 and 4 neutropenia. In addition, weight based dosing in pediatric patients weighing less than 45 kg [see *Dosing and Administration, Section 2.3, Table 1*] provides exposures comparable to those in adults receiving two 6 mg doses one week apart.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenesis studies have been performed with pegfilgrastim.

Pegfilgrastim did not affect reproductive performance or fertility in male or female rats at cumulative weekly doses approximately 6 to 9 times higher than the recommended human dose (based on body surface area).

13.3 Reproductive and Developmental Toxicology

Pregnant rabbits were dosed with pegfilgrastim subcutaneously every other day during the period of organogenesis. At cumulative doses ranging from the approximate human dose to approximately 4 times the recommended human dose (based on body surface area), treated rabbits exhibited decreased maternal food consumption, maternal weight loss, as well as reduced fetal body weights and delayed ossification of the fetal skull; however, no structural anomalies were observed in the offspring from either study. Increased incidences of post-implantation losses and spontaneous abortions (more than half the pregnancies) were observed at cumulative doses approximately 4 times the recommended human dose, which were not seen when pregnant rabbits were exposed to the recommended human dose.

Three studies were conducted in pregnant rats dosed with pegfilgrastim at cumulative doses up to approximately 10 times the recommended human dose at the following stages of gestation: during the period of organogenesis, from mating through the first half of pregnancy, and from the first trimester through delivery and lactation. No evidence of fetal loss or structural malformations was observed in any study. Cumulative doses equivalent to approximately 3 and 10 times the recommended human dose resulted in transient evidence of wavy ribs in fetuses of treated mothers (detected at the end of gestation but no longer present in pups evaluated at the end of lactation).

14 CLINICAL STUDIES

14.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy

Neulasta was evaluated in three randomized, double-blind, controlled studies. Studies 1 and 2 were active-controlled studies that employed doxorubicin 60 mg/m² and docetaxel 75 mg/m² administered every 21 days for up to 4 cycles for the treatment of metastatic breast cancer. Study 1 investigated the utility of a fixed dose of Neulasta. Study 2 employed a weight-adjusted dose. In the absence of growth factor support, similar chemotherapy regimens have been reported to result in a 100% incidence of severe neutropenia (ANC < 0.5 × 10⁹/L) with a mean duration of 5 to 7 days and a 30% to 40% incidence of febrile neutropenia. 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, and the efficacy of Neulasta was demonstrated by establishing comparability to filgrastim-treated patients in the mean days of severe neutropenia.

In Study 1, 157 patients were randomized to receive a single subcutaneous injection of Neulasta (6 mg) on day 2 of each chemotherapy cycle or daily subcutaneous filgrastim (5 mcg/kg/day) beginning on day 2 of each chemotherapy cycle. In Study 2, 310 patients were randomized to receive a single subcutaneous injection of Neulasta (100 mcg/kg) on day 2 or daily subcutaneous filgrastim (5 mcg/kg/day) beginning on day 2 of each chemotherapy cycle.

Both studies met the major efficacy outcome measure of demonstrating that the mean days of severe neutropenia of Neulasta-treated patients did not exceed that of filgrastim-treated patients by more than 1 day in cycle 1 of chemotherapy. The mean days of cycle 1 severe neutropenia in Study 1 were 1.8 days in the Neulasta arm compared to 1.6 days in the filgrastim arm [difference in means 0.2 (95% CI -0.2, 0.6)] and in Study 2 were 1.7 days in the Neulasta arm compared to 1.6 days in the Filgrastim arm [difference in means 0.1 (95% CI -0.2, 0.4)].

A secondary endpoint in both studies was days of severe neutropenia in cycles 2 through 4 with results similar to those for cycle 1.

Study 3 was a randomized, double-blind, placebo-controlled study that employed docetaxel 100 mg/m² administered every 21 days for up to 4 cycles for the treatment of metastatic or non-metastatic breast cancer. In this study, 928 patients were randomized to receive a single subcutaneous injection of Neulasta (6 mg) or placebo on day 2 of each chemotherapy cycle. Study 3 met the major trial outcome measure of demonstrating that the incidence of febrile neutropenia (defined as temperature ≥ 38.2°C and ANC ≤ 0.5 × 10⁹/L) was lower for Neulasta-treated patients as compared to placebo-treated patients (1% versus 17%, respectively, p < 0.001). The incidence of hospitalizations

(1% versus 14%) and IV anti-infective use (2% versus 10%) for the treatment of febrile neutropenia was also lower in the Neulasta-treated patients compared to the placebo-treated patients.

Study 4 was a multicenter, randomized, open-label study to evaluate the efficacy, safety, and pharmacokinetics [see *Clinical Pharmacology* (12.3)] of Neulasta in pediatric and young adult patients with sarcoma. Patients with sarcoma receiving chemotherapy age 0 to 21 years were eligible. Patients were randomized to receive subcutaneous Neulasta as a single dose of 100 mcg/kg (n= 37) or subcutaneous filgrastim at a dose 5 mcg/kg/day (n=6) following myelosuppressive chemotherapy. Recovery of neutrophil counts was similar in the Neulasta and filgrastim groups. The most common adverse reaction reported was bone pain.

14.2 Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome

Efficacy studies of Neulasta could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Approval of this indication was based on efficacy studies conducted in animals and data supporting Neulasta's effect on severe neutropenia in patients with cancer receiving myelosuppressive chemotherapy [see *Dosage and Administration* (2.1)].

The recommended dose of Neulasta is two doses, 6 mg each, administered one week apart for humans exposed to myelosuppressive doses of radiation. For pediatric patients those weighing less than 45 kg, dosing of Neulasta is weight based and is provided in Table 1 [see *Dosage and Administration* (2.3)]. This dosing regimen is based on population modeling and simulation analyses. The exposure associated with this dosing regimen is expected to provide sufficient pharmacodynamic activity to treat humans exposed to myelosuppressive doses of radiation [see *Clinical Pharmacology* (12.3)]. The safety of Neulasta at a dose of 6 mg has been assessed on the basis of clinical experience in patients with cancer receiving myelosuppressive chemotherapy.

The efficacy of Neulasta for the acute radiation syndrome setting was studied in a randomized, placebo-controlled non-human primate model of radiation injury. Rhesus macaques were randomized to either a control (n=23) or treated (n=23) cohort. On study day 0, animals (n = 6 to 8 per irradiation day) were exposed to total body irradiation (TBI) of 7.50 ± 0.15 Gy delivered at 0.8 ± 0.03 Gy/min, representing a dose that would be lethal in 50% of animals by 60 days of follow-up (LD50/60). Animals were administered subcutaneous injections of a blinded treatment (control article [5% dextrose in water] or pegfilgrastim [300-319 mcg/kg/day]) on study day 1 and on study day 8. The primary endpoint was survival. Animals received medical management consisting of intravenous fluids, antibiotics, blood transfusions, and other support as required.

Pegfilgrastim significantly (at 0.0014 level of significance) increased 60-day survival in irradiated non-human primates: 91% survival (21/23) in the pegfilgrastim group compared to 48% survival (11/23) in the control group.

16 HOW SUPPLIED/STORAGE AND HANDLING

Neulasta single use prefilled syringe for manual use

Neulasta is supplied in a prefilled single use syringe for manual use containing 6 mg pegfilgrastim, supplied with a 27-gauge, 1/2-inch needle with an UltraSafe® Needle Guard.

The needle cap of the prefilled syringe contains dry natural rubber (a derivative of latex).

Neulasta is provided in a dispensing pack containing one sterile 6mg/0.6 mL prefilled syringe (NDC 55513-190-01).

Neulasta prefilled syringe does not bear graduation marks and is intended only to deliver the entire contents of the syringe (6 mg/0.6 mL) for direct administration. Use of the prefilled syringe is not recommended for direct administration for pediatric patients weighing less than 45 kg who require doses that are less than the full contents of the syringe.

Store refrigerated between 36° to 46°F (2° to 8°C) in the carton to protect from light. Do not shake. Discard syringes stored at room temperature for more than 48 hours. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once.

Neulasta Onpro™ kit

Neulasta Onpro kit is provided in a carton containing one sterile prefilled syringe and one sterile On-body Injector for Neulasta (NDC 55513-192-01).

The single use prefilled syringe contains 0.64 mL of solution that delivers 6 mg/0.6 mL of pegfilgrastim when used with the On-body Injector for Neulasta. The prefilled syringe is supplied with a 27-gauge, 1/2-inch needle with an UltraSafe® Needle Guard. The syringe does not bear graduation marks and is only to be used with the On-body Injector for Neulasta.

The needle cap of the prefilled syringe contains dry natural rubber (a derivative of latex).

Store Neulasta Onpro kit in the refrigerator at 36°F to 46°F (2°C to 8°C) until ready for use. Because the On-body Injector for Neulasta is at room temperature during the period of use, Neulasta Onpro kit should not be held at room temperature longer than 12 hours prior to use. Discard Neulasta Onpro kit if stored at room temperature for more than 12 hours.

Do not use the On-body Injector for Neulasta if its packaging has been previously opened.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Advise patients of the following risks and potential risks with Neulasta:

- Splenic rupture and splenomegaly
- Acute Respiratory Distress Syndrome
- Serious allergic reactions
- Sickle cell crisis
- Glomerulonephritis
- Capillary Leak Syndrome

Advise patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome) that efficacy studies of Neulasta for this indication could not be conducted in humans for ethical and feasibility reasons and that, therefore, approval of this use was based on efficacy studies conducted in animals [see *Clinical Studies* (14.2)].

Advise patients on the use of the On-body Injector for Neulasta:

- Review the Patient Information and Patient Instructions for Use with the patient and provide the instructions to the patient.
- Refer the patient to the dose delivery information written on the Patient Instructions for Use.
- Tell the patient when their dose delivery of Neulasta will begin and when their dose delivery should be completed.
- Advise the patient that serious allergic reactions can happen with Neulasta. Patients should have a caregiver nearby for the first use. Patients should plan to be in a place where they can appropriately monitor the On-body Injector for Neulasta during the approximately 45 minute Neulasta delivery and for an

hour after the delivery. Advise the patient to avoid traveling, driving, or operating heavy machinery during hours 26-29 following application of the On-body Injector for Neulasta.

- If the On-body Injector for Neulasta is placed on the back of the arm, remind the patient that a caregiver must be available to monitor the On-body Injector for Neulasta.
- If a patient calls the healthcare provider regarding any On-body Injector for Neulasta problems, the healthcare provider is advised to call Amgen at 1-800-772-6436.
- Advise the patient:
 - to call their healthcare provider immediately if the status light on the On-body Injector for Neulasta is flashing red (see the Patient Instructions for Use).
 - to inform their healthcare provider if the adhesive on the On-body Injector for Neulasta becomes saturated with fluid, or there is dripping, as this may be evidence of significant product leakage, resulting in inadequate or missed dose (see the Patient Instructions for Use).
 - to keep the On-body Injector for Neulasta dry for approximately the last 3 hours prior to the dose delivery start to better enable potential leak detection.
 - that the On-body Injector for Neulasta should only be exposed to temperatures between 41°F and 104°F (5°C-40°C)
 - to keep the On-body Injector for Neulasta at least 4 inches away from electrical equipment such as cell phones, cordless telephones, microwaves and other common appliances. Failure to keep the On-body Injector for Neulasta at least this recommended distance may interfere with operation and can lead to a missed or incomplete dose of Neulasta.
 - that if the needle is exposed after On-body Injector for Neulasta removal, place the used On-body Injector for Neulasta in a sharps disposal container to avoid accidental needle stick and call their healthcare provider immediately.
 - to remove the On-body Injector for Neulasta after the green light shines continuously and to place the used On-body Injector for Neulasta in a sharps disposal container (see the Patient Instructions for Use).
- Advise the patient:
 - do not reapply the On-body Injector for Neulasta if the On-body Injector for Neulasta comes off before full dose is delivered and instead call their healthcare provider immediately.
 - avoid bumping the On-body Injector for Neulasta or knocking the On-body Injector for Neulasta off the body.
 - do not expose the On-body Injector for Neulasta to medical imaging studies, e.g. X-ray scan, MRI, CT scan, ultrasound and oxygen rich environments such as hyperbaric chambers to avoid On-body Injector for Neulasta damage and patient injury.
- Advise the patient to avoid:
 - airport X-ray scans and request a manual pat down instead; remind patients who elect to request a manual pat down to exercise care to avoid having the On-body Injector for Neulasta dislodged during the pat down process.
 - sleeping on the On-body Injector for Neulasta or applying pressure on the On-body Injector for Neulasta as this may affect On-body Injector for Neulasta performance.
 - getting body lotions, creams, oils and cleaning agents near the On-body Injector for Neulasta as these products may loosen the adhesive.
 - using hot tubs, whirlpools, or saunas and avoid exposing the On-body Injector for Neulasta to direct sunlight as these may affect the drug.
 - peeling off or disturbing the On-body Injector for Neulasta adhesive before delivery of full dose is complete.



Neulasta® (pegfilgrastim)

Manufactured by:

Amgen Inc.

One Amgen Center Drive

Thousand Oaks, California 91320-1799

US License No. 1080

Patent: <http://pat.amgen.com/neulasta/>

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1-800-77-AMGEN (1-800-772-6436)

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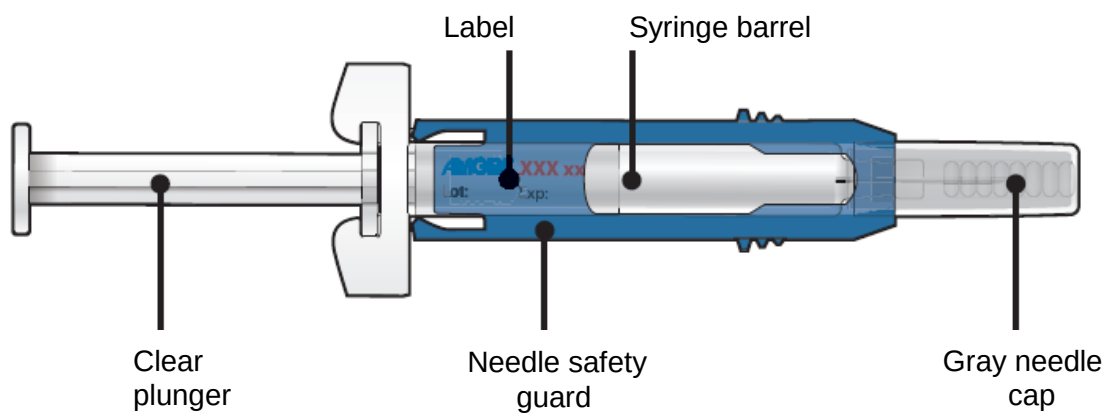
v1X

Neulasta® (pegfilgrastim) Onpro™ kit

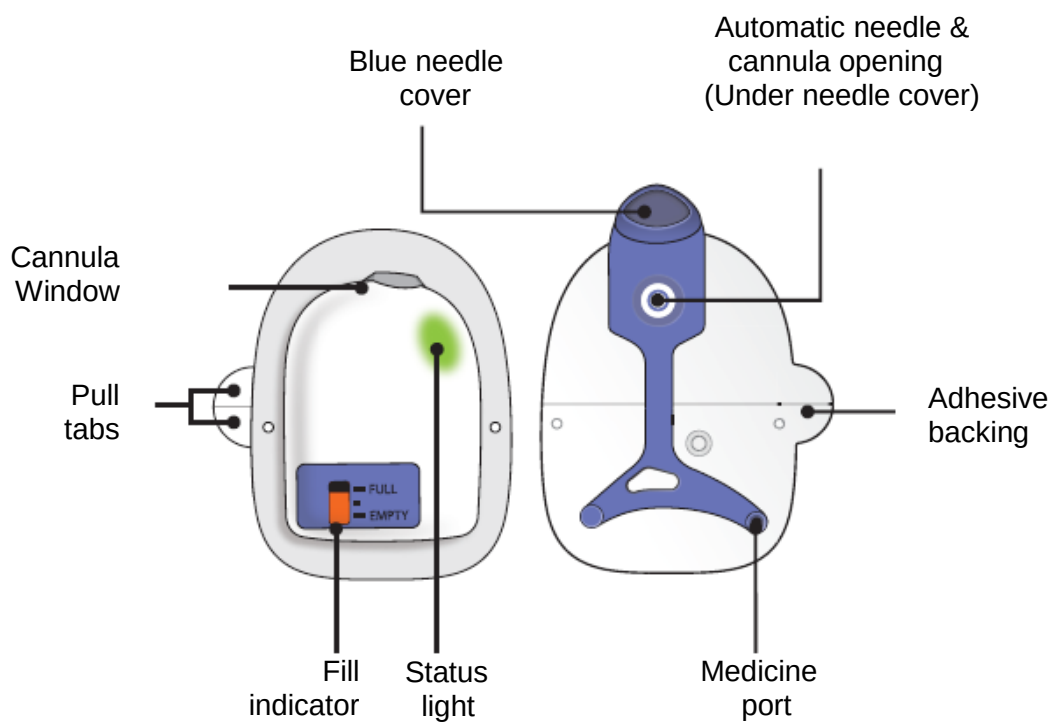
Healthcare Provider Instructions for Use

Guide to Parts

Neulasta Prefilled Syringe with Manual Needle Guard



On-body Injector for Neulasta



Important

READ THE FOLLOWING INSTRUCTIONS BEFORE USING THE ON-BODY INJECTOR

Warning: Do not use Neulasta Onpro kit to deliver any other drug product.

-  See Prescribing Information for information on Neulasta.
-  The On-body Injector is for adult patients only.
-  Store Neulasta Onpro kit in the refrigerator at 36°F to 46°F (2°C to 8°C) until ready for use. If Neulasta Onpro kit is stored at room temperature for more than 12 hours, do not use. Start again with a new Neulasta Onpro kit.
-  Keep the prefilled syringe in the Neulasta Onpro kit carton until use to protect from light.
-  For patients who have had severe skin reactions to acrylic adhesives, consider the benefit:risk profile before administering pegfilgrastim via the On-body Injector for Neulasta.
-  The On-body Injector should be applied to intact, non-irritated skin on the abdomen or back of the arm. The back of the arm may only be used if there is a caregiver available to monitor the status of the On-body Injector.
-  DO NOT:
 -  freeze Neulasta Onpro kit.
 -  shake the prefilled syringe.
 -  separate the components of Neulasta Onpro kit until ready for use.
 -  modify the On-body Injector.
 -  warm Neulasta Onpro kit components using a heat source.
 -  use Neulasta Onpro kit if expiry date on the carton or any of the Neulasta Onpro kit components has passed.
 -  use if the name Neulasta does not appear on the Neulasta Onpro kit carton.
 -  attempt to reapply On-body Injector.
 -  use if either the On-body Injector or prefilled syringe is dropped. Start again with a new Neulasta Onpro kit.

For all questions, call Amgen at 1-800-772-6436. If a patient calls you regarding any On-body Injector problems, call Amgen at 1-800-772-6436.

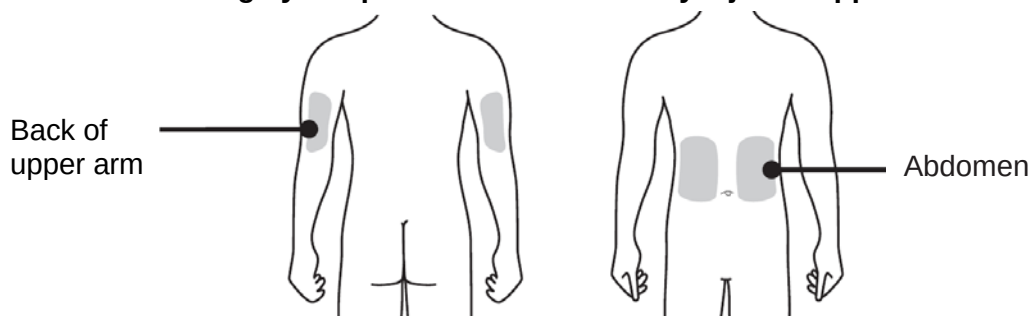
Step 1: Prepare

A Remove Neulasta Onpro kit from refrigerator. Check to make sure it contains:

- One Neulasta prefilled syringe
- One On-body Injector for Neulasta
- Neulasta package insert
- Instructions for use:
 - for healthcare provider
 - for patient
- Reference guide

⊘ DO NOT use On-body Injector if its packaging has been previously opened.

B Wash hands thoroughly. Prepare and clean On-body Injector application site.



Choose the flattest site for On-body Injector application. Consult with your patient regarding their ability to remove and monitor the entire On-body Injector.

You can use:

- Left or right side of abdomen, except for a 2-inch area right around navel.
- Back of upper arm, only if there is a caregiver available to monitor the status of the On-body Injector.

Choose an area larger than the adhesive pad, and clean it with an alcohol swab. Allow skin to completely dry.

⊘ DO NOT touch this area again before attaching On-body Injector.

You should avoid:

- ✗ Areas with scar tissues, moles, or excessive hair. In case of excessive hair, carefully trim hair to get On-body Injector close to skin.
- ✗ Areas where belts, waistbands, or tight clothing may rub against, disturb, or dislodge On-body Injector.
- ✗ Surgical sites.
- ✗ Areas where On-body Injector will be affected by folds in skin.



The following is an overview of On-body Injector preparation steps. Read this section first.

When ready, proceed to Step 2: Get Ready Section.

Before you apply On-body Injector to your patient, locate medicine port on blue needle cover to fill the On-body Injector with Neulasta.

Please note: During filling, beeping will sound and the On-body Injector will be activated.

After activation, you will have 3 minutes to:

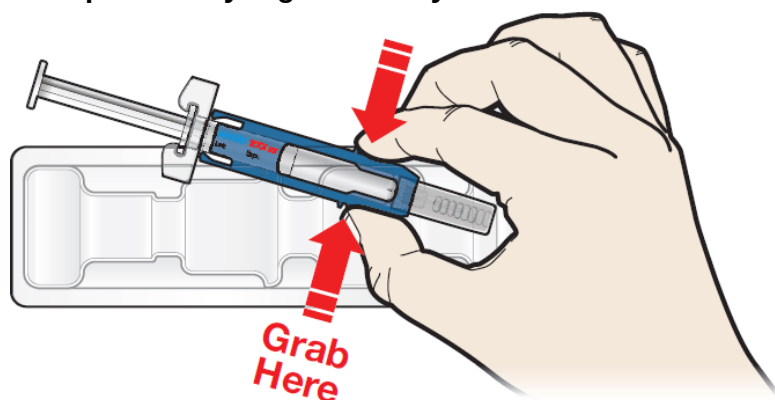
1. Completely empty syringe contents into medicine port.
2. Remove syringe from port and pull down needle safety guard over the exposed needle.
3. Remove blue needle cover from back of On-body Injector.
4. Peel away the two pieces of white adhesive backing from the back of the On-body Injector.
5. Attach On-body Injector to back of patient's upper arm or abdomen.

On-body Injector will deploy cannula in 3 minutes, even if not applied to patient. If not on patient's body in 3 minutes, do not use the On-body Injector. Start again with a new Neulasta Onpro kit.

When you feel you are ready, please continue...

Step 2: Get Ready

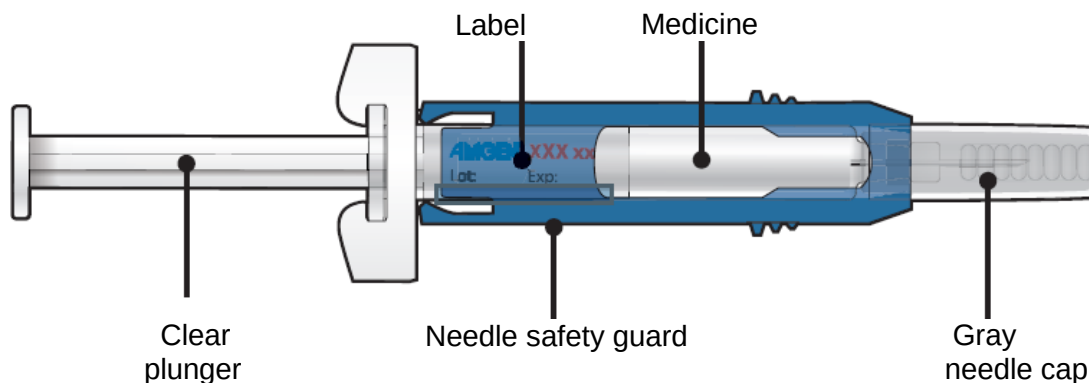
A Remove Neulasta prefilled syringe from tray.



For safety reasons:

- ⊘ DO NOT grasp gray needle cap.
- ⊘ DO NOT put the gray needle cap back onto syringe.
- ⊘ DO NOT grasp clear plunger.

B Inspect medicine and Neulasta prefilled syringe. The Neulasta liquid should always be clear and colorless.

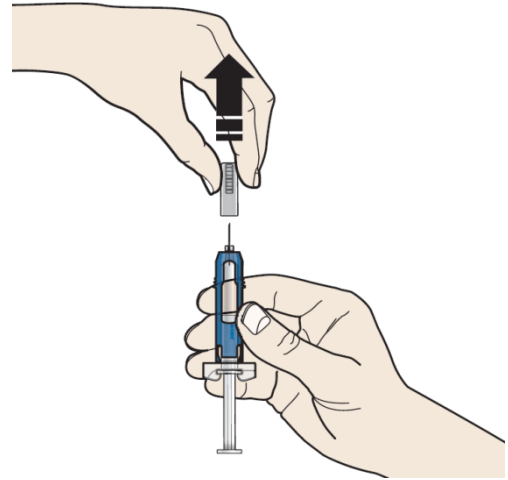


- ⊘ DO NOT use Neulasta prefilled syringe if:
 - ✗ Liquid contains particulate matter or discoloration is observed prior to administration.
 - ✗ Any part appears cracked or broken.
 - ✗ The gray needle cap is missing or not securely attached.
 - ✗ The expiration date printed on the label has passed.
- ⊘ DO NOT remove gray needle cap until ready to fill On-body Injector.
- ⊘ DO NOT pull needle safety guard down over the needle until filling is complete.
- ❗ In all the above cases, start again with a new Neulasta Onpro kit. Call Amgen at 1-800-772-

6436.

! The prefilled syringe gray needle cap contains dry natural rubber, which is derived from latex.

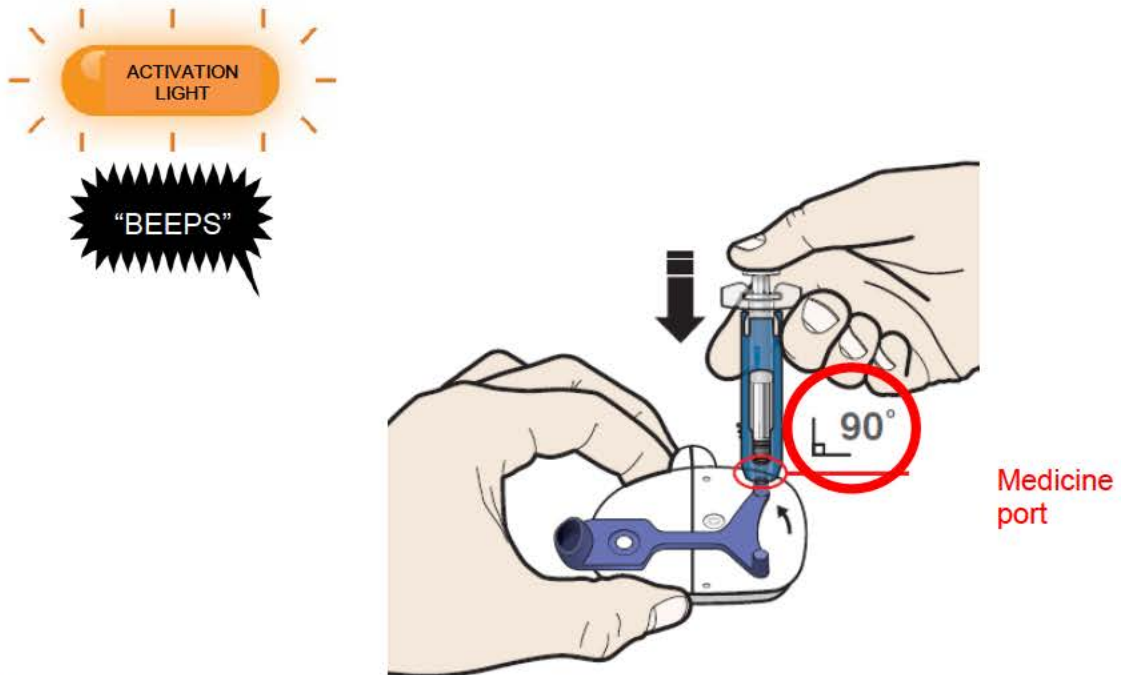
C **Carefully remove gray needle cap straight out from the syringe and away from your body. Check syringe, and remove air bubbles.**



! Take care to expel air only and not medicine.
A small droplet at the tip of the needle during air purging is normal.

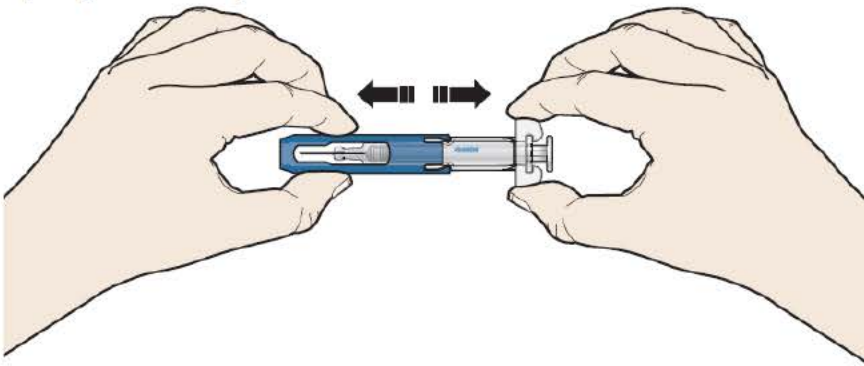
⊘ DO NOT recap syringe.

- D** Using blue needle cover, to avoid bending the needle and spilling medicine, insert syringe needle at 90 degrees all the way into medicine port. Slowly empty the entire syringe contents. Remove empty syringe from the medicine port. When beeping sounds and the status light flashes amber, the 3-minute countdown begins.

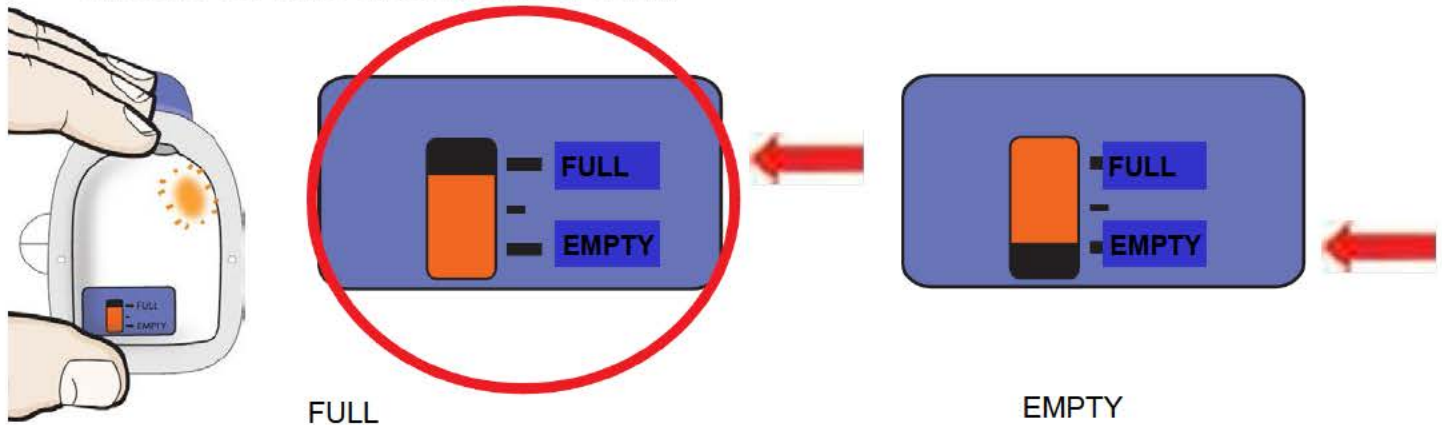


- ⊘ DO NOT insert needle into medicine port at other than a 90 degree angle
- ⊘ DO NOT insert needle more than once.
- ⊘ DO NOT remove blue needle cover before filling the On-body Injector.

- E** Pull needle safety guard down until it clicks and covers needle. Dispose of empty syringe in a sharps container.



F Check to see if the On-body Injector is full.



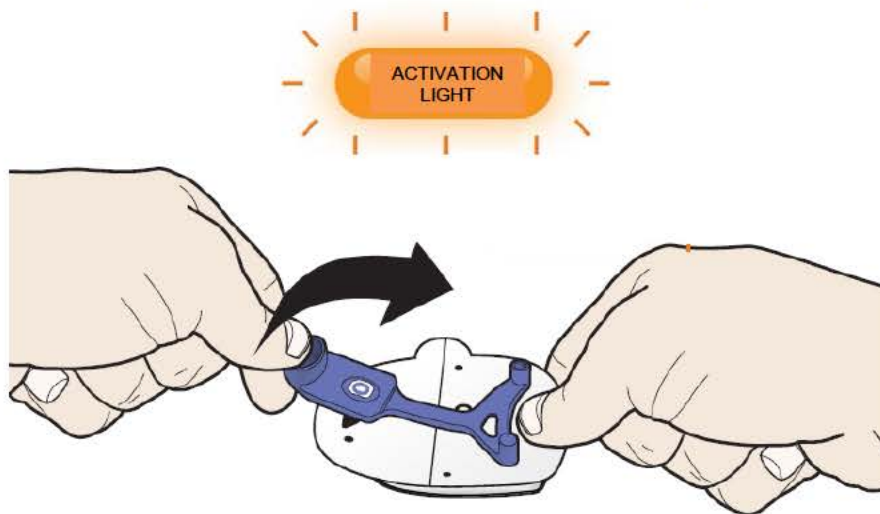
You should see:

- amber status light flashing.
- black line next to FULL on the fill indicator

If this is not the case, do not use. Start again with a new Neulasta Onpro kit, and call Amgen at 1-800-772-6436.

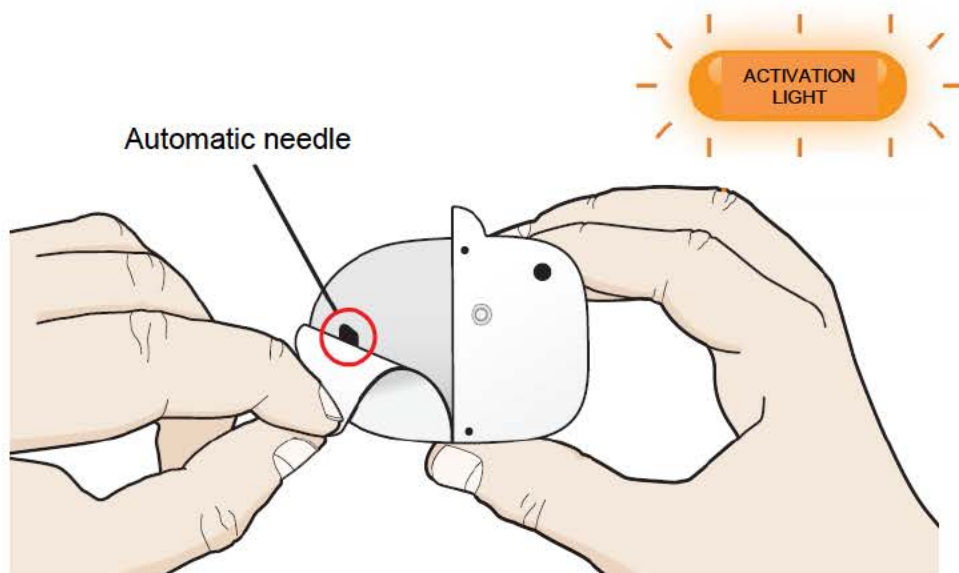
Step 3: Apply

A Firmly lift and remove blue needle cover away from On-body Injector.



A drop of medicine may be visible on needle tip when blue needle cover is removed.

- B To expose the adhesive pad, use both pull tabs, one at a time, to peel the two pieces of white adhesive backing away from On-body Injector.**

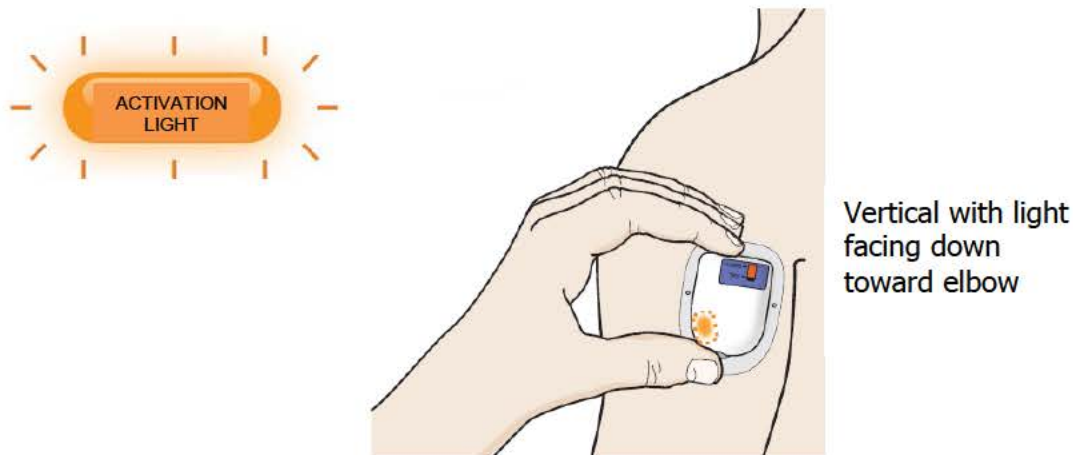


- ⊘ DO NOT touch or contaminate automatic needle area.
- ⊘ DO NOT pull off adhesive pad or fold it.
- ⊘ DO NOT use if the needle or cannula is extended past the adhesive or is extended before the On-body Injector is placed on patient.

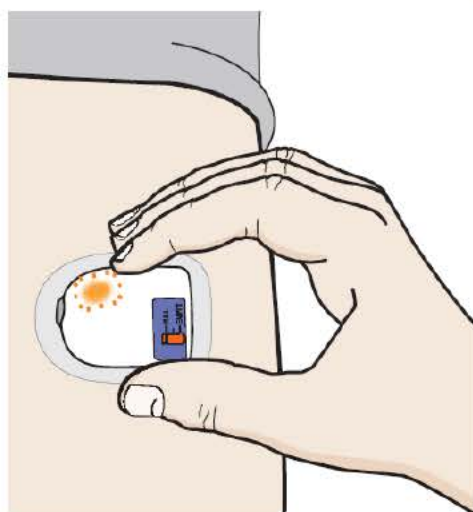
! In all cases, start again with a new Neulasta Onpro kit. Call Amgen at 1-800-772-6436.

- C Apply On-body Injector securely to patient with entire On-body Injector visible so it can be monitored by patient or caregiver.**
Before cannula deploys, place On-body Injector on your selected site, and run your finger around entire adhesive pad to make sure it is securely attached.

Back of Upper Arm



Horizontal
with light
facing
navel

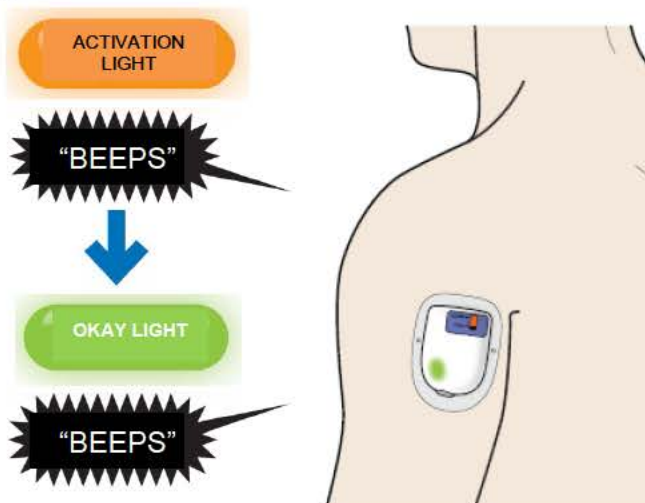


Abdomen



STOP! Do not worry if On-body Injector is quiet. When 3 minutes are up, On-body Injector will beep.

- D** Beeping will tell you the cannula is about to insert. You may hear a series of clicks. This is okay.
A long beep will sound, and the status light will turn to green. This means the cannula insertion is complete.



If the adhesive folds over near the cannula window or there are folds anywhere that prevent the On-body Injector from securely adhering, remove the On-body Injector. Start again with a new Neulasta Onpro kit and call Amgen at 1-800-772-6436.

Step 4: Finish

- A Fill in the Dose Delivery Information section in the patient instructions. Be sure to include when the On-body Injector was applied, when the dose will begin, and your contact information. Review this information with the patient.**

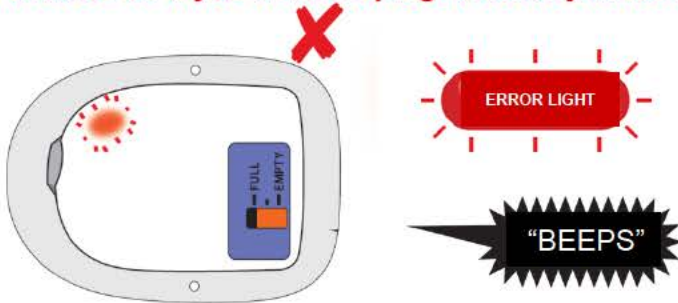
Review each step in the patient instructions with your patient. Give your patient the instructions, and reference guide to take home.

Before your patient goes home, make sure your patient understands:

- The On-body Injector will always flash a slow green light to let them know it is working properly.
- **After approximately 27 hours, beeps will signal that the dose delivery will begin in 2 minutes.**
- **When the dose delivery starts it will take about 45 minutes to complete. During this time, the On-body Injector will flash a fast green light.**
- The patient should remain in a place where they can monitor the On-body Injector for the entire dose delivery. The patient should avoid activities and settings that may interfere with monitoring during the dosing of Neulasta administered by the On-body Injector. For example, avoid traveling, driving, or operating heavy machinery during hours 26-29 following application of the On-body Injector (this includes the approximately 45-minute delivery period plus an hour post-delivery).
- If the patient has an allergic reaction during the delivery of Neulasta, the patient should remove the On-body Injector and call his or her healthcare provider or seek emergency care right away.
- If placed on the back of the arm, remind the patient that a caregiver must be available to monitor the On-body Injector.
- When the dose delivery is complete, the patient or caregiver will hear a beep and see a solid green light.
- Always dispose of the empty On-body Injector in a sharps disposal container as instructed by your healthcare provider or by state or local laws.
- Keep the On-body Injector at least 4 inches away from electrical equipment such as cell phones, cordless telephones, microwaves and other common appliances. Failure to keep the On-body Injector at least this recommended distance may interfere with operation and can lead to a missed or incomplete dose of Neulasta.

Attention!

What to do if you hear beeping or when you look at status light and it is flashing red.

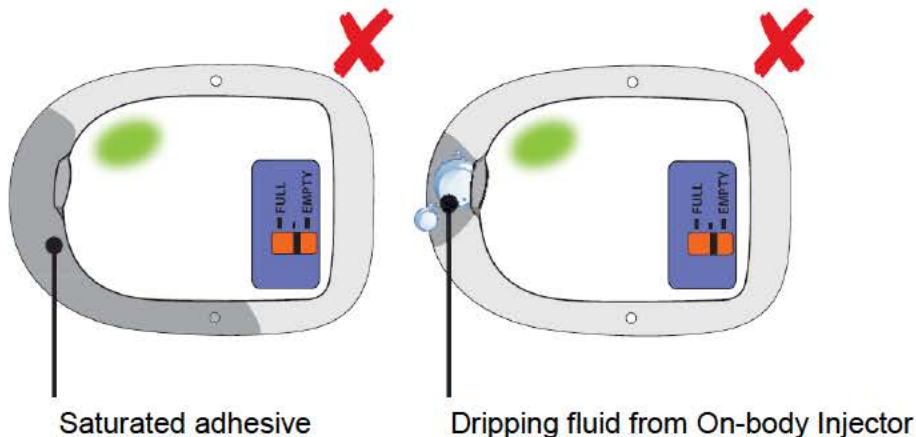


If at any time the On-body Injector beeps continuously for 5 minutes, and the status light is flashing red, take the On-body Injector off of the patient.

- ⊗ DO NOT apply On-body Injector to patient if red error light is on.
- ⊗ DO NOT leave On-body Injector on patient if red error light is on.

In all cases, do not use. Start over with a new Neulasta Onpro kit, and call Amgen at 1-800-772-6436.

What to do if the adhesive becomes saturated with fluid or the On-body Injector is dripping.



If patient reports an On-body Injector leak, they might not have received full dose. Schedule a follow-up appointment, and report the incident to Amgen at 1-800-772-6436.

Neulasta® (pegfilgrastim)

Manufactured by:

Amgen Inc.

One Amgen Center Drive

Thousand Oaks, California 91320-1799

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www.neulasta.com 1-800-772-6436 (1-800-77-AMGEN)

Issued: 09/2015

v3

Do not expose the On-body Injector for Neulasta to the following environments as the On-body Injector may be damaged and the patient could be injured:

- MRI
- X-ray
- CT-Scan
- Ultrasound
- Oxygen rich environments such as hyperbaric chambers

Symbol	Meaning
	Do not reuse this On-body Injector. Single-use only
	Refer to Instructions for Use
	Do not use if packaging is damaged.
	Temperature Limitation
	Humidity Limitation
	Expiration Date (use by date)
	Reference/model number
	Lot Number
	Type BF medical device (protection from electrical shock)
	Sterilized by ethylene oxide
	Waterproof up to 8 feet for 1 hour
	Prescription use only
	Not MRI-safe
	On-body Injector for Neulasta® (pegfilgrastim)
	Neulasta® (pegfilgrastim) Prefilled Syringe

Electromagnetic Compatibility

The information contained in this section (such as separation distances) is, in general, specifically written in regard to the On-body Injector for Neulasta. The numbers provided will not guarantee faultless operation but should provide reasonable assurance of such. This information may not be applicable to other medical electrical equipment; older equipment may be particularly susceptible to interference.

General Notes:
Medical electrical equipment requires special precautions regarding electromagnetic compatibility (EMC), and needs to be installed and put into service according to the EMC information provided in this document.

Portable and mobile RF communications equipment can affect medical electrical equipment.

Cables and accessories not specified within the instructions for use are not authorized. Using cables and/or accessories may adversely impact safety, performance, and electromagnetic compatibility (increased emission and decreased immunity).

Care should be taken if the On-body Injector for Neulasta is used adjacent to other electrical equipment; if adjacent use is inevitable, the On-body Injector for Neulasta should be observed to verify normal operation in this setting.

Electromagnetic Emissions		
The On-body Injector for Neulasta is intended for use in the electromagnetic environment specified below. The user of the On-body Injector for Neulasta should ensure that it is used in such an environment.		
Emissions	Compliance according to	Electromagnetic environment
RF Emissions (CISPR 11)	Group 1	The On-body Injector for Neulasta uses RF energy only for its internal function. Therefore, its RF emissions are very low and are not likely to cause any interference in nearby equipment.
CISPR B Emissions Classification	Class B	

Electromagnetic Immunity			
The On-body Injector for Neulasta is intended for use in the electromagnetic environment specified below. The user of this equipment should ensure that it is used in such an environment.			
Immunity Test	IEC 60601 Test Level	Compliance Level	Electromagnetic Environment – Guidance
ESD IEC 61000-4-2	±6kV Contact ±8kV Air	6kV Contact ±8kV Air	Floors should be wood, concrete or ceramic tile. If floors are synthetic, the r/h should be at least 30%.
Power Frequency 50/60 Hz Magnetic Field IEC 61000-4-8	3A/m	3A/m	Power frequency magnetic fields should be that of typical commercial or hospital environment.
Radiated RF Fields 61000-4-3	3 V/m 80 MHz to 2.5 GHz	(E1)=3V/m	Portable and mobile communications equipment should be separated from the On-body Injector for Neulasta by no less than the distances calculated/listed below: $D = (3.5/V1)(\sqrt{P})$ 150 kHz to 80 MHz $D = (3.5/E1)(\sqrt{P})$ 80 to 800 MHz $D = (7/E1)(\sqrt{P})$ 800 MHz to 2.5 GHz Where P is the max power in watts and D is the recommended separation distance in meters. Field strengths from fixed transmitters, as determined by an electromagnetic site survey, should be less than the compliance levels (V1 and E1). Interference may occur in the vicinity of equipment containing a transmitter.

Recommended separation distances between portable and mobile RF communications equipment and the On-body Injector for Neulasta

You can help prevent electromagnetic interference by maintaining a minimum distance between portable and mobile RF communications equipment (transmitters) and the On-body Injector for Neulasta, as recommended below, according to the maximum power of the communication equipment.

Rated maximum output power of transmitter, in watts	Separation distance according to frequency of transmitter, in meters		
	150 kHz to 80 MHz $D=(3.5/V1)(\sqrt{P})$	80 to 800 MHz $D=(3.5/E1)(\sqrt{P})$	800 MHz to 2.5 GHz $D=(7/E1)(\sqrt{P})$
0.01	0.11667	0.11667	0.23333
0.1	0.36894	0.36894	0.73785
1	1.1667	1.1667	2.3333
10	3.6894	3.6894	7.3785
100	11.667	11.667	23.333

{SIDE 1 Information}

Patient Instructions for Use

On-body Injector for Neulasta Description

The On-body Injector for Neulasta is intended for delivery of Neulasta. The On-body Injector is small, for one-time use, lightweight, battery-powered, and waterproof up to 8 feet for 1 hour. Your healthcare provider will use a prefilled syringe with Neulasta to fill the On-body Injector prior to applying it. The prefilled syringe with Neulasta and the On-body Injector are provided to your healthcare provider as part of Neulasta Onpro™ kit. The On-body Injector is applied directly to your skin using a self-adhesive backing. The On-body Injector informs you of its status with sounds and lights.

The On-body Injector contains electronic components as well as: a plastic housing, acrylic adhesive, batteries, a cannula introducer (needle) and a cannula. The On-body Injector is approximately: 2.4 in long, 1.6 in wide, 0.7 in height (62 mm long, 41 mm wide, 17 mm height).

Warnings

- **Before** you receive Neulasta, tell your healthcare provider if you:
 - o Have sickle cell trait or sickle cell disease
 - o Have problems with your kidneys
 - o Have any other medical problems
 - o Are pregnant or plan to become pregnant. It is not known if Neulasta may harm your unborn baby.
 - o Are breastfeeding or plan to breastfeed. It is not known if Neulasta passes into your breastmilk.
- **DO NOT** take Neulasta if you have had a serious allergic reaction to pegfilgrastim (Neulasta®) or to filgrastim (Neupogen®).
- Tell your healthcare provider if you are allergic to latex. A prefilled syringe is used to fill the On-body Injector by your healthcare provider prior to applying the On-body Injector. The prefilled syringe gray needle cap contains dry natural rubber, which is derived from latex. Latex may be transferred to your skin.
- Tell your healthcare provider if you have had severe skin reactions to acrylic adhesives.
- The On-body Injector is for adult patients only.
- Avoid activities and places that may interfere with monitoring during the dosing of Neulasta administered by the On-body Injector. For example, **AVOID** traveling, driving, or operating heavy machinery during hours 26-29 following application of the On-body Injector for Neulasta (this includes the 45-minute dose delivery period plus an hour post-delivery). If you must travel by airplane **before** the approximately 45-minute dose delivery period with the On-body Injector, avoid airport X-ray scans. Request a manual pat down instead. Use care during a manual pat down to help prevent the On-body Injector from being accidentally removed. For more information go to <http://www.tsa.gov/traveler-information/travelers-disabilities-and-medical-conditions>
- If you have an allergic reaction during the delivery of Neulasta, remove the On-body Injector by grabbing the edge of the adhesive pad and peeling off the On-body Injector. Get emergency medical help right away.
- Call your healthcare provider immediately if you have severe pain or skin discomfort around your On-body Injector.

- Call your healthcare provider right away if you have pain in your left upper stomach area or left shoulder area. This pain could mean your spleen is enlarged or ruptured.
- Call your healthcare provider or get emergency medical help right away if you get any of these symptoms of acute respiratory distress syndrome (ARDS): fever, shortness of breath, trouble breathing, or a fast rate of breathing.
- Call your healthcare provider right away if you experience any of these symptoms of kidney injury (glomerulonephritis): puffiness in your face or ankles, blood in your urine or brown colored urine or you notice you urinate less than usual.
- Keep children away from the used On-body Injector.
- You should only receive a dose of Neulasta on the day your healthcare provider tells you.
- You should not receive your dose of Neulasta any sooner than 24 hours after you finish receiving your chemotherapy. The On-body Injector for Neulasta is programmed to deliver your dose about 27 hours after your healthcare provider places the On-body Injector on your skin.
- **DO NOT** expose the On-body Injector to the following because the On-body Injector may be damaged and you could be injured:
 - MRI
 - X-ray
 - CT-Scan
 - Ultrasound
 - Oxygen rich environments, such as hyperbaric chambers
- **DO NOT** use hot tubs, whirlpools, or saunas while wearing the On-body Injector. This may affect your medicine.
- **DO NOT** expose the On-body Injector to direct sunlight. If the On-body Injector is exposed to direct sunlight for more than 1 hour, it may affect your medicine. Wear the On-body Injector under clothing.
- **DO NOT** sleep on the On-body Injector or apply pressure during wear, especially during dose delivery. This may affect the On-body Injector performance.
- **DO NOT** peel off or disturb the On-body Injector's adhesive before your full dose is complete. This may result in a missed or incomplete dose of Neulasta.

Precautions

Environmental:

- Keep the On-body Injector dry for the last 3 hours prior to the dose delivery start.
- Only expose the On-body Injector to temperatures between 41°F and 104°F (5°C-40°C).
- Keep the On-body Injector at least 4 inches away from electrical equipment such as cell phones, cordless telephones, microwaves and other common appliances. Failure to keep the On-body Injector at least this recommended distance may interfere with operation and can lead to a missed or incomplete dose of Neulasta.

Activity Related:

- Avoid getting body lotions, creams, oils or cleaning agents near the On-body Injector as these products may loosen the adhesive.
- Be careful not to bump the On-body Injector or knock the On-body Injector off your body.

Biohazard:

Properly dispose of the On-body Injector:

- The On-body Injector contains batteries, electronics, and a needle. The On-body Injector should be placed in a sharps disposal container, with an appropriate sized opening, regardless of whether or not the needle is exposed. Follow instructions provided by your healthcare provider or by state or local laws.
- To participate in Amgen's voluntary disposal program, please call 1-844-MYNEULASTA (1-844-696-3852) or visit www.neulasta.com to enroll.
- For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to FDA's website at: <http://www.fda.gov/safesharpsdisposal>.

Risks

You can avoid most risks related to using the On-body Injector for Neulasta by following the Patient Instructions for Use. Immediately call your healthcare provider if any of the following occur:

- The adhesive becomes noticeably wet (saturated) with fluid, or you see dripping
- If the On-body Injector fill indicator is not at the empty position after On-body Injector removal (You should see a black line next to the EMPTY indicator.)
- The On-body Injector comes off from the skin before or during a dose delivery (**DO NOT re-apply it.**)
- Status light is flashing red
- Allergic reaction
- Persistent or worsening redness or tenderness at the application site (may be a sign of infection)
- Severe pain or skin discomfort around your On-body Injector
- Any concern about your medication
- If the needle is exposed after On-body Injector removal

{SIDE 2 Information}

On-body Injector for Neulasta® (nu-las-tah) (pegfilgrastim) Injection

Patient Instructions for Use

Dose Delivery Information

Your On-body Injector was applied:

Day	Time	AM / PM
-----	------	---------

Your dose delivery will start around:

Day	Time	AM / PM
-----	------	---------

Name of Healthcare Provider:

Last, First

Healthcare Provider contact number:

On-body Injector lot number:

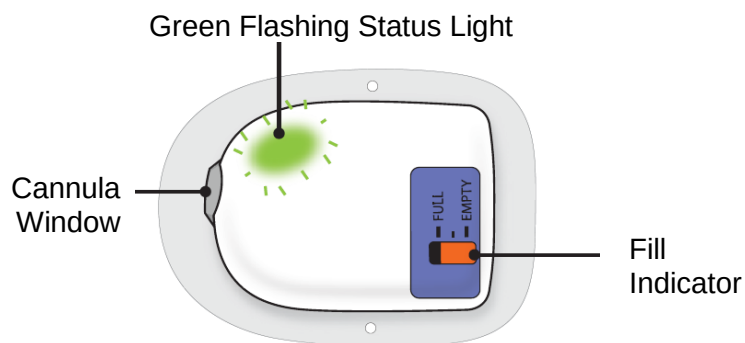
Important Information

-  This On-body Injector delivers Neulasta with an under-the-skin (subcutaneous) injection. See Patient Information for medicine information.
-  If you have concerns about your medication, call your healthcare provider immediately. Serious allergic reactions can happen with Neulasta. Ask your caregiver to be nearby for the first use.
-  Plan to be in a place where you or your caregiver can appropriately monitor the On-body Injector for Neulasta during the approximately 45 minute Neulasta delivery and for an hour after the delivery.
-  Avoid activities and places that may interfere with monitoring during the dosing of Neulasta administered by the On-body Injector (hours 26-29).

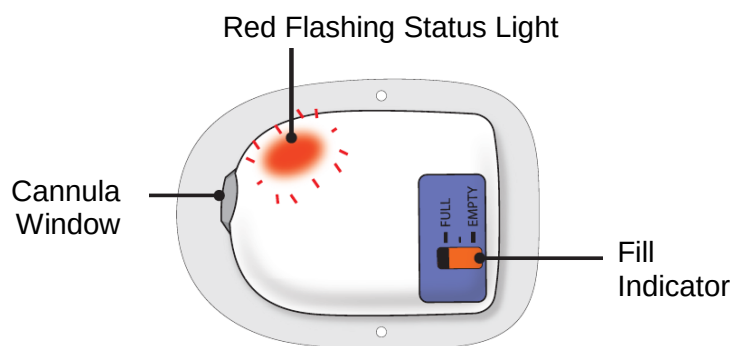
- !** If you have an allergic reaction during the delivery of Neulasta, remove the On-body Injector by grabbing the edge of the adhesive pad and peeling off the On-body Injector. Get emergency medical help right away.
 - !** The On-body Injector should be applied to intact, non-irritated skin on the stomach area (abdomen) or back of the arm. The back of the arm may only be used if there is a caregiver available to monitor the status of the On-body Injector.
 - !** Call your healthcare provider immediately if you have severe pain or skin discomfort around your On-body Injector.
 - !** Be careful not to bump the On-body Injector or knock the On-body Injector off your body.
 - !** Avoid getting body lotions, creams, oils or cleaning agents near the On-body Injector as these products may loosen the adhesive.
 - !** Keep the On-body Injector dry for the last 3 hours prior to the dose delivery start.
 - !** Only expose the On-body Injector to temperatures between 41°F and 104°F (5°C and 40°C).
 - !** After On-body Injector removal, properly dispose of it in a sharps disposal container as instructed by your healthcare provider or by state or local laws.
 - !** Keep the On-body Injector at least 4 inches away from electrical equipment such as cell phones, cordless telephones, microwaves and other common appliances. Failure to keep the On-body Injector at least this recommended distance may interfere with operation and can lead to a missed or incomplete dose of Neulasta.
- ⊘ DO NOT:**
- ×** use hot tubs, whirlpools, or saunas while wearing the On-body Injector. This may affect your medicine.
 - ×** expose the On-body Injector to direct sunlight. If the On-body Injector is exposed to direct sunlight for more than 1 hour, it may affect your medicine. Wear the On-body Injector under clothing.
 - ×** sleep on the On-body Injector or apply pressure during wear, especially during dose delivery. This may affect On-body Injector performance.
 - ×** peel off or disturb the On-body Injector adhesive before your full dose is complete. This may result in a missed or incomplete dose of Neulasta.

A healthcare provider who is familiar with Neulasta should answer your questions. For general questions or support call 1-844-MYNEULASTA (1-844-696-3852) or visit www.neulasta.com.

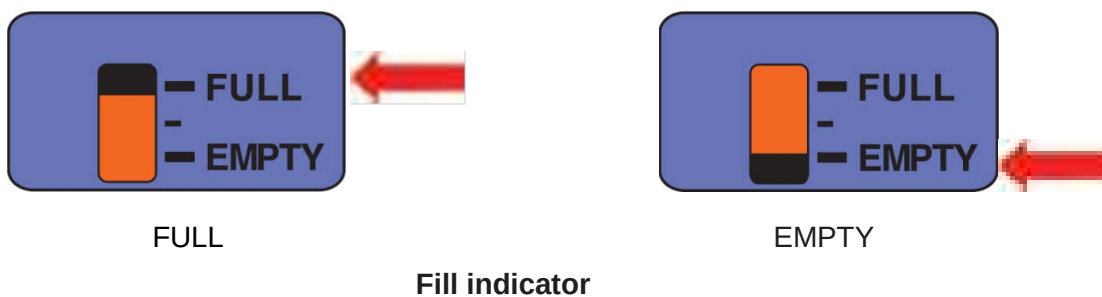
Guide to Parts for On-body Injector for Neulasta



The On-body Injector is working properly.

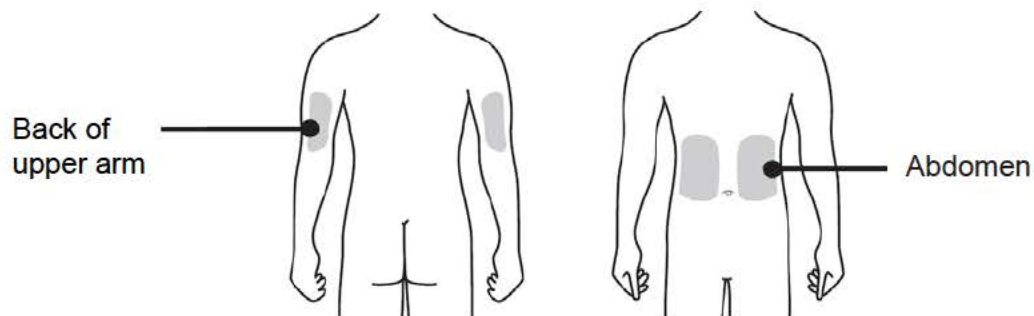


If at any time you hear beeping, check the status light. If it is flashing red, call your healthcare provider immediately.



After your dose delivery is complete, check to see if the black line on your On-body Injector fill indicator is at empty.

On-body Injector Placement



Step 1: Monitor On-body Injector

- A** Check your status light occasionally for approximately 27 hours. Since it flashes slowly, watch for at least 10 seconds. If the status light is flashing green, it is okay.

! If at any time you hear beeping, check the status light. If it is flashing red, call your healthcare provider immediately.

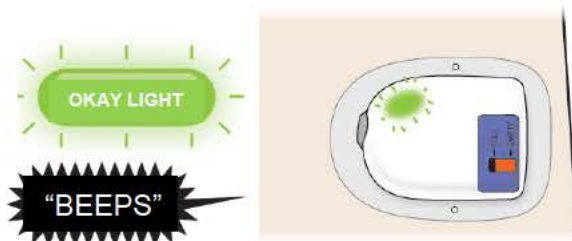


If the On-body Injector for Neulasta was placed on the back of your arm, a caregiver must be available to monitor the status of the On-body Injector.



- B** After approximately 27 hours, your On-body Injector will beep to let you know your dose delivery will begin in 2 minutes. When the dose delivery starts, it will take about 45 minutes to complete. During this time, the On-body Injector will flash a fast green light.

! If at any time you hear beeping, check the status light. If it is flashing red, call your healthcare provider immediately.

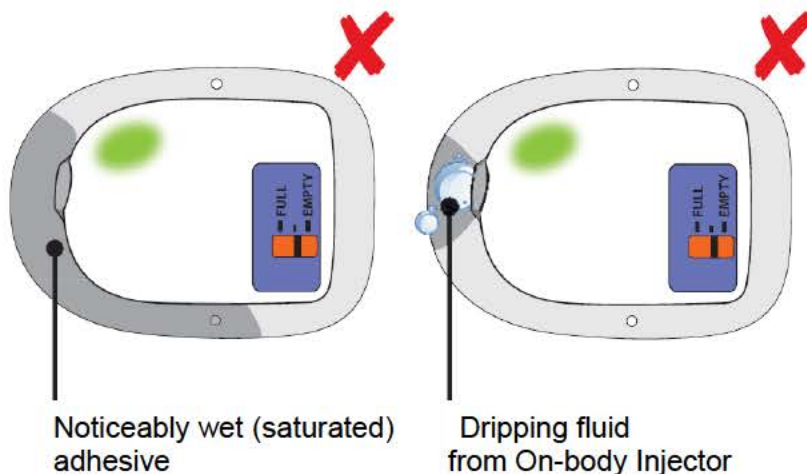


⊘ **DO NOT** remove the On-body Injector before the dose delivery is complete.

Step 2: Monitor Dose Delivery



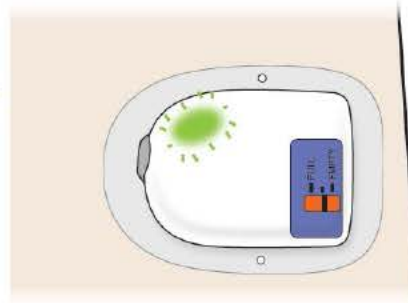
For the next 45 minutes, monitor your On-body Injector frequently for leaks during dose delivery. If the On-body Injector was placed on the back of your arm, a caregiver must be available to monitor your On-body Injector.



If the adhesive becomes noticeably wet (saturated) with fluid, or you see dripping, call your healthcare provider immediately.

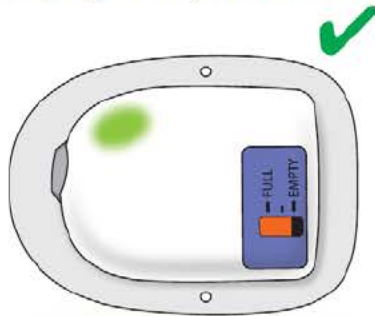
A Your dose delivery will take around 45 minutes to complete.

- You may hear a series of clicks. This is okay.
- A beep will sound when the dose delivery is complete.

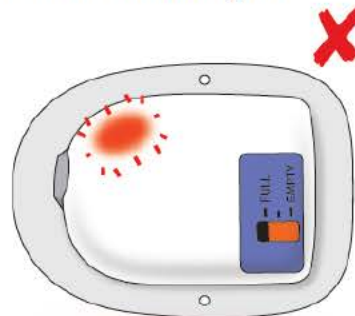


Step 3: Remove On-body Injector When Dose Delivery Is Complete

A When beeping starts, check to see the color of the status light.



Check to see if the status light is **SOLID GREEN** or has switched off. This means the dose is complete. Remember, **any time you see a leak, call your healthcare provider immediately.** If the dose is complete, go to the next step.



If you see the status light is flashing red, your On-body Injector is not functioning properly. Call your healthcare provider immediately, as you may not have received a full dose.

B Grab the edge of the adhesive pad. Slowly peel off the On-body Injector.

- If medicine has leaked or the adhesive is noticeably wet (saturated), call your healthcare provider immediately as you may not have received your full dose.
- Remove any extra adhesive using soap and water.



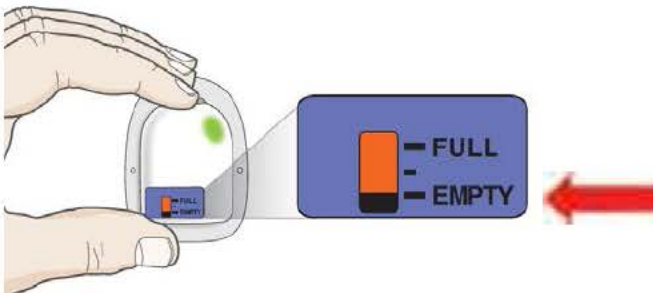
⊘ **DO NOT** grasp the On-body Injector itself to try to pull it off of your body.

Step 4: Finish



Check to see if your On-body Injector is empty.

- You should see a black line next to the EMPTY indicator. If the On-body Injector is not empty, call your healthcare provider immediately.



- Check your status light again. Watch for at least 10 seconds. If the status light is solid green or it has switched off, it is okay.
 - If you hear beeping, or when you check the status light and it is flashing red, call your healthcare provider immediately.
- !** After On-body Injector removal, place the On-body Injector in a sharps disposal container whether the needle is exposed or not. If the needle is exposed, call your healthcare provider immediately.

A Record the end state of your On-body Injector.

- Mark the box of the description that represents your On-body Injector after it has been used.

☐ Status light is solid green or the status light has switched off. This means that the delivery is complete.

☐ On-body Injector leaked, call your healthcare provider immediately.

☐ Status light is red, call your healthcare provider immediately.

B Properly dispose of the On-body Injector.

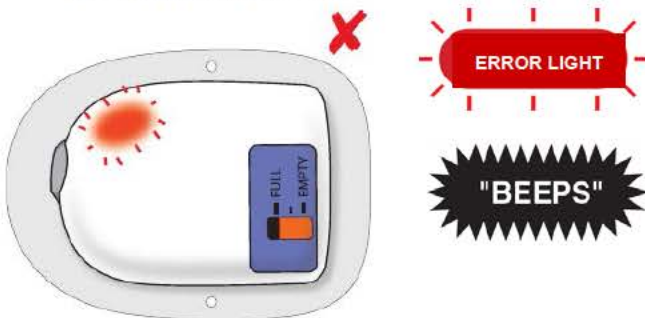
- The On-body Injector contains batteries, electronics, and a needle. Dispose of it in a sharps disposal container as instructed by your healthcare provider or by state or local laws.
- To participate in Amgen's voluntary disposal program, please call 1-844-MYNEULASTA (1-844-696-3852) or visit www.neulasta.com to enroll. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to FDA's website at: <http://www.fda.gov/safesharpsdisposal>.

! Keep children away from the used On-body Injector.

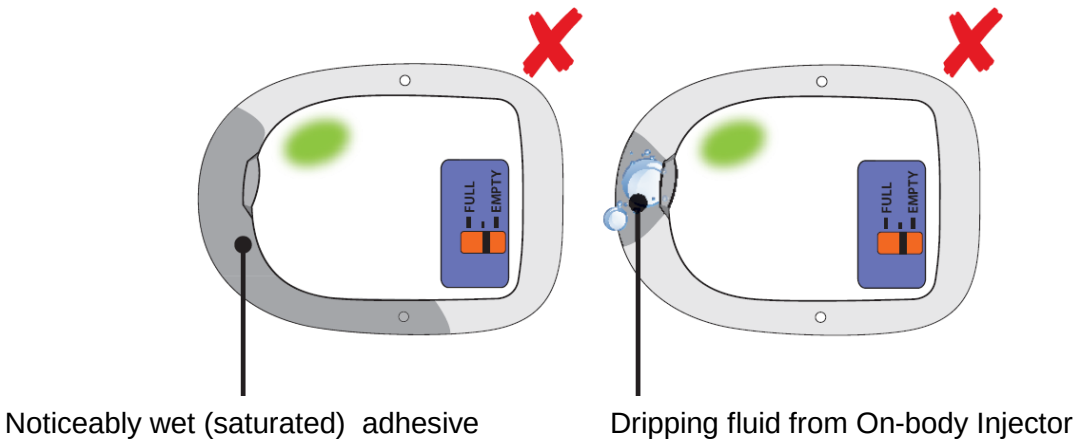
Attention!

What to do if you hear beeping or when you look at the status light and it is flashing red.

! If the status light is flashing red, you may not have received your full dose. Call your healthcare provider immediately.



What to do if the On-body Injector adhesive becomes noticeably wet (saturated) with fluid, or you see dripping.



- ! If the adhesive becomes saturated with fluid, or you see dripping, your medicine may have leaked out.
- ! Even with a leak, the status light may remain green and the fill indicator may be at EMPTY.
- ! Call your healthcare provider immediately as you may not have received your full dose.

Note: It is normal to see a few drops of fluid at the application site, but not normal to see a noticeably wet (saturated) adhesive.

What do I do if the On-body Injector comes off before the full dose is delivered?

Call your healthcare provider immediately if the On-body Injector at any time comes away from your skin before your full dose delivery, **DO NOT** reapply it.

What if there is blood at my application site after the On-body Injector has been removed?

If there is blood, press a clean cotton ball or gauze pad on the application site. Apply an adhesive bandage if needed.

What if my application site is red or tender after On-body Injector removal?

Call your healthcare provider immediately if you experience persistent or worsening redness or tenderness at the application site, as this can be a sign of infection.



Neulasta® (pegfilgrastim)

Manufactured by:

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799
US License No. 1080

Patent: <http://pat.amgen.com/neulasta/>

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www.neulasta.com

1-844-MYNEULASTA (1-844-696-3852) Issued: 11/2015 vX

Patient Information
Neulasta® (nu-las-tah)
(pegfilgrastim)
injection
On-body Injector for Neulasta

Read this Patient Information before you receive Neulasta and each time you receive Neulasta with the On-body Injector for Neulasta. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I need to know about receiving Neulasta with the On-body Injector for Neulasta?

- **See the Instructions for Use for the On-body Injector for Neulasta for detailed information about the On-body Injector for Neulasta and important information about your dose delivery that has been written by your healthcare provider.**
 - o Know the time that delivery of your dose of Neulasta is expected to start.
 - o Avoid traveling, driving, or operating heavy machinery during hour 26 through hour 29 after the On-body Injector for Neulasta is applied. Avoid activities and places that may interfere with monitoring during the **45-minute** period that Neulasta is expected to be delivered by the On-body Injector for Neulasta, and for 1 hour after delivery.
- A caregiver should be with you the first time that you receive Neulasta with the On-body Injector for Neulasta.
- **If you have an allergic reaction during the delivery of Neulasta, remove the On-body Injector for Neulasta by grabbing the edge of the adhesive pad and peeling off the On-body Injector for Neulasta. Get emergency medical help right away.**
- **You should only receive a dose of Neulasta on the day your healthcare provider tells you.**
- **You should not receive your dose of Neulasta any sooner than 24 hours after you finish receiving your chemotherapy.** The On-body Injector for Neulasta is programmed to deliver your dose about 27 hours after your healthcare provider places the On-body Injector for Neulasta on your skin.
- **Do not** expose the On-body Injector for Neulasta to the following because the On-body Injector for Neulasta may be damaged and you could be injured:
 - MRI
 - X-ray
 - CT-Scan
 - Ultrasound
 - Oxygen rich environments, such as hyperbaric chambers

- Avoid airport X-ray scans. Request a manual pat down instead. Use care during a manual pat down to help prevent the On-body Injector for Neulasta from being accidentally removed.
- **Keep the On-body Injector for Neulasta at least 4 inches away from electrical equipment such as cell phones, cordless telephones, microwaves and other common appliances.** If the On-body Injector for Neulasta is too close to electrical equipment, it may not work correctly and can lead to a missed or incomplete dose of Neulasta.
- The On-body Injector is for adult patients only.
- **Call your healthcare provider right away if the:**
 - On-body Injector for Neulasta comes off before or during a dose delivery. **Do not re-apply it.**
 - On-body Injector for Neulasta is leaking.
 - adhesive on your On-body Injector for Neulasta becomes noticeably wet (saturated) with fluid, or there is dripping. This may mean that Neulasta is leaking out of your On-body Injector for Neulasta. If this happens you may only receive some of your dose of Neulasta, or you may not receive a dose at all.
 - On-body Injector for Neulasta status light is flashing red.

What is Neulasta?

Neulasta is a prescription medicine used to help reduce the chance of infection due to a low white blood cell count, in people with certain types of cancer (non-myeloid), who receive anti-cancer medicines (chemotherapy) that can cause fever and low blood cell count.

Who should not take Neulasta?

Do not take Neulasta if you have had a serious allergic reaction to pegfilgrastim (Neulasta®) or to filgrastim (Neupogen®).

What should I tell my healthcare provider before receiving Neulasta?

Before you receive Neulasta, tell your healthcare provider if you:

- have sickle cell trait or sickle cell disease
- have had severe skin reactions to acrylic adhesives
- are allergic to latex
- have problems with your kidneys
- have any other medical problems
- are pregnant or plan to become pregnant. It is not known if Neulasta may harm your unborn baby.

Pregnancy Registry: There is a pregnancy registry for women who become pregnant during treatment with Neulasta. The purpose of this registry is to collect information about the health of you and your baby. You are encouraged to enroll in this registry. Your healthcare provider may enroll you, or you may enroll by calling 1-800-AMGEN (1-800-772-6436).

- are breastfeeding or plan to breastfeed. It is not known if Neulasta passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive Neulasta?

See the Instructions for Use for detailed information about how you will receive a dose of Neulasta with the On-body Injector for Neulasta, and how to remove and dispose of the On-body Injector for Neulasta.

- **See the section “What is the most important information I need to know about receiving Neulasta with the On-body Injector for Neulasta?”**
- Neulasta is given as an injection under the skin (subcutaneous). Your healthcare provider will use a prefilled syringe with Neulasta to fill the On-body Injector prior to applying it. The prefilled syringe with Neulasta and the On-body Injector are provided to your healthcare provider as part of Neulasta Onpro™ kit. The On-body Injector for Neulasta will be applied to the stomach area (abdomen) or back of your arm by your healthcare provider. If the On-body Injector for Neulasta was placed on the back of your arm, a caregiver must be available to monitor the On-body Injector for Neulasta.
- Your healthcare provider should place the On-body Injector for Neulasta on an area of your skin that does not have swelling, redness, cuts, wounds, or abrasions. Tell your healthcare provider about any skin reactions that happen in the On-body Injector for Neulasta application area after it has been applied.
- The On-body Injector for Neulasta is programmed to deliver your dose about 27 hours after your healthcare provider places the On-body Injector for Neulasta on your skin.
- The dose of Neulasta will be delivered over about 45 minutes. During dose delivery and for 1 hour after delivery, it is best to stay in a place where you or a caregiver can monitor the On-body Injector for Neulasta to make sure you receive your full dose of Neulasta and watch for symptoms of an allergic reaction.
- Keep the On-body Injector for Neulasta dry for about the last 3 hours before the dose delivery is expected to start. This will help you to better detect possible leaking from the On-body Injector for Neulasta.
- Only expose the On-body Injector for Neulasta to temperatures between 41°F to 104°F (5°C to 40°C).

What should I avoid while the On-body Injector for Neulasta is in place?

While the On-body Injector for Neulasta is in place you should avoid:

- traveling, driving or operating heavy machinery during hour 26 through hour 29 after the On-body Injector for Neulasta is applied.

- sleeping on the On-body Injector for Neulasta or applying pressure on the On-body Injector for Neulasta. The On-body Injector for Neulasta may not work properly.
- bumping the On-body Injector for Neulasta or knocking it off your body.
- getting body lotion, creams, oils, and skin cleansing products near the On-body Injector for Neulasta. These products may loosen the adhesive that holds the On-body Injector for Neulasta onto your body.
- using hot tubs, whirlpools, or saunas, and direct sunlight. These may affect Neulasta.
- peeling off or disturbing the On-body Injector for Neulasta adhesive before you receive your full dose of Neulasta.

What are possible side effects of Neulasta?

Neulasta can cause serious side effects, including:

- **Spleen rupture.** Your spleen may become enlarged or may rupture during treatment with Neulasta. A ruptured spleen can cause death. Call your healthcare provider right away if you have pain in your left upper stomach area or left shoulder area. This pain could mean your spleen is enlarged or ruptured.
- **A serious lung problem called Acute Respiratory Distress Syndrome (ARDS).** Call your healthcare provider or get emergency medical help right away if you get any of these symptoms of ARDS: fever, shortness of breath, trouble breathing, or a fast rate of breathing.
- **Serious allergic reactions.** Get emergency medical help right away if you get any of these symptoms of a serious allergic reaction with Neulasta: shortness of breath, wheezing, dizziness, swelling around the mouth or eyes, fast pulse, sweating, and hives.

If you have an allergic reaction during the delivery of Neulasta, remove the On-body Injector for Neulasta by grabbing the edge of the adhesive pad and peeling off the On-body Injector for Neulasta. Get emergency medical help right away.

- **Sickle cell crises.** Severe sickle cell crises, and sometimes death, can happen in people with sickle cell trait or disease who receive filgrastim, a medicine similar to Neulasta (pegfilgrastim).
- **Kidney injury (glomerulonephritis).** Kidney injury has been seen in patients who received Neulasta. You should notify your healthcare provider right away if you experience puffiness in your face or ankles, blood in your urine or brown colored urine or you notice you urinate less than usual.
- **Increased white blood cell count (leukocytosis).** Your doctor will check your blood during treatment with Neulasta.

- **Capillary Leak Syndrome.** Neulasta can cause fluid to leak from blood vessels into your body's tissues. This condition is called "Capillary Leak Syndrome" (CLS). CLS can quickly cause you to have symptoms that may become life-threatening. Get emergency medical help right away if you develop any of the following symptoms:
 - o swelling or puffiness and are urinating less often
 - o trouble breathing
 - o swelling of your stomach-area (abdomen) and feeling of fullness
 - o dizziness or feeling faint
 - o a general feeling of tiredness

The most common side effect of Neulasta is pain in the bones and in your arms and legs.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Neulasta. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of Neulasta

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. If you would like more information about Neulasta, talk with your healthcare provider or pharmacist. You can ask your pharmacist for information about Neulasta that is written for health professionals.

For more information, go to www.neulasta.com or call 1-844-696-3852 (1-844-MYNEULASTA).

What are the ingredients in Neulasta?

Active ingredient: pegfilgrastim

Inactive ingredients: acetate, polysorbate 20, and sodium, sorbitol in Water for Injection.

This Patient Information has been approved by the U.S. Food and Drug Administration.



Neulasta® (pegfilgrastim)

Manufactured by:

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799
US License No. 1080

Patent: <http://pat.amgen.com/neulasta/>

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www.neulasta.com

1-844-MYNEULASTA (1-844-696-3852)

Issued: 11/2015

vX

Neulasta®

Pegfilgrastim

Information for Patients and Caregivers

This patient package insert provides information and instructions for people who will be receiving Neulasta or their caregivers. This patient package insert does not tell you everything about Neulasta. You should discuss any questions you have about treatment with Neulasta with your doctor.

What is Neulasta?

Neulasta is a man-made form of granulocyte colony-stimulating factor (G-CSF), which is made using the bacteria *Escherichia coli*. G-CSF is a substance produced by the body. It stimulates the growth of neutrophils (**nu**-tro-fils), a type of white blood cell important in the body's fight against infection.

Who should not take Neulasta?

Do not take Neulasta if you have had:

- A serious allergic reaction to Neulasta® (pegfilgrastim) or to Neupogen® (filgrastim).

What important information do I need to know about receiving Neulasta?

Occasionally, pain and redness may occur at the injection site. If there is a lump, swelling, or bruising at the injection site that does not go away, talk to the doctor.

Neulasta should only be injected on the day the doctor has determined and should not be injected until approximately 24 hours after receiving chemotherapy.

If your child weighs less than 45 kg, do not use the prefilled syringe for direct administration of Neulasta. The Neulasta prefilled syringe is not designed to allow for direct administration of doses less than 6 mg.

The needle cover on the single-use prefilled syringe contains dry natural rubber (latex), which should not be handled by persons sensitive to this substance.

What should I tell my healthcare provider before taking Neulasta?

If you have a sickle cell disorder, make sure that your doctor knows about it before you start using Neulasta. If you have a sickle cell crisis after getting Neulasta, tell your doctor right away.

If you have a problem with your kidneys, make sure that your doctor knows about it before you start using Neulasta as you may need more frequent urine tests.

If you have any questions, talk to your doctor.

Why am I given Neulasta if I was exposed to radiation?

Exposure to high levels of radiation damages bone marrow. Damage to the bone marrow can be deadly. Neulasta increases your chance of survival.

Effectiveness of Neulasta in increasing survival after radiation exposure was only studied in animals. Neulasta given after deadly radiation levels could not be studied in people.

What are possible serious side effects of Neulasta?

- **Spleen Rupture.** Your spleen may become enlarged and can rupture while taking Neulasta. A ruptured spleen can cause death. The spleen is located in the upper left section of your stomach area. Call your doctor right away if you have pain in the left upper stomach area or left shoulder tip area. This pain could mean your spleen is enlarged or ruptured.
- **A serious lung problem called Acute Respiratory Distress Syndrome (ARDS).** Call your doctor or seek emergency care right away if you have shortness of breath, trouble breathing, or a fast rate of breathing.
- **Serious Allergic Reactions.** Neulasta can cause serious allergic reactions. These reactions can cause shortness of breath, wheezing, dizziness, swelling around the mouth or eyes, fast pulse, sweating, and hives. If you start to have any of these symptoms, call your doctor or seek emergency care right away. If you have an allergic reaction during the injection of Neulasta, stop the injection. Call your doctor right away.
- **Sickle Cell Crises.** You may have a serious sickle cell crisis if you have a sickle cell disorder and take Neulasta. Serious and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving filgrastim, a medicine similar to Neulasta (pegfilgrastim). Call your doctor right away if you have symptoms of sickle cell crisis such as pain or difficulty breathing.
- **Kidney injury (glomerulonephritis).** Kidney injury has been seen in patients who received Neulasta. Call your doctor right away if you experience puffiness in your face or ankles, blood in your urine or brown colored urine or you notice you urinate less than usual.
- **Increased white blood cell count (leukocytosis).** Your doctor will check your blood during treatment with Neulasta.
- **Capillary Leak Syndrome.** Neulasta can cause fluid to leak from blood vessels into your body's tissues. This condition is called "Capillary Leak Syndrome" (CLS). CLS can quickly cause you to have symptoms that may become life-threatening. Get emergency medical help right away if you develop any of the following symptoms:
 - swelling or puffiness and are urinating less often
 - trouble breathing
 - swelling of your stomach-area (abdomen) and feeling of fullness
 - dizziness or feeling faint
 - a general feeling of tiredness

What are the most common side effects of Neulasta?

The most common side effect you may experience is aching in the bones and muscles. If this happens, it can usually be relieved with a non-aspirin pain reliever, such as acetaminophen.

What about pregnancy or breastfeeding?

Neulasta has not been studied in pregnant women, and its effects on unborn babies are not known. If you take Neulasta while you are pregnant, it is possible that small amounts of it may get into your baby's blood. It is not known if Neulasta can get into human breast milk. If you are pregnant, plan to become pregnant, think you may be pregnant, or are breastfeeding, you should tell your doctor before using Neulasta. If you become pregnant during Neulasta treatment, you are encouraged to enroll in Amgen's Pregnancy Surveillance Program. You should call 1-800-77-AMGEN (1-800-772-6436) to enroll.

HOW TO PREPARE AND GIVE A NEULASTA INJECTION

If your child weighs less than 45 kg, do not use the prefilled syringe for direct administration of Neulasta. The Neulasta prefilled syringe is not designed to allow for direct administration of doses less than 6 mg.

Neulasta is provided in a prefilled syringe. **Neulasta should be stored in its carton to protect from light until use.** If you are giving someone else Neulasta injections, it is important that you know how to inject Neulasta. Before getting your Neulasta injection, always check to see that:

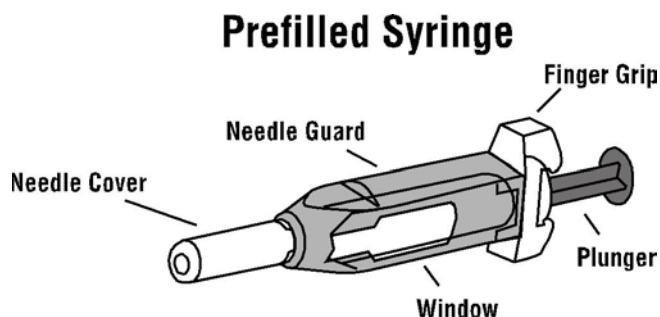
- The name Neulasta appears on the carton and prefilled syringe label.
- The expiration date on the prefilled syringe has not passed. **You should not use a prefilled syringe after the date on the label.**
- The Neulasta liquid should always be clear and colorless. Do not use Neulasta if the contents of the prefilled syringe appear discolored or cloudy, or if the prefilled syringe appears to contain lumps, flakes, or particles.

IMPORTANT: TO HELP AVOID POSSIBLE INFECTION, YOU SHOULD FOLLOW THESE INSTRUCTIONS.

Setting up for an injection

Note: The needle cover on the single-use prefilled syringe contains dry natural rubber (latex), which should not be handled by persons sensitive to this substance.

1. Find a clean, flat working surface, such as a table.
2. Remove the carton containing the prefilled syringe of Neulasta from the refrigerator. Allow Neulasta to reach room temperature (this takes about 30 minutes). Remove the syringe from the carton before injection. Each prefilled syringe should be used only once. **DO NOT SHAKE THE PREFILLED SYRINGE.** Shaking may damage Neulasta. If the prefilled syringe has been shaken vigorously, the solution may appear foamy and it should not be used.
3. Assemble the supplies you will need for an injection:
 - Neulasta prefilled syringe with transparent (clear) plastic blue needle guard attached



- An alcohol swab and a cotton ball or gauze

Alcohol Swab



Cotton Ball



- Puncture-proof disposal container

4. Wash your hands with soap and warm water.

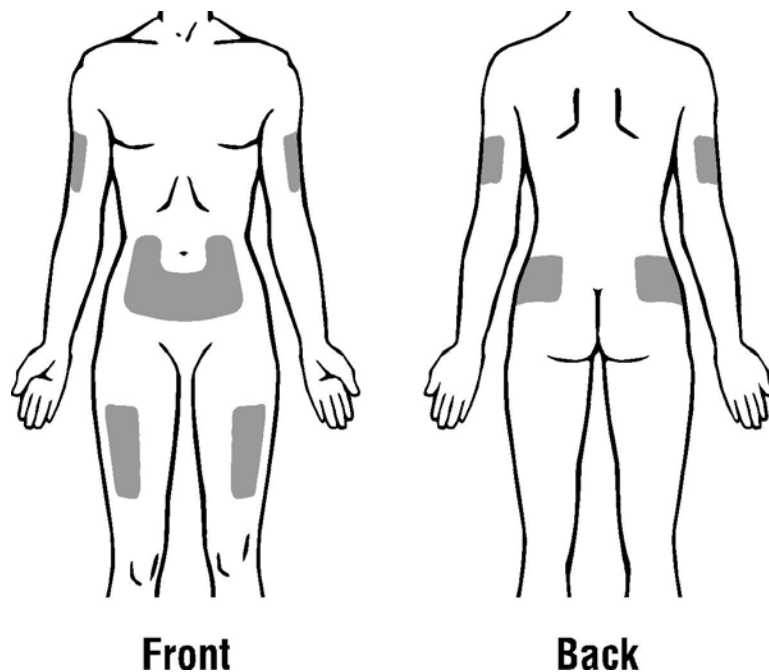


HOW TO PREPARE FOR INJECTION OF NEULASTA

5. Remove the prefilled syringe from the package and the tray. Check to see that the plastic blue needle guard is covering the barrel of the glass syringe. **DO NOT** push the blue needle guard over the needle cover before injection. This may activate or lock the needle guard. If the blue needle guard is covering the needle that means it has been activated. **DO NOT** use that syringe. Dispose of that syringe in the puncture-proof disposal container. Use a new prefilled syringe. **Do not activate the needle guard prior to injection.**
6. Hold the syringe barrel through the needle guard windows with the needle pointing up. Holding the syringe with the needle pointing up helps to prevent medicine from leaking out of the needle. Carefully pull the needle cover straight off.
7. Check the syringe for air bubbles. If there are air bubbles, gently tap the syringe with your fingers until the air bubbles rise to the top of the syringe. Slowly push the plunger up to force the air bubbles out of the syringe.
8. Gently place the prefilled syringe with the window flat on your clean working surface so that the needle does not touch anything.

Selecting and preparing the injection site

9. Choose an injection site. Four recommended injection sites for Neulasta are:
 - The outer area of the upper arms
 - The abdomen, except for the two-inch area around the navel
 - The front of the middle thighs
 - The upper outer areas of the buttocks

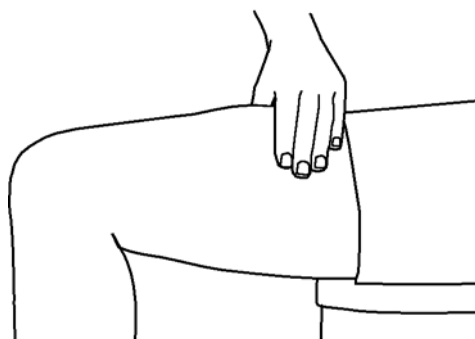


10. Clean the injection site with an alcohol swab.

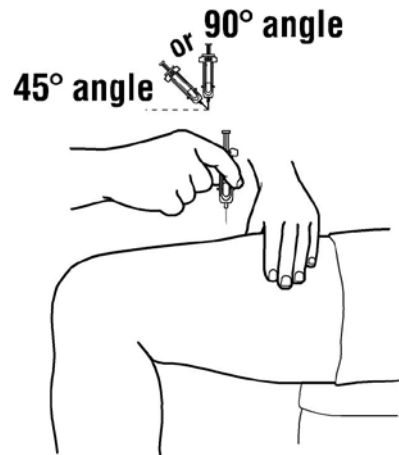


Injecting the dose of Neulasta

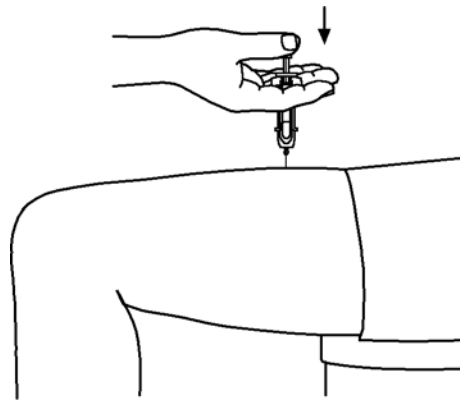
11. Pick up the prefilled syringe from your clean, flat working surface by grabbing the sides of the needle guard with your thumb and forefinger.
12. Hold the syringe in the hand you will use to inject Neulasta. Use the other hand to pinch a fold of skin at the cleaned injection site. Note: Hold the syringe barrel through the needle guard windows when giving the injection.



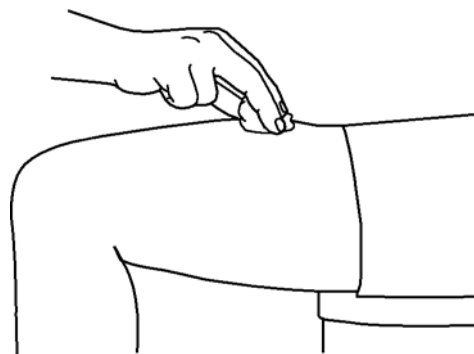
13. Holding the syringe like a pencil, use a quick “dart-like” motion to insert the needle either straight up and down (90 degree angle) or at a slight angle (45 degrees) into the skin.



14. Inject the prescribed dose subcutaneously as directed by your doctor, nurse, or pharmacist.



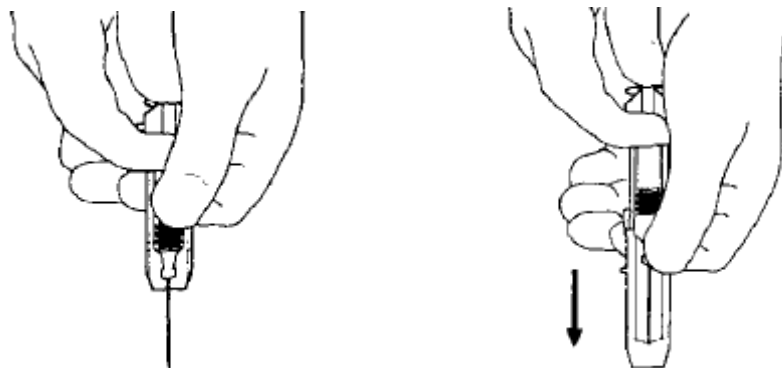
15. When the syringe is empty, pull the needle out of the skin and place a cotton ball or gauze over the injection site and press for several seconds.



16. Use a prefilled syringe with the needle guard only once.

Activating the Needle Guard after the injection has been given

17. After injecting Neulasta from the prefilled syringe, do not recap the needle. Keep your hands behind the needle at all times. While holding the clear plastic finger grip of the syringe with one hand, grasp the blue needle guard with your free hand and slide the blue needle guard over the needle until the needle is completely covered and the needle guard clicks into place. **NOTE: If an audible click is not heard, the needle guard may not be completely activated.**



18. Place the prefilled syringe with the activated needle guard into a puncture-proof container for proper disposal as described below.

Disposal of prefilled syringes and needle guards

You should always follow the instructions given by your doctor, nurse, or pharmacist on how to properly dispose of containers with used syringes and needle guards. There may be special state and local laws for disposal of used needles and syringes.

- Do not throw the container in the household trash. Do not recycle.
- DO NOT put the needle cover (the cap) back on the needle.
- Place all used needle covers and syringes in a hard plastic container with a screw-on cap or in a metal container with a plastic lid such as a coffee can labeled “used syringes.” If a metal container is used, cut a small hole in the plastic lid and tape the lid to the metal container. If a hard plastic container is used, always screw the cap on tightly after each use.
- Do not use glass or clear plastic containers.
- When the container is full, tape around the cap or lid to make sure the cap or lid does not come off.
- **Always** keep the container out of the reach of children.

How should Neulasta be stored?

Neulasta should be stored in the refrigerator at 2° to 8°C (36° to 46°F), but not in the freezer. Neulasta should be protected from light, so you should keep it in its carton until you are ready to use it. Avoid shaking Neulasta. If Neulasta is accidentally frozen, allow it to thaw in the refrigerator before injecting. However, if it is frozen a second time, do not use. Neulasta can be left out at room temperature for up to 48 hours. Do not leave Neulasta in direct sunlight. For all questions about storage, contact your doctor, nurse, or pharmacist.

What are the ingredients in Neulasta?

Each syringe contains pegfilgrastim in a sterile, clear, colorless, preservative-free solution containing acetate, sorbitol, polysorbate 20, and sodium.

AMGEN®

Neulasta® (pegfilgrastim)

Manufactured by:

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

Patent: <http://pat.amgen.com/neulasta/>

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www.neulasta.com

1-800-77-AMGEN (1-800-772-6436)

Revised: 11/2015

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125031Orig1s180

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	11/10/2015
From	Libero Marzella MD, PhD
Subject	Division Director Summary Review
BLA #	125031
Supplement #	180
Applicant Name	Amgen Inc.
Date of Submission	02/13/2015
PDUFA Goal Date	11/15//2015
Proprietary Name / Established (USAN) Name	Neulasta PEG Filgrastim
Dosage Form / Strengths/ Route of Administration	Injection Single use prefilled syringe for manual use 6mg/0.6 mL Subcutaneous injection
Indication	Increase survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic sub-syndrome of acute radiation syndrome)
Action	Approval

Material Reviewed OND Action Package, including:	Names of discipline reviewers
Medical Officer Review 10/14/2015	William Dickerson, MD
Pharmacology Toxicology Review 10/21/2015	Yanli Ouyang, PhD
Statistical Review 11/02/2015	Lan Huang, PhD
Clinical Pharmacology Review OCP/DCP-V, DPM 10/26/2015	Lian Ma, PhD
Consultative Reviews: -Clinical OHOP/DHP 08/06/2015, 11/06/2015	Patricia Dinndorf, MD
-Drug Utilization OSE/DEP-II 10/08/2015	Kusum Mistry, PharmD
-FAERS OSE/DPV-II 08/27/2015	Kathleen Phelan, RPh
Labeling Reviews: DMIP	Nushin Todd, MD
OSE/DMEPA 10/23/2015	Ebony Ayres, PharmD
OND/DPMH 11/06/2015	Erica Radden, MD
Cross Discipline Team Leader Summary 10/30/2015	Alex Gorovets, MD

DCP-V = Division of Clinical Pharmacology V
 DEP-II = Division of Epidemiology II
 DHP = Division of Hematology Products
 DMEPA = Division of Medication Error Prevention and Analysis
 DMIP = Division of Medical Imaging Products
 DPM = Division of Pharmacometrics
 DPMH = Division of Pediatric and Maternal Health
 DPV-II = Division of Pharmacovigilance II
 FAERS = FDA Adverse Event Reporting System
 OCP = Office of Clinical Pharmacology
 OHOP = Office of Hematology and Oncology Products
 OND = Office of New Drugs
 OPDP = Office of Prescription Drug Promotion
 OSE = Office of Surveillance and Epidemiology

1. Introduction

Product

Neulasta (Pegfilgrastim) is a covalent conjugate of recombinant methionyl human

granulocyte colony-stimulating factor (r-metHuG-CSF, Filgrastim) and monomethoxypolyethylene glycol. Filgrastim is a 175 amino acid protein with an amino acid sequence identical to G-CSF (except for an N-terminal methionine). Endogenous human G-CSF is produced by monocytes, fibroblasts and endothelial cells and regulates the production of neutrophils in the bone marrow by affecting the proliferation, differentiation, and functions of neutrophil precursor cells.

Pegfilgrastim and Filgrastim are classified pharmacologically as leukocyte growth factors. The mechanism of action of these drugs is based on the same biological activity. Both drugs bind to specific cell surface receptors thereby stimulating proliferation, differentiation, commitment, and end cell functional activation. Pegfilgrastim has a half-life ranging from 15 to 80 hours after subcutaneous injection whereas the half-life of Filgrastim ranges from 2 to 4 hours. Neulasta is supplied in a prefilled single-use syringe for manual use. The syringe contains 6 mg pegfilgrastim in 0.6 ml.

Objective

This review summarizes my assessment of the approvability of the efficacy supplement submitted on 2/13/2015 by Amgen Inc. (the Applicant) to add an indication for use of Neulasta in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic sub-syndrome of acute radiation syndrome) to increase survival. Neulasta is indicated for use in patients with cancer receiving myelosuppressive chemotherapy.

Clinical considerations

The lethal form of the hematopoietic syndrome of acute radiation syndrome manifests after acute radiation exposure > 2 Gy with the sequelae of myelosuppression namely neutropenia, thrombocytopenia, and anemia that can result in death from infection and bleeding. The onset and severity of the hematopoietic sub-syndrome (HS) is dependent on the radiation absorbed dose and on concomitant conditions such as traumatic or burn injury and internal contamination with radioactive material. Acute radiation syndrome (ARS) following radiation absorbed doses > 10 Gy is uniformly fatal. Survival following HS-ARS is dependent on the recovery of the hematopoietic stem and progenitor cells so that production of mature, functional neutrophils, and platelets can occur.

Neutrophil recovery is inversely related to radiation exposure and can occur 3 to 4 weeks following radiation exposure. G-CSF (Filgrastim) acts by enhancing neutrophil recovery and Filgrastim is indicated in patients receiving myelosuppressive chemotherapy, or undergoing bone marrow transplantation or progenitor cell mobilization, as well as patients with idiopathic neutropenia. Filgrastim is the only drug indicated for treatment of the hematopoietic sub-syndrome of ARS. Supportive care consisting of fluid and nutritional support and specific treatment with antimicrobials and blood products (platelets and erythrocytes) is an important aspect of the clinical management of patients with bone marrow suppression. Full supportive care has been used in non-human primate models of ARS to evaluate the efficacy of leukocyte growth factors. Supportive care increases survival in animal models of ARS and may be important for supplementing the lineage specific effects of G-CSF (see FDA pharmacology/toxicology review by Dr. Ouyang).

Leukocyte growth factors (G-CSF and GM-CSF) are approved for use to reduce severe neutropenia and its sequelae include G-CSFs filgrastim (neupogen), tbo-filgrastim (Granix), filgrastim-sndz (Zarxio), and pegfilgrastim (Neulasta); and GM-CSF sargramostim (Leukine).

2. Background

Regulatory considerations

Priority review. This supplemental application was granted priority review designation because the proposed use of Neulasta in patients acutely exposed to myelosuppressive radiation would fill an unmet medical need. Neulasta is expected to provide a practical advantage in a mass casualty nuclear or radiation incident because the prolonged duration of action of the drug allows for administration of two drug doses one week apart. Neupogen on the other hand requires daily administration with monitoring of absolute neutrophil counts (ANC).

Sources of data. Efficacy studies of Neulasta could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. The review of the present BLA supplement relied on efficacy studies conducted in animals under the Animal Rule and on data supporting Neulasta's effect on severe neutropenia in patients with cancer receiving myelosuppressive chemotherapy. The Agency also relied on a drug utilization review, a review of the scientific literature, a review of FAERS (FDA Adverse Event Reporting System) and results of population modeling and simulation for assessment of safety and extrapolation of efficacy of Neulasta in pediatric patients.

Applicant's right of reference. The Applicant provided a letter of authorization that granted them the right of reference to animal efficacy studies sponsored by the National Institute of Allergy and Infectious Diseases (NIAID). Through this authorization FDA reviewed the reports already submitted by NIAID to their (b)(4) and relied on these data for the assessment of the changes to the Neulasta labeling proposed by the Applicant.

Orphan drug designation. Neulasta received orphan drug designation on November 20, 2013 for the proposed use of treatment of subjects at risk of developing myelosuppression after a radiological or nuclear incident. Therefore, this application is exempt from requirements under the Pediatric Equity Research Act.

Pre-EUA. The Biomedical Advanced Research and Development Authority (BARDA) submitted a Pre-Emergency Use Authorization (Pre-EUA) request for consideration for Neulasta on 2/21/13. An approval action for this supplement obviates the need of a EUA.

Indicated population. Neulasta was first approved in 2002 and is presently indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Product presentation. Neulasta is supplied as a single-use prefilled syringe containing 6 mg/0.6 mL. The syringe lacks graduation marks that would allow for the direct administration of doses less than 0.6 mL (6 mg). Therefore, preparation and dispensing of Neulasta for indirect administration to pediatric patients weighing less than 45 kg require manipulation of the prefilled syringe or dose approximation, posing the risk of medication errors. Development of a pediatric dosing recommendations in the absence of a suitable drug presentation was an important issue in the review of the supplement.

Animal rule. Approval of a marketing application under the animal rule requires that the following four requirements are met. I concur with the unanimous assessment by the FDA reviewers in the following disciplines: clinical, pharmacology toxicology, clinical pharmacology and statistics that

the Applicant has met the following requirements.

1. *Reasonably well-understood pathophysiological mechanism of radiation injury and biological plausibility for pegfilgrastim efficacy.* The pathophysiological mechanism of radiation injury and the mechanism of action of G-CSFs are well understood. Radiation injures rapidly dividing cells including neutrophil progenitor cells. Animal models of the hematopoietic sub-syndrome of acute radiation syndrome are characterized primarily by bone marrow suppression with consequent neutropenia, thrombocytopenia, anemia and mortality. The myelosuppression in the animal models is similar to the myelosuppression induced by chemotherapy in patients with cancer. G-CSFs are lineage specific and accelerate the recovery of severe neutropenia in animals and humans. G-CSFs are not species specific and Filgrastim and Pegfilgrastim have been studied in various animal models of acute radiation injury.
2. *The treatment effect is demonstrated in more than one animal species expected to react with a response predictive for humans.* The unanimous assessment by the pharmacology/toxicology, clinical and statistical reviewers (Drs. Ouyang, Dickerson, and Huang) is that a survival benefit of Pegfilgrastim has been demonstrated in an adequate and well controlled efficacy study in non-human primates (NHP) who received one dose of Pegfilgrastim 20-26 hours after total body irradiation and a second dose on day 8. The NHP received supportive medical care and were euthanized according to pre-specified veterinary care criteria.

Furthermore, studies in (b)(4) mice in a murine animal model of total-body or partial-body irradiation also demonstrated a survival benefit of Pegfilgrastim compared to untreated controls (see pharmacology toxicology review by Dr. Ouyang).

3. *The nonhuman primate study efficacy endpoint (overall survival at 60 days post total body irradiation) is directly related to the desired benefit in humans.* See the clinical review by Dr. Dickerson for a detailed discussion of the clinical relevance of the animal model and the efficacy outcomes. In addition to improved survival a key secondary pharmacodynamic endpoint, namely duration of severe neutropenia, was also met by the NHP studies of Filgrastim and Pegfilgrastim. In the treated animals both drugs improved the time to recovery of neutrophil counts compared to untreated control animals.
4. *The pharmacokinetic (PK) and pharmacodynamic (PD) data from nonhuman primates and humans allow selection of an effective dose in humans.* The supplemental application contains a comprehensive population model that integrates the neutrophil counts and survival data for nonhuman primates treated with pegfilgrastim, and the pharmacokinetic and the neutrophil counts data from adult and pediatric patients, and data from healthy volunteers receiving pegfilgrastim. Using the developed model, simulations were conducted with multiple scenarios to predict the effect of radiation exposure and pegfilgrastim treatment on neutrophil counts and survival in humans. See the clinical pharmacology review by Dr. Ma for a summary of the data and independent simulations based on a modified PK/PD model. The results of these simulations and risk/benefit consideration led to the conclusion that two 6 mg doses of Pegfilgrastim administered one-week apart should be recommended in the labeling.

2. CMC

This section is not applicable. No new data on product quality or microbiological quality were provided and none were needed.

3. Nonclinical Pharmacology/Toxicology

I concur with the recommendation by the FDA reviewer Dr. Ouyang that this supplemental application be approved from the pharmacology/toxicology perspective based on animal efficacy studies for which the Applicant has a right of reference. No new preclinical safety data was provided and none is needed.

Dr. Ouyang considers the NHP model used in the efficacy studies to be reliable and finds the results of the principal efficacy study convincing. The study was titled “AXG21: A 60-Day Efficacy Study of Subcutaneous Pegfilgrastim (Neulasta) to Treat the ARS-HS Following an LD50/60 of TBI in Rhesus Macaques.” The study was performed at a single laboratory, did not include PK measurements and was not designed to evaluate gender differences in treatment outcomes. However, no gender-related differences have been observed in PK of pegfilgrastim in human and in other animal studies.

The study was designed as a two arms, randomized, and blinded study and overall survival was the primary endpoint. The study was conducted under GLP. Male rhesus macaques were exposed to LD_{50/60} TBI. The treatment arm received Neulasta (300 mcg/kg/week x two doses starting 20-26 hours after radiation). Both arms received veterinary care guided by clinical observations and laboratory data. Care consisted of analgesics, anti-ulceratives, anti-diarrheals, anti-emetics, antibiotics, anti-pyretics, nutritional support, hydration fluids, and blood transfusions. The planned interim analysis showed that Neulasta improved survival (91% (21/23) vs. 48% (11/23) in the control arm, two-sided Chi-square test, $p = .0014$).

Dr. Ouyang also cites the following studies in NHP and murine models of ARS as supportive evidence of mechanism of action and efficacy of pegfilgrastim.

1. Study AXG15, the pivotal study for the approval of Filgrastim for HS-ARS. In this study NHP received a total body irradiation dose of 7.5 Gy, delivered at a rate of 0.8 Gy/min using a 6 MV linear accelerator radiation source. The animals received supportive care consisting of intravenous fluids, antimicrobials and blood products. Filgrastim (10 mcg/kg daily SC) at 0.023 level of significance increased 60-day overall survival. Survival was 79% (19/24) in the Filgrastim group compared to 41% (9/22) in the control group.
2. Mouse screening or pilot efficacy studies conducted under (b)(4) and for which summary reports were provided. The Applicant acquired a letter of authorization to allow FDA to use the information to support the present BLA efficacy supplement.
 - a) *ES1152 (ES2014.203): Effects of Neulasta on survival end points using the PBI BM2.5 model in (b)(4) mice (N=60) without antibiotic support.* In this partial body irradiation model Neulasta increased overall survival compared to control. Thirty day survival rates post 13 Gy PBI were 80%, 50% or 20% in 1mg/kg Neulasta, 0.1 mg/kg Neulasta, or vehicle control groups, respectively. The rates post 13.5 Gy PBI were 45%, 25% or 5%, respectively.

- b) *ES1151: The effect of Neulasta on survival end points using the TBI model in (b)(4) mice with antibiotic supportive care.* This study used a similar design to study ES1152. Neulasta did not increase survival after 13Gy or 14Gy TBI. No animal survived beyond day 13.
- c) *IU2013.225M [N=44] and IU2013.239M [N= 110]: Hematopoietic Screening Assay for Radio mitigating Activity of 2 doses of Subcutaneously Administered Neulasta (1 mg/kg on days 1 and 8) after Exposure to the LD50/30 Dose of Radiation (b)(4) Mice (b)(4).* Pooled data from the two studies showed that Neulasta, at 1 mg/kg subcutaneously administered at 24+4 hr. and on Day 8 post LD50/30 TBI, significantly increased survival compared to vehicle controls (76.9% (40/52) vs. 33.3% (34/102).

Finally Dr. Ouyang summarizes the following three key reports from the literature among the publications submitted by the Applicant to the sBLA.

1. *NHP study by Farese et al. Radiat. Res. 178: 403–413, 2012.* In this study NHP received an LD10/30 dose of TBI with supportive care and pegfilgrastim (300 mcg/kg) either on Day 1 or Days 1 and 7 post TBI, or filgrastim (10 mcg/kg/daily starting on Day 1 post TBI and continued till neutrophil recovery. Pegfilgrastim on Days 1 and 7 was superior to pegfilgrastim on Day 1 and to daily filgrastim in improving neutrophil recovery.
2. *Murine study by Chua et al. Health Phys. 106: 21-38, 2014.* In this study the activity of two different pegylated G-CSF (MAXYG34 and Neulasta) was evaluated in a mouse (C57BL/6) model of lethal H-ARS. Only the outcomes of Neulasta relative to control are presented here. Neulasta (1 mg/kg) increased survival in mice post LD_{50/30} TBI (7.96 Gy). The same survival results were observed when Neulasta was administered either as one dose (20 to 28 hour post TBI) or two doses (Days 1 and 7 after TBI).

The survival rates were 55% (11/20) in the control arm and 95% in the Neulasta arms administered either as one dose (19/20) or two doses post TBI (19/20). Dose ranging showed similar activity of a single dose of Neulasta ranging from 0.1 to 1 mg/kg administered on Day 1 post LD_{90/30} TBI (8.7 Gy). The survival rates were 0% (0/30), 57% (17/30), 43% (13/30), and 47% (14/30) for 0 (vehicle control), 0.1, 0.3, and 1.0 mg/kg Neulasta, respectively.

3. *Murine study by Kiang et al. Oxid. Med. Cell Longev. 2014:481392, 2014.* In this publication, the effect of Neulasta on survival and neutrophil counts was evaluated in B6D2F1/J female mice. The mice were exposed to 9.5 Gy TBI and injected subcutaneously with 1 mg/kg Neulasta or vehicle on days 1, 8 and 15 post TBI (N = 20-22 per group). Neulasta increased survival 100% vs. 68% in the control arm. In addition, Neulasta increased neutrophil counts compared to control on day 30 post TBI.

Dr. Ouyang describes the lack of efficacy of filgrastim when treatment is begun 48 hours after radiation exposure. Study AXG 22 was stopped for futility when an interim analysis showed that Neupogen, (10 mcg/kg daily) at 44 to 52 hr, following a LD_{50/60} TBI, did not increase overall survival (52% vs. 50%) compared to untreated controls. Study weakness included lack of Neupogen active control group (start of treatment at 24 hr.) and imbalance in a serious viral infection favoring the untreated controls. The results of this study are concerning and further studies are warranted to

characterize the loss of LGF treatment effect with time elapsed after radiation exposure.

4. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology reviewer Dr. Ma that the efficacy supplement be approved with the recommended dosing regimen for HS-ARS of two 6 mg doses administered one-week apart in patients weighing 45 kg or more. Among patients weighing less than 45 kg, a 100 mcg/kg dose is recommended for patients weighing less than 10 kg; a weight-tiered based dosing is recommended for patients weighing from 10 kg to less than 45 kg. The dosing regimen for patients weighing less than 45 kg is also applicable to the chemotherapy-induced neutropenia indication.

The following considerations drove the selection of pegfilgrastim dose.

- The pharmacokinetics of Pegfilgrastim is not available in patients acutely exposed to myelosuppressive doses of radiation.
- The final animal rule guidance recommends the selection of human doses that provide PK exposures higher than the PK exposures observed in animals in the efficacy studies. Given the uncertainties of extrapolating efficacy from animals to humans this approach would insure that the dose for humans mimics the therapeutic effects seen in animals.
- Pharmacokinetic simulations showed that doses of Pegfilgrastim ranging from 6 to 18 mg did not exceed the PK exposures associated with the effective dose of Pegfilgrastim (300mcg/kg) used in the NHP efficacy study.
- The safety of doses of Pegfilgrastim higher than 6 mg has not been adequately evaluated. On the other hand, the 6 mg dose is considered safe in both adult patients and healthy subjects based on postmarketing experience.
- Treatment with doses of Pegfilgrastim higher than 6 mg would increase the risk of leukocytosis in a mass radiological incident setting in which reliable assessment of radiation absorbed doses is not available.
- A PD endpoint, namely duration and magnitude of severe neutropenia, was therefore chosen as the predictor for overall survival and endpoint for dose selection.

The sponsor developed a population model that included the neutrophil counts and survival for NHPs treated with pegfilgrastim, and PK and neutrophil counts primarily from adult and pediatric patients receiving Pegfilgrastim. Results of these simulations suggest that when considering the time-course of the ANC profile, doses higher than 6 mg or different dosing frequencies are unlikely to increase the 60-day survival rate (b)(4)

However when the predicted benefit in efficacy is assumed to relate to duration of severe (grade 4) neutropenia, the results of the simulations appear to support a regimen of 6 mg given at day 1 and day 8 for patients weighing 45 kg or more.

The PK/PD relationship of pegfilgrastim in pediatrics appear to be consistent with that in adults. Simulations support a dose of 100 mcg/kg in patients weighing less than 45 kg. To facilitate dispensing and administration of Pegfilgrastim in a mass casualty situation, the clinical pharmacology reviewers developed a weight tiered dosing for patients weighing between 10 and 44 kg (4 mg for 31-44 kg body weight; 2.5 mg for 21 – 30 kg; 1.5 mg for 10 - 20 kg) and showed that the PK exposures would be similar to those in adults. Among patients weighing less than 10 kg the

weight-tiered approach is undesirable because of the risk of overdosing those at the lowest end of the range of body weights and underdosing those with higher body weights. For these patients a 100 mcg/kg dose is recommended.

In the case of Neupogen, simulations conducted using a population pharmacokinetic model indicated that the exposures to Filgrastim at a dose of 10 mcg/kg in patients acutely exposed to myelosuppressive doses of radiation would exceed the exposures at a dose of 10 mcg/kg in irradiated non-human primates. This higher dose was recommended in the labeling for use in HS-ARS because the clinical safety experience for Neupogen administered at 10 mcg/kg daily and at 5 mcg/kg daily for their indicated uses was similar. In addition, literature reports of patients receiving Neupogen at a dose of 10 mcg/kg daily for the treatment of radiation accidents did not raise safety concerns.

5. Clinical Microbiology

This section is not applicable to this submission.

6. Clinical/Statistical-Efficacy

I concur with the recommendations by the statistical and clinical reviewers (Drs. Huang and Dickerson) that this supplemental application be approved. The Applicant did not provide any new clinical data and none was needed.

The efficacy of Neulasta was established in a single-center, randomized, blinded, placebo-controlled study (AXG21) in a non-human primate model of radiation injury. The FDA reviewers summarize the study as follows.

The efficacy of Neulasta for the acute radiation syndrome setting was studied in a randomized, placebo-controlled non-human primate model of radiation injury. The planned sample size was 78 animals, but the study was stopped at the interim analysis with 46 animals because of efficacy. Rhesus macaques were randomized to control (n=23) or treated (n=23) group. On study day 0, animals (n = 6 to 8 per irradiation day) were exposed to total body Irradiation of 750 ± 15 cGy delivered at 80 ± 3.0 cGy/min, representing an LD50 dose after 60 days follow-up. Pegfilgrastim significantly (p-value from exact chi-square test of $0.0031 < \text{the alpha level allocated for the interim analysis } 0.0107$) reduced 60-day mortality in the irradiated non-human primates. The statistical reviewer verified the primary efficacy analysis of study on chi-square test on the survival rate on day 60.

Dr. Huang summarizes the secondary analyses of the primary efficacy outcome as follows. The logrank test for the two Kaplan Meier survival curves (Neulasta vs. control) had a nominal p-value of 0.011, in favor of Neulasta. The Neulasta group had a hazard ratio of 0.13 (95% CI [0.03, 0.56]) compared with control group, from a Cox model with treatment as the covariate.

A mechanistically important secondary efficacy outcome, namely recovery of neutrophil counts generally favored Neulasta. During the 60 day study period, 13/23 (56%) of animals in control group and 22/23 (96%) animals in the Neulasta group recovered from $\text{ANC} < 500/\mu\text{L}$ and

ANC<1000/uL. The Neulasta group had shorter time to ANC recovery for the recovered animals. The median time to recovery to ANC ≥ 500 /uL for all animals was 27 days for control and 18 days for Neulasta. The median time to recovery to ANC ≥ 1000 /uL for all animals was 35 days for control and 20 days for Neulasta. The logrank test had nominal p-value <0.001 for the difference between the two time to recovery curves (Neulasta vs. control). The Neulasta group had fewer transfusions. The number of transfusions ranged from 1 to 7 for the control arm (average of 3), and from 0 to 5 for the Neulasta arm (average of 2).

The FDA primary reviewers and the cross-discipline reviewer (Dr. Gorovets) identify the following limitations in the efficacy data.

- Efficacy study conducted at single laboratory (deemed GLP-compliant) variability of treatment effect cannot be estimated
- Single pivotal study in single species (generally supportive studies in other species)
- Almost all studies conducted in male animals, gender-specific safety and efficacy cannot be evaluated
- Efficacy with delay in start of treatment not studied (activity for Filgrastim not shown if treatment begun 24 after radiation exposure)
- Efficacy in presence of traumatic or burn injury not known
- Efficacy in absence of supportive therapy not established
- Optimal dose selection based on limited data (further exploration desirable)
- Efficacy at various myelosuppressive doses of radiation including sub-lethal doses uncertain
- Efficacy in patients subjected to continuous radiation exposure (e.g. internal contamination) not known

The FDA reviewers also cite the following operational limitations in a radiation nuclear casualty setting:

- Reliable radiation exposure estimates to identify indicated population likely unavailable (should not delay treatment)
- Supportive care likely not immediately available (reduction in treatment response likely)

I concur with the reviewer's assessment that all the data limitations listed above do not call into question the reliability of the data or diminish the importance of the Pegfilgrastim treatment effect.

7. Safety

I concur with the clinical and cross discipline reviewers that the safety profile of Neulasta is well understood based on the pre- and post-marketing data and that the risks are acceptable for patients with ARS. It is likely that some healthy subjects will receive Neulasta in a mass casualty situation because of incorrect estimates of radiation exposure. Studies in healthy adults have shown that the safety profile of Neulasta is consistent with the profile established in the indicated populations. The risk is acceptable because of the overall survival benefit in the population with radiation-induced myelosuppression. The long term safety of Neulasta with respect to delayed manifestations of acute radiation injury is not known.

The following serious adverse reactions including fatalities are attributed to the use of Neulasta and are cited in the prescribing information: splenic rupture; acute respiratory distress syndrome; anaphylaxis and other allergic reactions; sickle crisis in patients with sickle cell disease; promotion of growth of malignant cells; cutaneous vasculitis. Leukocytosis with counts $\geq 100,000/\text{mm}^3$ has been observed. The most common reactions to Neulasta are bone pain and pain in the extremities.

8. Advisory Committee Meeting

A meeting of Advisory Committee was not considered necessary because the sBLA did not raise new scientific issues.

On May 3, 2013 FDA sought the advice of the Medical Imaging Drugs Advisory Committee (MIDAC) and the Oncologic Drugs Advisory Committee (ODAC) regarding the animal study sponsored by NIAID to assess the efficacy of Filgrastim for the treatment of acute exposure to myelosuppressive doses of radiation. The discussion at that meeting is applicable to the assessment of this sBLA and is summarized below.

The advisory committee (AC) was nearly unanimous in its opinion that Filgrastim was reasonably likely to produce clinical benefits in humans exposed to radiation following a radiological or nuclear incident. The AC felt that the pathophysiological mechanism of radiation induced bone marrow injury and its reduction by Filgrastim are understood and that growth of stem cells not killed by radiation exposure is stimulated by leukocyte growth factors (LGFs). Some committee members noted that the experience with chemotherapy induced neutropenia is applicable to radiation induced marrow injury. Committee members also agreed that the animal study survival endpoint is clearly related to a desired benefit in humans and that shortening the absolute neutrophil count recovery time is a useful supportive endpoint.

Some committee members noted that the availability of supportive care will likely affect the survival benefit of LGF administration. Additionally, it was noted that the impact of secondary injuries and the ability to treat these will also likely impact survival outcomes. Some members expressed concerns about how long the LGF therapy could be delayed before the treatment effect is lost.

There was concern that the total body irradiation carried out in the NIAID study does not replicate all the radiation exposures potentially experienced in a nuclear incident. Committee members stated that the safety of LGF administration is unclear in a situation where ongoing radiation exposure is likely.

9. Pediatrics

I concur that with the unanimous recommendations by the clinical, CTDL and clinical pharmacology reviewers (see Drs. Dickerson , Gorovets and Ma's reviews) and the consultative reviews by the Divisions of Hematology (Dr. Dinndorf) and Pediatric and Maternal Health (Dr. Radden) that Neulasta be approved for use in all pediatric patients with HS-ARS and in patients in the indicated oncology population weighing less than 45 kg.

No new pediatric data have been provided in this efficacy supplement. The approval decision is based on efficacy studies conducted in animals, clinical studies supporting the use of Neulasta in the approved indications and a pediatric efficacy and PK study in patients with sarcoma. In addition FDA conducted a review of the scientific literature (see Dr. Dinndorf's review), drug utilization review (see Dr. Mistry's review) and a review of the FAERS database (Phelan RPh) and concluded that there is evidence of utilization of Neulasta across all pediatric age groups and that there is no evidence of a difference in the safety profile of pegfilgrastim in adults and pediatric patients. Three reports of incorrect dosing in pediatric oncology patients were identified due to the lack of a suitable drug presentation for use in patients weighing less than 45 kg. The Division of Medication Error Prevention and Analysis (see review by Dr. Ayres) made a number of recommendations to revise the labeling to minimize the risk of inaccurate dosing. These recommendations including the statement that the prefilled syringe lacks graduation marks and should not be used for direct administration of drug to patients weighing less than 45 kg. These recommendations are implemented in the final labeling. DMEPA recommends pharmacovigilance reviews to assess the effect of these new labeling changes on medication errors

I conclude that that the labeling as revised provides adequate instructions for use of Neulasta in pediatric patients.

10. Other Relevant Regulatory Issues

The Applicant has agreed to provide a clinical protocol for a postmarketing study as required by the animal rule.. The protocol will be finalized after approval of this efficacy supplement according to the agreed timelines. No restrictions to ensure safe use are needed.

11. Labeling

The DMIP associate director for labeling Dr. Todd led the revisions of the prescribing information. The required information for animal efficacy studies has been added to the labeling as required by the animal rule (see appended final labeling). A finding of safety and effectiveness of Neulasta was made for pediatric patients of all ages on the basis of various data sources and analyses. Pediatric dosing and administration labeling was developed for both the ARS and the oncology indication. A proposal by the Applicant (b)(4)

12. Decision/Action/Risk Benefit Assessment

I concur with the unanimous recommendation by the FDA reviewers that this efficacy supplement be approved to provide a new indication for Neulasta to increase survival in patients acutely exposed to myelosuppressive doses of radiation (the hematologic sub-syndrome of acute radiation syndrome).

Neulasta provides for an unmet medical need in a mass casualty radiological/nuclear incident because the prolonged duration of action of the drug allows for administration of two doses one week apart. Neupogen on the other hand requires daily administration with monitoring of neutrophil counts.

The approval of this supplement is based on an adequate and well-controlled animal efficacy study and supportive studies that establish that the drug is reasonably likely to produce clinical benefit in humans. The efficacy of Neulasta was established in a single-center, randomized, blinded, placebo- controlled study in a non-human primate model of radiation injury. Neulasta increased 60-day survival; Neulasta improved survival (91% (21/23) vs. 48% (11/23) in the control arm).

Partial extrapolation of Neulasta efficacy from human data was also made. Pegfilgrastim decreases the incidence of febrile neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. Pegfilgrastim was also as effective as Filgrastim in reducing the duration of severe neutropenia caused by chemotherapy relative to historical controls not receiving LGF treatment. The finding of safety for the ARS indication relied on the demonstration of human safety in the approved indication. The safety of Neulasta is well established and serious reactions are uncommon.

The selection of the optimum dose of Neulasta for ARS is based on limited data. A human dose that provides for PK exposure greater than the exposure in the NHP efficacy studies cannot be recommended due to lack of safety data. The safety of doses of Pegfilgrastim higher than 6 mg has not been adequately evaluated. When the predicted benefit in efficacy is assumed to relate to duration of severe (grade 4) neutropenia, the results of the simulations appear to support a regimen of 6 mg given at day 1 and day 8 for patients weighing 45 kg or more.

The PK/PD relationship of Pegfilgrastim in pediatrics appears to be consistent with that in adults. Simulations support a dose of 100 mcg/kg in patients weighing less than 45 kg. To facilitate dispensing and administration of Pegfilgrastim in a mass casualty situation, a weight tiered dosing for patients weighing between 10 and 44 kg was developed. Preparation and dispensing of Neulasta for the indirect administration to patients weighing less than 45 kg will require manipulation of the prefilled syringe or dose approximation. Despite these shortcomings the risk benefit of Pegfilgrastim is favorable in this patient subgroup as well. FDA will periodically monitor reports of medication errors in oncology patients after the approval of this supplement to determine if a safety issue exists and regulatory action is needed.

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/s/

LIBERO L MARZELLA
11/13/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125031Orig1s180

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: BLA125031/S180
Neulasta® (pegfilgrastim)

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Adebayo Laniyonu
Albert Deisseroth
Alexander Gorovets
Ebony Ayres
Erica Radden
Frank Lutterodt
Lan Huang
Libero Marzella
Luning Zhuang
Nitin Mehrotra
Nushin Todd
Thomas Gwise
William Dickerson
Yanli Ouyang

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125031Orig1s180

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 26, 2015
From	Alex Gorovets, MD
Subject	Cross-Discipline Team Leader Review
BLA #/Supplement#	125031/180
Applicant	Amgen
Date of Submission	02/13/2015
PDUFA Goal Date	11/13/2015
Proprietary Name / Established (USAN) names	NEULASTA/Pegfilgrastim
Dosage forms / Strength	6 mg by subcutaneous injection (0.6 ml prefilled syringe)
Proposed Indication	Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)
Recommended:	<i>Approval</i>

1. Introduction

The subject of this Cross Disciplinary Team Leader (CDTL) review is the supplemental Biologic License Application (BLA) 125031 for Neulasta (pegfilgrastim), a pegylated form of filgrastim, a granulocyte-colony stimulating factor (G-CSF), marketed in US since 2002 for use in patients with chemotherapy induced neutropenia, now being proposed for use in patients at risk for developing a hematopoietic (sub)-syndrome of an Acute Radiation Syndrome (HS-ARS) following an exposure to radiation during a nuclear incident including mass casualties and other situations involving radiation injury.

The applicant is Amgen, the manufacturer of Neulasta as well as Neupogen, the original, non-pegylated filgrastim. The main clinical difference between Neulasta and Neupogen in the chemotherapy indication is that the former is given once during a chemotherapy cycle whereas the latter is given daily. Neupogen dosing is weight based; (b)(4)

Neupogen has been approved for the ARS indication on 3/30/15, with weight based dosing instructions for patients of all ages.

As in the case of Neupogen the current application relies on data from a pivotal efficacy study conducted under the Animal Rule because studies involving potentially lethal radiation exposure could not be conducted in humans. The application also relies on the existing human safety data from the approved indication and other supportive data in animals and humans.

Again as in the case of Neupogen, the pivotal efficacy study of Neulasta in non-human primates (NHPs) was carried out by NIH with Amgen having the right of reference to the data.

The proposed indication as currently worded states the following: “*Neulasta is indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)*”. Although it is the same indication for which Neupogen is already approved, the use of Neulasta provides a potentially significant practical advantage especially in the setting of mass casualty because of its prolonged duration of action making daily injections unnecessary. The review of the current supplement has been designated as a Priority review.

This CDTL review document addresses the review issues brought about by multiple disciplines. Although there are no new clinical data, the applicant has performed new pharmacometric analyses and modeling to arrive at the appropriate human dose for the new indication. The most challenging review issue has involved the use of Neulasta in pediatric patients and is addressed in Section 10 below. The opinions from different disciplines are summarized there as well. The amendment submitted by the applicant in July addressing the pediatric issue was deemed a major amendment and review was extended by three months.

2. Background

The reference is being made to the 3/16/15 CDTL review of the Neupogen application for the ARS indication. The Background section of that review contains information on ARS, myelosuppression and the use of growth factors and is not reproduced here again.

A further account of the regulatory history of Neulasta development is provided by Drs. William Dickerson and Yanli Ouyang, the primary clinical and Pharmacology-Toxicology reviewers, respectively. Like Neupogen, Neulasta has received orphan designation in 2013 for “treatment of subjects at risk of developing myelosuppression after a radiological or nuclear incident”. Unlike Neupogen, it is not included in the CDC’s Strategic National Stockpile. Biomedical Advanced Research and Development Authority (BARDA) has submitted a Pre-Emergency Use Authorization (Pre-EUA) request for consideration for Neulasta on 2/21/13 (EUA #18) but there has been no further development in that application.

3. CMC/Device

There are no new CMC data in this application. Neulasta is supplied in single-dose prefilled syringes.

4. Nonclinical Pharmacology/Toxicology

The application does not contain any new Pharmacology-Toxicology data related to product safety. However the nonclinical efficacy data represent the main data source for this application’s review.

The efficacy of Neulasta for the acute radiation syndrome setting was studied in a randomized, placebo-controlled non-human primate model of radiation injury. This NIH model has been

previously reviewed by the FDA and was also used in the Neupogen studies. The model is considered to be well characterized and is included in the description of the study below.

In the pivotal, GLP-compliant, efficacy study of Neulasta, Rhesus macaques were randomized to either a control (n=23) or treatment (n=23) arm. On study day 0, animals were exposed to total body irradiation (TBI) of 750 ± 15 cGy delivered at 80 ± 3.0 cGy per minute, representing an LD50/60 dose. Animals were blindly administered subcutaneous injections of either a control (5% dextrose in water) or pegfilgrastim (300 mcg per kg) on study day 1 and on study day 8. All animals received medical management consisting of intravenous fluids, antibiotics, blood transfusions, nutrition and other support as required, according to pre-determined criteria for use. The primary endpoint was survival. The key secondary endpoint, as outlined by Dr. Ouyang, was the duration of severe neutropenia ($ANC < 500/\text{mcL}$).

Pegfilgrastim significantly improved survival: 91% [21/23] in the treatment arm vs. 48% [11/23] in the control arm ($p = 0.0014$). The median number of days with $ANC < 500/\text{mcL}$ was 14 in the treatment arm and 18 in the control arm. The primary statistical reviewer, Dr. Huang, has verified the data and analyses provided by the applicant.

The NHP efficacy data, as summarized by Dr. Ouyang, are supported by several mice studies showing an improved survival in animals treated with pegfilgrastim.

5. Clinical Pharmacology/Biopharmaceutics

As in the case of Neupogen, in accordance with the pre-submission FDA request, the applicant has provided in the current Neulasta application the pharmacometric simulation for dose explorations by developing a population model integrating available nonclinical and clinical data. Based on this modeling, the applicant has proposed the dose of pegfilgrastim for HS-ARS (b)(4)

The FDA Pharmacometric review team, Drs. Lian Ma and Nitin Mehrotra, have performed independent modeling (b)(4)

As outlined by the reviewers, according to the dose selection considerations from the “Animal Rule”, because of the “uncertainty associated with extrapolating animal efficacy data to humans, human dose should provide exposures that exceed those observed in animal efficacy studies with fully effective dose”. Such considerations have led the FDA to recommend a Neupogen dose for the ARS indication (b)(4)

Here, the pharmacokinetic simulations have indicated that 6 mg dose of Neulasta might not be adequate to produce optimal benefit in humans exposed to radiation because it does not result in exposures exceeding the exposures associated with the NHP dose (300 mcg/kg) at which efficacy has been demonstrated. (b)(4)

(b)(4). Based on the simulation results, even a higher dose (18 mg) in humans would not provide exposures fully exceeding the exposures observed in the NHP studies. In addition, there is limited human safety experience with 18 mg dose level.

Therefore, considering the mechanism of action of pegfilgrastim and involving an interdisciplinary discussion, the focus has shifted to the pharmacodynamic (PD) endpoint, absolute neutrophil count (ANC), as the target for dose selection. The reviewers' independent simulation has shown that the 18 mg dose regimen and regimen of the two 6 mg doses one-week apart will likely lead to faster ANC recovery post-nadir (b)(4). For the clinically relevant ANC endpoints (e.g. duration of grade 4 neutropenia), the regimen of 6 mg one week apart (b)(4).

The reviewers correctly note that from a safety perspective, the 6 mg dose is considered safe in both adult patients and healthy subjects given the long clinical experience with this dose since the drug's approval in 2002. There is very limited clinical experience with higher doses of Neulasta (e.g. 18 mg) and given its prolonged action the potential risk of excessive leukocytosis would not be warranted.

Given the presented results of the pharmacometric analyses this reviewer does not find major clinically significant differences (b)(4).

The pharmacometric review team has also proposed a weight tiered dosing for the pediatric patients and adults weighing less than 45 kg. They have found that the PK/PD relationship in pediatric appears to be consistent with that in adults and proposed selecting a dose in pediatrics that produces similar PK to that of adults with 6 mg one week apart dosing regimen.

As discussed further in Section 10 of this document, the same weight-tiered based dosing regimen could be also proposed for the chemotherapy induced neutropenia (CIN) indication. For the CIN indication, as currently labeled, observed pediatric PK data are available at the dose of 100 mcg per kg. Based on pharmacokinetic simulations, it appears that the exposures achieved with the proposed weight-tiered based dosing are similar to those of 100 mcg per kg dose in pediatrics.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

No new clinical data have been submitted with this application and no new statistical analyses of clinical data have been performed. The statistical reviewer has concentrated on the nonclinical efficacy data verification. The clinical reviewer in addition to clinically interpreting the results of the nonclinical efficacy studies has summarized the literature based experience in relation to pediatric use. The data support the proposed use of Neulasta for HS-ARS.

The reviewers have summarized the key aspects of the “Animal Rule” as applicable to Neupogen and the ARS indication:

- Reasonably well-understood pathophysiological mechanism of radiation injury and biological plausibility for filgrastim efficacy
- Pivotal data generated in a well-characterized model in nonhuman primates expected to be predictive of the response in humans
- Pivotal nonhuman primate study endpoint (survival) directly related to the desired benefit in humans
- Pharmacokinetic (PK) and pharmacodynamic (PD) data from nonhuman primates and humans allows selection of an effective dose in humans

The latter point has been discussed in the Clinical Pharmacology section.

8. Safety

Safety profile of Neulasta for the ARS indication is derived from its safety profile in the approved indication. The commonly reported adverse reaction is bone pain. The labeled contraindication is a history of a serious allergic reaction to pegfilgrastim or filgrastim. The Warning and Precautions include fatal splenic rupture, acute respiratory distress syndrome, anaphylaxis, fatal sickle cell crises.

9. Advisory Committee Meeting

No AC meeting has been planned.

10. Pediatrics

The currently approved indication for use of Neulasta in patients with CIN is silent on the age of the patients. However the Pediatric Section of the currently approved label states that “In pediatric patients with chemotherapy induced neutropenia, safety and effectiveness of Neulasta have not been established”.

For the new ARS indication, the applicant has proposed

(b)(4)

The currently approved label does contain pediatric dosing information in the Pediatric section in the report on the pK and safety study in 37 pediatric sarcoma patients. The age groups ranged from 0 to 21, pK was similar to the one in adults and there were no new safety signals. The weight based dose of 100 mcg per kg was derived from the adult studies of Neulasta in patients with breast cancer which was thought to be equivalent to the flat dose of 6 mg which was eventually selected for marketing.

It has also been generally acknowledged that there is an off-label use of Neulasta in children with cancer in this country using the 100 mcg per kg dose by drawing the necessary volume from the prefilled syringe or from an intermediary sterile container, with a new dose usually prepared by a pharmacist. To the best of our knowledge there are no other presentations of Neulasta marketed anywhere else in the world.

In view of the important public health aspect of this issue the review team has reviewed the additional pediatric information provided by the applicant and conducted an independent literature search and review. Consultations were obtained from the Oncology/Hematology colleagues and the OSE colleagues, both from the pharmacovigilance and drug utilization groups in relation to the pediatric use of Neulasta, summarized by Dr. Dickerson in the clinical review. These were in addition to the consultations from DMEPA (medication errors) and DPMH (pediatrics).

The conclusion from all this review activity is that Neulasta is used safely and effectively in a variety of pediatric cancer patients. The most common dose is 100 mcg per kg. The utilization has been clearly demonstrated. The use is generally safe however there have been three all-time reports of medication errors resulting in administering higher than intended volume resulting in a significant leukocytosis which has resolved without clinical consequences.

An additional review issue has developed involving the recommendations from the Pediatric (the review is not in DARRTS yet) and Hematology/Oncology colleagues. Both disciplines strongly feel that the Neulasta label (b)(4)

those weighing < 45 kg for both the ARS and the CIN indications. A telephone discussion with the applicant took place on 9/25/15 and the labeling negotiations are ongoing. FDA has provided the labeling recommendations to the applicant and the subsequent clarifications. There has been no response from the applicant as of today.

It should be also noted that the recommendations from DMEPA and DPMH are somewhat different. DPMH position (see above) has been made in various communications but not finalized yet. DMEPA (review is in DARRTS) is concerned about a possible rise in the medications errors because the available presentation is a syringe without gradations making accurate draws of volumes less than 0.6 ml somewhat difficult. The proposed label would say that this presentation is not for direct administration of lesser volumes, implying that there is a need for a transfer, but that might not be enough. DMEPA does agree that the benefit outweighs the risk in the pediatric ARS population and is more concerned with changes involving the CIN population recommending mitigation of this potential risk by an increase in pharmacovigilance in the pediatric patients if the labeling changes are approved. It appears that once the labeling is finalized these two positions can be reconciled.

So at this time the labeling recommendations are based on the modeling performed by the Pharmacometrics team and involve a tiered approach: 4 mg for 31-44 kg body weight; 2.5 mg for 21 – 30 kg; 1.5 mg for 10 - 20 kg; and 100 mcg per kg for those weighing less than 10 kg. As noted, the currently approved presentation of Neulasta does not allow a direct

administration of a dose less than 6 mg. It should be also noted that the current formulation of Neulasta in the prefilled syringe (6 mg in 0.6 mL) is not designed for administering doses of less than 1 mg (i.e. at 100 mcg per kg to those weighing less than 10 kg).

11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues.

12. Labeling

Labeling negotiations are ongoing and changes are proposed to the Indication, D&A, pediatric, clinical pharmacology and clinical studies sections. The content is expected to reflect what is described in the corresponding sections of this document.

13. Recommendations/Risk Benefit Assessment

The CDTL recommendation is to approve the use of Neulasta for increasing “survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)”.

There is an unmet medical need for treatment of patients at risk of developing ARS after sustaining radiation injury to reduce mortality, usually from life threatening infections that can develop in a setting of a severe radiation induced neutropenia occurring as a result of bone marrow suppression. Although Neupogen has been just approved for the same indication, the additional benefit of Neulasta is that its use could be more easily accomplished in a mass casualty situation as it would involve only two injections of Neulasta instead of daily injections of Neupogen.

The efficacy of Neulasta for the ARS indication has been demonstrated in the nonclinical study conducted under the Animal rule in the NHPs in a GLP compliant facility. It showed an over 40% survival benefit of Neulasta over control. In addition to the primary efficacy analysis of survival the study was also successful in the secondary pharmacodynamic endpoints assessing neutropenia. The effectiveness in the ARS indication is supported by the established effectiveness of Neulasta in patients undergoing chemotherapy and there has been a long history of clinical use of Neulasta. As the mechanism of action of Neulasta is the same as with Neupogen the known benefit of Neupogen in ARS is further supportive of the benefit of Neulasta in ARS.

The risks of Neulasta are well described in the product labeling and in addition to serious allergic reactions splenic rupture and alveolar hemorrhage are of particular concern. Both are fortunately rare. Given its long history of clinical use Neulasta is considered to be fairly safe. As with Neupogen, the problem arises with the uncertainty of its use in healthy people, especially in possible “worried well”. Therefore estimating the radiation exposure is particularly important to avoid unnecessary treatment. The prolonged duration of action of Neulasta while constituting the main benefit of using Neulasta in treatment of ARS also constitutes its main risk. Once started the treatment cannot be easily reversed by simply stopping the drug if let’s say the white count keeps on going up. Of note however the high

counts (even close to 100,000) are rarely associated with adverse clinical reactions and resolve spontaneously without known consequences.

Overall the benefits of Neulasta in the new indication of ARS clearly outweigh possible risks. Additional risk/benefits considerations involving the proposed pediatric use are addressed above in the Pediatric section and are primarily related to the lack of the adequate presentation to administer Neulasta to children and small adults.

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/s/

ALEXANDER GOROVETS
10/30/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125031Orig1s180

CLINICAL REVIEW

Application Type	Supplemental Biologic Licensing Agreement
Application Number(s)	SBLA 125,031 SD-1137 eCTD sequence 0230
Priority or Standard	Priority
Submit Date(s)	2/13/2015
Received Date(s)	2/13/2015
PDUFA Goal Date	Original 8/15/2015 Revised 11/13/2015
Division / Office	DMIP/ ODEIV
Reviewer's Name	William Dickerson, M.D.
Review Completion Date	October 14, 2015
Established Name	Neulasta® (pegfilgrastim)
(Proposed) Trade Name	N/A
Therapeutic Class	Leukocyte Growth Factor
Applicant	Amgen
Formulation(s)	6mg in 0.6ml prefilled syringe
Dosing Regimen	
Indication(s)	Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic

Syndrome of Acute Radiation Syndrome)

Intended Population(s)	All patients with suspected or confirmed exposure to radiation doses greater than 2 gray (Gy).
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Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of Amgen's supplemental Biologics License Application (sBLA) to add to the indication for Neulasta® (pegfilgrastim) to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).

1.2 Risk Benefit Assessment

The risk benefit assessment favors approval. The data clearly show that the risk of adverse events from the use of Neulasta in healthy volunteers and in patients treated with Neulasta for the presently approved indication is relatively small. The benefit for the use of Neulasta for treating patients exposed to myelosuppressive doses of radiation can be extrapolated from animal studies.

Risk:

The risk from use of Neulasta in oncology patients has been shown to be minimal. Per the sponsor, the efficacy and safety profile of pegfilgrastim has been well characterized in over (b)(4) patients worldwide with minimal side effects since Neulasta's approval by the FDA in 2002. Leukocyte Growth Factors (LGFs) including filgrastim, sargramostim, and pegfilgrastim have also been used for treatment of radiation accident victims. In all cases, serious adverse events have been very rare.

Concern About Risk:

I have had some concern about the risk of using Neulasta in children because the FDA approved label for Neulasta dated 09/2015 states in Section 8.4, Pediatric Use, that "Safety and effectiveness of Neulasta in pediatric patients have not been established." However, after reviewing supportive literature, information provided in the product labeling, and reviews of pediatric utilization data and FAERS data, I believe that the use of Neulasta is safe in children as well as in adults for the treatment of the hematopoietic syndrome of the Acute Radiation Syndrome. However, since Neulasta is only available in a 6 mg/ 0.6 mL presentation for adults, dosing children at 100 mcg/ kg will be difficult. At the time of this review, our FDA Division of Medical Imaging Product and Amgen have not yet come to an agreement on pediatric dosing. Please see my sections 6.1.8.2, and 7.6.3 for my further discussion on the use of Neulasta in Pediatrics.

The Neulasta label revised 09/2015 states in its Section 5 Warnings and Precautions that a health care provider should be concerned that Neulasta may contribute to 5.1 Splenic Rupture, 5.2 Acute Respiratory Distress Syndrome, 5.3 Serious Allergic Reactions, 5.4 Allergies to Acrylics (for the On-body injector), 5.5 Severe Sick Cell Crises in Patients with Sick Cell Disorders, 5.6 Glomerulonephritis, 5.7 Leukocytosis,

5.8 Capillary Leak Syndrome, and 5.9 Potential for Tumor Growth Stimulatory Effects on Malignant Cells. Fortunately, these situations have rarely, if ever, developed. The Neulasta label states in Section 6 Adverse Reactions, that the most common adverse reactions occurring in $\geq 5\%$ of patients or $\geq 5\%$ higher in the pegfilgrastim arm than in a placebo controlled arm are bone pain and pain in an extremity.

Benefit:

In the oncology setting Neulasta has been shown to reduce the period of neutropenia in patients with bone marrow suppression due to chemotherapy. I agree with Amgen and others who believe that the mechanism of action for pegfilgrastim to stimulate granulopoiesis is independent of the type of injury. I believe that neutropenia due to chemotherapy is similar to radiation-induced neutropenia, and response to Neulasta for these conditions appears similar.

Since efficacy studies of Neulasta could not be conducted in humans with acute radiation syndrome, animal studies were necessary. **AXG21** was a randomized, blinded, placebo-controlled study in non-human primates (NHPs) exposed to an acute dose of total body irradiation (TBI) which was predicted to be lethal to 50% of the animals within 60 days (LD 50/60). Half the animals were given Neulasta, and all the animals received extensive supportive care. The AXG21 trial was titled “**A Sixty-Day Efficacy Study Of Subcutaneous Pegfilgrastim (Neulasta®) To Treat The Hematopoietic Syndrome Of The Acute Radiation Syndrome (ARS-HS) Following an LD50/60 of Total-body Irradiation (TBI) in Rhesus Macaques**”. This trial was sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) and was completed in March 2014. The conclusion of the trial was that survival of rhesus macaques following exposure to 7.50 Gy total-body irradiation was significantly improved (Chi-square test, $p = 0.0014$) by Neulasta (pegfilgrastim) administered at 300-319 mcg/kg/day subcutaneously on study day (SD) 1 and on SD 8. Sixty day all-cause mortality was reduced in the Neulasta cohort to 8.7% from 52.2% in the D5W-treated cohort. The 905-page report and protocol for AXG21, first author Kim Hankey, Ph.D., is included in the submission. (Reference: Amgen submission, Section 2.5, page 23, link from Hankey reference)

Trial **AXG21** for pegfilgrastim mirrors trial **AXG15** which was an NHP trial for Neupogen (filgrastim). AXG 15 showed a significant survival advantage for the NHPs receiving Neupogen (79%) versus controls (41%). The data from study AXG15 was presented to an FDA Advisory Committee in May 2013 which voted 17:1 that filgrastim therapy was reasonably likely to produce clinical benefits in humans exposed to radiation following a radiological/nuclear incident. In March 2015 Neupogen was approved by the FDA for the additional indication: “Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)”.

Concerns About Benefit:

-Effectiveness: Neulasta (a long-acting leukocyte growth factor) and Neupogen (a short acting leukocyte growth factor) have been shown in NHPs exposed to an LD 50/60 (lethal dose to 50% of subjects within 60 days) acute dose of radiation to improve survival. However, they may be less effective when radiation is combined with physical trauma (combined injury). Also, Neulasta and Neupogen have been shown to be effective when given with supportive care at an LD 50/60, but they may be less effective if given for other doses of radiation such as LD20/60, LD80/60, or without supportive care. The benefit may not contribute to long-term survival due to the delayed effects of radiation.

-Timing: Amgen recommends starting Neulasta (and Neupogen) early, within the first 2 weeks of radiation exposure (Reference Amgen submission, Module 2.7.2, page 17). For studies AXG21 (Neulasta) and AXG15 (Neupogen) the LGF was initiated at 24 hours post radiation exposure. NHP study AXG22 did not show a survival benefit when Neupogen was started 48 hours after exposure.

-Complexity: The management of acute radiation syndrome is complex. If there is a mass casualty incident with radiation exposure, it will be difficult to manage a large number of patients for radiation dose determination, treatment (b)(4) (b)(4) Neulasta or daily injections of Neupogen, extensive supportive care, and frequent blood counts to evaluate need for continued treatment. Education of providers and patients will be essential.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies (REMS)

No REMS are planned following approval of this submission.

1.4 Recommendations for Postmarket Requirements and Commitments

The sponsor has included in Section 5.3.5.4 of its 02/13/2015 submission an outline for a study titled: “A Phase 4 Study Evaluating the Efficacy and Safety of Neulasta® (pegfilgrastim) in the Setting of Hematopoietic Syndrome Following Acute Radiation Exposure.”

2 Introduction and Regulatory Background

2.1 Product Information

Neulasta® (pegfilgrastim) is a covalent conjugant of recombinant methionyl human granulocyte colony-stimulating factor (r-metHuG-CSF, filgrastim). To produce pegfilgrastim, a polyethylene glycol (PEG) molecule is covalently bound to the N-terminal methionyl residue of filgrastim. This binding essentially produces long-acting filgrastim. Similar to endogenous G-CSF, pegfilgrastim selectively stimulates granulopoietic cells of the neutrophil lineage. It acts at all stages of neutrophil

development to increase the proliferation and differentiation of neutrophils from progenitor cells. Pegfilgrastim also enhances the survival and function of mature neutrophils.

Neulasta is supplied as both a single use prefilled syringe containing 6 mg pegfilgrastim in 0.6 mL, and as the Neulasta Delivery Kit which includes both a single use prefilled syringe and one sterile on-body injector to deliver 6 mg pegfilgrastim in 0.6 mL.

Neulasta was initially approved by the FDA in 2002. It is indicated to decrease the incidence of infection, as manifested by febrile neutropenia (FN), in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs that have been associated with a clinically significant incidence of FN. Pegfilgrastim has not been approved for the treatment of chemotherapy-induced neutropenia (CIN) in pediatrics. In addition, pegfilgrastim is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

The sponsor is now applying for an additional indication which is for (b)(4)

The sponsor has submitted this application for approval under the Animal Rule (21 CFR 601.90).

2.2 Table of Currently Available Treatments for Proposed Indications

Table 1 Currently Available Treatments for Proposed Indications

FDA approved leukocyte growth factors (LGFs) with similar or slightly different indications are the following:

<u>Brand (generic) name</u>	<u>Class of drug</u>	<u>Approved FDA Indication</u>
Granix® (tbo-filgrastim)	Granulocyte Colony Stimulating Factor (G-CSF)	Only indicated in adults for reduction in duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia
Leukine® (sargramostim)	Granulocyte Macrophage Colony Stimulating Factor (GM-CSF)	Adults only: 1. Use Following Induction Chemotherapy in Acute Myelogenous Leukemia 2. Use in Mobilization and Following Transplantation of Autologous Peripheral Blood Progenitor Cells

<u>Brand (generic) name</u>	<u>Class of drug</u>	<u>Approved FDA Indication</u>
		3. Use in Myeloid Reconstitution After Autologous Bone Marrow Transplantation 4. Use in Myeloid Reconstitution After Allogeneic Bone Marrow Transplantation 5. Use in Bone Marrow Transplantation Failure or Engraftment Delay
Neulasta® (pegfilgrastim)	Pegylated G-CSF	Only indicated in adults “to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.”
Neupogen® (filgrastim)	G-CSF	1. Decrease incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever 2. Reduce time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with acute myeloid leukemia (AML) 3. Reduce duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation 4. Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis

<u>Brand (generic) name</u>	<u>Class of drug</u>	<u>Approved FDA Indication</u>
		5. Reduce incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic adult and pediatric patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia 6. (Approved 3/2015) Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)
Zarxio® (filgrastim-sndz) (biosimilar filgrastim)	G-CSF	Approved 3/2015 as a biosimilar of filgrastim for the first 5 indications for which Neupogen is approved.

2.3 Availability of Proposed Active Ingredient in the United States

Neulasta is readily available in limited quantities for oncology patients at most medical centers. However, the need for Neulasta after a nuclear or radiologic incident would far exceed the supply at any medical center. The Strategic National Stockpile (SNS) includes stockpiles of Neupogen and Leukine for use in case of a radiologic or nuclear mass casualty disaster. Neupogen is at present the only drug approved by the FDA for the treatment of the Acute Radiation Syndrome. The use of Leukine from the SNS would require an Emergency Use Authorization. I expect that in the future if this supplemental BLA is approved, that Neulasta will also be stockpiled in the SNS.

2.4 Important Safety Issues With Consideration to Related Drugs

-Granix (tbo-filgrastim) is a G-CSF which is biologically similar to Neupogen. Granix was approved by the FDA in 2013 for only one indication (see Table 1 in Section 2.2 above). There is limited experience with this drug in the USA, but more experience overseas.

Since this drug has been widely used for several years, I believe that it is fairly safe with usage as indicated. However, the “Warnings and Precautions” section from the FDA approved label includes the following topics for possible adverse events: Splenic Rupture, Acute Respiratory Distress Syndrome (ARDS), Allergic Reactions, Use in Patients with Sickle Cell Disease, Capillary Leak Syndrome, and Potential for Tumor Growth Stimulatory Effects on Malignant Cells. These “Warnings and Precautions” are similar to the “Warnings and Precautions” in the presently approved Neulasta label.

The 09/2015 version of the Neulasta label also warns about possible glomerulonephritis.

-Leukine (sargramostim) is different chemically from Neupogen and Neulasta and has different indications than Neupogen and Neulasta (see Table 1 in Section 2.2 above). Leukine is a type of granulocyte macrophage colony stimulating factor (GM-CSF) which acts more broadly than G-CSF, and may cause more side effects. Also, Leukine, like Neulasta, is FDA approved only for adults, while Neupogen is FDA approved for both adults and children.

Since this drug has been widely used for several years, I believe that it is fairly safe with usage as indicated. However, the “Warnings” section from the FDA approved label includes the following topics for possible adverse events: Pediatric Use, Fluid Retention, Respiratory Symptoms, Cardiovascular Symptoms, and Renal and Hepatic Dysfunction.

-Neupogen (filgrastim) is the most widely used granulocyte colony stimulating factor (G-CSF) and, like Neulasta, is produced by Amgen. Neupogen has been FDA approved since 1991 and currently is approved for the 6 indications described above (see Table 1 in Section 2.2 above). Neupogen, like Granix, Leukine and Zarxio, requires daily injections,

Since this drug has been widely used for over 20 years with rare serious adverse effects, it is quite safe with usage as indicated. However, the “Warnings and Precautions” section from the FDA approved label includes the following topics for possible adverse events: Splenic Rupture, Acute Respiratory Distress Syndrome, Serious Allergic Reactions, Sick Cell Disorders, Alveolar Hemorrhage and Hemoptysis, Capillary Leak Syndrome, Patients with Severe Chronic Neutropenia, Thrombocytopenia, Leukocytosis, Cutaneous Vasculitis, Potential Effect on Malignant Cells, Simultaneous Use with Chemotherapy and Radiation Therapy Not Recommended, and Nuclear Imaging.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The history of Neulasta is related to the history of Neupogen since they are related chemically except for the fact that Neulasta is a pegylated, long-acting form of Neupogen. In February 1991 the FDA initially approved filgrastim with the indication to decrease the incidence of infection, as presented by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs that have been associated with a clinically significant incidence of febrile neutropenia. Additional indications have been approved by the FDA since then and are described in Section 2.2 above.

In 2002 the FDA approved Neulasta (pegfilgrastim) for only one indication-as a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of

febrile neutropenia. The dosage for Neulasta has been 6 mg administered subcutaneously in adults only, once per chemotherapy cycle. Neulasta is not to be administered between 14 days before and 24 hours after administration of cytotoxic chemotherapy. The FDA-approved label for Neulasta states in section 8.4 Pediatric Use, that “Safety and effectiveness of Neulasta in pediatric patients have not been established.”

In October 2005, the CDC submitted a preliminary Emergency Use Authorization (EUA) request regarding filgrastim (Neupogen) for the treatment of Acute Radiation Syndrome (ARS) in response to a nuclear/radiological attack. Animal studies had suggested a clinical benefit for the use of a G-CSF for treatment of radiation induced neutropenia for several years. This EUA (b)(4) was prepared for activation should a mass casualty nuclear or radiation incident occur.

In December 2006 the National Institute of Allergy and Infectious Diseases (NIAID) submitted to the FDA a proposal for Good Laboratory Practice (GLP) murine and non-human primate (NHP) studies, both pilot and pivotal, to identify whether or not filgrastim provides a survival benefit if given after a species receives a life-threatening dose of radiation. These proposed animal studies were designated as pre-IND-100,228 and meetings were held with the FDA to assist with design of the studies.

In July 2011 NIAID reported the results of IND-100,228 **Study AXG15** which was titled “A sixty-day efficacy study of subcutaneous filgrastim (Neupogen) to treat the hematopoietic syndrome of the acute radiation syndrome (ARS-HS) following an LD50/60 of total body irradiation (TBI) in Rhesus Macaques.” LD50/60 is the lethal dose of radiation to 50% of animals within 60 days. For this trial’s Rhesus Macaques the LD50/60 was approximately 7.5 gray (Gy). The results showed a significant survival advantage to the use of Neupogen in non-human primates (NHPs) exposed to a dose of radiation which was lethal within 60 days to 50% of the control group. This pivotal efficacy study, performed by the University of Maryland, showed 21% lethality to NHPs exposed to an LD 50/60 dose of radiation and treated with Neupogen and best supportive care, versus a 59% mortality for the cohort of NHPs which received best supportive care only. Neupogen dose was 10 mcg/kg/day starting 22-26 hours post LD 50/60 TBI. All animals were euthanized according to the prespecified criteria except for three animals in the control arm that were found dead between Days 11-18.

Based on the results of this trial, the Division of Medical Imaging Products requested an inspection of the study’s facility at the University of Maryland in Baltimore, MD, and also requested an Advisory Committee be convened to discuss the role of leukocyte growth factors in humans following an otherwise lethal dose of radiation.

December 4-14, 2012 the FDA inspected the University of Maryland’s research facility to audit Study AXG15 (Neupogen) of IND 100,228. The entire 39-page FDA report with responses by the University of Maryland staff was entered in DARRTS under IND 100,228 on April 19, 2013 by Niraj Mehta. The FDA investigators found the study

compliant with Good Laboratory Practice (GLP). In spite of a number of shortcomings listed in the inspection report, the FDA determined that the findings in the AXG15 report were reasonable.

On May 3, 2013 FDA's Medical Imaging Drugs Advisory Committee (MIDAC) and Oncologic Drugs Advisory Committee (ODAC) met jointly, to discuss the safety and efficacy of currently approved leukocyte growth factors (LGFs) as potential treatments for radiation-induced myelosuppression associated with a radiological/nuclear incident. This joint FDA Advisory Committee meeting was scheduled subsequent to FDA's review of nonhuman primate study efficacy data submitted by NIAID under preIND-100,228.

The NIAID data demonstrated efficacy of filgrastim in the treatment of the Hematopoietic Syndrome of the Acute Radiation Syndrome. Based on the information presented at that meeting, **the Advisory Committee voted 17:1 that filgrastim therapy was reasonably likely to produce clinical benefits in humans exposed to radiation following a radiological/nuclear incident.** In addition, the committee overall agreed that this efficacy could be generalized to the use of other leucocyte growth factors, including Neulasta, Leukine and Tbo-filgrastim. (See also Section 9.3 Advisory Committee Meeting.)

On November 19, 2013 Amgen met with the FDA for a Type B pre-sBLA meeting to discuss the way forward for a sBLA. At that meeting Amgen agreed that they would develop a population model integrating available nonclinical and clinical data to estimate human survival benefit. The minutes of this meeting are in DARRTS under (b)(4). Amgen has submitted their population models with this Neulasta supplemental BLA submission.

On November 20, 2013 the FDA granted "Orphan Drug" designation to Amgen for pegfilgrastim for the treatment of subjects at risk of developing myelosuppression after a radiological/nuclear incident. (Per Amgen's cover letter, this Orphan Drug designation is OD#13-4130.) Since Amgen has received Orphan Drug designation, PREA requirements are waived.

On September 30, 2014 Amgen (b)(4) to their Neupogen BLA. (b)(4) was for an efficacy supplement to add to the Neupogen label an indication (b)(4).

On February 13, 2015 Amgen submitted this sBLA under the Animal Rule (21 CFR 601.90) for pegfilgrastim for the (b)(4).

Priority Review was requested and designated.

In March 2015 the FDA approved Amgen's sBLA for Neupogen for the new indication: "Increase survival in patients acutely exposed to myelosuppressive doses of

radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)”

2.6 Other Relevant Background Information

No new clinical studies were conducted in support of this sBLA.

The original submission was to be reviewed within 6 months (due August 13, 2015). On June 4, 2015 we sent Amgen an Information Request asking for a review of all safety information on the use of Neulasta in children. “This review should include all information from Amgen sponsored studies, a review of the literature, and a review of all safety data bases available to Amgen.” Amgen responded July 7 that they had performed the following literature search:

“The MEDLINE, BIOSIS, and Embase literature databases were searched on 12 June 2015 for publications pertaining to weight based dosing in pediatric patients. The search was conducted using a mixture of controlled vocabulary and keywords including, but not limited to: (“Neupogen”, “filgrastim”, “Granulokine”, “lenograstim”, “Neulasta”, “pegfilgrastim”, “g-csf”, “granulocyte colony stimulating factor?”, “rhu-gcsf”, “r-methug-csf”) and (“weight based”). The search was limited to publications in the English language. Abstracts identified in the search were reviewed for relevance, and the complete articles were obtained and assessed for all abstracts that referred to adverse events in studies or case reports with pediatric patients administered granulocyte colony stimulating factor (G-CSF) where the weight was provided.” (Reference: Amgen 1.11.3- Response to FDA Information Request 04 June 2015, p. 4).

(b)(4)

(Reference Amgen 1.11.3- Response to FDA Information Request 04 June 2015, pp 6-7, Section 2.1.3.2 Safety Analysis – Literature).

Our Division then sent Amgen another information request on July 7, 2015 where we requested copies of all their references for our own review. Amgen complied with that request. Since review of Amgen’s references required additional time to complete review of this sBLA, on July 23, 2015 our Division Director, Libero Marzella, MD, PhD, informed Amgen that we were extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date was changed to November 13, 2015.

Reviewer’s Comments: Patricia Dinndorf, M.D. of the Division of Hematology Oncology Products, and I, reviewed the above articles provided by Amgen. We did not identify any article significantly supportive or critical of the use of Neulasta in children. Therefore we reviewed a literature search through the FDA’s library. Of 84 articles identified by the FDA Library, 22 were especially useful and supportive of the use of Neulasta in children (none were against such use). These 22 articles are listed in my Section 9.1.1, “References supporting the use of

pegfilgrastim in pediatrics”. Actually, 12 of the 22 identified by the FDA library were described by Amgen in their module “1.11.3 – Response to FDA information Request of 23 March 2015” which the FDA received May 1, 2015. (See my Section “6.1.8.2.3 Amgen Response to Information Request (IR) of 23 March 2015”).

Several organizations recommend the use of Colony Stimulating Factors for the treatment of radiation induced neutropenia. These organizations include the American Society of Clinical Oncology (ASCO), the Armed Forces Radiobiology Research Institute (AFRRI), the Radiation Emergency Assistance Center/ Training Site (REAC/TS), and the World Health Organization - Radiation Emergency Medical Preparedness and Assistance Network (WHO-REMPAN).

Both Neupogen and Leukine are included in the CDC’s Strategic National Stockpile and are available for distribution in case of an emergency.

Some of the FDA’s BLA, IND, and EUA submissions for leukocyte growth factors are as follows (See also Section 2.2 and Section 2.4 above):

Granix (tbo-filgrastim):

-BLA-125294, a G-CSF similar to Neupogen, is sponsored by Sicor Biotech.

Leukine (sargramostim):

-BLA-103362 is a granulocyte-macrophage colony stimulating factor (GM-CSF), sponsored by Genzyme Inc.

-Pre-EUA 17 is the pre-Emergency Use Authorization (EUA) for the use of Leukine after a radiation or nuclear mass casualty incident. This EUA used to be sponsored by the Biomedical Advanced Research and Development Authority (BARDA), but is now sponsored by CDC.

(b)(4)

Neulasta (pegfilgrastim)

-BLA-125031 is sponsored by Amgen, Inc. The efficacy supplement to this BLA is the topic of this review

(b)(4)

-Pre-EUA 18 is sponsored by BARDA

Neupogen (filgrastim):

-BLA-103353 is sponsored by Amgen.

(b)(4)

(b)(4) sponsored by NIAID, is for animal studies with radiation. AXR01, AXG15

(b)(4)

-AXR01 and AXG15 were both submitted on July 22, 2010 as completed studies.

-AXR01 was titled, "A Pilot Study to Define the Dose Response Curve in Rhesus Macaques Exposed to Increasing Doses of Total Body Ionizing Radiation and Receiving Supportive Care."

-AXG15 was titled, "A Sixty-Day Efficacy Study of Subcutaneous Filgrastim (Neupogen) to Treat the Hematopoietic Syndrome of the Acute Radiation Syndrome (ARS-HS) Following an LD 50/60 of Total Body Irradiation (TBI) in Rhesus Macaques." AXG15 was the primary study presented at an FDA Advisory Committee in May 2013. I describe it extensively in Section 6 of this review

-AXG22 final report was submitted to the FDA on September 29, 2014. It is titled: "A sixty-day efficacy study of subcutaneous **delayed** filgrastim (neupogen) administration to treat the hematopoietic syndrome of the acute radiation syndrome (ARS-HS) following an LD50/60 of total body irradiation (TBI) in Rhesus Macaques." (See Sections 1.2 and 5.3 for results of AXG15 and AXG22)

Zarxio® (filgrastim-sndz)

-BLA 125553 is sponsored by Sandoz, INC. This drug was approved in March 2015 as a biosimilar to filgrastim.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

-Acceptable

3.2 Compliance with Good Clinical Practices

-Amgen's production facility in Thousand Oaks, CA, has been inspected in the past and was found to be compatible with Good Clinical Practices (GCP).

-No new clinical data was provided with this submission which relies on the FDA's "Animal Rule". NIAID's studies AXG15 (for Neupogen) and AXG21 (for Neulasta) were conducted in a manner compatible with Good Laboratory Practice (GLP). See Section 2.5 above, for details on the result of the FDA's inspection of the AXG15 study test facility December 4-14, 2012. The facility used for testing AXG15 is the same facility which was used for testing AXG21.

3.3 Financial Disclosures

Per sponsor: “Not Applicable”, since no new study was or will be performed.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The supplement did not address any CMC issues.

4.2 Clinical Microbiology

The supplement did not address any microbiology issues.

4.3 Preclinical Pharmacology/Toxicology

Module 2.4 of the submission is titled “Nonclinical Overview – Acute Radiation Syndrome”. I have provided below the sponsor’s conclusions.

“The pivotal GLP-compliant radiation survival study with pegfilgrastim in nonhuman primates (NHP) was conducted at the University of Maryland School of Medicine, under contract to the National Institute of Allergy and Infectious Diseases (NIAID). Additional support for the efficacy of pegfilgrastim in HS-ARS comes from published reports of studies conducted in mice and rhesus monkeys.....” (Reference Amgen Submission Module 2.4 page 5)

Key Conclusions from the Nonclinical Information

“Pegfilgrastim significantly increased 60-day survival compared to vehicle in a well-characterized NHP model of radiation injury (91.3% [21 of 23] survival in the pegfilgrastim group vs 47.8% [11 of 23] survival in the control group) when administered at 300 to 319 µg/kg subcutaneously (SC) once on study day 1 (20 to 28 hours after radiation exposure on study day 0), and again on study day 8. Pegfilgrastim significantly decreased duration of grade 3 and 4 neutropenia (absolute neutrophil count [ANC] < 500/µL and ANC < 100/µL, respectively, and shortened recovery to ANC > 1000/µL). The duration of thrombocytopenia and time to recovery of platelet counts (PLT) ≥ 20,000/µL was also significantly reduced by pegfilgrastim treatment.” (Reference Amgen Submission Module 2.4 pages 5-6)

Dose in Animals

In study 960135 Amgen reported:

“The pharmacokinetics of pegfilgrastim exhibited nonlinearity. As the dose increased

from 100 to 1000 µg/kg, the mean clearance values decreased from 17.5 to 8.6 mL/h/kg. Although the drug exposure increased more than dose proportionally, the ANC responses increased less than dose proportionally. As the dose increased from 100 to 1000 µg/kg, the mean AUC_ANC increased from 4490 to 6150 cells x 10⁹ h/L. The ANC response declined to baseline level at the end of the study.” (Reference: Sponsor’s submission, Section 2.4 page 20)

Per sponsor’s Study 100841,
“Compared with the control group, pegfilgrastim at 100 or 300 µg/kg after IV or SC administration significantly shortened the duration of neutropenia and improved the ANC at nadir For the 100 µg/kg pegfilgrastim groups, no significant differences between the IV and SC groups were observed in the duration of neutropenia, the ANC at nadir, and time to ANC recovery. For the 300 µg/kg pegfilgrastim groups, the duration of neutropenia and the ANC at nadir between IV and SC groups were similar; however, the time to ANC recovery was significantly shorter after SC than after IV administration. Compared with the 300 µg/kg filgrastim groups, pegfilgrastim at 300 µg/kg after IV or SC administration significantly shortened the duration of neutropenia; the ANC at nadir was generally improved after pegfilgrastim administration.” (Reference: Amgen submission, Section 2.4, page 25)

Reviewer’s Comment:

I note that the sponsor tested doses ranging from 100 µg/kg to 1000 µg/kg in NHPs. This compares with the FDA label fixed dose of 6 mg for all adults. This dose for adults is equivalent to 100 µg/ kg for a 60 kg adult, or 50 µg/kg for a 120 kg adult.

Toxicology

“Toxicology evaluations were conducted to support the original Product License Application. In brief, toxicology findings were related to exaggeration of pharmacologic effects (dose-dependent increases in white cell counts, increased neutrophils, increased myeloid:erythroid ratio in bone marrow, extramedullary granulopoiesis in liver and spleen, and dose-related increases in spleen weight) and reversed after discontinuation of treatment. Increased abortion and embryo lethality associated with signs of maternal toxicity were observed at high doses in pregnant rabbits. No adverse effects on fetal development or fertility were observed in rats. (Reference: Amgen module 2.4 page 6)

Nonclinical toxicology is also described in Section 13 of the FDA-approved label for Neulasta. The label states that no carcinogenicity or mutagenesis studies have been performed with pegfilgrastim. The label also states “Pegfilgrastim did not affect reproductive performance or fertility in male or female rats at cumulative weekly doses approximately 6 to 9 times higher than the recommended human dose (based on body surface area)”.

The label states that for Reproductive and Developmental Toxicology, in pregnant rabbits, “Increased incidences of post-implantation losses and spontaneous abortions

(more than half the pregnancies) were observed at cumulative doses approximately 4 times the recommended human dose, which were not seen when pregnant rabbits were exposed to the recommended human dose.”

4.4 Clinical Pharmacology

Amgen describes Clinical Pharmacology in 2 areas of its submission. The 2 areas are Module 2.5- Clinical Overview- Acute Radiation Syndrome, subsection 3, and Module 2.7.2 –Summary of Clinical Pharmacology- Acute Radiation Syndrome.

In Module 2.5 Amgen proposes

(b)(4)

”

The FDA requested Amgen submit a population model. That model was submitted in Amgen’s Section 4 of Module 2.7.2 and was reviewed in depth by our Clinical Pharmacology reviewers. Please see the recommendations of our pharmacometrics staff below in my Section 6.1.8, “Analysis of Clinical Information Relevant to Dosing Recommendations.”

4.4.1 Mechanism of Action

No new data on the mechanism of action of Neulasta has been submitted. The Neulasta label states in Section 12.1 that it is a colony-stimulating factor that acts on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end cell functional activation.

Module 2.5 states that:

“.....After SC administration, serum pegfilgrastim concentrations reach a maximum approximately 24 hours later. After being absorbed into the systemic circulation, pegfilgrastim initiates its pharmacological effects by binding to the cell-surface G-CSF receptor on neutrophils, which is followed by internalization and degradation of the drug-receptor complex and is referred to as neutrophil-mediated clearance. The biological activity and mechanism of action of pegfilgrastim are identical to filgrastim as demonstrated by in vitro studies. However, in vivo testing in mice confirmed that pegfilgrastim increased ANC (ie, PD response) for a substantially longer period of time than filgrastim This prolonged effect stems from the covalent attachment of the PEG moiety, which causes pegfilgrastim’s hydrodynamic radius to be too large to be filtered by the glomerulus, thus virtually removing the kidneys as an elimination pathway. Therefore, the predominant pathway for elimination of pegfilgrastim becomes neutrophil-mediated clearance. Thus, the serum concentration of pegfilgrastim begins to decline at the onset of neutrophil recovery.”

Module 2.7.2 –Summary of Clinical Pharmacology states:

“In vitro studies have shown that the biologic activity and mechanism of action of pegfilgrastim are identical to those of filgrastim, and in vivo studies in animals and humans have demonstrated that a single dose of pegfilgrastim produces a sustained elevation of ANC comparable to multiple daily doses of filgrastim.”

4.4.2 Pharmacodynamics

The approved label for Neulasta does not include a section for pharmacodynamics. Per Module 2.7.2 Summary of Clinical Pharmacology - Acute Radiation Syndrome, Pharmacodynamics of Filgrastim and Pegfilgrastim are described on page 7 as follows: “Granulocyte colony-stimulating factor (G-CSF) exerts its pharmacological effect by binding to the G-CSF receptor (G-CSFR) that is present on peripheral neutrophils and precursor cells in the bone marrow. G-CSF produces dose-dependent increases in the number of total circulating neutrophils by 2 mechanisms: cytokinesis and accelerated granulopoiesis Filgrastim is a human G-CSF produced by recombinant DNA technology. Studies in cancer patients have shown a decrease in ANC during the first 30 to 60 minutes after filgrastim administration, which may be due to neutrophil margination to endothelial cells. This is followed by a steep increase in ANC above normal levels within 4 hours after dosing, which is predominately due to de-margination and mobilization of mature neutrophils from a bone marrow storage pool. Sustained increase of ANC after repeated dosing is due to acceleration of neutrophil granulopoiesis by mitotic expansion and decreased maturation time of neutrophil precursors. Depending on the peak ANC achieved, ANC return to normal levels within 1 to 7 days after discontinuation of dosing. No evidence of withdrawal effects of filgrastim discontinuation, including rebound neutropenia, has been reported. Neutrophils produced during a proliferative response to filgrastim have demonstrated normal or enhanced functional properties, as shown in assays of phagocytosis and chemotaxis **In vitro studies have shown that the biologic activity and mechanism of action of pegfilgrastim are identical to those of filgrastim, and in vivo studies in animals and humans have demonstrated that a single dose of pegfilgrastim produces a sustained elevation of ANC comparable to multiple daily doses of filgrastim.**”

4.4.3 Pharmacokinetics

Pharmacokinetic (PK) information was provided by the sponsor both in the approved label and in their submission. PK analysis was also performed by our Clinical Pharmacology staff who will enter it in our FDA archive system, DARRTS.

The label which is presently approved has the following information in Section 12.3 Pharmacokinetics:

“The pharmacokinetics of pegfilgrastim were studied in 379 patients with cancer. The pharmacokinetics of pegfilgrastim were nonlinear and clearance decreased with increases in dose. Neutrophil receptor binding is an important component of the clearance of pegfilgrastim, and serum clearance is directly related to the number of neutrophils. In addition to numbers of neutrophils, body weight appeared to be a factor. Patients with higher body weights experienced higher systemic exposure to pegfilgrastim after receiving a dose normalized for body weight.

A large variability in the pharmacokinetics of pegfilgrastim was observed. The half-life of Neulasta ranged from 15 to 80 hours after subcutaneous injection. In healthy volunteers, the pharmacokinetics of pegfilgrastim were comparable when delivered subcutaneously via a manual prefilled syringe versus via the On-body Injector for Neulasta.

No gender-related differences were observed in the pharmacokinetics of pegfilgrastim, and no differences were observed in the pharmacokinetics of geriatric patients (≥ 65 years of age) compared with younger patients (< 65 years of age)..... The pharmacokinetics of pegfilgrastim were studied in pediatric patients with sarcoma..... Renal dysfunction had no effect on the pharmacokinetics of pegfilgrastim..... The pharmacokinetic profile in patients with hepatic insufficiency has not been assessed.” (Reference: Approved label, Section 12.3)

Module 2.5 of the submission, Clinical Overview-Acute Radiation Syndrome, states on pages 17-19:

“.....the predominant pathway for elimination of pegfilgrastim becomes neutrophil-mediated clearance. Thus, the serum concentration of pegfilgrastim begins to decline at the onset of neutrophil recovery.....The PK of pegfilgrastim depends on the ANC profile and not on the type of injury (radiation or chemotherapy) that results in neutropenia. Therefore, the PK-PD characteristics of pegfilgrastim are expected to be similar in the HS-ARS and CIN settings.”

Dosing Regimen Recommendation for Adult Patients with HS-ARS:

“Based on the projection of the ARS model from NHPs to humans, Amgen

(b)(4)

Dosing Regimen Recommendation for Pediatric Patients with HS-ARS:

“Pegfilgrastim has not been approved for treatment of CIN in pediatrics; however, Amgen has conducted a phase 2 study for pediatric patients with sarcoma with a single 100 $\mu\text{g/kg}$ dose of pegfilgrastim or daily SC doses of filgrastim at 5 $\mu\text{g/kg}$ after chemotherapy. **The body weight-based dose of pegfilgrastim was chosen based on results in adult patients with breast cancer: a single SC dose of pegfilgrastim at 100 $\mu\text{g/kg}$ is as safe and non-inferior in reducing neutropenia and its**

complications as are daily injections of filgrastim at 5 µg/ kg..... Results from this pediatric study show that:

(1) The overall efficacy profile was similar after a single dose of pegfilgrastim at 100 µg/kg and daily doses of filgrastim at 5 µg/kg/day and was comparable with the experience in adults.

(2) The PK/PD relationship of pegfilgrastim in pediatric patients is similar to that in adults.

(b)(4)

Module 2.7.2 of the submission (Summary of Clinical Pharmacology) states:
“After SC administration, the absorption of pegfilgrastim from the SC site is slower than that of filgrastim; the time to reach the maximum pegfilgrastim concentration is approximately 24 hours after SC administration of 6 mg pegfilgrastim in humans. Pegylation of filgrastim renders renal clearance insignificant,....” (Reference: Module 2.7.2 page 9.)

Amgen’s stated the following in its prediction of overall **survival in humans in the HS-ARS setting (Reference Module 2.7.2, page 41):**

(b)(4)

Reviewer’s Comment: Although the 09/2015 approved label for Neulasta does not include an

(b)(4)

Amgen describes Population Modeling in Module 2.5 Clinical Overview Section 3.4. In Module 2.7.2 Summary of Clinical Pharmacology Section 4.2. Amgen states that the Overall Survival (OS) model in NHPs “.....adequately described the available data and confirmed that the OS for NHPs depends on the duration and depth of ANC suppression in NHPs exposed to lethal levels of radiation with (91.3% survival) and without (47.8% survival) pegfilgrastim administration. ANC is a valid surrogate to predict OS in irradiated NHPs because it explains 73% (95% CI: 38.7% to 99.9%) of pegfilgrastim treatment effect on OS.....”

The pharmacokinetics of Neulasta is not available in patients acutely exposed to myelosuppressive dose of radiation. Based on limited pharmacokinetics data in irradiated non-human primates, the area under the time-concentration curve (AUC), reflecting the exposure to pegfilgrastim in non-human primates at 300 mcg/kg dose of Neulasta appears to be similar to or exceed that in adult humans at 6 mg per chemotherapy cycle. Although the “Animal Rule” recommends that human exposure to a therapeutic drug exceed that achieved with an effective dose in an animal model, simulations conducted using a population pharmacokinetic model indicate that human exposures to pegfilgrastim at a dose of 6 mg on day 1 and day 8 for patients who might be acutely exposed to myelosuppressive doses of radiation are predicted to be less than the pharmacokinetics of NHP exposures at a dose of 300 mcg/kg on days 1 and 8. However, our clinical pharmacologists believe the human exposure to Neulasta at 6 mg on day 1 and day 8 after a radiation event result in comparable pharmacodynamics activity to the dose of 300 mcg/ kg in NHPs in reducing severe neutropenia.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2 Table of Studies/ Clinical Trials

<u>NAME</u>	<u>DETAILS</u>
“Animal Studies Showing the Effect of Pegfilgrastim on Animals Exposed to Sublethal and Lethal Doses of Radiation”	Amgen Module 2.4 (Non-clinical overview), has Table 2 on page 12 of submission which lists six animal studies that provide data that pegfilgrastim can improve survival after lethal irradiation. However, only two of the studies were conducted under GLP regulations, and the number of animals used in other studies was usually small, especially for NHPs. (See my Table 3 below)

NAME	DETAILS
Filgrastim and Pegfilgrastim Studies in Non-human Primates and Humans	Amgen Module 2.7.2 (Summary of Clinical Pharmacology), Figure 1 on page 10, lists 6 NHP studies, and 4 studies in healthy adults, 4 studies in adult patients, and 2 studies in pediatric patients. A summary of the individual studies is provided on pages 10 to 16 of module 2.7.2. In general, these studies showed that pegfilgrastim in doses ranging from 30 mcg/kg up to 300 mcg/kg were safe, and had similar efficacy and safety as daily doses of filgrastim. (See my Figure 1 below).
Study AXG15	A 60-Day Efficacy Study of Subcutaneous Filgrastim (Neupogen) to Treat the Hematopoietic Syndrome of The Acute Radiation Syndrome (ARS-HS) Following an LD50/60 of TBI in Rhesus Macaques, sponsored by NIAID.
Study AXG21	This is the pivotal trial for approval of pegfilgrastim for HS-ARS. This was a 60-Day Efficacy Study Of Subcutaneous Pegfilgrastim (Neulasta) To Treat The Hematopoietic Syndrome Of The Acute Radiation Syndrome (ARS-HS) Following An LD50/60 Of Total Body Irradiation (TBI) In Rhesus Macaques. Sponsored by NIAID.
Study AXG22	A 60-day Efficacy Study Of Subcutaneous Delayed Filgrastim (Neupogen) Administration To Treat The Hematopoietic Syndrome Of The Acute Radiation Syndrome (ARS-HS) Following An LD50/60 Of Total Body Irradiation (TBI) In Rhesus Macaques.
Gluzman-Poltorak et al, 2014	“Recombinant interleukin-12, but not granulocyte-colony stimulating factor, improves survival in lethally irradiated nonhuman primates in the absence of supportive care: evidence for the development of a frontline radiation medical countermeasure.”
FDA label for Neulasta	The FDA approved label for Neulasta has in Section 14, Clinical Studies, a summary of three randomized, double blind, controlled studies which support the use of Neulasta for the approved indication-“.....to decrease the incidence of

NAME	DETAILS
	infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.”

Table 3 Animal Studies Showing the Effect of Pegfilgrastim on Animals Exposed to Sublethal and Lethal Doses of Radiation

Author	Species	Radiation & Treatment	Radiation Source	Filgrastim Dose & Schedule	Key Results
Chua et al, 2014	Mouse C57/BL6	776 - 904 cGy (LD _{50/30} - LD _{70/30})	¹³⁷ Cs	Pegfilgrastim 100, 300, or 1000 µg/kg SC on day 1 or 1000 ug/kg on days 1 and 7 after TBI	Pegfilgrastim improved survival after TBI. One dose of pegfilgrastim on day 1 was as effective as two doses, on days 1 and 7.
Kiang, et al, 2014	Mouse B6D2F1/J	950 cGy + skin burn (15% body surface area) (Pain meds)	⁶⁰ Co	Filgrastim 10 µg/kg/day SC day 1 through 14; or pegfilgrastim 1000 µg/kg SC on days 1, 8 and 15 after TBI	Filgrastim and pegfilgrastim improved survival after radiation alone but only filgrastim improved survival after radiation combined with skin burn.
Farese et al, 2003	Monkey (Rhesus)	920 cGy+ autologous bone marrow transplantation, Supportive care	250 kVp x-ray	Pegfilgrastim single dose (300 or 100 µg/kg SC or IV, respectively)	Single doses of pegfilgrastim reduced duration of neutropenia, improved ANC nadir and time to recovery.
Hérodin, et al, 2007	Monkey (cynomolgus)	700 cGy Supportive care	⁶⁰ Co	Pegfilgrastim 300 µg/kg SC, 2 hrs and 8 days after TBI	Pegfilgrastim shortened the duration of neutropenia. Effects on survival were not reported in this study.
Farese et al, 2012b	Monkey (Rhesus)	600 cGy (LD _{10/30}) Supportive care	LINAC 2 MV photon source	Pegfilgrastim 300 µg/kg SC on day 1 or days 1 and 7 after TBI	Pegfilgrastim improved the speed of hematopoietic recovery after TBI. Administration of pegfilgrastim on days 1 and 7 was most effective in this study.
Hankey, 2014	Monkey (Rhesus)	750 cGy (LD _{50/60}) Supportive care	LINAC 2 MV photon source	Pegfilgrastim 300 µg/kg/day SC days 1 and 8 after TBI	Pegfilgrastim reduced 60-day mortality and decreased duration of neutropenia and thrombocytopenia compared to controls.

ANC = absolute neutrophil count; BID = twice daily; cGy = centiGray; G-CSF = granulocyte colony-stimulating factor; IV = intravenous; LDx/y = lethal dose for x% of animals by day y; SC = subcutaneous

^a Supportive care included fluids, antibiotics, and blood cell transfusions unless otherwise indicated. If nothing is specified, the study did not include supportive care.

(Reference: The above table is Amgen’s Table 2 in Module 2.4 Nonclinical Overview – Acute Radiation Syndrome)

Figure 1 Filgrastim and Pegfilgrastim Studies in Non-human Primates and Humans

2.7.2 – Summary of Clinical Pharmacology - Acute Radiation Syndrome
Pegfilgrastim Page 10

Figure 1. Filgrastim and Pegfilgrastim Studies in Non-human Primates and Humans

NHP Studies		Clinical Studies	
Healthy NHPs	Irradiated NHPs	Healthy Subjects	Patients
*PK94006 *PK97018	*Farese 2003 Farese 2012 Farese 2013 (Study AXG15) *Hankey 2014 (*Study AXG21)	Adult 91170 930243 *970230 *980230	Adult *970144 *980147 *980226 *990749 Pediatric 8814 *990130

* = pegfilgrastim studies; NHP = non-human primate

(Reference: The above figure is Amgen's Figure 1 in Module 2.7.2 – Summary of Clinical Pharmacology – Acute Radiation Syndrome)

5.2 Review Strategy

My review strategy was as follows:

- Review the sponsor's submission with close attention to the clinical risk-benefit of use of Neulasta for the treatment of the hematopoietic syndrome of the acute radiation syndrome (HS-ARS).
- Review the sponsor's FDA-approved label information
- Review the recommendations of the Advisory Committee on the use of Leukocyte Growth Factors for Radiation Injury which met on May 3, 2013.
- Review the "Animal Rule" to ensure regulatory compliance (See Section 6, Efficacy Summary).
- I requested the sponsor provide a literature review of the use of Neulasta in children.
- I also requested the FDA library perform a literature search to further identify the use

of Neulasta in children.

- We requested the FDA's Office of Surveillance and Epidemiology (OSE) to conduct a search on the utilization data of Neulasta in children,
- We requested the FDA's OSE to provide reports of adverse events on the use of Neulasta in children which had been reported in the FDA Adverse Event Reporting System (FAERS).
- We requested the FDA's Division of Hematology Products (DHP) to comment on known pediatric use of Neulasta in oncology indications (label and off-label), and any known issues associated with such use. We also asked our DHP colleagues to comment on any known dosing regimens of Neulasta in children and adults (label and off-label) and on the dosing considerations for the proposed ARS indication.
- We also asked the Division of Pediatrics and Mental Health (DPMH) for a consultation report on labeling and possible use of Neulasta in children.

5.3 Discussion of Individual Studies/Clinical Trials

Reviewer's Comments: My Table 3 (Amgen's Table 2 above from Module 2.4) includes references to 6 animal studies showing the effect of pegfilgrastim on animals exposed to radiation. The studies were published between 2003 and 2014. Two of the studies were in mice, and four in monkeys. Various doses of radiation were given. The animals were then treated with supportive care with or without pegfilgrastim. In general, those animals who received filgrastim or pegfilgrastim had an increased survival, or at least a decreased period of neutropenia versus the animals who received only supportive care. The only pegfilgrastim study which was GLP compliant was the one by Hankey (AXG21). A summary of some of the trials follows.

KIANG, et al, 2014: The mouse study by Kiang et al showed that "filgrastim and pegfilgrastim improved survival after radiation alone but **only filgrastim improved survival after radiation combined with skin burn.**" I have provided the details of Kiang's study in my Section 9.1.2, Other References below.

FARESE et al, 2012b showed that Pegfilgrastim improved the speed of hematopoietic recovery after TBI. Pegfilgrastim at 300 mcg/kg on days 1 and 7 after radiation was more effective than pegfilgrastim at 300 mcg/kg only on day 1, or filgrastim daily at 10 mcg/kg.

HANKEY, 2014, is a publication which describes Study AXG21 which is the pivotal trial for the use of Pegfilgrastim for HS-ARS. (See STUDY AXG21 below).

-STUDY AXG15 was the pivotal efficacy study which supported the efficacy supplement for **filgrastim (Neupogen) for HS-ARS** which was approved by the FDA in March 2015. This trial, sponsored by NIAID, had for the primary endpoint, a comparison of the number of Rhesus Macaques surviving at day 60. Neupogen at 10 mcg/kg/day starting 22-26h post LD 50/60 TBI improved survival [79% (19/24) versus 41% (9/22) in the control arm. All animals were euthanized

according to prespecified criteria except for three animals in the control arm that were found dead between Days 11-18. (Reference: Farese et al, 2013, and Amgen's module 2.4, page 11)

*-STUDY AXG21 was also sponsored by NIAID, and tested the efficacy of **pegfilgrastim (Neulasta) for treatment of ARS-HS**. It was submitted to the FDA as a final report on 3/25/2014. Prior to irradiation, animals were randomized to either a control (n = 23) or treated (n = 23) cohort. On Study Day (SD) 0, the NHPs were exposed to TBI at a targeted dose of 7.50 Gy. Following TBI, animals were administered SC injections of either the control article (Dextrose 5% in Water [D5W]) or Neulasta at 300-319 mcg/kg/d on SD 1 (20-28 hrs) and on SD 8. All animals were monitored for complete blood count (CBC), body weight (BW), core body temperature (CBT) and hydration status for 60 days. Animals received medical management consisting of intravenous (IV) fluids, antibiotics, blood transfusions, nutrition and other support as required. An interim analysis showed highly significant improvement in **survival in the Neulasta cohort (91.3% [21/23], [Chisquare test, p = 0.0014] as compared to the controls (47.8% [11/23])**. Since this crossed the boundary for testing for efficacy, these were the final data. (Reference: Hankey, 2014, and Amgen's module 2.4, pages 12-13).*

*-STUDY AXG22, also sponsored by NIAID, is titled: "A sixty-day efficacy study of subcutaneous delayed **filgrastim (Neupogen)** administration to treat the hematopoietic syndrome of the acute radiation syndrome (ARS-HS) following an LD50/60 of total body irradiation (TBI) in Rhesus Macaques." The results of this study show that **neupogen, started approximately 48 hours after radiation exposure, did not significantly improve 60-day survival** as compared to the placebo. (Reference: Farese et al, 2014, and Amgen's module 2.4 page 7)*

-FDA approved label for Neulasta: Section 14, Clinical Studies, states:

"Neulasta was evaluated in three randomized, double-blind, controlled studies. Studies 1 and 2 were active-controlled studies that employed doxorubicin 60 mg/m² and docetaxel 75 mg/m² administered every 21 days for up to 4 cycles for the treatment of metastatic breast cancer. Study 1 investigated the utility of a fixed dose of Neulasta. Study 2 employed a weight-adjusted dose. In the absence of growth factor support, similar chemotherapy regimens have been reported to result in a 100% incidence of severe neutropenia (ANC < 0.5 x 10⁹/L) with a mean duration of 5 to 7 days and a 30% to 40% incidence of febrile neutropenia. 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, and the efficacy of Neulasta was demonstrated by establishing comparability to filgrastim-treated patients in the mean days of severe neutropenia.

In Study 1, 157 patients were randomized to receive a single subcutaneous injection of Neulasta (6 mg) on day 2 of each chemotherapy cycle or daily

subcutaneous filgrastim (5 mcg/kg/day) beginning on day 2 of each chemotherapy cycle.

In Study 2, 310 patients were randomized to receive a single subcutaneous injection of Neulasta (100 mcg/kg) on day 2 or daily subcutaneous filgrastim (5 mcg/kg/day) beginning on day 2 of each chemotherapy cycle.

Both studies met the major efficacy outcome measure of demonstrating that the mean days of severe neutropenia of Neulasta-treated patients did not exceed that of filgrastim-treated patients by more than 1 day in cycle 1 of chemotherapy. The mean days of cycle 1 severe neutropenia in Study 1 were 1.8 days in the Neulasta arm compared to 1.6 days in the filgrastim arm [difference in means 0.2 (95% CI -0.2, 0.6)] and in Study 2 were 1.7 days in the Neulasta arm compared to 1.6 days in the Filgrastim arm [difference in means 0.1 (95% CI -0.2, 0.4)].

A secondary endpoint in both studies was days of severe neutropenia in cycles 2 through 4 with results similar to those for cycle 1.

Study 3 was a randomized, double-blind, placebo-controlled study that employed docetaxel 100 mg/m² administered every 21 days for up to 4 cycles for the treatment of metastatic or non-metastatic breast cancer. In this study, 928 patients were randomized to receive a single subcutaneous injection of Neulasta (6 mg) or placebo on day 2 of each chemotherapy cycle. Study 3 met the major trial outcome measure of demonstrating that the incidence of febrile neutropenia (defined as temperature $\geq 38.2^{\circ}\text{C}$ and ANC $\leq 0.5 \times 10^9/\text{L}$) was lower for Neulasta-treated patients as compared to placebo-treated patients (1% versus 17%, respectively, $p < 0.001$). The incidence of hospitalizations (1% versus 14%) and IV anti-infective use (2% versus 10%) for the treatment of febrile neutropenia was also lower in the Neulasta-treated patients compared to the placebo-treated patients.”

(Reference: Neulasta label dated 09/2015 v16)

-Gluzman-Poltarak, 2014, showed no improvement in survival for G-CSF (filgrastim) after radiation injury when no supportive care was provided.

Please see my Reviewer’s Comments for these trials in my section 9.1.2 Other References. I agree with the sponsor that “Radiation injury in humans is likely to present with variable exposure, confounding injuries and co-morbidities. G-CSF has been shown to increase survival after radiation injury..... population modeling based on human and nonhuman primate data shows potential for benefit of G-CSF and pegylated G-CSF over a range of radiation exposures or chemotherapy injury, a window of time of initiating treatment and a range of doses While these two publications (i.e. Kiang and Gluzman-Poltarak) highlight that there may be conditions in which G-CSF will not be effective, the weight of evidence suggests that G-CSF has the potential to improve survival after radiation injury.” (Reference: Amgen submission, module 2.4, page 8.)

6 Review of Efficacy

Efficacy Summary (Reference Amgen's Module 2.5 Section 4)

No new clinical efficacy studies of pegfilgrastim were conducted in support of the proposed indication. Efficacy studies of Neulasta could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Efficacy for the use of Neulasta in the Acute Radiation Syndrome (ARS) setting of myelosuppression is based on the results of the **non-human primate study AXG21. The title of study AXG21 was “A Sixty-Day Efficacy Study of Subcutaneous Pegfilgrastim (Neulasta®) to Treat the Hematopoietic Syndrome of the Acute Radiation Syndrome (ARS-HS) Following an LD 50/60 of Total Body Irradiation (TBI) in Rhesus Macaques.”** This study showed a survival advantage for the use of Neulasta in non-human primates exposed to a dose of radiation which was lethal in 50% of the control animals. This study is pivotal and is supportive because it satisfies the regulatory guidance of the “Animal Rule” (21 CFR 601.90, Subpart H).

The key aspects of the “Animal Rule” are:

1. Reasonably well-understood pathophysiological mechanism of radiation injury and biological plausibility for filgrastim efficacy
2. Pivotal data generated in a well-characterized model in nonhuman primates expected to be predictive of the response in humans
3. Pivotal nonhuman primate study endpoint (survival) directly related to the desired benefit in humans
4. Pharmacokinetic (PK) and pharmacodynamic (PD) data from nonhuman primates and humans allows selection of an effective dose in humans

Section 2.4 of the Amgen submission (Nonclinical Overview, Acute Radiation Syndrome, pages 5 and 6 describes the results of study AXG21 as follows:

“Pegfilgrastim significantly increased 60-day survival compared to vehicle in a well characterized NHP model of radiation injury (91.3% [21 of 23] survival in the pegfilgrastim group vs 47.8% [11 of 23] survival in the control group) when administered at 300 to 319 µg/kg subcutaneously (SC) once on study day 1 (20 to 28 hours after radiation exposure on study day 0), and again on study day 8. Pegfilgrastim significantly decreased duration of grade 3 and 4 neutropenia (absolute neutrophil count [ANC] < 500/µL and ANC < 100/µL, respectively, and shortened recovery to ANC > 1000/µL). The duration of thrombocytopenia and time to recovery of platelet counts (PLT) ≥ 20,000/µL was also significantly reduced by pegfilgrastim treatment.”

Reviewer's Comment: I believe that the AXG21 trial satisfies the criteria of the Animal Rule described above. Based on the efficacy demonstrated in study AXG21 and the regulatory framework of the Animal Rule, I believe that Neulasta will be effective in humans for the additional indication of treatment of radiation-induced myelosuppression (Hematopoietic Syndrome of the Acute Radiation Syndrome, HS-ARS).

6.1 Indication

The draft additional indication statement in the sponsor's submission is:

(b)(4)

(b)(4) Efficacy studies of Neulasta could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Approval of this indication was based on efficacy studies conducted in animals.” (Reference: Draft Label in Amgen's submission dated February 2015)

Reviewer's Comment: I disagree

6.1.1 Methods

The AXG21 study was designed as a two arm, randomized, blinded study conducted under GLP. The study was powered to show a 30% difference in 60-day survival between control and Neulasta arms using a two-tailed chi square test at a 5% significance level.

Rhesus Macaques were exposed to a LD50/60 total body irradiation (TBI). Neulasta was subcutaneously administered once per week for two weeks at 300-319 mcg/kg/dose. There were two doses, first dose administered at 20-26h after the TBI and the second dose on day 8. The Neulasta dose and dose regimen in this study were selected based on a previous PK/PD study, in which administration of Neulasta at 300 mcg/kg/dose on day 1 and day 7 post TBI was most effective at improving neutrophil recovery. Dextrose 5% in Water (D5W) was used as a control agent.

Extensive medical management and supportive care, including whole blood transfusion and prophylactic antibiotic treatment, were provided according to the

prespecified criteria. The primary endpoint was overall survival. Secondary endpoints included, but were not limited to, durations of neutropenia, thrombocytopenia, and febrile neutropenia (FN). The interim efficacy analysis was conducted after 58% of the animals had completed the study. The study was then terminated.

The interim analysis revealed that Neulasta significantly improved overall survival [91.3% (21/23) Neulasta arm vs. 47.8% (11/23) in the control arm, $p = 0.0014$. Animals were euthanized in a blinded manner according to prespecified criteria. **Some key secondary endpoints were met, which included, but were not limited to, the following:**

1. Shortened the duration of neutropenia with the median duration of ANC < 500/mcL: 14 days in the Neulasta arm vs. 18 days in the control arm, and ANC < 100/mcL: 8 vs. 12 days).
2. Shortened the time to recovery from neutropenia with the median time-to-recovery to ANC > 500/mcL: 18 in the Neulasta arm vs. 23 days in the control arm; ANC > 1,000/mcL: 20 vs. 25 days)
3. Shortened duration of thrombocytopenia with the median duration of PLT < 20,000/mcL: 11 in the Neulasta arm vs. 16 days in the control arm)
4. Shortened the time to recovery from thrombocytopenia (the median time-to recovery to PLT $\geq$ 20,000/mcL: 20 days in the Neulasta arm vs. 26 days in the control arm)
5. Reduced numbers of blood transfusions with a total of 47 in the Neulasta arm vs. 80 in the control arm
6. Reduced the mean percent of days when animals had Febrile Neutropenia (FN) (mean 11% of days in the Neulasta arm vs. 18% of days in the control arm, $p = 0.0488$)
7. Reduced supportive care including the mean frequency of antibiotic administration with the mean frequency of antibiotic administration: 34% in the Neulasta arm vs. 61% in the control arm, $p < 0.0001$

6.1.2 Demographics

Not applicable since efficacy was determined by animal study AXG21.

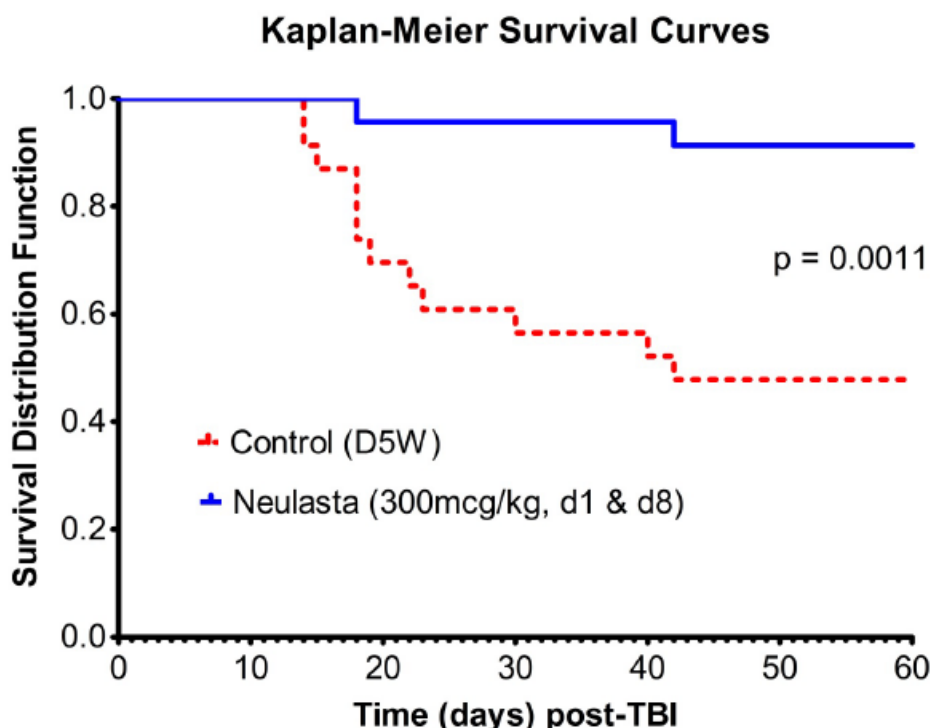
6.1.3 Subject Disposition

Animals were euthanized if still surviving 60 days after radiation.

6.1.4 Analysis of Primary Endpoint(s)

Pegfilgrastim significantly increased 60-day survival compared to vehicle in a well-characterized NHP model of radiation injury (91.3% [21 of 23] survival in the pegfilgrastim group vs 47.8% [11 of 23] survival in the control group) when administered at 300 to 319 $\mu\text{g/kg}$ subcutaneously (SC) once on study day 1 (20 to 28 hours after radiation exposure on study day 0), and again on study day 8.
(Reference: Amgen submission, Module 2.4 Nonclinical Overview)

Figure 2 Kaplan-Meier Survival Curves



Survival of rhesus macaques administered Neulasta (n = 23) or control, D5W, (n = 23) as a function of time after 7.50 Gy TBI. The log-rank test of these data shows that the difference between the survival curves is statistically and highly significant ($P = 0.0011$). (Reference: Amgen Module 4.2.1.1 AXG21, Final Report, page 43 of 69).

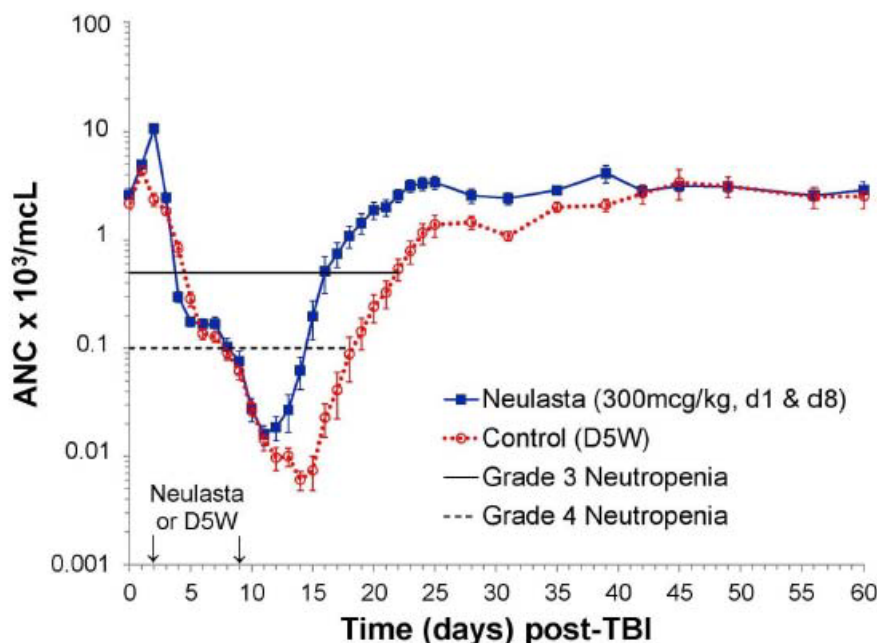
6.1.5 Analysis of Secondary Endpoints(s)

Secondary objectives included evaluation of mean survival time (MST) of decedents, ANC nadir, first and last day of neutropenia, duration of neutropenia, time to recovery to $ANC > 500/\text{mcL}$ and $ANC > 1,000/\text{mcL}$, incidence of absolute neutropenia, PLT nadir, first day of thrombocytopenia, duration of thrombocytopenia, time to recovery from thrombocytopenia, first day and number of transfusions, first day and frequency of FN, frequency of fever, incidence of infection, frequency of antibiotic administration, and spleen measurements. Other evaluations include incidence of antibiotic resistance, incidence and severity of diarrhea, incidence and severity of body weight loss, and incidence of significant pathology in tissues collected at necropsy.

“Following exposure to lethal doses of TBI, reduction of circulating ANC was faster in the Neulasta-treated NHP than in the D5W-treated animals where ANC decreased to $< 500/\text{mcL}$ by $SD 4 \pm 0.1$ (mean $\pm$ SEM) and $SD 5 \pm 0.1$, respectively. The difference in the first day that $ANC < 500/\text{mcL}$ between the two cohorts was statistically significant (Mantel-Haenszel chi-square test, $p = 0.0009$). The ANC continued to decrease to $< 100/\text{mcL}$ by $SD 8 \pm 0.4$ and $SD 7 \pm 0.4$ in both test and control cohorts, respectively; however, this difference was not statistically significant.

Neulasta significantly increased the ANC nadir to $10/\text{mcL} \pm 3$ from $2/\text{mcL} \pm 1$ in the D5W cohort (Wilcoxon rank sum test, $p = 0.0377$) but did not significantly affect the incidence of absolute neutropenia (ANC = $0/\text{mcL}$) which was 47.83% (11/23) and 65.22% (15/23) of Neulasta- and D5W-treated animals, respectively.”
(Reference: AXG21 and Amgen module 4.2.1.1 pages 39-40 and 44-45 of 905.)

Figure 3 Absolute Neutrophil Count in Rhesus Macaques Following 750 cGy Irradiation and treatment with Neulasta or D5W on days 1 and 7



Mean ($\pm$ SEM) neutrophil count $\times 10^3/\mu\text{L}$ in the peripheral blood of rhesus macaques administered Neulasta® ($n = 23$) or 5% dextrose in water ($n = 23$) as a function of time after TBI.

ANC = absolute neutrophil count; D5W = 5% dextrose in water; SEM = standard error of the mean; TBI = total body irradiation.

Source: Amgen Module 2.4, page 14, and Study Report AXG21

6.1.6 Other Endpoints

Study AXG 21 describes primary and secondary endpoints on pages 39-40 of 905. No other endpoints are described. However, descriptive statistics are given such as

Incidence of antibiotic resistance in blood/tissue, culture positive microbial cultures, incidence of diarrhea, severity of diarrhea, incidence of significant pathology in the bone marrow, heart, lung, liver, spleen, kidney, thymus, lymph nodes, and small and large intestine after necropsy. There were no significant histopathology findings attributable to Neulasta treatment among the surviving NHPs. (Reference pp 54-60 of 902 pages and 67 of 902 pages.)

Reviewer's Comment: The clinical items described above as "Other Endpoints" were isolated, and I do not believe of any clinical significance.

6.1.7 Subpopulations

AXG21 involved a total of 46 rhesus macaques (23 males/group), (b)(4)
(b)(4), 3.9–5.5 kg body weight, were used.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Two big issues are 1. Dose for humans for treatment of HS-ARS, and 2. Treatment of children. I discuss below these two issues. See also my Section 4.4.3, Pharmacokinetics, above.

6.1.8.1 Dose for humans

It is impossible to determine exactly the best human dose for Neulasta for radiation sickness since there have not been, nor probably will there ever be, pharmacokinetic data on humans exposed to radiation and treated with Neulasta. According to the Animal Rule, pharmacokinetic and pharmacodynamic data from nonhuman primates (NHP's) and humans should allow selection of an effective dose. The dose given in AXG21 to NHP's was 300 mcg/kg on days 1 and 8 after radiation. The dose provided in the approved Neulasta label is for 6 mg as a single dose for all adults at risk of developing a neutropenic fever after receiving myelosuppressive chemotherapy. (b)(4)

The "Animal Rule" recommends that in terms of drug exposure the dose to humans be higher, if possible, than the equivalent dose used in non-human primates. For example, the pegfilgrastim dose to NHPs in AXG21 was 300 mcg/ kg. Therefore, one might expect that the dose in humans would be more than 300 mcg/ kg. However, our division is proposing a dose of 6 mg for anyone weighing at least 45 kg, and 100 mcg/kg for those weighing less than 45 kg. This is based on the recommendations of our pharmacometric staff: 6 mg for a 60 kg adult would be equivalent to 100 mcg/ kg, but for a 120 kg adult, a dose of 6 mg would equal 50 mg/ kg. Our pharmacometric

staff is recommending the dose of 100 mcg/ kg in children, or 6 mg per person weighing at least 45 kg because such doses have been safely and effectively used in children and adults receiving chemotherapy. The safety profile of higher doses in humans is unknown.

6.1.8.2 Treatment of children

Although Amgen (b)(4) in a nuclear or radiologic disaster, it will be more effective and efficient to give only 2 doses of Neulasta one week apart (b)(4) Supporting our recommendation are a Consultation Report from the Division of Hematology Product, FAERS data, and data on utilization in pediatrics. We have also requested a consultation report from the Division of Pediatrics and Maternal Health (DPMH) which we had not received at the time of this review. Amgen provided responses to our pediatric Information Requests of 23 March 2015 and 9 July 2015. I discuss these items separately below. I will first provide the information provided by Amgen in the Neulasta label, "Section 8.4 Pediatric Use".

6.1.8.2.1. Neulasta Label

Label dated 09/2015, Section 8.4, Pediatric Use, states:

"Safety and effectiveness of Neulasta in pediatric patients have not been established. The adverse reaction profile and pharmacokinetics of pegfilgrastim were studied in 37 pediatric patients with sarcoma. The mean ($\pm$ standard deviation [SD]) systemic exposure (AUC_{0-inf}) of pegfilgrastim after subcutaneous administration at 100 mcg/kg was 22.0 ($\pm$ 13.1) mcg·hr/mL in the 6 to 11 years age group (n = 10), 29.3 ($\pm$ 23.2) mcg·hr/mL in the 12 to 21 years age group (n = 13), and 47.9 ($\pm$ 22.5) mcg·hr/mL in the youngest age group (0 to 5 years, n = 11). The terminal elimination half-lives of the corresponding age groups were 20.2 ($\pm$ 11.3) hours, 21.2 ($\pm$ 16.0) hours, and 30.1 ($\pm$ 38.2) hours, respectively. The most common adverse reaction was bone pain."

Reviewer's Comment: Although Amgen states in the above section of the label that "Safety and effectiveness of Neulasta in pediatric patients have not been established." Amgen also states that ".....pharmacokinetics of pegfilgrastim were studied in 37 pediatric patients with sarcoma." I will describe below some other information supporting the use of Neulasta in children.

6.1.8.2.2 Consultation Report from the Division of Hematology Products

We requested that our colleagues in the Division of Hematology Products (DHP) comment on the known pediatric use of Neulasta in the oncology setting. Their response was entered in the FDA's DARRTS archival system on 08/06/2015 and provided the following information:

Amgen was unable in the past to complete accrual of a randomized study to determine the safety and efficacy in the pediatric population. Labels prior to 2010 had stated: "The 6 mg fixed dose single-use syringe formulation should not be used in infants, children, and smaller adolescents weighing less than 45 kg."

Literature Review

On June 4, 2015 we sent Amgen an Information Request asking for a review of all safety information on the use of Neulasta in children. "This review should include all information from Amgen sponsored studies, a review of the literature, and a review of all safety data bases available to Amgen. (b)(4)

(Reference Amgen 1.11.3- Response to FDA
Information Request 04 June 2015, pp 6-7, Section 2.1.3.2 Safety Analysis –
Literature)

Our colleagues in DHP then reviewed a literature search provided by the FDA library. They found 22 articles (which I include in my Appendix 9.1.1) which describe the safety and dosing of Neulasta in pediatric patients as young as 4 months old. Most patients were treated at a dose of 100 mcg/kg but doses ranged from 55 mcg/kg to 300 mcg/kg. In randomized studies, it appears that pegfilgrastim at 100 mcg/ kg provided a similar response compared with filgrastim at a dose of 5-10 mcg/ kg/ day.

Our colleagues in DHP also reviewed the use of Pegfilgrastim in Children's Oncology Group (COG) protocols. There are current pediatric solid tumor protocols which allow or suggest use of pegfilgrastim as a post chemotherapy myeloid growth factor for the following pediatric malignancies: Neuroblastoma, Germ Cell Tumor, Hepatoblastoma, Lymphoma, Ewing Sarcoma, Osteosarcoma, Soft Tissue Sarcoma, and Wilms Tumor.

The DHP consult report concluded that:

- Pegfilgrastim is used in pediatric patients for post chemotherapy support and as an adjunct to stem cell mobilization.
- Patients as young as 4 months have been documented to receive pegfilgrastim without undue toxicity.
- There are no reports that suggest children experience unexpected, more severe, or more frequent adverse events than adults.
- The most frequent dose documented in the literature is 100 mcg/kg but higher doses up to 300 mcg/kg have been administered, as an adjunct to stem cell mobilization without undue toxicity.
- When pegfilgrastim was compared to filgrastim it was never assessed to be inferior.
- The dosing schedule of a single dose is a particular advantage in a pediatric population, as injections are frequently perceived as noxious in this population.

- Since Pegfilgrastim has the same mechanism of action in the pediatric population as in the adult population, efficacy can be extrapolated. There is adequate pediatric PK data in the label to guide dosing in children.
- Safety data cannot be extrapolated to the HS-ARS indication, but there has been sufficient use of pegfilgrastim in the pediatric population to demonstrate there are no safety signals that would preclude the use of this product in children.

6.1.8.2.3 Amgen Response 1 May 2015 to FDA Information Request (IR) of 23 March 2015

FDA Information Request of 23 March 2015 includes the following **FDA Request 4**:

“We request you provide information on the safety of the use of Neulasta® in children from neonate to adult (or < 18 years of age). Please include information from your database and any external sources you may find.”

Amgen’s response included analysis of Study 990130 and a literature review of the use of pegfilgrastim in children.

-Study 990130 was a study of single dose per cycle of pegfilgrastim or daily filgrastim as an adjunct to chemotherapy in pediatric sarcoma patients. 34 children were treated with pegfilgrastim in a 6:1 allocation to receive either pegfilgrastim at 100 mcg/kg or daily SC doses of filgrastim 5 mcg/kg. Per Amgen, “The most frequently reported > grade 3 adverse events in the 28 days to 23 month age group were febrile neutropenia (75%) and mucosal inflammation (75%). Anemia and febrile neutropenia were the most frequently reported > grade 3 adverse events in both the 2 year to 11 year age group and 12 to 18 year age group [anemia:67% both age cohorts; and febrile neutropenia 67% and 42%, respectively].”

Reviewer’s Comments: The adverse events described above are consistent with side effects of the chemotherapy, not pegfilgrastim.

Amgen’s response to FDA Information Request 4 includes a summary of 14 articles which describe the use of pegfilgrastim in children from age 0 to 23 who received pegfilgrastim after chemotherapy or for mobilization of stem cells. Adverse events for the most part were due to the underlying malignancy, or the common side effects of pegfilgrastim i.e. bone pain, as seen in adults. (See my section 9.1.1, References supporting the use of pegfilgrastim in pediatrics)

(Reference Amgen module 1.11.3, Response to IR of 23 March 2015, pages 17-35.)

Reviewer’s Comments: I have reviewed the abstracts of the 14 articles Amgen provided and it is my conclusion that these articles support the safe use of Neulasta in children.

6.1.8.2.4 Amgen Response 17 July 2015 to FDA Information Requests (IR) of 9 July 2015

On July 9, 2015 we sent Amgen two Information Requests.

In the first FDA IR we stated that [REDACTED] (b)(4)

[REDACTED] We also stated “.....we request copies of all the references you have found in your literature search and indicate which ones you have used in responding to our recent information request. We will conduct our own independent review of the literature.”

Amgen responded to the IR that they had reviewed forty-seven abstracts and their conclusion was that “.... [REDACTED]” (b)(4)

In the second FDA IR we stated that “We disagree with your response to Request 2 in our (previous) information request where you state that [REDACTED]” (b)(4)

Amgen responded that [REDACTED] (b)(4)

(Reference: Amgen Module 1.11.3 – Response to FDA Information Request 09 July 2015, pp.3-6 ,

Reviewer’s Comment: Although Amgen recommended that Neulasta [REDACTED] (b)(4)

[REDACTED] (See my section 4.4.3, Pharmacokinetics, above)

6.1.8.2.5 Pegfilgrastim Pediatric Data from the FDA Adverse Event Reporting System (FAERS)

-October 21, 2014 the FDA’s Office of Surveillance and Epidemiology completed a Pharmacovigilance Memo which provided an overview of the pediatric cases for pegfilgrastim in FAERS up until October 2014. .

The October 2014 memo summarizes 55 cases comprising 21 reports of labeled events (9 allergic reactions ranging from a rash to anaphylaxis, 7 exposures during pregnancy, 3 leukocytosis/increased white blood cell counts, 2 injection site reactions) and 34 reports of unlabeled events (20 hematologic events, 8 miscellaneous adverse events, 3 medication errors, and 3 cases of interest). Except for the cases of interest and the medication errors, the memo points out that the cases are confounded by disease and concomitant medications, making causal association with a specific drug difficult to determine.

The medication errors included overdosing of two patients, aged 1.5 and 2 years, who each received the full syringe containing 6 mg Neulasta followed by white blood cell counts above 50,000/mcL in both cases but no adverse clinical events. The prescribed doses were 1 mg and 100 mcg/kg for the 1.5-year-old and 2-year-old, respectively. According to the published case report, the dose of 6 mg was equivalent to 937 mcg/kg for the 2-year-old. In the third medication error, the physician suspected intramuscular rather than subcutaneous administration.

The cases of interest were a possible interaction with vincristine causing neurotoxicity, a case of febrile neutropenia, and a case of thrombocytosis. Neulasta may have contributed to the adverse events in the cases of interest but none were conclusive.

The reviewer concluded that the drug labeling accurately described warnings and precautions, and that: “There are no new significant safety concerns for Neulasta identified in the pediatric cases at this time.”

-August 28, 2015 an updated Pharmacovigilance Review stated that the FDA received seven new adverse event cases with pegfilgrastim since the 2014 memo. The new cases included **one potential dosing error report**. (The 2014 memo had included two dosing error reports.) This review identified one case in which a prefilled syringe containing 6 mg Neulasta was dispensed to fill a prescription for a 1.7-mg dose. The administered dose was an unknown dose less than 6 mg, but the child’s WBC count was 108.5 (no units) 3 days later.

These medication errors occurred with off-label use in pediatric patients; Neulasta is currently approved only for use in adults. The reviewer did not identify any new safety concerns in the remaining cases.

Reviewer’s Comment: The three dosing errors described above highlight the difficulty for providers to administer 100 µg/ kg from the 6 mg / 0.6 mL prefilled syringe. An additional presentation for pediatrics weighing less than 45 kg is highly recommended.

6.1.8.2.6 Data on utilization in pediatrics

We requested our colleagues in the FDA’s Office of Surveillance and Epidemiology to provide us with information about the use of Neulasta in children. Their Drug Utilization Review dated October 7, 2015 has the following Executive Summary.

EXECUTIVE SUMMARY

“.....the Division of Epidemiology (DEPI II) examined utilization of pegfilgrastim in pediatric patients based on U.S. non-federal hospital data and health plan claims data projected to the U.S commercially insured population from 2010 through 2014.

Our analyses of U.S. non-federal hospital data showed that (b)(4) **pediatric patients aged 0-17 years (less than 1% of total patients) had a hospital discharge billing**

for pegfilgrastim in 2014. During the five year period, **the use of pegfilgrastim in the pediatric population** (b)(4) **patients in 2010** (b)(4) **patients in 2014.** Patients aged 7-12 accounted for the largest proportion of pediatric use at (b)(4) (b)(4), followed by patients aged 13-17 years at (b)(4) of pediatric patients. However, the overall use of pegfilgrastim in pediatric patients in the hospital data may be underestimated as standalone pediatric and other specialty hospitals are not available in the hospital database.

Our analyses of U.S. health plan claims data projected to the U.S. commercially insured population showed that **approximately** (b)(4) **pediatric patients aged 0-17 years had a prescription and/or procedure claim for pegfilgrastim in 2014.** During the defined study period, the pediatric use of pegfilgrastim (b)(4) patients in 2010 to (b)(4) 2014. Patients aged 13-17 years accounted for the largest proportion of use at (b)(4) followed by patients aged 3-6 years at (b)(4) (b)(4). Based on the claims data, (b)(4) pediatric patients had a prescription and/or procedure claim for pegfilgrastim AND a claim for the selected diagnoses codes for radiotherapy in 2014.

The overall findings from these analyses show use of pegfilgrastim in the pediatric population during the examined time period although current labeling states that the safety and effectiveness in pediatric patients have not been established.”

REVIEWER’S COMMENT: *The data in the above Executive Summary are consistent with significant use of pegfilgrastim (Neulasta) in children from age 0-17 even though Neulasta is not approved for administration to children. This utilization data in combination with the above described safety data support expanding the label for Neulasta to include all age groups.*

6.1.8.2.7 Consultation Report from the Division of Pediatrics and Maternal Health

We have requested a consultation report from the FDA’s Division of Pediatrics and Maternal Health (DPMH) regarding the use of Neulasta in children. As of the time I completed this review, we had not yet received a report from DPMH. This and other consultation reports will be entered in the FDA’s DARRTS archival system when complete.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Neulasta has generally been used only once per chemotherapy cycle with myelosuppressive chemotherapy to reduce the incidence of febrile neutropenia. Such administration rarely lasts for more than a few months, and has a very safe track record. I know of no reduction of efficacy or tolerance of effects with repeated use.

6.1.10 Additional Efficacy Issues/Analyses

In summary, AXG15 and AXG21 are the two most significant studies which directly or indirectly support the effective use of Neulasta administration for the treatment of HS-ARS in humans.

AXG21 is the pivotal trial for Neulasta which showed a survival advantage in NHPs. The NHPs exposed to radiation and then treated with Neulasta had a 92% 60-day survival versus 48% 60-day survival for the NHPs exposed to radiation and then treated with D5W.

AXG15 is the pivotal trial for Neupogen which shows a survival advantage in NHPs. The NHPs exposed to radiation and then treated with Neupogen had a 79% 60-day survival versus 41% 60-day survival for the NHPs exposed to radiation and then treated with D5W. This trial indirectly supports the use of Neulasta for the treatment of HS-ARS, since Neupogen and Neulasta appear to have a similar mechanism of action. The main difference between the drugs is that Neupogen is a short-acting leukocyte growth factor which requires a daily injection, while Neulasta is a long-acting leukocyte growth factor which only requires a weekly injection.

Both of the above trials were GLP trials which included extensive supportive care. More information about each trial is described above in my Sections 1.2, 2.5, 5.1, 5.3, and 6.

7 Review of Safety

Safety Summary (Reference Amgen's Module 2.5 Section 5)

Reviewer's Safety Summary Comment: Although the sponsor did not submit any new clinical data, and although the approved label does describe contraindications, warnings and precautions, and adverse reactions, I believe that overall the product is safe based on extensive use for over 10 years.

7.1 Methods

No New Clinical Data Was Submitted. Clinical safety information to support the use of Neulasta (pegfilgrastim) in the Acute Radiation Syndrome (ARS) setting was primarily drawn from existing clinical safety data from human studies previously conducted to support approval of pegfilgrastim in other indications. No new clinical studies were conducted in support of the ARS indication. As such, a clinical summary of safety, and an integrated summary of safety were not included with the submission. (Reference Amgen's submission section 1.11.3 - Response to FDA Information Request of 23 March 2015)

The sponsor relies on a database of extensive, safe use since 2002 when Neulasta was initially approved by the FDA. This lengthy period of observation and follow-up of (b)(4) patients who received the drug world-wide provides assurance of the overall safety of Neulasta in the indicated population. Some trials on healthy subjects were performed in the past and are described below.

7.2 Adequacy of Safety Assessments

No New Clinical Data Submitted

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

No New Clinical Data Submitted

7.2.2 Explorations for Dose Response

Our FDA Clinical Pharmacologists and Pharmacokinetic Staff worked diligently to make a recommendation for a dose of Neulasta for the radiation indication. They have recommended a dose for ARS-HS of 6 mg on days 1 and 8 after a radiation exposure of 2 Gray or more for adults and children weighing ≥ 45 kg, and a dose of 100 mcg/kg on days 1 and 8 after a radiation exposure for those weighing less than 45 kg. (See Section 4.4.3 Pharmacokinetics, above)

7.2.3 Special Animal and/or In Vitro Testing

No Clinical Data Submitted

7.2.4 Routine Clinical Testing

No Clinical Data Submitted

7.2.5 Metabolic, Clearance, and Interaction Workup

The approved label dated 09/2015 states in section 8.6 Renal Impairment “In a study of 30 subjects with varying degrees of renal dysfunction, including end stage renal disease, renal dysfunction had no effect on the pharmacokinetics of pegfilgrastim. Therefore, pegfilgrastim dose adjustment in patients with renal dysfunction is not necessary.....”

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

No Clinical Data Submitted

7.3 Major Safety Results

No New Clinical Data Submitted. Section 5, Overview of Safety, of the submission states:

“In a placebo-controlled clinical trial in patients receiving pegfilgrastim after nonmyeloablative cytotoxic chemotherapy, the most common adverse reactions occurring in $\geq 5\%$ of patients and with a between-group difference of $\geq 5\%$ higher in the pegfilgrastim group were bone pain and pain in the extremity (Neulasta USPI 2014). Leukocytosis was observed with a frequency of $< 1\%$, and no complications attributable to leukocytosis were reported. Warnings described in the USPI include peripheral blood progenitor cell mobilization use, splenic rupture, acute respiratory distress syndrome, allergic-type reactions, and sickle cell crises in patients with sickle cell disorders. Precautions in the USPI include simultaneous use with chemotherapy or radiation therapy and potential effects on malignant cells. The possibility that pegfilgrastim can act as a growth factor for any tumor type cannot be excluded.”

7.3.1 Deaths

The Neulasta label states in Section 5, Warnings and Precautions, that fatalities can occur due to splenic rupture following the administration of Neulasta. The label also states that fatalities can occur in patients with sickle cell disorders receiving filgrastim, the parent compound of pegfilgrastim.

7.3.2 Nonfatal Serious Adverse Events

The Neulasta label states in in Section 6, Adverse Reactions, that the following serious adverse reactions may occur:

- Splenic Rupture
- Acute Respiratory Distress Syndrome
- Serious Allergic Reactions
- Allergy to Acrylics (for those using the On-body Injector)
- Sickle Cell Disorders
- Glomerulonephritis
- Leukocytosis
- Capillary Leak Syndrome
- Potential Stimulatory Effect on Malignant Cells

7.3.3 Dropouts and/or Discontinuations

No Clinical Data Submitted

7.3.4 Significant Adverse Events

In addition to what I described above in Sections 7.3.1 and 7.3.2, the Neulasta label states in Section 6.1 Clinical Trials Experience that the most common adverse reactions occurring in $\geq 5\%$ of patients and with a between-group difference of $\geq 5\%$ higher in the pegfilgrastim arm in placebo controlled clinical trials are **bone pain and pain in extremity**. Per the label, section 6.3 Postmarketing Experience includes the above reactions, and **Sweet's Syndrome (Acute Febrile Neutrophilic Dermatitis)**

(b)(4)

7.3.5 Submission Specific Primary Safety Concerns

Reviewer's Comment: *I have 2 main concerns.*

My first concern is the use of Neulasta in children less than 45 kg. The only presentation available is the pre-filled syringe of 6 mg Neulasta in 0.6 mL. It will be logistically difficult to administer doses of 100 μg / kg to children weighing less than 45 kg.

My second concern is the operational aspect of administering Neulasta in a mass casualty situation due to a nuclear or radiological disaster. Few health care providers have treated patients with the Acute Radiation Syndrome, and there are nuances which make treatment complex. The approval of this submission is based on the efficacy demonstrated in NHPs exposed to an acute, LD 50/60, dose of radiation with Neulasta started at approximately 24 hours after radiation exposure and with a high level of supportive care provided. The reality of radiation exposure would be more complex, e.g. radiation combined with trauma or burns (combined injury) from a nuclear detonation, or protracted radiation from radioactive fallout or from internal or external contamination from a "dirty bomb" or a nuclear reactor incident. Neulasta will have to be stockpiled in the Strategic National Stockpile (SNS). Since the SNS already has a stockpile of Neupogen and Leukine for HS-ARS, providers will have to decide which leukocyte growth factor to use, and will need to be knowledgeable about their use. We must not underestimate the complexity of dealing with a radiological or nuclear disaster.

7.4 Supportive Safety Results

Neulasta has an impressive safety record with over 10 years of clinical use involving more than (b)(4) patients in over 100 countries worldwide. (Reference Amgen Module 2.5, page 4)

7.4.1 Common Adverse Events

Per Amgen, bone pain is the only commonly observed adverse event with administration of Neulasta. In a placebo-controlled clinical trial in patients receiving pegfilgrastim after nonmyeloablative cytotoxic chemotherapy, the most common

adverse reactions occurring in $\geq 5\%$ of patients and with a between-group difference of $\geq 5\%$ higher in the pegfilgrastim group were bone pain and pain in the extremity. Leukocytosis was observed with a frequency of $< 1\%$, and no complications attributable to leukocytosis were reported. (Reference Amgen Module 2.5, page 20)

7.4.2 Laboratory Findings

No Clinical Data Submitted. Per the label, Section 5.7 Leukocytosis, White blood cell (WBC) counts of $100 \times 10^9/L$ or greater have been observed in patients receiving pegfilgrastim. Monitoring of complete blood count (CBC) during pegfilgrastim therapy is recommended.

7.4.3 Vital Signs

No Clinical Data Submitted

7.4.4 Electrocardiograms (ECGs)

No Clinical Data Submitted

7.4.5 Special Safety Studies/Clinical Trials

No Clinical Data Submitted

7.4.6 Immunogenicity

No Clinical Data Submitted.

Per the label, section 6.2 Immunogenicity states:

“As with all therapeutic proteins, there is a potential for immunogenicity. Binding antibodies to pegfilgrastim were detected using a BIAcore assay. The approximate limit of detection for this assay is 500 ng/mL. Pre-existing binding antibodies were detected in approximately 6% (51/849) of patients with metastatic breast cancer. Four of 521 pegfilgrastim-treated subjects who were negative at baseline developed binding antibodies to pegfilgrastim following treatment. None of these 4 patients had evidence of neutralizing antibodies detected using a cell-based bioassay. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Neulasta with the incidence of antibodies to other products may be misleading.”

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No Clinical Data Submitted.

7.5.2 Time Dependency for Adverse Events

No Clinical Data Submitted

7.5.3 Drug-Demographic Interactions

No Clinical Data Submitted

7.5.4 Drug-Disease Interactions

No Clinical Data Submitted

7.5.5 Drug-Drug Interactions

Amgen states that drug-drug interactions between pegfilgrastim and antibiotics have not been reported. (Reference Module 2.5, page 18) Coadministration of pegfilgrastim with Aranesp (an erythropoietin-stimulating agent) and Stemgen (a stem cell factor) has been reported to treat human radiation accident casualties. No drug-drug interactions were reported. (Reference Module 2.7.2, pages 17-18).

7.6 Additional Safety Evaluations

No Clinical Data Submitted

7.6.1 Human Carcinogenicity

No Clinical Data Submitted,
Per the 09/2015 label, section 13.1, Carcinogenesis, Mutagenesis, Impairment of Fertility, “No carcinogenicity or mutagenesis studies have been performed with pegfilgrastim.”

7.6.2 Human Reproduction and Pregnancy Data

No Clinical Data Submitted,
Per the 09/2015 label, section 13.1 “....Impairment of Fertility,..... Pegfilgrastim did not affect reproductive performance or fertility in male or female rats at cumulative weekly doses approximately 6 to 9 times higher than the recommended human dose.....”

Per the label, section 13.3 Reproductive and Developmental Toxicology, “Pregnant rabbits were dosed with pegfilgrastim subcutaneously every other day during the period of organogenesis. At cumulative doses ranging from the approximate human dose to approximately 4 times the recommended human dose (based on body surface area), treated rabbits exhibited decreased maternal food consumption, maternal weight loss, as well as reduced fetal body weights and delayed ossification of the fetal skull; however, no structural anomalies were observed in the offspring from either study. Increased incidences of post-implantation losses and spontaneous abortions (more than half the pregnancies) were observed at cumulative doses approximately 4 times the recommended human dose, which were not seen when pregnant rabbits were exposed to the recommended human dose.”

The label also describes three studies in pregnant rats dosed with pegfilgrastim at doses equivalent to three to ten times the human dose. There was transient evidence of wavy ribs in fetuses of treated mothers, but no evidence of fetal loss or structural malformation observed.

7.6.3 Pediatrics and Assessment of Effects on Growth

Neulasta is not approved by the FDA for use in children. There is no evidence that the off-label use of Neulasta has effected the growth of children. I will explain below why I recommend that Neulasta be approved for use in children.

Per the 09/2015 Label Section 8.4 Pediatric Use:

“Safety and effectiveness of Neulasta in pediatric patients have not been established. The adverse reaction profile and pharmacokinetics of pegfilgrastim were studied in 37 pediatric patients with sarcoma. The mean ($\pm$ standard deviation [SD]) systemic exposure (AUC_{0-inf}) of pegfilgrastim after subcutaneous administration at 100 mcg/kg was 22.0 ($\pm$ 13.1) mcg·hr/mL in the 6 to 11 years age group ($n = 10$), 29.3 ($\pm$ 23.2) mcg·hr/mL in the 12 to 21 years age group ($n = 13$), and 47.9 ($\pm$ 22.5) mcg·hr/mL in the youngest age group (0 to 5 years, $n = 11$). The terminal elimination half-lives of the corresponding age groups were 20.2 ($\pm$ 11.3) hours, 21.2 ($\pm$ 16.0) hours, and 30.1 ($\pm$ 38.2) hours, respectively. The most common adverse reaction was bone pain.”

Module 2.5 Section 3.3 “Dosing Regimen Recommendation for Pediatric Patients with HS-ARS” states the following:

“Pegfilgrastim has not been approved for treatment of CIN (chemotherapy induced neutropenia) in pediatrics; however, Amgen has conducted a phase 2 study for pediatric patients with sarcoma with a single 100 μ g/kg dose of pegfilgrastim or daily SC doses of filgrastim at 5 μ g/kg after chemotherapy. The body weight-based dose of pegfilgrastim was chosen based on results in adult patients with breast cancer: a single SC dose of pegfilgrastim at 100 μ g/kg is as safe and non-inferior in reducing neutropenia and its complications as are daily injections of filgrastim at 5 μ g/kg Results from this pediatric study show that:

(1) The overall efficacy profile was similar after a single dose of pegfilgrastim at 100 µg/kg and daily doses of filgrastim at 5 µg/kg/day and was comparable with the experience in adults.

(2) The PK/PD relationship of pegfilgrastim in pediatric patients is similar to that in adults.

Since the mechanism of action of pegfilgrastim is independent of the type of injury and the PK-PD relationship of pegfilgrastim, as projected by the ARS model from NHPs to humans....., is similar between pediatrics and adults, **Amgen** (b)(4)

Amgen's Section 3.2 of Module 2.7.2 Summary of Clinical Pharmacology) says in part:

“..... (b)(4)

Reviewer's Comments

Amgen above recommends administering Neulasta (b)(4)

In my section 6.1.8.2 “Treatment of Children” above I showed that the label, Consultation Report from the Division of Hematology Products, Literature Review, data on utilization in pediatrics and Pediatric FAERS data indicate that Neulasta is being used in pediatrics (b)(4) and is safe in that age group.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No clinical data submitted. Information on Neulasta overdosage is included in the label Section 10 OVERDOSAGE which states the following:

“The maximum amount of Neulasta that can be safely administered in single or multiple doses has not been determined. Single subcutaneous doses of 300 mcg/kg have been administered to 8 healthy volunteers and 3 patients with non-small cell lung cancer without serious adverse effects. These patients experienced a mean maximum absolute

neutrophil count (ANC) of $55 \times 10^9/L$, with a corresponding mean maximum WBC of $67 \times 10^9/L$. The absolute maximum ANC observed was $96 \times 10^9/L$ with a corresponding absolute maximum WBC observed of $120 \times 10^9/L$. The duration of leukocytosis ranged from 6 to 13 days.....”

Reviewer’s Comment: I believe the potential for Overdose, Abuse, Withdrawal or Rebound is very low.

7.7 Additional Submissions / Safety Issues

Section 5 of the Label, “Warnings and Precautions”, has information on the following topics:

5.1 Splenic Rupture

5.2 Acute Respiratory Distress Syndrome

5.3 Serious Allergic Reactions

(b)(4)

Healthy Subjects:

The pegfilgrastim clinical study safety data in healthy volunteers was based on 72 healthy subjects who received at least 1 dose of pegfilgrastim in 1 of 3 studies (970230, 980230, or 20020114) (See my Table 4 below).

Table 4 Amgen Clinical Studies in Healthy Subjects

Study Identifier Protocol Number	Phase and Study Design	Dose and route of administration	Number of pegfilgrastim Treated Healthy Subjects (n)
970230	A phase I study of pegfilgrastim or subcutaneous (SC) daily filgrastim in healthy subjects	Subjects were enrolled into 1 of 4 dose cohorts to receive a single SC dose of pegfilgrastim at 30, 60, 100, or 300 µg/kg	32
980230	A phase I study comparing SC injection and intravenous (IV) infusion of pegfilgrastim or SC daily filgrastim in healthy subjects	Comparison of a single administration of either SC or IV pegfilgrastim (30 or 60 µg/kg) to daily SC filgrastim (NEUPOGEN®; 5 µg/kg/day)	33
20020114	This phase 1, open-label, single-dose study was designed to evaluate the pharmacokinetics of 6.0 mg pegfilgrastim in subjects with various degrees of renal function ^a .	Subjects received 6.0 mg pegfilgrastim administered by SC injection	7

SC = subcutaneous; IV = intravenous.

^a. In study 20020114 there were a total of 31 subjects, of which 7 were healthy subjects.

(Reference Amgen, Section 1.11.3 Response to FDA Information Request of 23 March 2015, page 8)

Study 970230

Study 970230 was a phase 1, open-label, dose-escalation, single-center study designed to evaluate the safety, pharmacodynamics, and pharmacokinetics of a single weight-based dose of pegfilgrastim in normal healthy subjects. **The most frequently reported treatment-emergent adverse events occurring in the > 6 mg group in descending order of frequency by preferred term were headache 10 out of 11 subjects (91%), back pain 5 out of 11 subjects (46%), and myalgia, nausea, and oropharyngeal pain 3 out of 11 subjects (27%).**

Study 980230

Study 980230 was a phase I study comparing weight based dosing of subcutaneous injection and intravenous infusion of pegfilgrastim or subcutaneous daily filgrastim in healthy volunteers. One out of 13 subjects (8%) reported a grade 3 event of arthralgia in the 4-6 mg group. **The most frequently reported treatment-emergent adverse events occurring in the 4-6 mg group in descending order of frequency by preferred term were back pain 9 out of 13 subjects (69%), headache 7 out of 13 subjects (54%), and arthralgia 4 out of 13 subjects (31%).** No subject received a dose greater than 6 mg in this study.

Study 20020114

Study 20020114 was a phase 1, open-label, single-dose study designed to evaluate the pharmacokinetics of fixed dose 6.0 mg pegfilgrastim in subjects with various degrees of renal function. **The most frequently reported treatment-emergent adverse events in descending order of frequency by preferred term were headache 4 out of 7 subjects (57%) and arthralgia 3 out of 7 subjects (43%).**

(Reference: the above studies are described on pp 10-11 of Amgen's module 1.11.3-Response to FDA Information Request of 23 March 2015)

Summary of the above 3 studies in healthy volunteers

"...no fatal or serious adverse events were reported. There was 1 event of syncope that occurred in the < 4 mg dose level that led to a study discontinuation. Grade 3 adverse events occurred at all dose levels across the 3 studies except the < 4 mg dose level. The grade 3 adverse event of arthralgia occurred in the 4 to 6 mg dose levels, the grade 3 adverse event of back pain occurred in the 6 mg dose level and the grade 3 adverse event of headache occurred at the > 6 mg dose levels. The most frequent and consistently reported treatment emergent adverse events across the studies and dose levels were headache and arthralgia." (Reference Amgen Module 1.11.3 – Response to FDA Information Request of 23 March 2015, pages 15-16)

Reviewer's comment: The above studies suggest that if Neulasta is administered in a mass casualty scenario to patients who did not receive a significant radiation dose, e.g. the worried well, the most common significant (grade 3) adverse events will be headache and arthralgia.

8 Postmarket Experience

Adverse drug reactions identified in the postmarketing experience include splenic rupture and splenomegaly, sickle cell crisis, leukocytosis, hypersensitivity reactions, acute respiratory distress syndrome (ARDS), glomerulonephritis, capillary leak syndrome, injection site reactions, Sweet's syndrome (acute febrile neutrophilic dermatosis), (b)(4) (Reference 09/2015 label section 6.3 Postmarketing Experience.) Please see also my section 6.8.1.2 for post marketing experience in children.

9 Appendices

9.1 Literature Review/References

I have divided my references into 2 groups. The first group are references identified by Patricia Dinndorf, M.D. of the Division of Hematology Products which support a

pediatric indication (see my above section 6.1.8.2.2). Twelve of these references are also referred to by Amgen in their module “1.11.3 – Response to FDA Information Request of 23 March 2015”. (See my section 6.1.8.2.3). The second group of references are other references which support the use of granulocyte colony stimulating factors (G-CSF), such as pegfilgrastim, for the treatment of the hematopoietic syndrome of the acute radiation syndrome (HS-ARS).

9.1.1 References supporting the use of pegfilgrastim in pediatrics

Anaya Aguirre S E, Wanzke Del Angel V, et al., Randomized double-blind controlled trial (RCT) of pegfilgrastim as prophylactic therapy in pediatric patients with solid tumors during myelosuppressive chemotherapy, J Clin Oncol 2011; 29(15)

Andre N, Kababri M E, et al., Safety and efficacy of pegfilgrastim in children with cancer receiving myelosuppressive chemotherapy. Anti-Cancer Drugs 2007;18(3): 277-281.

Andre N, Milano E, et al., Safety of pegfilgrastim in children. Ann Pharmacother 2008 42(2): 290.

Beaupain B, Leblanc T, et al., Is pegfilgrastim safe and effective in congenital neutropenia? An analysis of the French severe chronic neutropenia registry Pediatr Blood Cancer 2009; 53:1068–1073.

Borinstein S C, Pollard J, Winter L, Hawkins DS, Pegfilgrastim for prevention of chemotherapy-associated neutropenia in pediatric patients with solid tumors. Pediatr Blood Cancer 2009;53: 375–378.

Cardenoux C, Demeocq F, et al., Pegfilgrastim Plus AMD 3100 for Stem-Cell Mobilization in Children (letter). Pediatr Blood Cancer 2010; 55:769.

Cesar S, Zanazzo A G, et al., A Phase II study on the safety and efficacy of a single dose of pegfilgrastim for mobilization and transplantation of autologous hematopoietic stem cells in pediatric oncohematology patients. Transfusion 2011; 51:2480-2487.

Choi L M, Guelcher C, Guerrera M, Novel treatment for severe congenital neutropenia with pegfilgrastim (letter). Blood 2007; 110 (12): 4134.

Dallorso S, Berger M, et al., Prospective single-arm study of pegfilgrastim activity and safety in children with poor-risk malignant tumours receiving chemotherapy Bone Marrow Transplant 2008; 42: 507–513.

Dufour C, Cappelli C B, et al., Similar favorable outcome of pegfilgrastim overdose in patients with different age and underlying disease Haematologica 2010: 95(4): 684-685.

Fioredda F, Calvillo M, et al., Pegfilgrastim in children with severe congenital neutropenia. *Pediatr Blood Cancer* 2010; 54:465–467.

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Reviewer's Comment: This article reports on study AXG15 which I have described in several locations above.

-Farese AM, Cohen MV, Stead RB, Jackson III W, and MacVittie TJ. Pegfilgrastim administered in an abbreviated schedule significantly improved neutrophil recovery after high dose, radiation-induced myelosuppression in rhesus macaques. *Radiat Res*. 2012; 178:403-413.

Reviewer's Comment: The abstract of this article states: ".....Animals were exposed to potentially lethal 6 Gy total-body X radiation. After irradiation all animals received supportive care and were administered either pegfilgrastim at 300 mcg/kg on day 1 or day 1 and day 7 post exposure, or filgrastim at 10 mcg/kg/

day initiated on day 1 post exposure and continued daily through neutrophil recovery..... Administration of pegfilgrastim at day 1 and day 7 was most effective at improving neutrophil recovery compared to daily administration of filgrastim or a single injection of pegfilgrastim on day 1, after severe, radiation-induced myelosuppression in rhesus macaques."

-Gluzman-Poltorak Z, Vainstein V, Basile LA. Recombinant interleukin-12, but not granulocyte-colony stimulating factor, improves survival in lethally irradiated nonhuman primates in the absence of supportive care: evidence for the development of a frontline radiation medical countermeasure. *American Journal of Hematology*.2014; 89:868-873.

Reviewer's Comment: This article is discussed by Amgen in module 2.4, Non-Clinical Overview, pages 7-8. G-CSF was tested as a comparator with rIL-12. G-CSF did not improve survival in this study. Per Amgen, a key difference between this study and AXG15 was that these authors did not use supplemental medical management of radiation-related symptoms (anti-ulcerative agents, antibiotics, antipyretics, blood transfusions or fluid support). I agree with Amgen, that while this publication indicates that "..... there may be conditions in which G-CSF will not be effective, the weight of evidence suggests that G-CSF has the potential to improve survival after radiation injury."

-Gluzman-Poltorak Z, Vainstein V, Basile LA. Association of Hematological Nadirs and Survival in a Nonhuman Primate Model of Hematopoietic Syndrome of Acute Radiation Syndrome. *Radiation Research*, 184(2):226-230, 2015.

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-Hankey KG, Farese AM, Blaauw EC, et al, Pegfilgrastim improves survival of lethally irradiated nonhuman primates. *Radiation Research*, 183 (6): 643-655, 2015.

Reviewer's Comment: This article is a summary of study AXG21.

Kiang JG, Zhai M, Liao P-J, Bolduc DL, Elliott TM, Gorbunov NV. Pegylated G-CSF inhibits blood cell depletion, increases platelets, blocks splenomegaly, and improves survival after whole-body ionizing irradiation but not after irradiation combined with burn. *Oxidative Medicine and Cellular Longevity*. 2014. <http://dx.doi.org/10.1155/2014/481392> Accessed September 8, 2015.

Reviewer's Comment: In this study, B6D2F1/J female mice were divided into groups treated with no irradiation, 9.5 Gy whole body radiation, or 9.5 Gy radiation plus a 15% total-body-surface-area skin burn (Combined Injury). Survival after 30 days for mice injured with radiation alone was 68%, for mice

injured with radiation and skin burn was 50%, for mice receiving radiation and pegylated G-CSF (peg G-CSF) was 100%, and for mice treated with peg G-CSF after combined injury was 50% (no survival benefit from the peg G-CSF).

In a separate protocol mice receiving only radiation injury had a 0% survival, mice receiving combined injury had a 5% survival, and those mice receiving G-CSF (Neupogen) with radiation injury had a 25% survival, while mice receiving G-CSF with combined injury had a 20% 30-day survival. The article concluded “In summary, skin burns increased radiation-induced mortality and body-weight loss.” In this study pegylated G-CSF improved survival in mice with only radiation injury but not with combined injuries, but G-CSF improved survival in both mice with only radiation injury and mice with combined injury. (See also my comments in my Section 5.3 above.)

-Moroni M, Ngudiankama BF, Christensen C, et al. The Göttingen minipig is a model of the hematopoietic acute radiation syndrome: G-colony stimulating factor stimulates hematopoiesis and enhances survival from lethal total-body gamma-irradiation. *Int J Radiation Oncol Biol Phys.* 2013;86:986-992.

Reviewer’s Comment: This article is mentioned by Amgen in module 2.4, Non-Clinical Overview, page 8. The study “.....did not use antibiotics, fluid support, blood transfusions, or anti-inflammatory agents, and demonstrated that G-CSF increased survival after total body irradiation at a lethal dose in 70% of the animals by day 30 (LD70/30).”

-Pulsiper MA, Chitphakdithai P, Logan BR, et al. Lower risk for serious adverse events and no increased risk for cancer after PBSC vs BM donation. *Blood.* 2014;123:3655-3663.

-Radiation Emergency Assistance Center/Training Site (REAC/TS). The Medical Aspects of Radiation Incidents. 2013; <https://orise.orau.gov/files/reacts/medical-aspects-of-radiation-incidents.pdf>. Last accessed September 8, 2015.

-Radiation Emergency Medical Management. 2015: www.remm.nlm.gov Last accessed October 13, 2015.

Reviewer’s Comment: This website, produced by the U.S. Dept of Health and Human Services, provides excellent guidance with algorithms and other multimedia on the medical management of the Acute Radiation Syndrome.

-Singh VK, Romaine PL, Seed TM, Medical countermeasures for radiation exposure and related injuries: characterization of medicines, fda-approval status and inclusion into the strategic national stockpile. *Health Phys.* 108(6): 607-630; 2015.

-Waselenko JK, MacVittie TJ, Blakely WF, et al. Medical management of the acute radiation syndrome: recommendations of the Strategic National Stockpile Radiation Working Group. *Ann Intern Med.* 2004;140(12):1037-1051.

9.2 Labeling Recommendations

I recommend that this supplemental BLA for Neulasta be approved and that the label be revised to include the following indication which is the same indication which was approved for Neupogen in March 2015.

Proposed new indication:

NEULASTA is a leukocyte growth factor indicated to

- Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)

The appropriate dosage for the above indication has not yet been agreed to between Amgen and the FDA. My recommendation for the Neulasta dosage for the treatment of HS-ARS in victims exposed to at least 2 Gray of whole body radiation is 6 mg for victims weighing ≥ 45 kg administered twice on days 1 and 8 after radiation exposure, and 100 mcg/ kg for victims < 45 kg administered twice on days 1 and 8 after radiation exposure.

I recommend that the label include in Section 15 REFERENCES, a few references which describe the medical management of the Acute Radiation Syndrome. A radiologic or nuclear incident could be catastrophic with massive casualties. There is much more to management of a radiation casualty than simply providing Neulasta and supportive care. Biodosimetry would need to be utilized to determine approximate radiation dose. Internal contamination with radionuclides would require drugs for decorporation, and the possible risk from the administration of Neulasta with chronic radiation exposure is unknown. An excellent reference which was developed by the Department of Health and Human Services (HHS) is the Radiation Emergency Medical Management website which is available at www.remm.nlm.gov. Other excellent references include that of the CDC and REAC/TS. These references are listed above in Section 9.1.2 Other References.

Since our recommendation for approval of Neulasta for the treatment of HS-ARS is based on the “Animal Rule”, we will include in the draft label the following information which is required by 21 CFR 601.91(b)(3):

“Information to be provided to patient recipients. For biological products or specific indications approved under this subpart, applicants must prepare, as part of their proposed labeling, labeling to be provided to patient recipients. The patient labeling must explain that, for ethical or feasibility reasons, the biological product's approval was based on efficacy studies conducted in animals alone and must give the biological product's indication(s), directions for use (dosage and administration), contraindications, a description of any reasonably foreseeable risks, adverse reactions, anticipated benefits, drug interactions, and any other relevant information required by FDA at the

time of approval. The patient labeling must be available with the product to be provided to patients prior to administration or dispensing of the biological product for the use approved under this subpart, if possible."

9.3 Advisory Committee Meetings

On May 3, 2013 FDA's Medical Imaging Drugs Advisory Committee (MIDAC) and Oncologic Drugs Advisory Committee (ODAC) met jointly, to discuss the safety and efficacy of currently approved leukocyte growth factors (LGFs) as potential treatments for radiation-induced myelosuppression associated with a radiological/nuclear incident. This joint FDA Advisory Committee meeting was scheduled subsequent to FDA's review of nonhuman primate study efficacy data submitted by NIAID under preIND-100,228 Study AXG15. The NIAID data demonstrated efficacy of filgrastim in the treatment of the Hematopoietic Syndrome of the Acute Radiation Syndrome. Based on the information presented at that meeting, **the Advisory Committee voted 17:1 that filgrastim therapy was reasonably likely to produce clinical benefits in humans exposed to radiation following a radiological/nuclear incident.** In addition, the committee recommended that this efficacy could be generalized to the use of other leukocyte growth factors, including Neulasta, Leukine and tbo-filgrastim. (See also My [Section 2.5 Summary of Presubmission Regulatory Activity Related to Submission](#), and [Section 6 Review of Efficacy](#) which describes NHP Study AXG15)

On Jan 7, 2015 the FDA's Oncology Drug Advisory Committee (ODAC) met to discuss the biosimilar drug of filgrastim sponsored by Sandoz, named filgrastim-sndz. The ODAC voted 14-0 to recommend approval of this biosimilar filgrastim which had been marketed by Sandoz in Europe since 2009. In March 2015 the drug was approved with the brand name Zarxio™.

Reviewer's Comment: Note that although Neupogen was approved in March 2015 for the additional indication to: ""Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)", Zarxio is approved for the other indications of Neupogen, but not for the treatment of the Hematopoietic Syndrome of the Acute Radiation Syndrome.

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/s/

WILLIAM E DICKERSON
10/14/2015

ALEXANDER GOROVETS
10/14/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125031Orig1s180

PHARMACOLOGY/TOXICOLOGY REVIEW

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number: 125031
Supporting document/s: 1137 (ES 180)
Applicant's letter date: 2/13/15
CDER stamp date: 2/13/15
Product: Neulasta (Pegfilgrastim, recombinant human G-CSF)
Indication: Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)
Applicant: Amgen Inc.
Review Division: Division of Medical Imaging Products (DMIP)
Reviewer: Yanli Ouyang, MD, PhD, DABT
Supervisor/Team Leader: Adebayo Laniyonu, PhD
Division Director: Louis (Libero) Marzella, MD, PhD
Project Manager: Frank A Lutterodt

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of sBLA 125031 are owned by Amgen Inc. or are data for which Amgen Inc. has obtained a written right of reference. Any information or data necessary for approval of sBLA 125031 that Amgen Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of sBLA 125031.

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1 Executive Summary

1.1 Introduction

Neulasta (pegfilgrastim) is a covalent conjugate of filgrastim and 20 kD monomethoxypolyethylene glycol with a longer half-life (ranged from 15 to 80 hours after subcutaneous injection vs. 210 minutes for filgrastim). Neulasta was initially approved in 2002. Neulasta is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. The recommended dosage of Neulasta is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle in adults.

Filgrastim (Neupogen) is a 175 amino acid recombinant human granulocyte colony-stimulating factor (rhG-CSF) with a molecular weight of 18,800 daltons and virtually identical amino acid sequence to the endogenous G-CSF. G-CSF regulates the production of neutrophils within the bone marrow by binding to specific cell surface receptor and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functions.

Neupogen was initially approved in 1991 under BLA 103353. Neupogen is currently approved for multiple indications including cancer patients receiving myelosuppressive chemotherapy (5 mcg/kg/day) and cancer patients receiving bone marrow transplant (10 mcg/kg/day). In March 2015, neupogen was approved to increase survival in patients acutely exposed to myelosuppressive doses of radiation under the animal rule. The recommended dose of neupogen is 10 mcg/kg as a single daily subcutaneous injection. Neupogen should be administered as soon as possible after suspected or confirmed exposure to radiation doses greater than 2 gray (Gy) and should be continued until the absolute neutrophil count (ANC) remains greater than 1,000/mm³ for 3 consecutive days or the complete blood count (CBC) exceeds 10,000/mm³ after a radiation-induced nadir.

Under the current efficacy supplement, neulasta is indicated for increasing survival in patients acutely exposed to myelosuppressive doses of radiation. The recommended dose of neulasta

(b)(4)

The efficacy studies to support this efficacy supplement were conducted in animals under the animal rule (21 CFR 601.90) because human clinical trials cannot be ethically conducted.

1.2 Brief Discussion of Nonclinical Findings

Primary endpoint-survival

The pivotal efficacy study to support this efficacy supplement is the study AXG21. The primary endpoint, a comparison of the number of surviving Rhesus Macaques on day 60, is met in this study. Neulasta at 300 mcg/kg/week [a total of two doses, the first dose administered at 20-26 hr post LD_{50/60} total body irradiation (TBI), and the second dose on Day 8] increased overall survival [91.3% (21/23) vs. 47.8% (11/23) in the control arm, $p = 0.0014$]. All animals that underwent premature sacrifice were euthanized in a blinded manner according to the pre-specified euthanasia criteria.

The efficacy study for neupogen (AXG15) in Rhesus Macaques also supports this efficacy supplement. Neupogen at 10 mcg/kg/day starting 22-26 hr post LD_{50/60} TBI increased survival [79% (19/24) versus 41% (9/22) in the control arm, the Chi-square test two sided $p < 0.0079$ and Fisher's exact test two sided $p = 0.0147$].

Furthermore, studies in (b)(4) and (b)(4) mice also demonstrated the survival benefit of neulasta. Neulasta increased survival by 32% or greater in these mouse studies over the controls. Of interest, in a (b)(4) mouse study, neulasta increased the survival in similar manner (40% or greater) either given one dose (22-28 hr post LD_{50/30} TBI) or two doses (Days 1 and 7) at 1 mg/kg or one dose (22-28 hr post LD_{90/30} TBI) at 0.1 mg/kg, 0.3 mg/kg, or 1.0 mg/kg. However, neulasta increased the survival in a dose dependent manner in another (b)(4) mouse study, in which mice were exposed to 13 Gy partial body irradiation with approximately 2.5% of the bone marrow shielded (PBI BM2.5). Thirty day survival rates were 80%, 50%, or 20% in 1 mg/kg Neulasta (subcutaneously administered once at about 24 hours post 13 Gy PBI BM2.5), 0.1 mg/kg Neulasta, or vehicle control groups, respectively. Neulasta at either 1 mg/kg or 0.1 mg/kg did not increase the 30 day survival in (b)(4) mice post 13 or 14 Gy TBI, which caused 100% mortality within 13 days post TBI.

Key secondary endpoint- the duration of severe neutropenia

In both studies AXG 21 and AXG15 aforementioned, neulasta and neupogen reduced duration of neutropenia and improved neutrophil recovery, meeting the key secondary endpoint. The median days with ANC < 500/mcL was 14 days in the neulasta or neupogen arm and 18 days in the control arm.

1.3 Recommendations

1.3.1 Approvability

An approval is recommended under the Animal Rule based on the totality of available efficacy and safety data in animals and humans from a nonclinical perspective. In addition, neulasta dose regimen has practical advance over neupogen (two doses vs. daily dose with ANC monitoring). Both safety and efficacy are established and further described below.

Safety

Neulasta has been approved since 2002. Nonclinical and clinical safety information is available in the current label. Extensive safety profile has been established.

Efficacy

According to the FDA draft Guidance for Industry titled “Product Development Under the Animal Rule” published in May 2014

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM399217.pdf>), FDA may grant marketing approval based on adequate and well-controlled animal efficacy studies when the results of those studies establish that the drug is reasonably likely to produce clinical benefit in humans.

The Animal Rule states that FDA will rely on evidence from animal studies to provide substantial evidence of effectiveness only when all of the four criteria described below are met.

First, there is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product. Both the pathophysiological mechanism of radiation injury and mechanism of action of G-CSF are reasonably well-understood. Radiation of animals leads to mortality and neutropenia, which is similar to human.

Second, the effect is demonstrated in more than one animal species expected to react with a response predictive for humans. The survival benefit of neulasta was demonstrated in mice and nonhuman primates (NHPs). In a relatively well-characterized NHP model aforementioned, neulasta significantly increased the 60-day overall survival when administered at approximately 24 hr and on Day 8 post a LD_{50/60} TBI.

In addition, neulasta significantly reduced duration of neutropenia and improved neutrophil recovery in all animal species studied.

Neupogen was approved for increasing survival in patients acutely exposed to myelosuppressive doses of radiation under the animal rule on March 30, 2015.

Relevant to the setting of Hematopoietic Subsyndrome of Acute Radiation Syndrome, neulasta is approved to decrease the incidence of infection and reduce the duration of neutropenia and neutropenia-related clinical sequelae including cytotoxic chemotherapy induced myelosuppression, which is mechanistically similar to radiation-induced myelosuppression.

Taken together, the primary and key secondary endpoints are met. The labeling emphasized that neulasta should be administered as soon as possible and reflected the importance of timely administration of neulasta post radiation exposure.

Third, the animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity. The animal study endpoints: increased survival and neutrophil recovery, are clearly related to the desired benefit in humans.

Fourth, the data or information on the kinetics and pharmacodynamics (PD) of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans. Although limited pharmacokinetic (PK) data in irradiated animals are available, available PK and PD data in animals and humans allows selection of an effective dose in humans, which is reviewed under the pharmacometrics review.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

There is no change in nonclinical-related sections. The efficacy labeling is under the review.

2 Drug Information

2.1 Drug

Generic Name
Neulasta (pegfilgrastim)

Molecular Weight
Approximately 39 kD

Pharmacologic Class
Leukocyte growth factor

2.2 Relevant INDs, NDAs, BLAs and DMFs

BLA 103353 for filgrastim

(b)(4) for Neulasta and pre-IND 100228 for Neupogen; Letters of Authorization (LOA) were provided for both pre-INDs.

2.3 Drug Formulation

There are two Neulasta presentations:

1. Neulasta for manual subcutaneous injection is supplied in 0.6 mL prefilled syringes.

2. On-body Injector for Neulasta is supplied with a prefilled syringe containing 0.64 mL of Neulasta in solution that delivers 0.6 mL of Neulasta when used with the On-body Injector for Neulasta.

The delivered 0.6 mL dose from either the prefilled syringe for manual subcutaneous injection or the On-body Injector for Neulasta contains 6 mg pegfilgrastim (based on protein weight) in a sterile, clear, colorless, preservative-free solution (pH 4.0) containing acetate (0.35 mg), polysorbate 20 (0.02 mg), sodium (0.02 mg), and sorbitol (30 mg) in Water for Injection, USP.

2.4 Comments on Novel Excipients

N/A

2.5 Comments on Impurities/Degradants of Concern

N/A

2.6 Proposed Clinical Population and Dosing Regime

Neulasta is proposed to increase survival in patients acutely exposed to myelosuppressive doses of radiation. The recommended dose of neulasta

(b)(4)

2.7 Regulatory Background

Major regulatory events are listed below in addition to meetings between FDA and the Sponsor.

1. 2002: Neulasta (pegfilgrastim) approved by FDA for treatment of neutropenia.
2. May 3, 2013: Advisory Committee meeting
3. November 20, 2013: Orphan Designation

3 Studies Submitted

3.1 Studies Reviewed

AXG21: A 60-Day Efficacy Study of Subcutaneous Pegfilgrastim (Neulasta) to Treat the ARS-HS Following an LD_{50/60} of TBI in Rhesus Macaques

AXG15: A 60-Day Efficacy Study of Subcutaneous Filgrastim to Treat the Hematopoietic Syndrome of the Acute Radiation Syndrome (ARS-HS) Following an LD_{50/60} of TBI in Rhesus Macaques.

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

ARX01: A Pilot Study to Define the Dose-Response Curve in Rhesus Macaques Exposed to Increasing Doses of Total Body Irradiation (TBI) and Receiving Supportive Care.

AXG15: A 60-Day Efficacy Study of Subcutaneous Filgrastim to Treat the Hematopoietic Syndrome of the Acute Radiation Syndrome (ARS-HS) Following an LD_{50/60} of TBI in Rhesus Macaques.

AXG22: A 60-day efficacy study of subcutaneous delayed filgrastim administration to treat the ARS-HS following an LD_{50/60} of TBI in Rhesus Macaques

ES2014.203_Neulasta PBI2.5: Effects of Neulasta on survival endpoints using the PBI BM2.5 model

ES2014.204: Effects of Neulasta on survival endpoints using the TBI model in (b)(4) mice with antibiotic support

IU2012.215M. (b)(4): Pilot study to define the dose response curve in (b)(4) Mice (b)(4) exposed to increasing doses of total-body ionizing radiation in the presence and absence of levofloxacin on days 1-30 post-exposure; combined data from cohorts 1, 2, and 3

IU2013.225M: Hematopoietic screening assay for radiomitigating activity of 2 doses of subcutaneously administered Neulasta (1 mg/kg on days 1 and 8) after exposure to the LD_{50/30} or LD_{70/30} dose of radiation for (b)(4) Mice (b)(4)

IU2013.225M and IU2013.239M: Hematopoietic screening assay for radiomitigating activity of 2 doses of subcutaneously administered Neulasta (1 mg/kg on days 1 and 8) after exposure to the LD_{50/30} dose of radiation for (b)(4) Mice (b)(4)

4 Pharmacology

4.1 Primary Pharmacology

Background

Neulasta (pegfilgrastim) is a covalent conjugate of filgrastim and 20 kD monomethoxypolyethylene glycol with a longer half-life (ranged from 15 to 80 hr after subcutaneous injection vs. 210 minutes for filgrastim). Neulasta was initially approved in 2002. Neulasta is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. The recommended dosage of Neulasta is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle in adults.

Neupogen (filgrastim) is a 175 amino acid recombinant human granulocyte colony-stimulating factor (rhG-CSF) with a molecular weight of 18,800 daltons and virtually identical amino acid sequence to the endogenous G-CSF. G-CSF regulates the production of neutrophils within the bone marrow by binding to specific cell surface receptor and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functions.

Neupogen was initially approved in 1991 under BLA 103353. Neupogen is currently approved for cancer patients receiving myelosuppressive chemotherapy (5 mcg/kg/day), cancer patients receiving bone marrow transplant (10 mcg/kg/day), cancer patients undergoing peripheral blood progenitor cell mobilization (10 mcg/kg/day), patients with congenital neutropenia (6 mcg/kg SC twice daily), and patients with cyclic or idiopathic neutropenia (5 mcg/kg/day). Neupogen is mainly indicated to decrease the incidence of infection and reduce the duration of neutropenia and neutropenia-related clinical sequelae.

Mechanism of action of G-CSF

According to the package insert (PI) for neulasta, pegfilgrastim is a CSF that acts on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end cell functional activation.

G-CSF is a lineage-specific CSF. G-CSF regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functions (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody-dependent killing, and the increased expression of some cell surface antigens). G-CSF is not species-specific and has been shown to have minimal direct in vivo or in vitro effects on the production or activity of hematopoietic cell types other than the neutrophil lineage.

Mechanism of radiation Injury- Hematopoietic Subsyndrome of the Acute Radiation Syndrome

Hematopoietic Subsyndrome of the Acute Radiation Syndrome (HS-ARS) is a consequence of exposure to radiation dose greater than 1 Gy (The Medical Aspects of Radiation Incidents, <https://orise.orau.gov/files/reacts/medical-aspects-of-radiation-incidents.pdf>, and FDA Advisory Committee Meeting briefing document, <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee/UCM350152.pdf>).

Radiation damages cells, generally most severe in rapidly reproducing cell types such as hematopoietic stem cells and progenitor cells. HS-ARS in humans is characterized by dose-dependent bone marrow depression leading to neutropenia, thrombocytopenia, and anemia. The HS-ARS is dose- and time-dependent, with increasing mortality and morbidity as exposure dose increase. The time of onset and severity of HS-ARS depends on the level of radiation exposure. Clinical manifestations of HS-ARS can be

seen following radiation exposures of 2 Gy to 10 Gy. The approximate LD_{50/60} (the most widely used endpoint for HS-ARS) for humans is 3.25 to 4.50 Gy without medical management. However, when medical management such as intravenous fluids, antibiotics, and blood products is provided, the LD_{50/60} can increase to 6.0 to 7.0 Gy.

Death due to HS-ARS from infection or excessive bleeding occurs within 2 to 3 weeks after exposure. Survival following HS-ARS is dependent on the recovery of the hematopoietic stem and progenitor cells so that production of mature, functional neutrophils, and platelets can occur. Neutrophil recovery is inversely related to radiation exposure and can occur 3 to 4 weeks following radiation exposure.

The rapid administration of G-CSF to enhance hematopoietic recovery is recommended by regulatory agencies including Centers for Disease Control and Prevention (<http://emergency.cdc.gov/radiation/neupogenfacts.asp>). CSFs including G-CSF have been used to treat ARS in individuals exposed to radiation accidentally. There is some anecdotal evidence for the safety and efficacy of G-CSF in the treatment of ARS, which was summarized in the FDA Advisory Committee Meeting briefing document (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee/UCM350152.pdf>). The U.S. Department of Health and Human Services' Office of the Assistant Secretary for Preparedness and Response awarded a 157.5 million contract to Amgen to purchase Neupogen for the US Strategic National Stockpile for use in the event of nuclear or radiological emergency under Project BioShield (<http://www.hhs.gov/news/press/2013pres/09/20130926a.html>).

Summary of FDA advisory committee meeting regarding leukocyte growth factors
(<http://www.fda.gov/advisorycommittees/committeesmeetingmaterials/drugs/medicalimagingdrugsadvisorycommittee/ucm334176.htm>)

On May 3, 2013, a joint meeting of the medical imaging drugs advisory committee (AC) and oncologic drugs AC was held to discuss the safety and efficacy of currently approved leukocyte growth factors (LGFs) including neupogen and neulasta as potential treatments for radiation-induced myelosuppression associated with a radiological/nuclear incident. A brief summary of key information is provided below.

The FDA briefing document included summaries of published reports of G-CSF use (mainly neupogen, a few studies using Neulasta) in animals with focus on the effect of G-CSF on survival and white blood cell (WBC) recovery in studies conducted in non-human primates (NHPs), dogs and mice (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee/UCM350151.pdf>). The review concluded that the results of published literature support the survival and WBC recovery benefit of rhG-CSF on HS-ARS. However, the radioprotective effect was dependent on factors such as radiation dose, G-CSF dose, treatment initiation time, and treatment duration. At that time, with the exception of the NHP study (AXG15) under pre-IND 100228, the survival studies were conducted in dogs and mice only. The survival benefit of rhG-CSF

treatment was consistently demonstrated in a radiation dose- and rhG-CSF dose-related manner.

rhG-CSF enhanced WBC recovery in all animal species and strains studied. The effects were measured mainly as reduced duration of neutropenia (a few days), reduced time to ANC recovery (a few days), Improved ANC nadir, increased WBC counts, and increased granulocyte/macrophage colony-forming units (GM-CFU) in bone marrow.

According to the summary minutes of the meeting (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee/UCM363898.pdf>), the committee members found a reasonably well-understood pathophysiological mechanism of radiation-induced bone marrow injury and its substantial reduction by filgrastim. Some committee members noted that the extensive data available from experience with chemotherapy-induced neutropenia (CIN) is generally applicable to radiation induced marrow injury.

Committee members agreed that the animal study primary endpoint (survival) is clearly related to a desired benefit in humans. Committee members also believed that reducing ANC recovery time is a useful supportive endpoint.

A majority of the committee members voted (17 yes and 1 no) that filgrastim therapy is reasonably likely to produce clinical benefits in humans exposed to radiation that is likely to induce myelosuppression during or following a radiological/nuclear incident.

In addition, the committee agreed that the animal-model based efficacy of filgrastim in the radiological/nuclear incident setting could be generalized to the use of other LGFs in that setting. The committee discussed BLA data that indicated, in the treatment of CIN, the three short-acting [Neupogen, Tbo-Filgrastim, and Leukine (sargramostin)] and one long-acting (Neulasta) LGF products appear to have similar effects on neutropenia. The committee also agreed that in the setting of a radiological/nuclear incident affecting a large number of people, where access to treatment facilities may be limited, it might be more practical to use a long-acting LGF.

Approval of Neupogen for HS-ARS

On March 30, 2015, DMIP approved Neupogen for increasing survival in patients acutely exposed to myelosuppressive doses of radiation (HS-ARS). This priority approval was based on an efficacy sBLA under the animal rule. The recommended dose of Neupogen is 10 mcg/kg as a single daily subcutaneous injection. Neupogen should be administered as soon as possible after suspected or confirmed exposure to radiation doses greater than 2 Gy and should be continued until ANC remains greater than 1,000/mm³ for 3 consecutive days or the complete blood count (CBC) exceeds 10,000/mm³ after a radiation-induced nadir.

Pivotal animal efficacy study

A pivotal animal efficacy study was conducted in Rhesus Macaques under the animal rule. The final study report was submitted and is reviewed below.

Study title: A Sixty-Day Efficacy Study of Subcutaneous Pegfilgrastim (Neulasta) to Treat the Hematopoietic Syndrome of the Acute Radiation Syndrome (ARS-HS) Following an LD_{50/60} of Total-body Irradiation (TBI) in Rhesus Macaques

Study no.: AXG21

Study report location: (b)(4)

Conducting laboratory and location: University of Maryland, Baltimore
School of Medicine, 10 South Pine Street,
MSTF 6-34D, Baltimore, MD 21201

Date of study initiation: 04 June 2012

GLP compliance: Yes*

QA statement: Yes

Drug, lot #, and % purity: Neulasta, lot #, 1028640, % purity, N/A

* Deviations from study protocol were tabulated in Appendix C. There were many deviations in medical management and supportive care mainly because of errors or oversights of technicians, miscommunication, misunderstanding, or documentation errors. In addition, some scheduled sample collections or tests were missed. According to the study report, these deviations did not impact the study. The reviewer agrees that the deviations recorded were not expected to significantly impact the study outcomes at least the primary endpoint.

Methods

Doses: 0 or 300-319 mcg/kg/dose^a
Frequency of dosing: 1/week, on SD 1 (20-26 hr) and on SD 8
(between 0800 hr and 1200 hr)
Route of administration: subcutaneous (SC)
Dose volume: 0.031 ± 0.001 mL/kg
Formulation/Vehicle: Dextrose 5% in Water (D5W)
Species/Strain: Monkey/rhesus macaques, (b)(4)
(b)(4)
Number/Sex/Group: 23/male/group^c
Age: three to four years
Weight: 3.9-5.5 kg
Satellite groups: None
Unique study design: Efficacy study under the animal rule

^a According to the study report, the proposed route and schedule of Neulasta administration was based on the currently approved indication of Neulasta for the treatment of cancer patients receiving myelosuppressive chemotherapy. The dose used reflected previous PK and PD analysis of pegfilgrastim in rhesus macaques following radiation-induced myelosuppression with and without autologous bone marrow transplantation (conducted by the same lab). The study report considered the dose to be bioequivalent to the dose proposed for humans (6 mg, SC, once per chemotherapy cycle).

^b Animals were obtained from two sources. (b)(4)

(b)(4)

(b)(4)

^c A maximum sample size of 78 animals was proposed for this study. The sample size was based on a two arm design with 80% power to detect a 30% difference in 60-day survival (50% in control, 80% in neulasta) using a two-tailed test at a 5% significance level. An interim analysis was performed after at least 58% of the animals completed the in-life phase of the study and the study was then terminated.

Reviewer comment

The study was conducted in males only, which causes potential concerns regarding the gender differences in the study outcomes. According to the PI of pegfilgrastim, no gender-related differences were observed in the human pharmacokinetics of pegfilgrastim. In addition, no gender-related differences were reported in the animal pharmacokinetics of pegfilgrastim. The combined PK or TK parameters were reported in the original BLA review and no gender difference was mentioned. These studies included a PK study in Rhesus monkeys (1 male and 2 females), a TK study in Cynomolgus monkeys (3-5/sex/group, 0, 75, 250, 750 mcg/kg/dose, SC, once/week, total five doses), and PK and TK studies in rats. Taken together, there is no evidence to indicate that there is a gender-related difference in survival benefit observed in this study.

Study design

The study was designed as a randomized and blinded study. The study was powered to show a 30% difference in 60-day survival using a two-tailed chi square test at a 5% significance level.

Blinding

All personnel involved in the study except for statisticians, Quality Assurance Unit personnel, archivist, and the Drug Managers (personnel preparing the control and drug articles) were blinded until the end of in-life phase.

The veterinary pathologist was blinded for individual animal histopathology examination and report. The veterinary pathologist was then unblinded to provide a written evaluation and conclusion based on the treatment arms.

Randomization

Animals were randomized to the control or neulasta arm in six to eight/per time point prior to each irradiation. The summary information of animal identification, source, irradiation date, and randomization is listed in the appendix (section 12). The code was provided to a designated unblinded member of the testing facility who was responsible

for maintaining the randomization schedule and overseeing the dosing based on the assigned arms.

Following the termination of the study, the randomization schedule was available to the Study Director.

Reviewer comment

Only slight imbalance was noted on two time points (on 7/16/12, 5 in the control arm vs. 3 in the neulasta arm; on 8/6/12, 3 in the control arm vs. 5 in the neulasta arm). The imbalance was not expected to impact study outcomes.

Baseline Assessment

During the post-quarantine evaluation period, baseline assessments were performed to assure the animals' inclusion. Post-quarantine evaluations included acclimation of animals to restraint, physical examination (PE), stool monitoring, measurements of BW, core body temperature (CBT), and hematology parameters. On the day of irradiation, animals were in good physical condition as evaluated by general appearance, heart rate, respiration rate, BW, CBT, and hydration status.

Radiation

Total body irradiation (TBI) using (b)(4)
(b)(4) 6-MV X-ray

Dose rate: approximately 80 cGy/min

n = 6 to 8 per irradiation day

Dose: 7.34 ± 0.189 Gy measured by OLSD in-vivo dosimetry, 2.1% lower than the prescribed midplane dose of 7.50 ± 0.15 Gy. See Table 1 for additional details. The dose was LD_{50/60} dose established in a previous study, which was reviewed by DMIP.

Table 1. Individual Radiation Doses

Irradiation Date	Group	ID	Radiation Dose (cGv)	Xiphoid				High Xiphoid			
				AP	PA	Sum	% Error	AP	PA	Sum	% Error
(b)(4)											

(b)(4)

Mean	734.0	-2.1
STDEV	18.9	

Medical Management and Supportive Care

Medical management and supportive care were provided to all animals as indicated by cageside and clinical observations. Medical management and supportive care included analgesics, anti-ulceratives, anti-diarrheals, anti-emetics, antibiotics, anti-pyretics, nutritional support, hydration fluids, and blood transfusions, and were described below.

Anesthesia

Ketamine HCl ((b)(4)) was administered intramuscularly prior to clinical observation procedures for minimizing stress and anxiety of animals, and for protecting animals and staff. If an animal responded poorly to ketamine alone, xylazine (b)(4) was added. If required, the effect of anesthetic agents was reversed by administering yohimbine (b)(4) (b)(4)

For CT scans, animals were anesthetized with ketamine and xylazine at the doses aforementioned.

Analgesics

Buprenorphine HCl (b)(4) (b)(4)) was administered from SD 5 through 35, and whenever mouth ulcers or bloody stools were observed. Mouth ulcers were cleansed with 10% chlorhexidine diacetate solution (b)(4)) or hydrogen peroxide, then rinsed with saline. Bupivacaine gel (b)(4) (b)(4) and the surgical lubricant (b)(4) were applied to ulcerated areas.

Anti-ulceratives

Sucralfate (Carafate, (b)(4)) was administered when bloody stool or mouth ulcers were observed.

Anti-diarrheals

After diarrhea was observed, loperamide hydrochloride (Imodium, (b)(4)) was administered for 3 days or less if diarrhea resolved. If diarrhea persisted for three consecutive days during Imodium treatment, diphenoxylate hydrochloride (Lomotil, (b)(4)) was administered for 3 days or less if diarrhea resolved. If diarrhea continued after Lomotil treatment for three days, Imodium treatment was resumed.

Anti-emetics

Ondansetron (b)(4) was administered twice on the day of irradiation (45 to 90 minutes prior to and following radiation exposure) to prevent radiation-induced nausea and vomiting. In addition, ondansetron (b)(4) was administered when emesis was observed.

Antibiotics/Antifungals

Prophylactic antibiotic treatment was initiated when ANC was < 500/mcL and continued until animals maintained ANC $\geq$ 500/mcL for 2 days. Enrofloxacin (Baytril, (b)(4)) was administered as a primary antibiotic. Gentamicin sulfate (b)(4) was added for up to four days when CBT $\geq$ 103°F. Renal function analysis was performed before, following, and occasionally during gentamicin administration by measurement of blood urea nitrogen (BUN) and creatinine.

Ceftriaxone (Rocephin, (b)(4)) or ertapenem (Invanz, (b)(4)) was also administered when microbial resistance to enrofloxacin or gentamicin was identified.

Metronidazole (b)(4) was administered for 10 to 14 days when there was a positive blood culture for gram negative anaerobes.

Fluconazole (b)(4) was administered for a minimum of 10 days when a fever persisted for more than five consecutive days.

Anti-pyretics

Carprofen (b)(4) was administered when CBT $\geq$ 104°F, and was continuously used for two days after the first day when CBT < 104°F.

Nutritional Support

A high protein shake (HPS, (b)(4)), consisting of (b)(4) liquid protein (b)(4) and MCT Oil (b)(4) was administered when animals were observed to loss $\geq 10\%$ of the baseline (SD 0) BW. The volume was reduced to 7 mL/kg if animals were also administered (b)(4) treated water for hydration.

When animals were not scheduled to be anesthetized but required nutritional support, the supplemental nutrition was provided as fresh fruit, vegetables, and snacks. Supplemental nutrition continued daily until the BW increased to $> 90\%$ of the baseline BW.

Hydration Support

Fluid support was provided as described below based on a dehydration grading system.

Mild: presence of tacky mucous membranes, skin tent time (STT) ≥ 2 but < 3 sec, or capillary refill time (CRT) ≥ 2 but < 3 sec. These animals were administered lactated Ringer's solution (b)(4), and treated water or oral electrolyte solution (OE, (b)(4)).

Moderate: mild plus dry mucous, $> 3\%$ increase in hematocrit (Hct) from the previous day (not transfusion-related), sunken eyes, STT ≥ 3 sec, or CRT ≥ 3 sec. These animals were administered LRS (b)(4), and treated water or OE (b)(4).

Severe: mild or moderate plus pale mucous membranes, $> 5\%$ increase in Hct from the previous day (not transfusion-related), a rapid and weak pulse, cold extremities, lethargy, or rapid breathing. These animals were administered the same treatment for animals with moderate dehydration plus a slow IV infusion of LRS (15 ± 5 mL/kg/h, 2-4 hours) followed by administration of treated water or OE (b)(4).

LRS (b)(4) was also administered after the irradiation procedure, during treatment with gentamicin, or CBT $\geq 103^\circ\text{F}$.

Blood transfusion

Whole blood, anti-coagulated with (b)(4), was obtained from healthy male monkeys with BW ≥ 7.0 kg. Blood was filtered through a (b)(4) strainer and irradiated at 25 Gy (b)(4) prior to use.

Whole blood was IV administered at (b)(4) using an (b)(4) blood filter when Hct decreased by $\geq 5\%$ with Hct $\leq 25\%$ over a 24-hour period, Hct $< 20\%$, PLT $< 20,000/\text{mcL}$ with Hgb < 6.7 g/dL, PLT $\leq 2,000/\text{mcL}$, or obvious signs of uncontrolled hemorrhage. In addition, whole blood was administered when Hct decrease by 7-10% over a 24-hour period or Hct $\leq 25\%$ with PLT $< 3,000/\text{mcL}$ for two consecutive days.

Reviewer comment

Extensive medical management and supportive care were provided. When such management and care were provided in a blinded manner according to the pre-specified criteria, they should not impact the study outcomes.

Euthanasia Criteria*Unscheduled Sacrifices*

Animals having one of the following conditions were euthanized:

1. Unrelieved pain or distress
2. Recumbent in the cage with decreased or absent responsiveness to touch
3. Seizure activity that did not respond to medication
4. Respiratory distress
5. Hemorrhage in excess of 20% of the estimated blood volume during a 24 hour period
6. CBT $\geq 106^{\circ}\text{F}$
7. CBT $< 96^{\circ}\text{F}$ for six hours
8. Loss of BW $\geq 25\%$ of baseline for three days
9. Extensive occurrences of self-mutilation

Animals having two of the following conditions were euthanized:

1. Tachypnea (respiration > 60 breaths per minute)
2. Abnormal activity: difficulty with ambulation, decreased food and water intake, self-mutilation, reluctance to move for > 2 hours
3. Clinical condition: severe dehydration that was not responsive to IV fluid therapy or unable to maintain a CBT above 97°F following 2-4 hours IV fluid therapy, shallow respiration, hyperthermia (CBT $> 105.5^{\circ}\text{F}$) that was not responsive to antipyretic therapy for > 72 hours, or evidence of eye or upper respiratory infections that were not responsive to antibiotic therapy for > 96 hours
4. Loss of BW $> 20\%$ of baseline BW for > 3 consecutive days
5. Abnormal appearance: rough coat, head down, tucked abdomen, pallor, or exudates around eyes or nose

Animals were sedated using ketamine (b)(4) then euthanized by IV injection of (b)(4)

Death was confirmed by lack of heartbeat, femoral or carotid artery pulse, and chest respiration.

Terminal Sacrifice

Animals survived through SD 60 were euthanized as described above on SD 61 to SD 67.

Reviewer comment:

Euthanasia criteria were clearly specified. When animals were euthanized in a blinded manner according to the pre-specified criteria, euthanasia should not introduce bias to survival.

Study endpoint and statistical analysis*Primary Endpoint*

The primary endpoint was survival. Differences in overall 60 days survival post TBI between the neulasta and control arms were compared using a chi-square test (two-tailed, null hypothesis at a 5% significance level).

Secondary Endpoint

Continuous data were summarized by the treatment arms using descriptive analysis including mean, StDev, SEM, median, and range. The following parameters were analyzed as continuous data. All animals were included into analyses regardless of survival status.

1. ANC nadir
2. The first day of neutropenia (ANC < 500/mcL or ANC < 100/mcL)
3. The last day of neutropenia after the nadir
4. Duration of neutropenia
6. Time to recovery to ANC > 500/mcL and ANC > 1,000/mcL after ANC nadir
7. PLT nadir
8. The first day of thrombocytopenia
9. Duration of thrombocytopenia and time to recovery to PLT > 20,000/mcL after PLT nadir
10. First day of FN
11. Frequency of FN, frequency of fever, and frequency of antibiotic administration expressed as a percentage of days animals on study
12. First day and numbers of blood transfusions per animal
13. Spleen weight and spleen weight/body weight at necropsy
14. Fold change in normalized spleen volume from baseline to SD 9 to 11 or to SD 60

Time-to-event data were summarized descriptively by the median, 25th and 75th percentiles and 95% confidence intervals, and graphically using Kaplan-Meier curves. Animals euthanized prior to the end of the in-life phase were censored on Day 60 for neutrophil- and platelet-related parameter analyses. The following parameters were analyzed as time-to-event data.

1. Overall survival from the day of irradiation to the day of death (Day 60 was used for animals survived until the terminal sacrifice.)
2. Duration of neutropenia
3. Duration of thrombocytopenia
4. Time to recovery to ANC > 500/mcL and ANC > 1,000/mcL after ANC nadir
5. Time to recovery to PLT > 20,000/mcL after PLT nadir

Categorical data [incidence data: infection, FN, CBT > 103°F, absolute neutropenia (ANC = 0/mcL), increased normalized spleen volume on SD 9-11 or on SD 60 relative to baseline volume, or splenic rupture] were presented as enumerations and percentages for all animals.

Other descriptive data described below were also presented as enumerations and percentages for all animals, which were calculated using Microsoft Excel 2010 (version 14.0.7106.5003) or calculators.

1. Incidence of antibiotic resistance in blood/tissue culture positive microbial cultures
2. Incidence of diarrhea
3. Severity of diarrhea
4. Incidence of pathology in the bone marrow, heart, lung, liver, spleen, kidney, thymus, lymph nodes, and small and large intestine after necropsy

Dichotomous outcomes were analyzed using either Fisher's exact or chi-square tests.

Continuous outcomes were compared between the treatment arms using Student's t test or Wilcoxon rank-sum test. Time-to-event survival curves were estimated for each treatment arm using the Kaplan-Meier product limit method, and were compared using the log-rank test. Survival curves were compared using the Cox proportional hazards regression model.

Exploratory analyses were conducted for effects of Neulasta on neutrophil and platelet indices compared with that of D5W. Trajectories of the laboratory values by treatment arms were graphically examined.

See Table 2 for a summary of scheduled events.

Table 2. Schedule of Select Events

Procedure	Study Day																
	-56 to -1	-30 to -1	-4 to -1	-3 to 0 pre-irrad.	0 pre-irrad.	0	1	2	3	4	5	6	7	8	9	10	11
Irradiation						X											
Restraint acclimation	X																
Physical Exam				X													
Chemistry ¹		X															
TA or CA injection						X								X			
CT scan ²		X														X	
Pegfilgrastim immunogenicity ³		X															
CBC, differential ⁴ (collected before dosing with TA/CA)		X	X		X		X	X	X	X	X	X	X	X	X	X	X
Cageside observations ⁵					X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical observations					X		X	X	X	X	X	X	X	X	X	X	X

¹Chemistry is collected up to 2X.
²CT scans are performed on any one day from SD(-30) through SD(-1), any one day from SD9-11, and on SD60, or prior to moribund sacrifice if an animal is found moribund before SD60.
³Blood is collected for immunogenicity one time from SD(-30) through SD(-1) and on SD60, or at the time of moribund sacrifice if an animal is found moribund before SD60. No sample will be collected on an animal found dead (expired).
⁴CBC, differential is collected at least 3X from SD(-30) through SD(-1) with one collection from SD(-4) through SD(-1)
⁵Cageside observations are performed at least twice daily.

Reviewer comment

The primary and secondary endpoints are appropriate.

Rules used to determine platelet recovery

To consider the effect of blood transfusions on platelets, duration of thrombocytopenia and time-to-recovery to $PLT \geq 20,000/\text{mcL}$ were calculated based on the following six rules.

Rule 1: Animals must recover to $PLT \geq 20,000/\text{mcL}$ according to the subsequent rules prior to death or at the end of the study to be included in calculations of the durations.

Rule 2: If there was no transfusion, recovery was the first day when $PLT \geq 20,000/\text{mcL}$ and PLT remained $\geq 20,000/\text{mcL}$ for 2 consecutive days.

Rule 3: If one transfusion was provided when $PLT < 20,000/\text{mcL}$, PLT on D1 and D2 post-transfusion were not considered recovered even if $PLT \geq 20,000/\text{mcL}$. If PLT remained $\geq 20,000/\text{mcL}$ on D3 through D5 post-transfusion, then D3 post-transfusion was considered the day of recovery to $PLT \geq 20,000/\text{mcL}$.

Rule 3a: Animals must survive for five days post-transfusion for recovery to be counted.

Rule 4: If multiple transfusions were provided prior to PLT recovery as stated in rule #3, the final transfusion was used as a starting point when determining when the recovery occurred.

Rule 5: If the first transfusion occurred on or after the day $PLT \geq 20,000/\text{mcL}$ and PLT remained $\geq 20,000/\text{mcL}$ on D1 through D3 post-transfusion, recovery to $PLT \geq 20,000/\text{mcL}$ was on the first day $PLT \geq 20,000/\text{mcL}$. The transfusion was considered no effect on PLT recovery.

Rule 6: For study days when a blood sample was not collected, the platelet value used in the determination of platelet recovery was estimated by linear interpolation using the preceding or following platelet counts.

Result

Primary endpoint-OS

Animals were observed twice per day by the husbandry staff for mortality, morbidity, and general health.

The research staff performed cageside observations according SOP (b)(4) twice per day with a minimum of six hours apart. Personnel performing cageside observations were blinded. Parameters evaluated during cageside observations included activity, posture, evidence of vomit, stool consistency, blood in stool, hemorrhage, respiratory activity, alopecia, seizure activity, and the presence of food in hopper

The research staff performed clinical observations daily from SD 0 through SD 25, then once at least on SD 28, 31, 35, 39, 42, 45, 49, 56, 60, and at the termination. Additional observations were performed as necessary for medical management and supportive care. Parameters evaluated include CBT, BW, hydration status, presence of mouth ulcers, petechia, ecchymosis, and swelling.

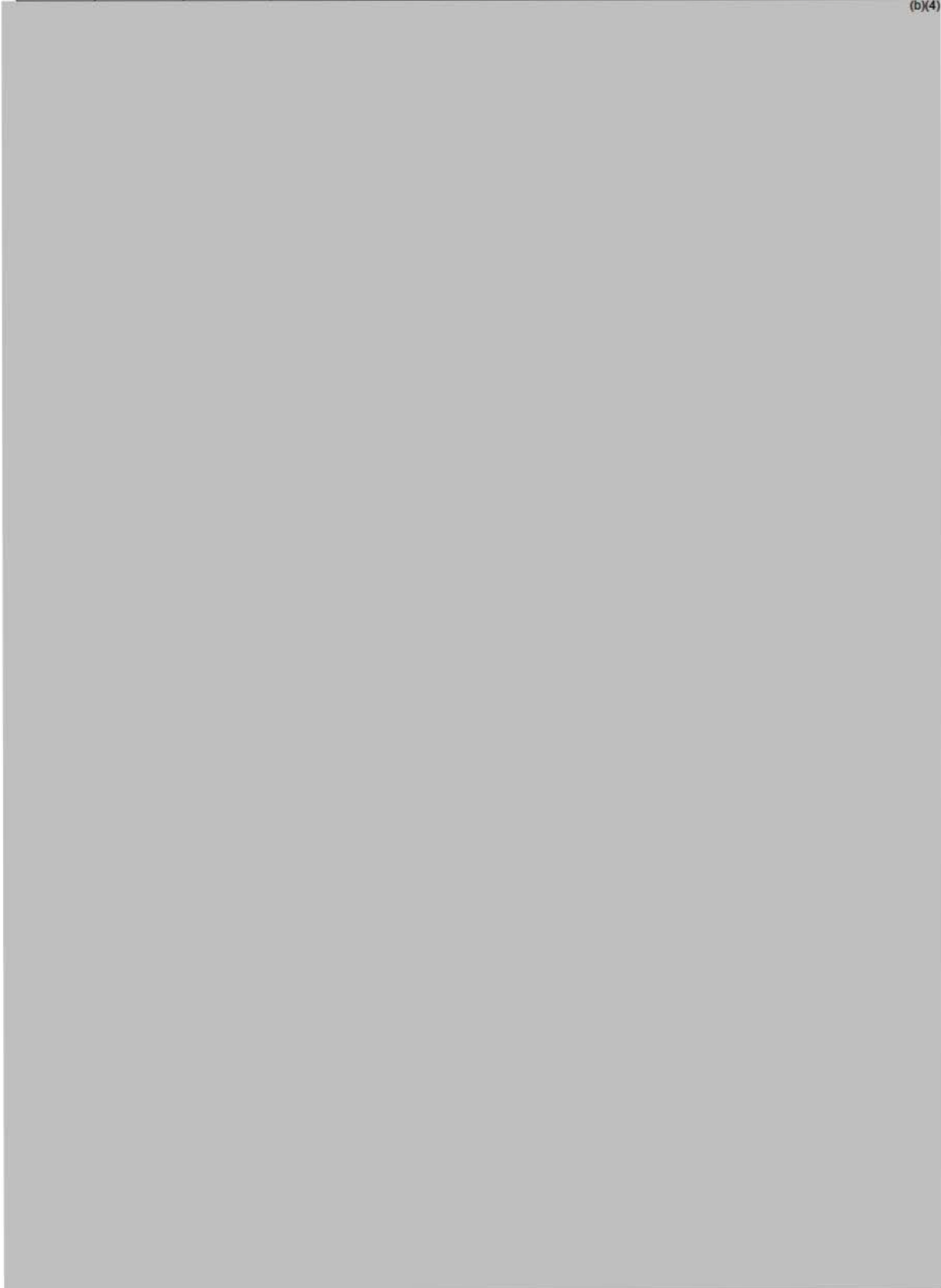
Animal fate

Only a summary table was provided at Appendix H. All animals that underwent unscheduled sacrifice were euthanized according to the euthanasia criteria aforementioned. The majority of animals were euthanized between SD14-SD23. Three only were euthanized on SD 40 or later, all because of weight loss $\geq 25\%$ of baseline weights.

Table 3. Summary of animal fate

Group	ID	Treatment	Date of Irradiation	Date of Death	SD	Disposition	Criteria for Euthanasia
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(b)(4)



Reviewer comment

All animals that underwent unscheduled sacrifice were euthanized according to the euthanasia criteria aforementioned. According to the study report, euthanasia was performed in a blinded manner.

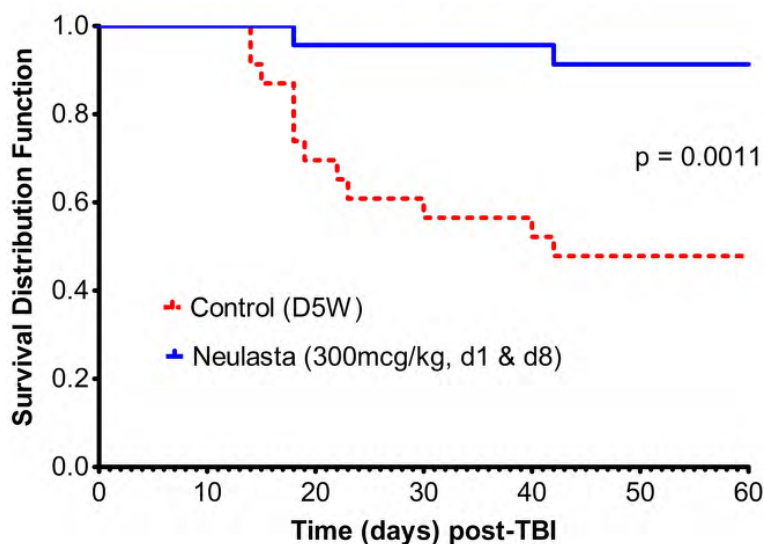
Survival

The interim efficacy analysis was conducted after 58% of the animals had completed in-life phase. This analysis was performed on unblinded animal fate data. The survival data were summarized in Table 4 and Figure 1. The interim analysis revealed that Neulasta, subcutaneously administered at 300-319 mcg/kg/dose on SD 1 (20-26 hr) and on SD 8 (between 0800 hr and 1200 hr) following a LD_{50/60} TBI, significantly increased overall survival [91.3% (21/23) vs. 47.8% (11/23) in the control arm, two-sided Chi-square test, $p = 0.0014$].

Table 4. Summary of Survival Data

Treatment	N	# Died	# Survived	Percent Died	Percent Survived	p value
D5W	23	12	11	52.2%	47.8%	0.0014
Neulasta	23	2	21	8.7%	91.3%	

Figure 1. Kaplan-Meier Survival Curves*



*Survival curve of rhesus macaques administered Neulasta (n = 23) or D5W (control, n = 23) as a function of time post LD_{50/60} TBI. The difference between the survival curves was statistically significant (log-rank test, $P = 0.0011$).

Reviewer comment

The primary endpoint was survival: Overall survival of animals in the neulasta arm needs to be at least 30% greater than that of animals in the control arm. The interim

analyses were performed on unblinded data with a fraction of 0.5897 (46/78 animals). The spending alpha was 0.0070 (the primary outcome was considered significant if p-value was less than 0.0070).

All animals that underwent premature death were euthanized in a blinded manner according to the pre-specified euthanasia criteria. Only two (2/23) animals were euthanized in the neulasta arm but 12 (12/23) were euthanized in the control arm. Therefore, neulasta significantly improved overall survival ($p=0.0014$, < 0.0070). The primary endpoint was met.

Secondary endpoint

Mean Survival Time of Decedents

Survival time of animals with unscheduled sacrifices was summarized in Table 5. There was no significant difference in the mean survival time between two arms ($p = 0.5172$, Wilcoxon rank sum test).

Table 5. Summary of Survival Time (days) of Decedents

Treatment	N	Mean	StDev	SEM	Median	Min	Max	Range
D5W	12	23	10	2.8	19	14	42	28
Neulasta	2	30	17	12	30	18	42	24

Hematology

Blood was collected from SD (-30) through SD (-1), SD 0 (prior to the irradiation), SD 1 prior to dosing, daily on SD 2 through 7, SD 8 prior to dosing, daily on SD 9 through 25, then on SD 28, 31, 35, 39, 42, 45, 49, 56, 60, and at the termination. CBCs and WBC differentials were measured and ANC were calculated. Results were summarized in Table 6 and illustrated by Figure 2 to Figure 4.

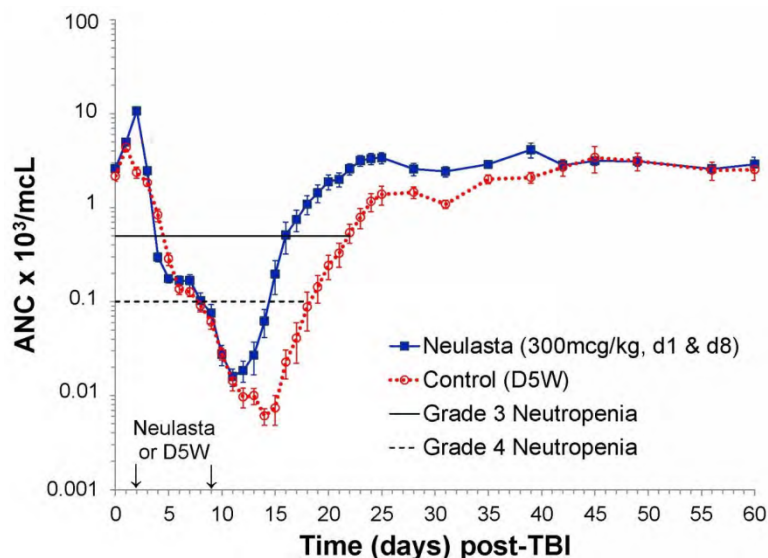
Neulasta mainly reduced the durations of ANC < 500/mcL (median: 14 vs. 18 days in the control arm) and ANC < 100/mcL (8 vs. 12 days in the control arm). As a result, neulasta improved the ANC recovery as evidenced by reduced median time-to-recovery to ANC > 500/mcL (18 vs. 23 days in the control arm) and ANC > 1,000/mcL (20 vs. 25 days in the control arm).

Table 6. Summary of Neutrophil Parameters

Parameter	Treatment	N	Mean $\pm$ SEM	Median	Range	p value
First day ANC < 500/mcl (SD)	D5W	23	5 $\pm$ 0.1	5	4-6	0.0009
	Neulasta	23	4 $\pm$ 0.1	4	4-5	
First day ANC < 100/mcl (SD)	D5W	23	7 $\pm$ 0.4	7	5-10	0.6304
	Neulasta	23	8 $\pm$ 0.4	8	4-11	
ANC nadir (/mcl)	D5W	23	2 $\pm$ 1	0	0-8	0.0377
	Neulasta	23	10 $\pm$ 3	4	0-66	
Last day ANC < 500/mcl [†] (SD)	D5W	14	22 $\pm$ 0.8	22	17-30	< 0.0001
	Neulasta	22	17 $\pm$ 0.5	17	14-23	
Last day ANC < 100/mcl [†] (SD)	D5W	16	19 $\pm$ 0.5	19	15-21	< 0.0001
	Neulasta	22	15 $\pm$ 0.4	15	12-19	
Duration ANC < 500/mcl [†] (days)	D5W	14	18 $\pm$ 0.8	18	13-26	< 0.0001
	Neulasta	22	14 $\pm$ 0.5	14	10-20	
Duration ANC < 100/mcl [†] (days)	D5W	16	12 $\pm$ 0.6	12	7-16	0.0002
	Neulasta	22	8 $\pm$ 0.7	8	2-15	
Time to Recovery of ANC $\geq$ 500/mcl [†] (days)	D5W	14	23 $\pm$ 0.8	23	18-31	< 0.0001
	Neulasta	22	18 $\pm$ 0.5	18	15-24	
Time to Recovery of ANC $\geq$ 1000/mcl [†] (days)	D5W	13	27 $\pm$ 1.6	25	20-41	0.0010
	Neulasta	21	20 $\pm$ 0.7	20	15-26	

[†]Analysis included all animals that recovered from neutropenia regardless of survival to SD 60.

Figure 2. ANC in Animals post TBI



Mean ($\pm$ SEM) ANC x 10³/mcl in the peripheral blood of rhesus macaques administered D5W (n = 23) or Neulasta (n = 23) as a function of time post TBI.

Figure 3. Kaplan-Meier Duration Curves for ANC < 500/mcL and ANC < 100/mcL

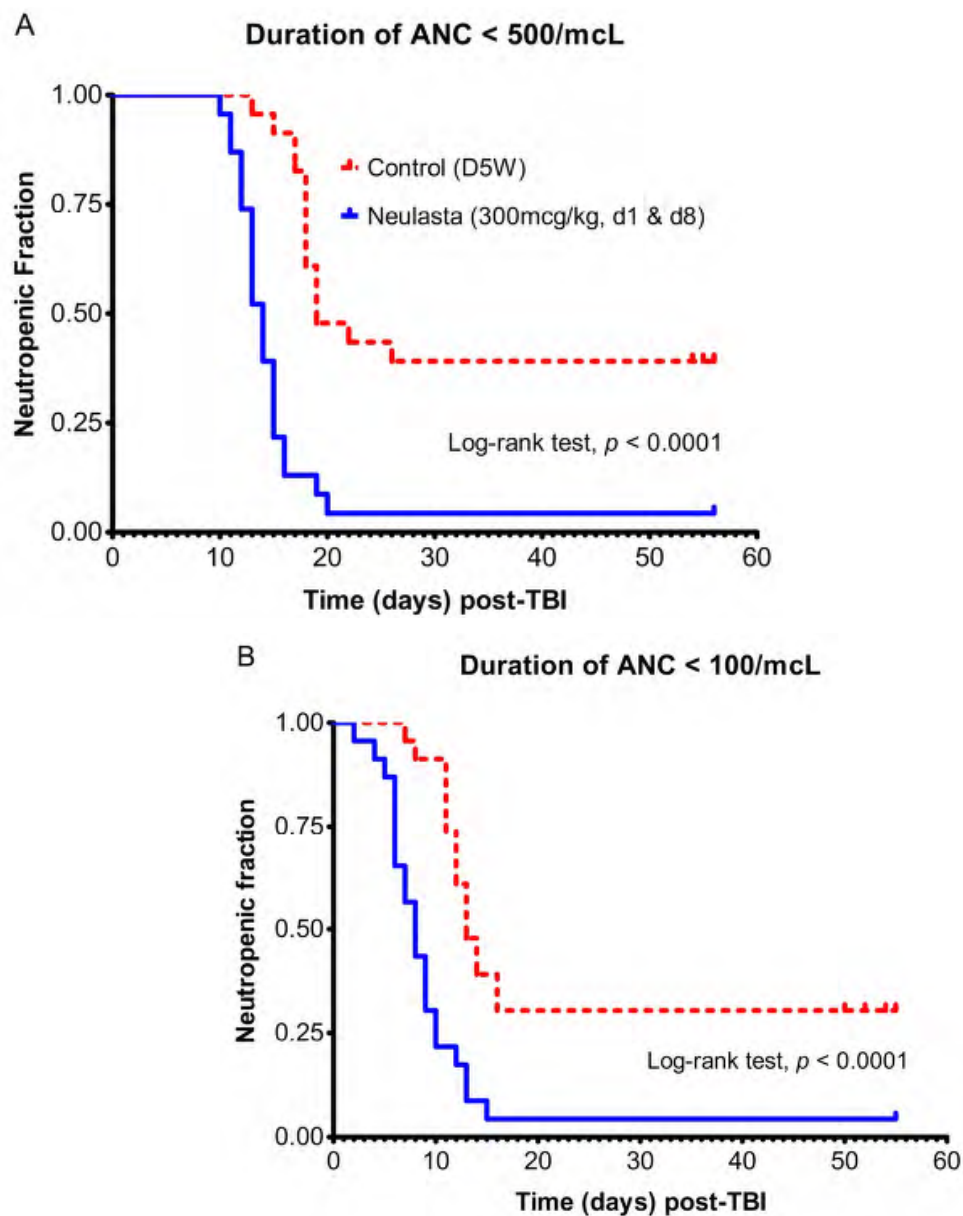
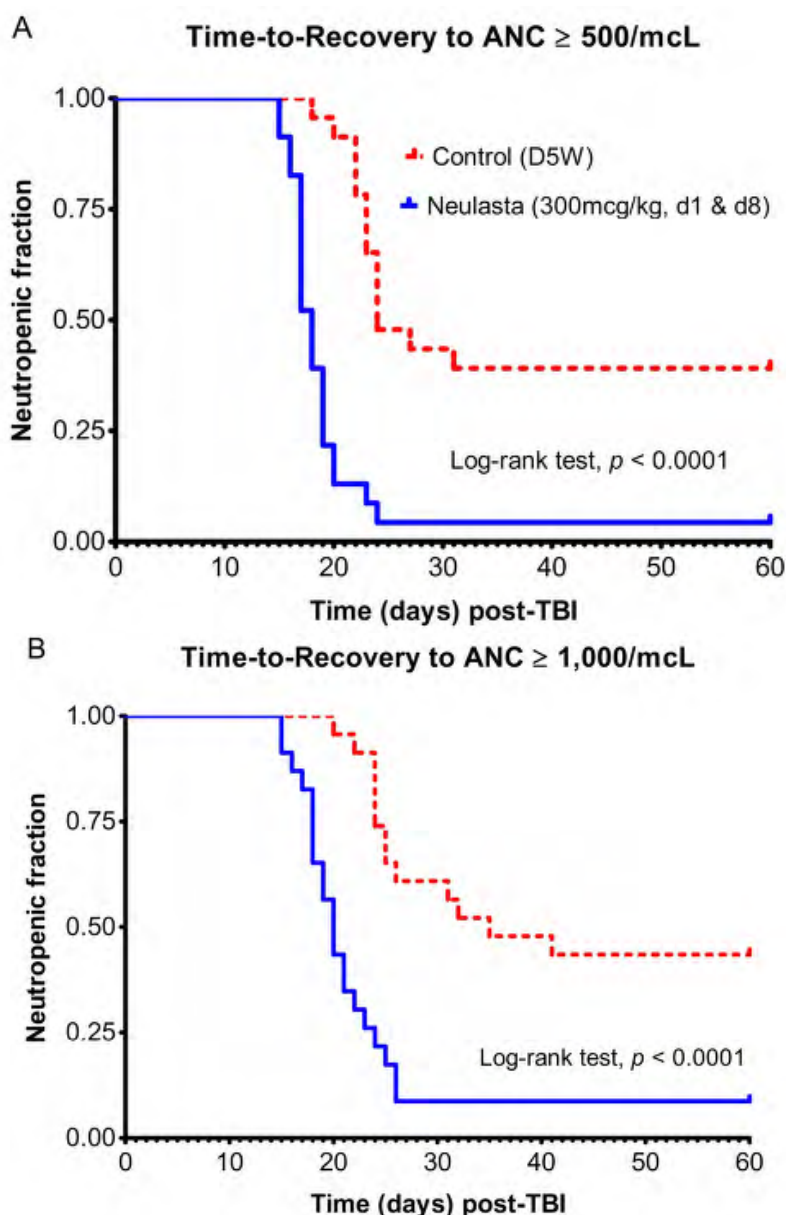


Figure 4. Kaplan-Meier Time-to-Recovery Curves for ANC in Animals post TBI

*Reviewer comment*

Reduced duration of severe neutropenia is used as a primary endpoint for approval of neulasta. According to the PI, in the absence of growth factor support, chemotherapy regimens used in the clinical trials have been reported to result in a 100% incidence of severe neutropenia ($\text{ANC} < 0.5 \times 10^9/\text{L}$) with a mean duration of 5 to 7 days and a 30% to 40% incidence of febrile neutropenia. The mean days of cycle 1 severe neutropenia were reduced to 1.8 or 1.7 days in the neulasta arm with 6 mg/dose or 100 mcg/kg/dose (once on Day 2 of a 21 day cycle), respectively. The mean days of cycle 1 severe neutropenia were reduced to 1.6 days in the filgrastim arm (5 mcg/kg/day). Similar results were achieved in cycles 2 through 4 (secondary endpoint).

Neulasta reduced the mean days of severe neutropenia in a similar magnitude (4 days) in this NHP study.

Platelet-Related Parameters & Transfusion Requirements

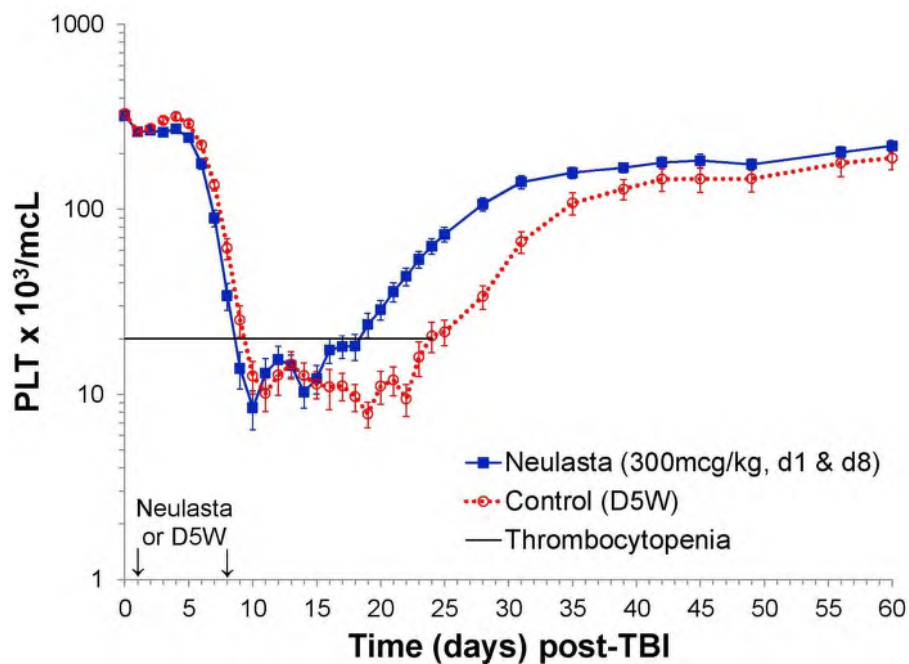
The results of platelet analyses were summarized in Table 7 and illustrated by Figure 5 and Figure 6. To minimize the transfusion-resulted increase in PLT, the rules aforementioned were applied to determine the duration of thrombocytopenia and time to recovery to PLT $\geq 20,000/\text{mcl}$.

Similar to ANC, neulasta mainly reduced duration of PLT $< 20,000/\text{mcl}$ (median: 11 vs. 16 days in the control arm). As a result, neulasta improved PLT recovery as evidenced by reduced median time-to-recovery to PLT $\geq 20,000/\text{mcl}$ (20 vs. 26 days in the control arm) and reduced average numbers of transfusions per animal (2 vs. 3 in the control arm, all animals, except for one in the neulasta arm, were administered at least one transfusion).

Table 7. Summary of Platelet Parameters

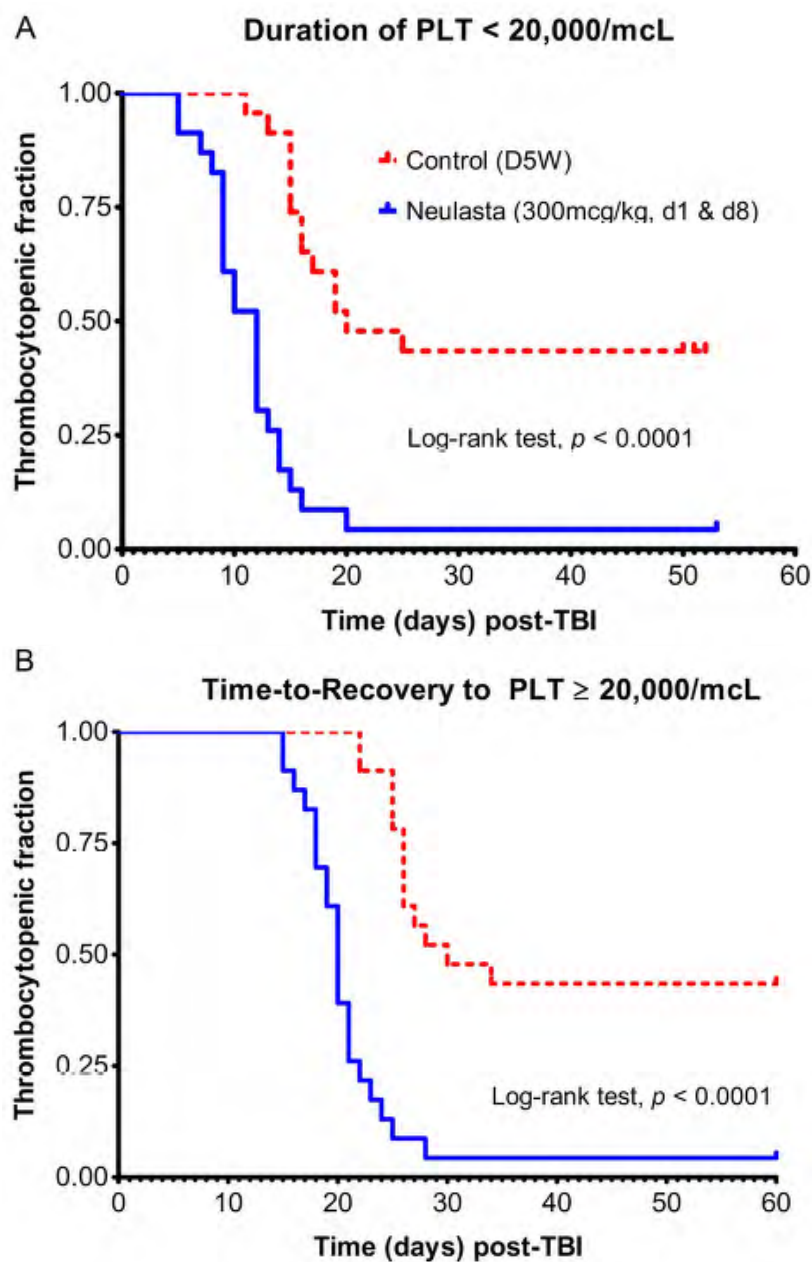
Parameter	Treatment	N	Mean $\pm$ SEM	Median	Range	p value
First day PLT $< 20,000/\text{mcl}$ (SD)	D5W	23	9 $\pm$ 0	9	8-11	0.0826
	Neulasta	23	9 $\pm$ 0	9	7-11	
PLT nadir (/mcl)	D5W	23	1696 $\pm$ 230	1000	0-4000	0.6146
	Neulasta	23	2087 $\pm$ 382	2000	0-8000	
Duration PLT $< 20,000/\text{mcl}^\dagger$ (days)	D5W	13	17 $\pm$ 1	16	11-25	< 0.0001
	Neulasta	22	11 $\pm$ 1	11	5-20	
Time to Recovery to PLT $\geq 20,000/\text{mcl}^\dagger$ (days)	D5W	13	26 $\pm$ 1	26	22-34	< 0.0001
	Neulasta	22	20 $\pm$ 1	20	15-28	
First day of transfusion (days)	D5W	23	11 $\pm$ 0.3	11	9-13	0.1076
	Neulasta	22	11 $\pm$ 0.2	10	9-13	
Number of transfusions (unit = 54 mL)	D5W	23	3 $\pm$ 0.3	3	1-7	0.0014
	Neulasta	23	2 $\pm$ 0.3	2	0-5	

[†]Analysis included all animals that recovered from thrombocytopenia regardless of survival to SD 60.

Figure 5. Mean ($\pm$ SEM) PLT $\times 10^3/\text{mCL}$ in Animals post TBI

Note: Transfusions elevated PLT nadir and the rate of recovery from thrombocytopenia.

Figure 6. Kaplan-Meier Duration and Time-to-Recovery Curves in Animals post TBI



Peripheral Blood Culture

Specimens for blood cultures were aseptically collected on the day when CBT $\geq 105^{\circ}\text{F}$, on the first day when FN (ANC $< 500/\text{mcL}$ and CBT $\geq 103^{\circ}\text{F}$) was observed, or at 24 hours after the first blood culture if FN persisted. An additional blood specimen was obtained if FN persisted for five consecutive days.

The results of blood cultures were summarized in Table 8 and Table 9.

Animals in the control arm had slightly higher incidence of at least one bacteria-positive blood cultures (18/23, 78%) than in the neulasta arm (15/23, 65%). But the difference was not statistically significant (Chi-square test, $p = 0.3259$).

Table 8. Summary of Blood Culture Results

Article	Peripheral Blood Cultures Performed		Peripheral Blood Cultures Negative for Bacteria		Number of NHP Having at Least One Bacteria-Positive Blood Culture		Cultures positive for Gram (-) Bacteria		Cultures positive for Gram (+) Bacteria		Cultures positive for Gram (-) and Gram (+) Bacteria	
	No./total	%	No./total	%	No./total	%	No./total	%	No./Total	%	No./total	%
Total	217		146/217	67	33/46	72	14/217	6	50/217	23	7/217	3
Control n=23	110/217	51	64/110	58	18/23	74	12/110	11	29/110	26	5/110	5
Test n= 23	107/217	49	82/107	77	15/23	65	2/107	2	21/107	20	2/107	2

Table 9. Peripheral Blood Culture Results from In-life Phase Specimens

Study Day	(b)(4)

N = no bacteria, + = Gram positive (+) organisms, - = Gram negative (-) organisms, + - = Gram + and Gram - organisms

The incidences of blood cultures with antibiotic resistant microbes were summarized in Table 10. The incidence of antibiotic resistant cultures was higher in the control arm than in the neulasta arm (70% vs. 39%).

Table 10. Antibiotic Resistance in Animals Treated with Antibiotics

Cohort	Baytril®		Gentamicin		Rocephin®		Invanz®		Total # NHP with antibiotic resistant blood culture results	
	No.	%	No.	%	No.	%	No.	%	No.	%
All animals	25/46	54	16/40	40	22/33	67	4/8	50	25/46	54
D5W	16/23	70	9/20	45	14/15	93	2/6	33	16/23	70
Neulasta	9/23	39	7/20	35	8/18	44	2/2	100	9/23	39

Blood and Tissue Microbial Culture at Necropsy

At necropsy, blood, kidney, lung, liver, and spleen samples were obtained aseptically, except for 2 animals in the control arm, and microbial cultures were performed. The results were summarized in Table 11.

Higher incidence of bacteria-positive cultures in both blood and tissues was observed in animals in the control arm than in the neulasta arm [24% (5/21) vs. 4% (1/23)], indicating animals in the control arm had more systemic infections than animals in the neulasta arm.

Table 11. Microbial Culture Results from Blood and Tissues Collected at Necropsy

ID	Cohort	Article	Disposition	Organ Site									
				Blood		Liver		Spleen		Lung		Kidney	
				Gram +	Gram -	Gram +	Gram -	Gram +	Gram -	Gram +	Gram -	Gram +	Gram -
(b)(4)													

Clinical Sign

Animals were observed and scored twice daily for activity, posture, evidence of vomit, stool consistency, blood in stool, hemorrhage, respiratory activity, alopecia, seizure activity, and the presence of food in hopper. Findings were separately described below.

Activity

Decreased activity was more frequently observed in animals in the control arm than in the neulasta arm (13/23 vs. 7/23). Absent activity (Grade 2) was observed in one animal in the control arm only. More days with limited activity (Grade 1) were observed in animals in the control arm than in the neulasta arm (31 days vs. 18 days).

Posture

Abnormal posture was more frequently observed in animals in the control arm than in the neulasta arm (16/23 vs. 8/23). Recumbent posture (Grade 2) was observed in one animal in the control arm only. More days with hunched posture (Grade 1) were observed in animals in the control arm than in the neulasta arm (40 days vs. 25 days).

Incidence and Severity of Diarrhea

There was no significant difference in incidence or severity of diarrhea between two arms. All animals, except one in the neulasta arm, experienced Grades 1, 2 or 3 diarrhea at some time points. The incidences of bloody diarrhea (Grade 3) were similar in both arms (5/23 in the neulasta arm vs. 4/23 in the control arm). However, more days with bloody diarrhea were observed in animals in the control arm than in the neulasta arm (16 days vs. 10 days).

Vomit

Vomiting (at least one episode) was more frequently observed in animals in the control arm than in the neulasta arm (15/23 vs. 8/23). Furthermore, more days with one episode of vomit (Grade 1) were observed in animals in the control arm than in the neulasta arm (21 days vs. 10 days).

Blood in Stool

Blood in stool was observed more frequently between SD 10 and SD 30 in both arms. Blood in stool was more frequently observed in animals in the control arm than that in the neulasta arm (22/23 vs. 18/23), but fewer days with blood in stool were observed in animals in the control arm than in the neulasta arm (8 days vs. 9 days).

Hemorrhage

Fusing blood or > 10 spots in cage (Grade 2) was more frequently observed in animals in the control arm than in the neulasta arm (3/23 vs. 1/23). Longer duration of hemorrhage was also noted in the control arm (between SD 8 to SD 39) than in the neulasta arm (between SD 9 and SD 26). The incidences of Grade 1 hemorrhage (≤ 10 blood spots) were comparable between the two arms (9/23 in the neulasta arm vs. 10/23 in the control arm). Grade 3 or life threatening hemorrhage was not observed in either arm.

Respiration

Normal respiration was observed in all animals.

Alopecia

Hair loss was first observed on SD 11 in both arms. Loss of coat was noted in more animals in the control arm than in the neulasta arm (16/23 vs 13/23). Fewer animals in the control arm recovered to a normal coat than in the neulasta arm (2/23 vs. 7/23).

Body Weights

Body weights were measured during the post-quarantine period, daily from SD 0 to SD 25, on SD 28, 31, 35, 39, 42, 45, 49, 56, 60, at termination, and on other days as required for medical management. Supplemental nutritional support was provided on the first day when body weight decreased to $\geq 10\%$ of the baseline.

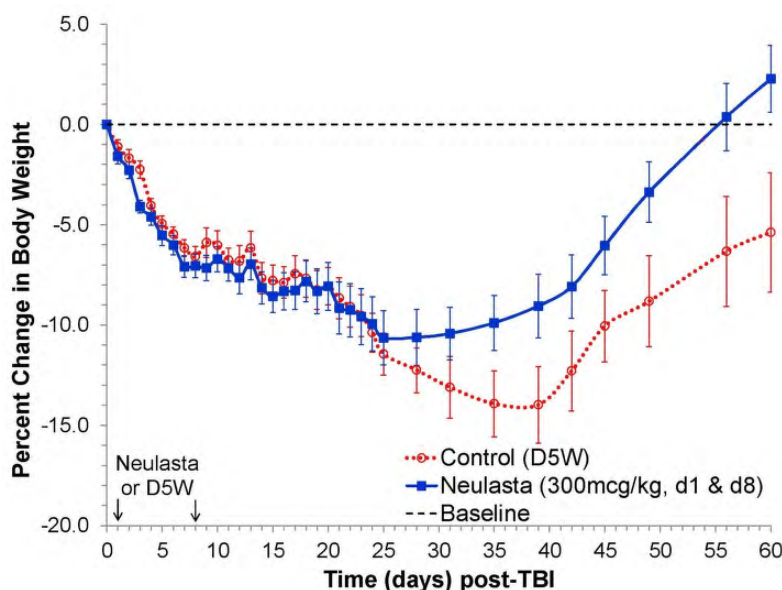
Incidence and severity of body weight loss were slightly greater in animals in the control arm than in the neulasta arm (Table 12). For example, three (3/23) animals in the control arm had a body weight loss $\geq 25\%$ of the baselines but one (1/23) only in the neulasta arm.

Table 12. Incidence and Severity of Body Weight Loss

Treatment	$\geq 10\%$ body weight loss			$\geq 25\%$ body weight loss		
	n/N	%	Mean No. Days $\pm$ SEM	n/N	%	Mean No. Days $\pm$ SEM
D5W	15/23	65.2%	13.7 $\pm$ 2.8	3/23	13.0%	1.3 $\pm$ 0.3
Neulasta	14/23	60.9%	16.4 $\pm$ 2.6	1/23	4.3%	1

The mean percent changes in body weight between SD 1 and SD 25 was similar between two arms (Figure 7). Starting between SD 25 and SD 28, animals in the neulasta arm constantly regained weight and returned to the baseline weight between SD 49 and SD 60. In contrast, animals in the control arm continued to lose weight until around SD 39 and mean body weight remained below the baseline weight at the end of study.

Figure 7. Percent Change in Body Weight Compared with Baseline Weight



Fever and Febrile Neutropenia (FN)

There were no significant differences in incidences of fever or FN (FN in 20/23 animals in each arm, Table 13). However, neulasta administration significantly reduced the days with FN (mean 11% of days in the neulasta arm vs. 18% of days in the control arm, Wilcoxon rank sum test, $p = 0.0488$).

Table 13. Incidence of Febrile Neutropenia or Fever

Treatment	Incidence of FN n/N, %	Mean $\pm$ SEM Days of FN expressed as % of days on study	Incidence of Fever n/N, %	Mean $\pm$ SEM Days of Fever expressed as % of days on study
D5W	20/23, 87%	18 $\pm$ 3	22/23, 96%	25 $\pm$ 3
Neulasta	20/23, 87%	11 $\pm$ 3	23/23, 100%	21 $\pm$ 3

Reviewer comment

Decrease in incidence of febrile neutropenia (defined as temperature $\geq 38.2^{\circ}\text{C}$ and ANC $\leq 0.5 \times 10^9/\text{L}$) was used as a primary endpoint for a clinical trial, according to PI of neulasta. In this trial, 928 patients were randomized to receive a single subcutaneous injection of neulasta (6 mg) or placebo on day 2 of each chemotherapy cycle. Incidence of febrile neutropenia was lower in neulasta-treated patients than in placebo-treated patients (1% vs. 17%, respectively, $p < 0.001$). Incidences of hospitalization (1% vs. 14%) and IV anti-infective use (2% vs. 10%) for treatment of febrile neutropenia were also lower in neulasta-treated patients than in placebo-treated patients.

Neulasta administration significantly reduced the days with FN (mean 11% of days in the neulasta arm vs. 18% of days in the control arm, $p = 0.0488$) in this NHP study, although incidences of FN were same (20/23 in each arm).

Spleen Volume

CT scans of the abdominothoracic cavity were performed once between SD (-30) to SD (-1) for baseline measurement, once between SD 9 and SD11, and once at the end of study (SD 63 to SD 65 for all animals survived to the scheduled sacrifice, $n = 11$ in the control arm and $n = 21$ in the neulasta arm, not on SD 60 as scheduled because of equipment malfunction on SD 60). CT scans were not performed for animals that underwent unscheduled euthanasia because of poor physical conditions of these animals. The CT images of the spleen were analyzed to quantify splenic size. The splenic size was reported as splenic volume in mL and was normalized according to body weights. The fold changes between baseline to SD 9 to SD11 and baseline to SD 63 to SD 65 in normalized spleen volumes were calculated. CT scans for SD 9 to SD11 were unusable for analysis in two animals in the control arm and one in the neulasta arm.

When compared with baseline spleen volume, decrease in splenic volume was noted in all animals on SD 9 to SD11, but there was no difference between two arms (t-test, $p = 0.9087$, Table 14). On SD 60 to 65, increased splenic volume was noted in more animals in the neulasta arm than in the control arms but the difference was not statistically significant (76% vs. 55%, Fisher's exact test, $p = 0.2515$). The mean fold increase was higher in the neulasta arm than in the control arm but not statistically significant (1.313 vs. 1.114, t-test, $p = 0.1204$).

Table 14. Summary of Changes in Splenic Volume

Treatment	Incidence of increased spleen volume at SD 9-11 n/N, %	Fold Change in normalized spleen volume at SD 9-11 Mean $\pm$ SEM	Incidence of increased spleen volume at SD 60-65 n/N, %	Fold Change in normalized spleen volume at SD 60-65 Mean $\pm$ SEM
D5W	0/21, 0%	0.713 $\pm$ 0.032	6/11, 55%	1.114 $\pm$ 0.083
Neulasta	0/22, 0%	0.708 $\pm$ 0.029	16/21, 76%	1.313 $\pm$ 0.077

Spleen Weight at Necropsy

The spleens of all animals were intact at necropsy, indicating no splenic rupture was observed.

Spleen weight and spleen weight/body weight were significantly greater in the neulasta arm than in the control arm (Table 15, mean: 7.1g and 0.115%, respectively, in the neulasta arm vs. 5.2 g and 0.087%, respectively, in the control arm, t-test, $p = 0.0024$ and $p = 0.0029$, respectively). However, time of necropsy could contribute to this

difference as more animals were sacrificed earlier in the control arm than in the neulasta arm [12 between SD 14 to SD 42 (mean SD 23) in the control arm vs. only two in the neulasta arm). At the terminal sacrifice, the difference in spleen weight between the two arms became smaller (mean: 7.4 g and 0.120%, respectively, in the neulasta arm, n=21, vs. 6.4 g and 0.106%, respectively, in the control arm, n=11, calculated by the reviewer based on data presented in Appendix Q).

Table 15. Summary of Spleen Weight at Necropsy

Treatment	N	Mean (g)	StDev (g)	SEM (g)	Median (g)	Min (g)	Max (g)	Range (g)
D5W	23	5.2	2.0	0.4	4.5	3.0	10.5	7.5
Neulasta	23	7.1	2.2	0.5	7.0	3.0	11.5	8.5
Spleen weight expressed as a percentage of the body weight								
Treatment	N	Mean (%)	StDev (%)	SEM (%)	Median (%)	Min (%)	Max (%)	Range (%)
D5W	23	0.087	0.028	0.006	0.075	0.048	0.150	0.102
Neulasta	23	0.115	0.032	0.007	0.114	0.051	0.164	0.113

Reviewer comment

Although the reported cases of splenic rupture associated with neulasta administration are rare, splenic rupture is a major safety concern for G-CSF products.

According to the PI, there were no serious adverse effects when neulasta at 300 mcg/kg was subcutaneously administered once to 8 healthy subjects and 3 patients with non-small cell lung cancer. These patients had a mean maximum ANC of $55 \times 10^9/L$, with a corresponding mean maximum WBC of $67 \times 10^9/L$. The maximum ANC was $96 \times 10^9/L$ and the corresponding maximum WBC was $120 \times 10^9/L$. The duration of leukocytosis ranged from 6 to 13 days.

According to the original BLA review for neulasta, in a cynomolgus monkey repeat dose toxicity study [3 animals/sex/group, 0, 75, 250, or 750 mcg/kg/dose, SC, once/week for 5 weeks (administered on Days 1, 8, 15, 22, and 29)], increased spleen weight was noted in all drug groups and the spleen weight trended toward recovery after 1 month recovery period in the 750 mcg/kg group (no other details provided, only control and 750 mcg/kg groups had recovery phase, 2/sex/group). Consistently, enlarged spleens, leukocytosis in the spleen, and foci of extramedullary hematopoiesis (erythroid precursors and megakaryocytes) in the spleen were noted in the drug groups.

Similarly, in a three and six months repeat dose toxicity study in rats [0, 100, 300, 1000 mcg/kg/dose, SC, once/week for 3 or 6 months, 14 or 27 doses, respectively), increased spleen weight was noted in all drug groups at both three and six month sacrifices. At 5 month sacrifice (after two month recovery period post three month dosing), no spleen weight increase in the 1000 mcg/kg group was mentioned in the review, assuming the spleen weight returned to normal. Enlarged spleens at ≥ 300 mcg/kg groups and dose-related myeloid hyperplasia in the spleen were also observed.

Myeloid hyperplasia in the spleen was not observed in the 1000 mcg/kg group at 5 month sacrifice (after two month recovery period post three month dosing).

Taken together, the risk of splenic rupture associated with 300 mcg/kg neulasta administration should be rare, if any, even for healthy subjects.

Medical Management and Supportive Care

Buprenorphine

There was no difference in buprenorphine administration between the two arms.

Bupivacaine

Fewer animals in the neulasta arm required the treatment with Bupivacaine for mouth ulcer (14 vs. 21 in the control arm).

Carafate

Fewer animals in the neulasta arm required the treatment with carafate for oral mucositis (14 vs. 21 in the control arm) and bloody stool (18 vs. 22).

Imodium and Lomotil

There was no difference in the frequency of administration of anti-diarrheals between the two arms.

Ondansetron

Fewer animals in the neulasta arm required additional treatment with ondansetron because of emesis (9 vs. 16 in the control arm).

Antibiotics

Antibiotics were administered prophylactically when ANC < 500/mcL.

Fewer antibiotic administrations were noted in the neulasta arm (the mean frequency of antibiotic administration: 34% vs. 61% in the controls arm, $p < 0.0001$, Wilcoxon rank sum, Table 16 and Table 17).

Table 16. Summary of Antibiotic Administration*

Treatment	N	Mean (%)	StDev (%)	SEM (%)	Median (%)	Min (%)	Max (%)	Range (%)
D5W	23	61	18	4	62	25	84	59
Neulasta	23	34	17	4	28	20	83	63

* Data were expressed as the mean percent of days each animal on study.

Table 17. Summary of Treatment with Specific Antibiotic

Antibiotic	Treatment	N	Mean # Days $\pm$ SEM			Mean % of Days $\pm$ SEM		
Baytril	D5W	23	16	$\pm$	1	50	$\pm$	5
	Neulasta	23	14	$\pm$	1	24	$\pm$	2
Gentamicin	D5W	20	5	$\pm$	0	17	$\pm$	2
	Neulasta	20	4	$\pm$	0	8	$\pm$	1
Rocephin	D5W	15	7	$\pm$	1	20	$\pm$	3
	Neulasta	18	7	$\pm$	1	15	$\pm$	3
Ertapenem	D5W	6	9	$\pm$	2	16	$\pm$	3
	Neulasta	2	6	$\pm$	1	9	$\pm$	1

Anti-pyretics

Fewer animals in the Neulasta arm required the treatment with fluconazole for fever lasted five or more consecutive days (4/23 vs. 8/23 in the control arm). However, more animals in the Neulasta arm required the treatment with Rimadyl for fever $> 104^{\circ}\text{F}$ (22/23 vs. 19/23 in the control arm).

Nutritional Supplementation

Similar numbers of animals in the both arms were administered the high protein shake for body weight loss ($\geq 10\%$ of baseline body weight and until weight loss was reduced to $< 10\%$, 16/23 in the neulasta arm vs. 17/23 in the control arm).

Hydration

All animals were administered fluid treatment (LRS by IV injection and treated water by oral gavage) because of mild or moderate dehydration. Severe dehydration was observed in two animals in the control arm only. These two animals required additional fluid treatment (LRS by IV infusion and treated water by oral gavage).

Transfusion

All animals, except for one in the neulasta arm, required at least one transfusion. However, fewer transfusions were required for animals in the neulasta arm (a total of 47 VS. 80 in the control arm). In addition, fewer animals required transfusions because of decreased Hct in the neulasta arm (9/23 vs. 16/23 in the control arm). However, there was no significant difference in incidences of transfusions required for platelet support between two arms (18/23 vs. 19/23 in the control arm).

Gross Pathology

At necropsy, gross pathology, including examination of the external surface of the body, palpation for superficial swellings, or for enlarged organs or masses within body

cavities, was performed on all animals either euthanized during the study or sacrificed at the termination of the study. All internal organs of the thoracic and abdominopelvic cavities (except for the reproductive organs) were examined for abnormalities, including hemorrhage, ulceration, and discoloration.

Fewer gross pathology findings were noted in the neulasta arm (185 findings vs. 355 findings in the control arm) at necropsy. Furthermore, abnormal gross observations were not observed in six animals in the neulasta arm but in one animal only in the control arm.

Hemorrhage was observed in fewer animals in the neulasta arm [14/23 (61%, one or two organs or tissues) vs. 20/23 (87%, one to four organs or tissues) in the control arm, Table 18]. In the control arm, majority of animals had hemorrhage in multiple organs or tissues (17 in two to four organs or tissues). Occasionally, hemorrhage was noted in areas with necrosis and ulceration, particularly in the GI system in the control arm.

Table 18. Summary of Gross & Microscopic Observations of Hemorrhage at Necropsy

Organ	Treatment	Number of NHP and Type of Observation			
		Gross	Gross+Microscopic	Microscopic	Total NHP
Heart	D5W	1	1	0	2
	Neulasta	0	0	0	0
Lung	D5W	7	2	2	11
	Neulasta	3	3	2	8
Liver	D5W	1	0	0	1
	Neulasta	0	0	0	0
Spleen	D5W	1	0	0	1
	Neulasta	0	0	0	0
Kidneys	D5W	16	0	0	16
	Neulasta	11	1	0	12
Large Intestine	D5W	6	6	0	12
	Neulasta	4	0	0	4
Small Intestine	D5W	9	3	0	12
	Neulasta	3	1	1	5
Thymus	D5W	0	0	1	1
	Neulasta	0	0	0	0
Lymph Node, Mesenteric	D5W	0	1	1	2
	Neulasta	0	0	1	1
Skin	D5W	8	1	0	9
	Neulasta	1	0	0	1

Enlarged spleens were observed in more animals in the neulasta arm than in the control arm [6/23 vs. 3/23]

In addition, the following findings were observed in fewer animals in the neulasta arm than in the control arm.

- Alopecia [2/23 (9%) vs. 9/23 (39%)]

- Ecchymosis and petechia of the skin (petechia in 1/23 vs. ecchymosis and petechial in 9/23)
- Enlarged mesenteric lymph nodes [3/23 (13%) vs. 6/23 (26%)]

Histopathology

Histopathology examination was conducted by a board-certified veterinary pathologist on all protocol-specified tissues from all 46 animals in a blinded fashion, except for thymuses from 14 animals (no thymic tissue was discernible on the slides), spleen from one animal (autolysis), and the ileum and jejunum from one animal (autolysis).

After completion of the “blind” histopathology evaluation, the pathologist was provided with the treatment code and summarized the original observations according to the treatment arms.

Microscopic observations were tabulated and summarized into two categories: moribund euthanasia and terminal euthanasia. The key findings are described below.

Moribund euthanasia

Lower incidence and severity of cellular and lymphoid depletion in the bone marrow and thymus were observed in animals in the neulasta arm than in the control arm (Table 19). For example, cellular depletion of the femur-derived bone marrow was observed in one animal (1/2) in the neulasta arm but 10 animals (10/12) in the control arm. Only mild depletion was observed in the neulasta arm; in contrast, marked depletion was observed in the majority of animals (6/10) in the control arm.

In addition, lesions, including hemorrhage, ulceration, and necrosis in the intestine, were observed in the control arm only.

Table 19. Summary of Selected Microscopic Findings from Tissue Collected at Moribund Euthanasia Necropsy

	Males	
Group	1	2
Dose (mcg/kg)	0	300-319
No. Animals Examined	12	2
Bone Marrow, Femur (No. Examined)	12	2
Depletion, cellular	(10) ^a	(1)
Mild	2	1
Moderate	2	0
Marked	6	0
Bone Marrow, Sternum (No. Examined)	12	2
Depletion, cellular	(9)	(1)
Minimal	0	1
Mild	2	0
Moderate	1	0
Marked	6	0
Intestine, Colon (No. Examined)	12	2
Hemorrhage, transmural	(4)	(0)
Moderate	2	0
Marked	2	0
Necrosis, transmural	(2)	(0)
Marked	2	0
Ulceration, mucosa, focal	(1)	(0)
Marked	1	0
Thymus (No. Examined)	11	2
Depletion, lymphoid	(10)	(1)
Mild	2	1
Moderate	3	0
Marked	5	0
Kidney, Left (No. Examined)	12	2
Degeneration / regeneration, tubular, multifocal	(4)	(0)
Minimal	1	0
Mild	1	0
Moderate	2	0

^a Numbers in parentheses represented the number of animals with the finding.

Terminal euthanasia

According to the Veterinary Pathology Contributing Scientist Report (Appendix L, by (b)(4) microscopic findings in the terminal euthanasia were incidental. The incidence and severity of the findings were similar in the control and neulasta arms.

Reviewer comment

Incidence and severity of important histopathology findings, such as cellular and lymphoid depletion and hemorrhage, were lower in the neulasta arm than in the control arm.

Grubb's Test

ANC values from the neulasta arm on SD 31 were statistically evaluated using a one-sided Grubbs' test to detect whether the minimum ANC value from the neulasta arm was an outlier.

The Grubbs' test revealed that the minimum ANC of $0.988 \times 10^3/\text{mcL}$ was not a statistical outlier. Thus, assessment of immunogenicity to neulasta was not needed according to the study report.

Reviewer comment

According to PI, four of 521 pegfilgrastim-treated subjects who were negative at baseline developed binding antibodies to pegfilgrastim following treatment. None of these 4 patients had evidence of neutralizing antibodies.

Toxicokinetics

Not conducted.

Dosing Solution Analysis

Concentration verification

Not conducted.

According to the study report, individual neulasta dosing syringes were prepared from stock neulasta prefilled syringes. (b)(4)



According to the PI of neulasta, neulasta should be stored refrigerated between 2° to 8°C (36° to 46°F) in the carton to protect from light. Syringes stored at room temperature for more than 48 hours should be discarded.

Reviewer comment

The concentration verification was not conducted, which is a deviation from GLP. Because neulasta was from the commercial manufacturer and a relative simple preparation only was conducted, such deviation might not significantly impact the study integrity.

Overall summary and discussion

This study is an animal efficacy study conducted under the animal rule. The study was designed as a two arms, randomized, and blinded study. The study was conducted under GLP. Rhesus Macaques were exposed to LD_{50/60} TBI. Neulasta was subcutaneously administered once per week for two weeks at 300-319 mcg/kg/dose (a total of two doses, first dose administered at 20-26h post TBI). The neulasta dose and dose regimen in this study were selected based on a previous PK/PD study, in which administration of neulasta at 300 mcg/kg on days 1 and 7 was more effective at improving neutrophil recovery. Dextrose 5% in Water (D5W) was used as a control agent.

The interim efficacy analysis was conducted on unblinded animal fate data after 58% of the animals had completed in-life phase. The interim analysis revealed that neulasta significantly improved overall survival [91.3% (21/23) vs. 47.8% (11/23) in the control arm, two-sided Chi-square test, $p = 0.0014$, < 0.0070], meeting the primary endpoint.

In addition, some key secondary endpoints were met, which included, but not limited to, the followings:

- Reduced duration of neutropenia
- Reduced time to recovery from neutropenia
- Reduced duration of thrombocytopenia
- Reduced time to recovery from thrombocytopenia
- Reduced number of transfusions
- Reduced mean percent of days when animals had FN
- Reduced supportive care, including the mean frequency of antibiotic administration

The approved dose regimen for neulasta is 6 mg administered subcutaneously once per chemotherapy cycle (in general, once on Day 2 of a 21 days cycle). Both 6 mg/dose and 100 mcg/kg/dose were used in clinical trials. Both regimens reduced duration of severe neutropenia in a similar manner. The current study used a single dose (300-319 mcg/kg/dose, once/week, two doses) and PK data were not collected. Lacking dose-exposure data in this study makes the selection of human dose more challenging. However, extensive PK and PD information in human is available for relevant indications. In addition, PK information in NHP, although limited, is available. The information can be used to support the selection of human dose. PK and PD simulation has been conducted and submitted and will be reviewed by pharmacometrics team. Such analysis will provide additional information to support the selection of human dose.

Mouse efficacy study

Mouse screening or pilot efficacy studies were conducted under (b)(4) and summary reports were submitted. The sponsor acquired a LOA to allow FDA to use the information to support the approval of the current sBLA. The studies are briefly reviewed below.

ES1152 (ES2014.203): Effects of Neulasta on survival end points using the PBI BM2.5 model in (b)(4) mice without antibiotic support

In this study, the effects of Neulasta on 30 day survival were evaluated in (b)(4) mice (20 males/group, 10-12 wk at irradiation, approximately 20-30 g). Mice were exposed to 13 or 13.5 Gy partial-body irradiation with approximately 2.5% of the bone marrow shielded (PBI BM2.5, the feet, tibia and fibula of one lower limb shielded). The study was conducted by (b)(4).

PBI was performed at 15:00 hr +/- 1 hr using an (b)(4) X-ray set (b)(4) at a dose rate of 0.812 Gy/min. Dosimetry results confirmed that the actual radiation doses were within 1% of the intended doses according to the study report.

Neulasta at 1 mg/kg or 0.1 mg/kg, or vehicle (0.9% NaCl + 0.1% Bovine Serum Albumin) was subcutaneously administered once at about 24 hr post PBI. Mice received acidified water from time of arrival throughout the study and acidified water-wetted food from day 4. Mice were checked twice daily from day 4 and euthanized when moribund (not additional details provided).

Neulasta increased overall survival (Figure 8, Table 20, and Table 21). Thirty day survival rates post 13 Gy PBI were 80%, 50% or 20% in 1mg/kg Neulasta, 0.1 mg/kg Neulasta, or vehicle control groups, respectively. The rates post 13.5 Gy PBI were 45%, 25% or 5%, respectively. According to the submission, after adjusting for radiation dose and using Cox Proportional Hazard Regression Model (Table 21), mice treated with 1 mg/kg Neulasta had significantly better overall survival than mice treated with 0.1 mg/kg Neulasta ($p=0.0283$) and mice treated with vehicle ($p=0.0003$). Mice treated with 0.1 mg/kg Neulasta had better overall survival than mice treated with vehicle ($p=0.0808$).

Figure 8. Kaplan-Meier survival curves

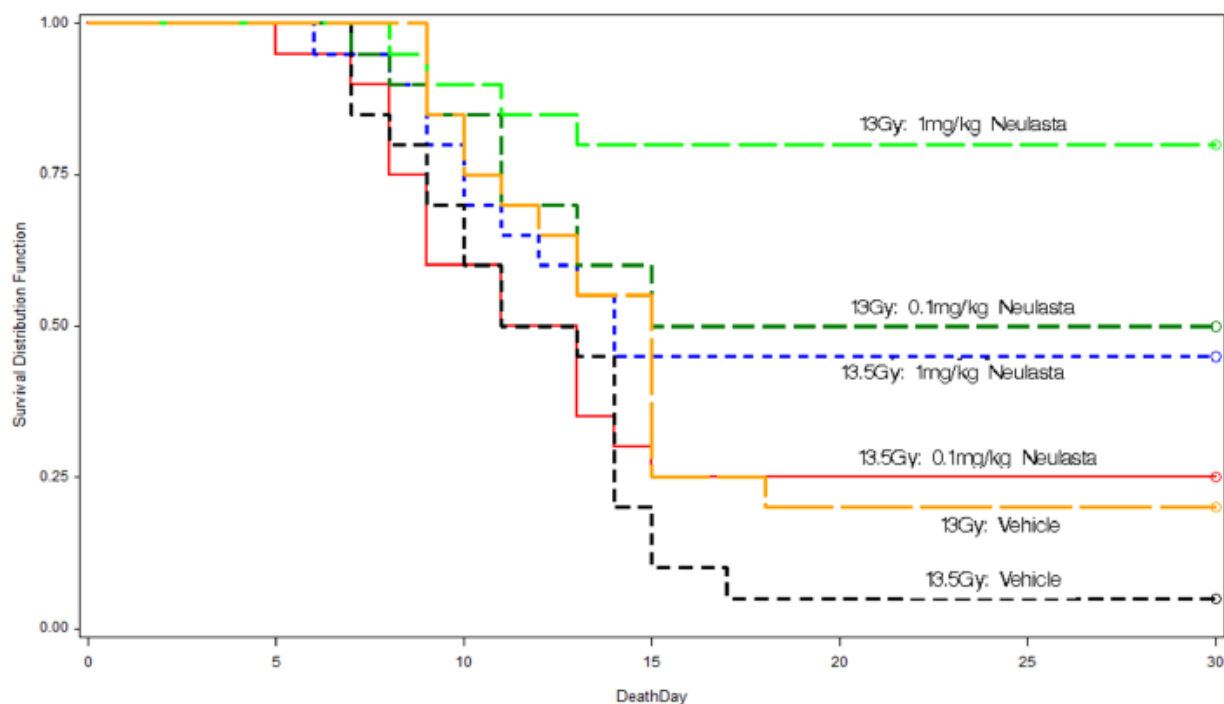


Table 20. Survival rates post-PBI

Radiation Dose	Treatment Group	N	% Alive Day 8	% Alive Day 9	% Alive Day 10	% Alive Day 11	% Alive Day 12	% Alive Day 13	% Alive Day 14	% Alive Day 30
13Gy	1mg/kg Neulasta	20	95	90	90	85	85	80	80	80
	0.1mg/kg Neulasta	20	90	85	85	70	70	60	60	50
	vehicle	20	100	85	75	70	65	55	55	20
13.5Gy	1mg/kg Neulasta	20	90	80	70	65	60	55	45	45
	0.1mg/kg Neulasta	20	75	60	60	50	50	35	30	25
	vehicle	20	80	70	60	50	50	45	20	5

The survival rates were highlighted in red when the rates were at least 15% higher than the rates in the corresponding vehicle groups.

Table 21. Cox Proportional Hazard Regression Model

Effect	Odds Ratio	95% Lower CL	95% Upper CL	P-value
1mg/kg Neulasta vs. 0.1mg/kg Neulasta	0.49	0.26	0.93	0.0283
1mg/kg Neulasta vs. Vehicle	0.34	-	0.56	0.0003
0.1mg/kg Neulasta vs. Vehicle	0.69	-	1.07	0.0808
13Gy vs. 13.5Gy	0.48	0.30	0.77	0.0022

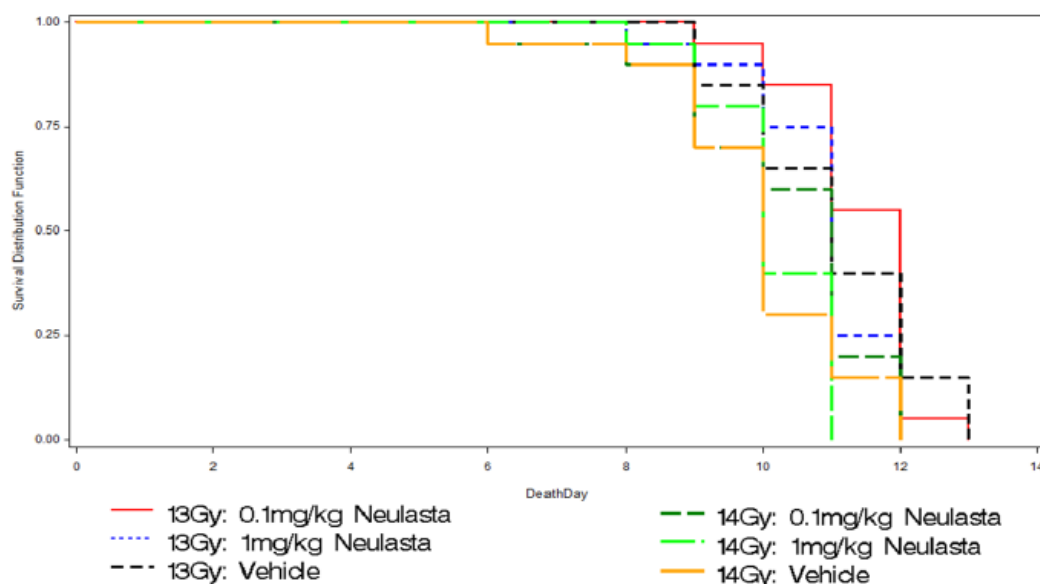
The model was performed as a one-sided test.

ES1151: The effect of Neulasta on survival end points using the TBI model in mice with antibiotic supportive care (b)(4)

This screening study used the same design as the study ES1152 aforementioned with two exceptions. First, the mice were exposed to 13 or 14 Gy TBI. Second, Levofloxacin (0.67 g/L) was added to the drinking water from day 1 (+24 hr).

Neulasta did not increase survival post 13Gy or 14Gy TBI (Figure 9). No animal survived beyond day 13.

Figure 9. Kaplan-Meier survival curves post-TBI



IU2013.225M and IU2013.239M: Hematopoietic Screening Assay for Radiomitigating Activity of 2 doses of Subcutaneously Administered Neulasta (1 mg/kg on days 1 and 8) after Exposure to the LD_{50/30} Dose of Radiation for (b)(4) Mice (b)(4)

These two screening studies were conducted by (b)(4) and pooled data were reported. (b)(4)

METHOD

Neulasta or vehicle administration

Neulasta at 1.0 mg/kg (20 mcg/20 g mouse) or vehicle (0.9% NaCl + 0.1% bovine serum albumin) was subcutaneously administered as 2 doses (1st at 24+4hr and 2nd on day 8) post LD_{50/30} TBI.

The dose was administered based on the average weight (separate average weights for males and females) weighted during the acclimation period. The volume of Neulasta was adjusted to deliver a dose of approximately 1.0 mg/kg to each mouse.

Animals and randomization

(b)(4) mice (b)(4) 8 wk at irradiation

Group:

Study IU2013.225M

1. Neulasta, n=22 (10F, 12M)
2. Vehicle, n=22 (10F, 12M)

Study IU2013.239M

1. Neulasta, n=30 (15F, 15M)
2. Vehicle, n=80 (40F, 40M)

Weight:

Males: 25.0 ± 2.9 grams; range = 17.4 – 33.7 grams

Females: 20.0 ± 2.8 grams; range = 14.5 – 27.46 grams

Mice were individually randomized to one of two treatment groups.

Supportive care

Mice were provided acidified water (pH 2.0-3.0) in bottles and fed certified commercial extruded laboratory animal chow (b)(4) throughout the study. On day 4 post TBI, mice were provided acidified autoclaved water in bottles and also in wetted chow (b)(4) in a Petri dish set in the bottom of the cage.

Satellite group

Study IU2013.225M

CBC with differential and peripheral smears was performed at baseline (n=8) and on study days 10, 20, 25, and 30 (n=6 at each time point).

Study IU2013.239M

CBC with differential and peripheral smears was performed at baseline (n=8) and on study days 2, 3, 6, 7, 9, 13, 16, and 23 (n=5 in the neulasta group and n=8 in the vehicle group at each time point).

In both studies, when possible, the same number of males and females in each group and in separate cages was selected for bleeding. Each mouse was bled a maximum of two times during the study and bleeds were at least 14 days apart.

Radiation

A dose of radiation equal to the LD_{50/30} was delivered as a single uniform total body gamma radiation from a ¹³⁷Cs radiation source (b)(4)

(b)(4) Mice were exposed in single chambers of a Plexiglas irradiation apparatus designed to hold 15-16 mice each. Pilot studies determined the LD_{50/30} dose of radiation to be 900cGy in the same test facility for (b)(4) mice. Mice were irradiated between 8:51 AM and 10:57 AM in groups of 5-15 mice. Each group of mice irradiated together in the same irradiation pie was roughly divided among all groups to ensure that each group received the same irradiation exposure.

Dose rate:

IU2013.225M: 99.253 cGy/min

IU2013.239M 100.118 cGy/min

In-Life assessment

Mice were monitored for survival once/day until euthanasia criteria (not specified in the report) were noted, then twice/day until day 30.

Primary Endpoint

Thirty day overall survival

Secondary Endpoint

Mean survival time (MST)

CBC analyses

RESULT

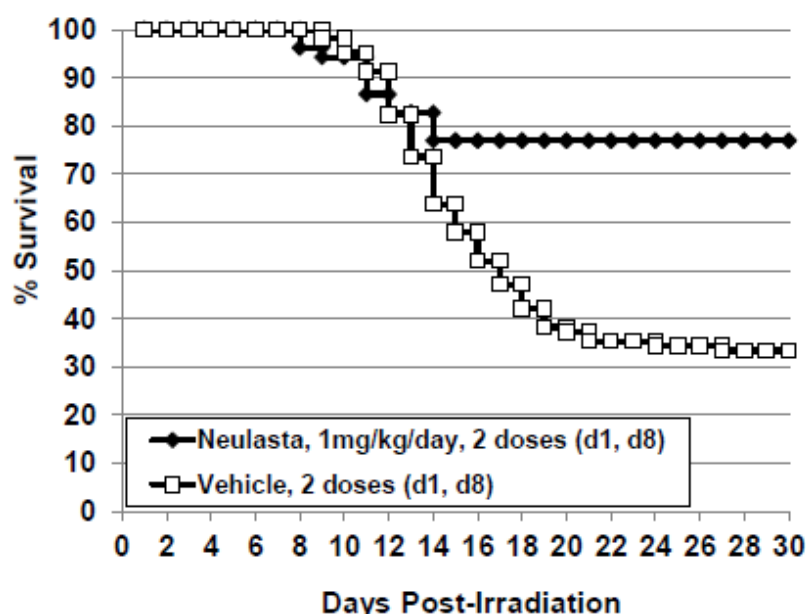
Survival

Neulasta, at 1 mg/kg subcutaneously administered at 24+4 hr and on Day 8 post LD_{50/30} TBI, significantly increased survival compared to vehicle controls [76.9% (40/52) vs. 33.3% (34/102), $p < 0.0001$, Table 22 and Figure 10].

Table 22. Thirty Day Survival, Mean Survival Time (MST), and Overall Survival Time

Group Description	Rad Dose	No. of Survivors/ Total	30 day Survival (%)		MST of Decedents (days)		P value TA vs. CA		
							30d Survival	MST	Overall Survival Time
Neulasta (1mg/kg on d1 and d8)	LD50 study 225	17/22	77.3	76.9	12.6	11.3	<0.0001	0.0017	<0.0001
	LD50 study 239	23/30	76.7		10.3				
Vehicle (2 doses on d1 and d8)	LD50 study 225	6/22	27.3	33.3	14.3	14.8			
	LD50 study 239	28/80	35.0		15.0				

Figure 10. Kaplan-Meier Survival Curves

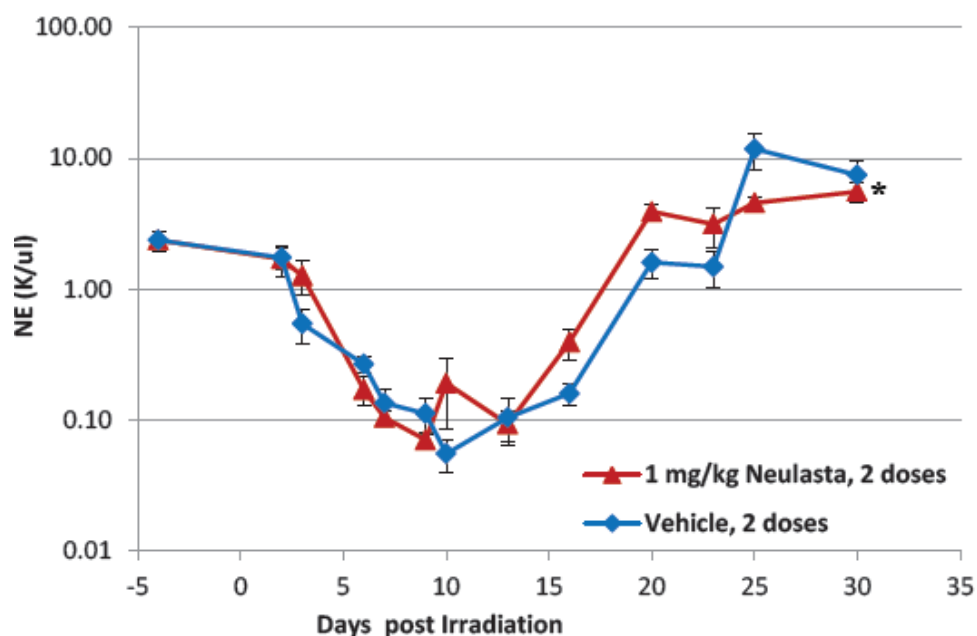


Pooled data from 900 cGy radiation dose groups. Mice were exposed to 900 cGy and injected subcutaneously with 1 mg/kg of Neulasta or the vehicle at about 24hr and on Day 8 post LD_{50/30} TBI. N=52 in the Neulasta group and n=102 in the vehicle group.

Absolute Neutrophil Count

Neulasta significantly increased recovery of neutrophils ($p \leq 0.01$, Figure 11)

Figure 11. ANC Curves



ANC (NE) data were pooled from 900 cGy dose groups from studies IU2013.225M and IU2013.239M. CBC were performed at baseline (day -3 or -4) and on study days 2, 3, 6, 7, 9, 10, 13, 16, 20, 23, 25, and 30 from randomly selected male and female mice in different cages, when possible. No mouse was bled more than twice and all blood draws on individual mice were at least 13 (study 239) or 14 (study 225) days apart. Data are presented as mean $\pm$ SEM. N= 16 mice for baseline bleed, n=4-8 for other time points with the exception of Day 25 (only 2 mice available in the control group because of bleed limitations).

*indicates significant increase in Neulasta-treated mice compared with vehicle-treated mice, $p \leq 0.01$.

Published reports of neulasta use in animals

The Sponsor also submitted a few publications and three key publications are reviewed separately below. Two publications with mouse studies had survival endpoint and one publication with NHP studies had ANC endpoint.

Chua HL, Plett PA, Sampson CH, et al. Survival efficacy of pegylated G-CSFs MAXYG34 and Neulasta in a mouse model of lethal H-ARS, and residual bone marrow damage in treated survivors. *Health Phys.* 2014; 106:21-38.

In this publication, the effect of Maxy-G34, a PEG-G-CSF (Maxygen, Inc) on survival was evaluated in C57BL/6 mice. Neulasta was used as a comparator. Neulasta related information is summarized below. Only 30 day survival was evaluated for neulasta in this publication.

Study design

According to the publication, C57BL/6 mice used in this publication were validated previously as a murine model of HS-ARS and the data were published¹. According to

this validation publication, C57BL/6 strain was chosen because of the moderate degree of radiosensitivity, well-defined hematopoietic system, and the recommendation by the Centers for Medical Countermeasures against Radiation Animal Models Workshop². According to the publication, studies with 20 mice per group were powered to detect a 30% reduction in mortality with 80% power using a two-tailed 5% significance level. The publication concluded “This well-characterized murine model is suitable for screening studies of candidate MCM and final pivotal efficacy studies performed under GLP for licensure of MCM to treat lethally-irradiated personnel exposed to radiation doses resulting in H-ARS.”

Animal

Specific pathogen-free C57BL/6 mice (50/50 male/female, Jackson Laboratory, Bar Harbor, ME) were received at 10 wk of age. Weights of mice in the survival studies ranged from 15.0-22.5 g for females and 20.0-28.0 g for males. Mice were provided with autoclaved acidified water and wet feed from Day 4 to Day 30 post irradiation. Irradiated mice were observed twice daily and scored on a scale of zero to three for signs meeting the criteria for early euthanasia based on the severity of hunched posture, squinted/closed eyes, and activity. Mice with scores of eight or nine underwent euthanasia. Overall, 11-67% of dead mice in these studies underwent humane euthanasia according to the publication.

Radiation

Mice were exposed in single chambers of a Plexiglas irradiation apparatus to single uniform TBI doses 7.96 Gy (estimate LD_{50/30}) or 8.7 Gy (estimate LD_{90/30}) gamma radiation from a ¹³⁷Cs radiation source (GammaCell 40; Nordion International, Kanata, Ontario, Canada) at 0.60-0.66 Gy/min. According to the aforementioned publication¹ the exposure was confirmed using Inlight Dot dosimeters (Landauer Inc., 2 Science Rd., Glenwood, IL 60425 USA). Reproducibility of individual dots was 3 ± 1% with accuracy of 4 ± 2%, well within the 10% industry standard for experimental radiation dosimetry. Lethality of mice irradiated in the morning was the closest to the predicted LD_{50/30} dose of radiation (54.4% lethality).

Neulasta and control

Neulasta was administered subcutaneously according to two different administration schedules.

¹ Plett PA, Sampson CH, Chua HL, Joshi M, Booth C, Gough A, Johnson CS, Katz BP, Farese AM, Parker J, MacVittie TJ, Orschell CM. Establishing a murine model of the hematopoietic syndrome of the acute radiation syndrome. *Health Phys* 103:343-355; 2012.

² Williams JP et al. Animal models for medical countermeasures to radiation exposure. *Radiat Res* 173:557-578; 2010.

Frist, one or two doses at 1.0 mg/kg: One dose was administered on Day 1 (20 to 28 hr) post TBI or two doses on Days 1 and 7 post TBI. According to the publication, 1 mg/kg used in this study was chosen based on doses used in chemotherapy myelosuppression models.

Second, dose response: 0.1 mg/kg, 0.3 mg/kg, or 1.0 mg/kg was administered once on Day 1 (20 to 28 hr) post TBI.

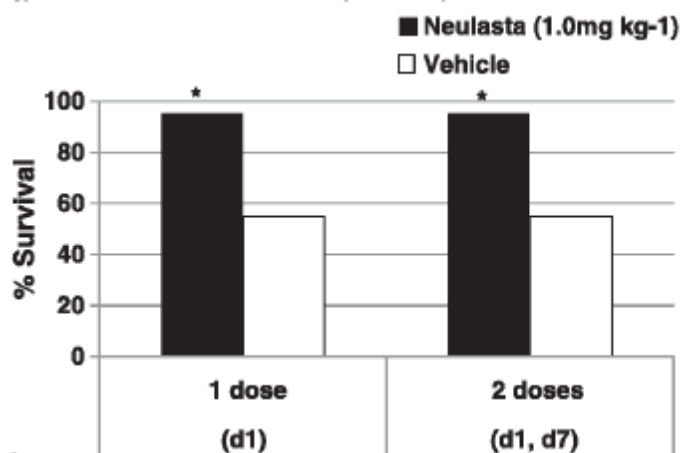
The control vehicle was 0.9% saline (w/v) + 0.1% BSA solution.

Result

One dose or two doses at 1 mg/kg

Neulasta at 1 mg/kg increased survival in mice post LD_{50/30} TBI (7.96 Gy, Figure 12). The same survival benefit was achieved when neulasta was administered either one dose (20 to 28 hr post TBI) or two doses (Days 1 and 7 post TBI). The survival rates were 55% (11/20) in the control arm and 95% in the neulasta arms administered either one dose (19/20, $p=0.003$) or two doses post TBI (19/20, $p = 0.004$).

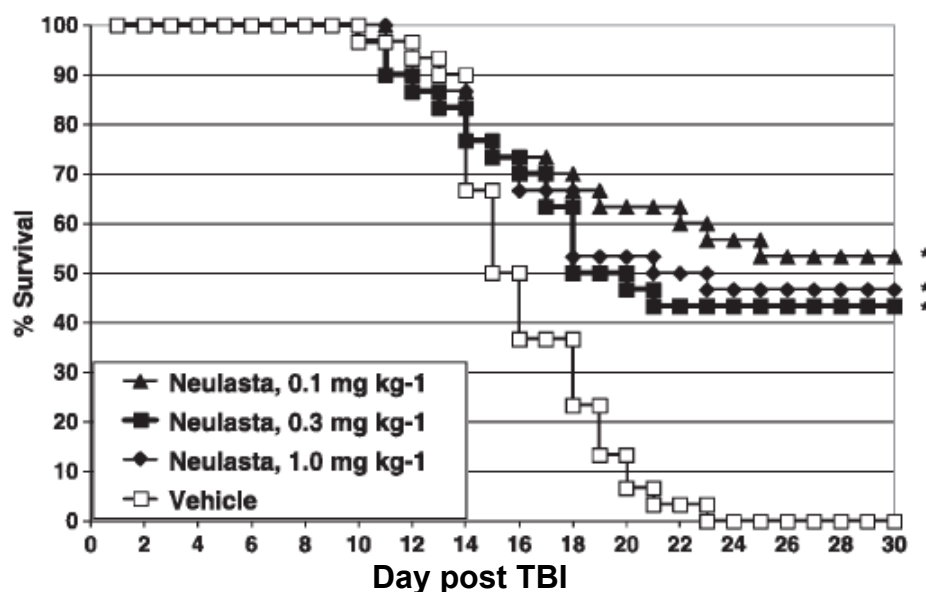
Figure 12. Survival in mice post LD_{50/30} TBI



Mice were exposed to 7.96 Gy TBI (estimated LD_{50/30}) and injected subcutaneously with one dose of 1.0 mg/kg Neulasta (filled bar) or the vehicle (open bar) on Day 1, or two doses on Days 1 and 7 post TBI. * $p<0.05$ the Neulasta groups vs. the vehicle groups, $n = 20$ per group. The figure is adopted from the publication.

Dose response

Neulasta increased survival in mice at 0.1 to 1 mg/kg administered on Day 1 (one dose) post LD_{90/30} TBI (8.7 Gy, Figure 13). The survival rates were 0% (0/30), 57% (17/30, $p < 0.001$), 43% (13/30, $p < 0.001$), or 47% (14/30, $p < 0.001$) at 0 (vehicle control), 0.1, 0.3, or 1.0 mg/kg Neulasta, respectively. There was no further survival benefit at higher doses in this study.

Figure 13. Survival curves of mice post LD_{90/30} TBI

Mice were exposed to 8.7 Gy TBI (estimated LD_{90/30}) and injected subcutaneously with one dose of Neulasta at 0.1, 0.3, or 1.0 mg/kg, or the vehicle on Day 1 post TBI. * p < 0.001 the neulasta groups vs. the vehicle group, n = 30 per group. The figure is adopted from the publication.

Reviewer comment

Neulasta increased survival by 40% or greater in mice at 0.1 to 1 mg/kg administered on Day 1 (one dose) or at 1 mg/kg on Day 1 (one dose) or on Days 1 or 7 (two doses) post TBI (LD_{50/30} or LD_{90/30}). Higher doses (0.3 mg/kg or 1 mg/kg vs. 0.1 mg/kg) or additional dose (two doses at 1 mg/kg vs. one dose) did not further increase survival.

In the 2012 publication,¹ Neupogen (125 mcg/kg, SC beginning 24 h post exposure and continuing daily to day 16) increased survival from 30% (LD_{70/30} in controls, n=30) to 60%.

The variability in control group survival among different experiments is noted. For example, 7.96 Gy was listed as estimated LD_{50/30} in some experiments but LD_{70/30} in other experiments. According to the publication, the variability in control group survival was an unintended consequence of the steep radiation dose response curve observed in inbred strains of mice such as C57Bl/6 used in this publication. The radiation dose response was evaluated in 2012 publication¹. The differential between the LD_{90/30} and LD_{10/30} doses was relatively small (0.72 to 1.45 Gy). According to the publications, the very steep curves mean that confidence intervals around the calculated LD_{XX/30} radiation doses span a larger fraction of the curve, thus pinpointing the LD_{XX/30} in subsequent experiments becomes difficult. Fortunately, based on the information provided in the publication, each neulasta study appears to be conducted under the same experiment.

Kiang JG, Zhai M, Liao P-J, Bolduc DL, Elliott TM, Gorbunov NV. Pegylated G-CSF

inhibits blood cell depletion, increases platelets, blocks splenomegaly, and improves survival after whole-body ionizing irradiation but not after irradiation combined with burn. Oxid Med Cell Longev. 2014; 2014:481392.

In this publication, the effect of neulasta on survival was evaluated in B6D2F1/J female mice and related information is summarized below. Thirty day survival and neutrophils were evaluated.

Study design

Animal

B6D2F1/J female mice (20–22 per group) were obtained from Jackson Laboratory (Bar Harbor, ME). Commercial rodent chow and acidified tap water were provided *ad libitum* at 12 to 20 weeks of age. Euthanasia was conducted in accordance with the recommendations and guidance of the American Veterinary Medical Association. Blood samples were collected on Day 30 post TBI.

Radiation

Mice were exposed to 9.5 Gy whole body bilateral ^{60}Co gamma-photon radiation, delivered at a dose rate of 0.4 Gy/min.

Neulasta and control

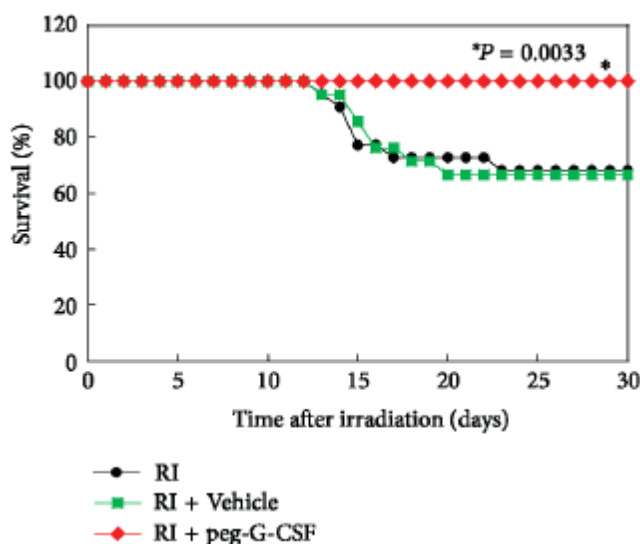
Neulasta was administered subcutaneously at 1000 mcg/kg (25 mcg/25g) on Days 1 (24 hr), 8, and 15 (3 doses) post TBI.

The control vehicle was sterile 0.9% sodium chloride solution for injection, USP.

Result

Neulasta, at 1 mg/kg administered subcutaneously on Days 1, 8, and 15 post TBI, increased survival in mice post 9.5 Gy TBI (100% vs. 68% in the control arm, $P = 0.0033$, Figure 14).

Figure 14. Survival in mice post TBI



Mice were exposed to 9.5 Gy TBI (RI) and injected subcutaneously with 1 mg/kg Neulasta or the vehicle on Days 1, 8 and 15 post TBI. n = 20-22 per group. The figure is adopted from the publication.

In addition, neulasta increased neutrophils in mice on Day 30 post TBI ($p < 0.05$, neulasta vs. control).

Reviewer comment

The survival benefit was demonstrated in two strains (C57BL/6 and B6D2F1/J). Based on the 2008 Centers for Medical Countermeasures against Radiation Animal Models Workshop², the small animal model should include at least two strains, such as the C57BL/6 and C3H/HeN strains. B6D2F1/J is one of the most common mouse strains used as well.

Farese, AM et al, 2012, Pegfilgrastim Administered in an Abbreviated Schedule, Significantly Improved Neutrophil Recovery after High-Dose Radiation-Induced Myelosuppression in Rhesus Macaques. Radiation Research, 178, 403–413

In this publication, male rhesus macaques were used to evaluate the effect of pegfilgrastim (neulasta) on neutrophil recovery when animals were exposed to 6 Gy total body X radiation (estimated $LD_{10/30}$ dose with supportive care). Animals were administered either pegfilgrastim at 300 mcg/kg on Day 1 (1 dose) or Days 1 and 7 (2 doses) post TBI, or filgrastim (neupogen) at 10 mcg/kg/day initiated on Day 1 post TBI and continued daily through neutrophil recovery. All animals were provided supportive care. Administration of pegfilgrastim on Days 1 and 7 was most effective on improving neutrophil recovery when compared to daily administration of filgrastim or a single injection of pegfilgrastim on Day 1 (Table 23). For example, the mean duration of ANC < 500 /mCL was 5.3 days in animals given 2 doses of pegfilgrastim but was much longer in animals given 1 dose (14.6 days) or control (19.4 days).

According to this publication, the PD modeling using the concentration-response relationships yielded EC₅₀ (effective plasma concentration producing a half-maximum response) estimates of 3.6 ng/mL for rhesus macaques. The 300 mcg/kg dose used approximated the projected EC₅₀.

Table 23. Filgrastim or Pegfilgrastim enhanced Neutrophil Recovery in Total-Body X-Irradiated Rhesus Macaques*

Treatment	ANC nadir (μL)	Duration (day) ANC < 100/μL	Duration (day) ANC < 500/μL	Time to recovery (day) 500/μL	Time to recovery (day) 2,000/μL	Antibiotic support (day)
Control, 0.1%AS	19.0 ± 5	9.4 ± 0.7	19.4 ± 1.8	24.4 ± 1.8	28.3 ± 2.6	20.9 ± 0.9
Filgrastim, qd	53.0 ± 17	2.8 ± 0.8 ^a	10.5 ± 1.3 ^a	16.8 ± 0.9 ^a	18.3 ± 0.9 ^a	14.3 ± 0.6 ^a
Peg-filgrastim, day 1	104 ± 17 ^a	1.7 ± 0.7 ^a	14.6 ± 1.7 ^b	20.0 ± 1.2	30.0 ± 4.2	14.7 ± 1.5 ^a
Peg-filgrastim, day 1 and day 7	244 ± 101 ^a	1.9 ± 0.7 ^a	5.3 ± 1.6 ^{a,c}	10.2 ± 2.6 ^{a,c}	18.1 ± 1.7 ^{a,d}	8.1 ± 2.2 ^a

* Monkeys were exposed to 6 Gy TBI and subcutaneously administered control protein (0.1% autologous serum, AS, n=10), filgrastim at 10 mcg/kg/d (n=4) until the ANC ≥ 2,000/mcL, pegfilgrastim at 300 mcg/kg (n=9) on Day 1 post TBI, or pegfilgrastim at 300 mcg/kg on Days 1 and 7 post TBI (n=9). Data represented mean values ± SEM. The duration of neutropenia was defined as days of ANC < 500/mcL or < 100/mcL and time to recovery was the number of days required for the ANC to reach ≥ 500/mcL or 2,000/mcL.

^a Statistically different from the AS-treated controls (P < 0.01).

^b Statistically different from the AS-treated controls (P < 0.05).

^c Statistically different from pegfilgrastim, day 1 only cohort (P < 0.01).

^d Statistically different from pegfilgrastim, day 1 only cohort (P ≤ 0.05).

The table is adopted from the publication.

Previously reviewed NHP studies for neupogen

Three relevant NHP studies were submitted to DMIP under pre-IND 100228 and the studies were reviewed previously. A Letter of Authorization (LOA) was provided to authorize FDA to use the data to support the review of the current sBLA. The study AXG15 is also submitted under the current sBLA as a pivotal efficacy study. These studies are summarized below.

ARX01: A Pilot Study to Define the Dose-Response Curve in Rhesus Macaques Exposed to Increasing Doses of Total Body Irradiation (TBI) and Receiving Supportive Care.

This study characterized the Rhesus Macaques TBI model. The study report was reviewed previously and the review was included in FDA briefing document for the FDA Advisory Committee Meeting

(<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee/UCM350151.pdf>).

In this study, LD_{30/60}, LD_{50/60}, and LD_{70/60} for HS-ARS in Rhesus macaques were determined. Animals (8 males/group) were exposed to 720, 755, 785, 805, 840, or 890 cGy TBI at a rate of 80 cGy/min using a 6 MV linear accelerator (LINAC) radiation source. Medical managements and supportive cares, including fluids, prophylactic antibiotics, and blood transfusions, were provided. The primary endpoint was survival at

60 days post TBI. The calculated LD_{30/60}, LD_{50/60}, and LD_{70/60} radiation doses were 709, 752, and 797 cGy, respectively. 750 cGy was then used as the targeted LD_{50/60} dose.

Review comment

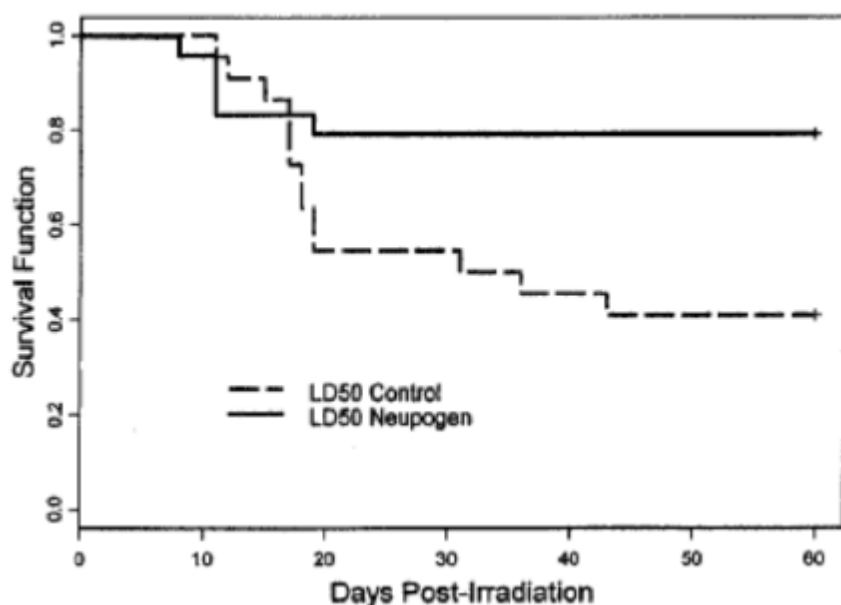
Animal models have been valuable in characterizing the damaging effects of radiation on hematopoiesis². Three species, mouse, canine and nonhuman primate (NHP), have been used in the majority of radiation studies on HS-ARS. Beagle is the predominant canine used and rhesus macaque (Macaca mulatta) is the main NHP used. Both beagle and rhesus macaque are considered well-characterized large animal models for which the lethal dose response relationships for the HS-ARS have been well established. Consistently, the mortality in rhesus macaque controls in three studies reviewed by FDA was relatively consistent (LD_{50/60}: 59% in AXG15, 52.2% in AXG21, and 50% in AXG22).

AXG15: A Sixty-Day Efficacy Study of Subcutaneous Filgrastim (Neupogen) to Treat the Hematopoietic Syndrome of the Acute Radiation Syndrome (ARS-HS) Following an LD_{50/60} of Total Body Irradiation (TBI) in Rhesus Macaques.

This study was the pivotal efficacy study to support Neupogen approval under the animal rule. The study is also submitted under the current sBLA as a pivotal efficacy study. The study was reviewed by clinical, nonclinical, and statistical reviewers previously and reviews were included in FDA briefing document for the FDA Advisory Committee Meeting ([http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drug s/MedicalImagingDrugsAdvisoryCommittee/UCM350151.pdf](http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drug%20s/MedicalImagingDrugsAdvisoryCommittee/UCM350151.pdf)). The key information is summarized below.

The primary endpoint, a comparison of the number of surviving at day 60, is met in this study. Neupogen at 10 mcg/kg/day starting 22-26 hr post LD_{50/60} TBI (7.4 ± 0.15 Gy delivered at 0.8 ± 0.03 Gy/min) increased survival [79% (19/24) versus 41% (9/22) in the control arm, the Chi-square test two sided p<0.0079 and Fisher's exact test two sided p=0.0147, Figure 15). All animals were euthanized according to the pre-specified criteria except for three animals in the control arm that were found dead between Days 11-18. The animal fate table is provided under the section 12.

Figure 15. Kaplan-Meier Survival Curves*



* the log rank test p-value for comparing the equality of the two curves 0.018.

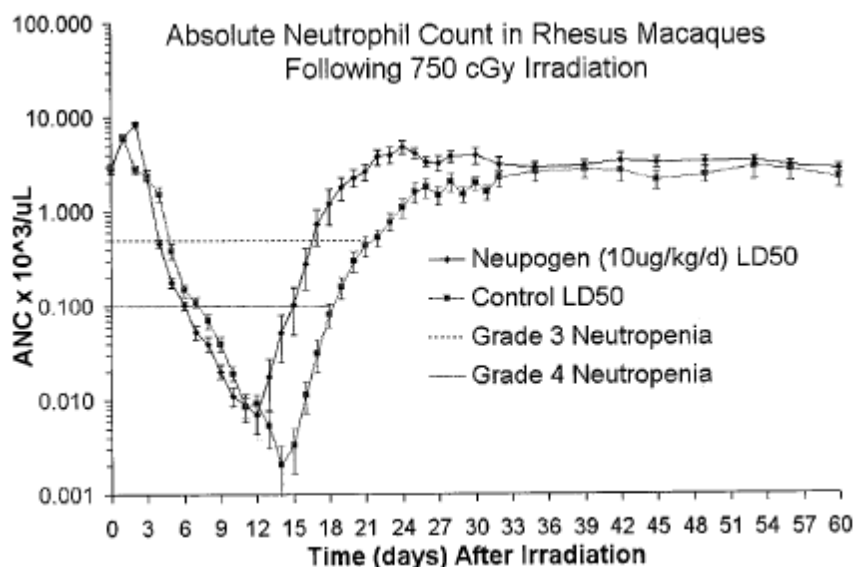
In addition, the key secondary endpoint, a comparison of the duration of severe neutropenia, is met. Neupogen reduced the duration of severe neutropenia by 4 days (Table 24 and Figure 16, defined as ANC < 500/mcL; median: 14 days in the neupogen arm versus 18 days in the control arm].

Table 24. Neutrophil-related parameters*

Tx		First day and range ANC < 500/ μ L or 100/ μ L		Duration (days and range) ANC < 500/ μ L or 100/ μ L		Recovery to ANC $\geq$ 1000/ μ L	ANC Nadir (/ μ L)
		< 500/ μ L	< 100/ μ L	< 500/ μ L	< 100/ μ L	$\geq$ 1000/ μ L	
Test Article	Mean $\pm$ SEM	4.3 $\pm$ 0.1	6.5 $\pm$ 0.3	14.3 $\pm$ 0.5	10.4 $\pm$ 0.6	19.7 $\pm$ 0.6	5 $\pm$ 2
	P value	Not done	Not done	<0.0001	0.009	<0.0001	0.115
	Median	NA	NA	14.0	10.0	20	0
	Range	SD3-5	SD4-9	9-19 days	4-14 days	15-25 days	NA
Control Article	Mean $\pm$ SEM	4.9 $\pm$ 0.2	7.1 $\pm$ 0.3	18.6 $\pm$ 0.8	12.3 $\pm$ 0.6	25.8 $\pm$ 0.9	1 $\pm$ 1
	Median	NA	NA	18.0	12.0	24.5	0
	Range	SD3-6	SD5-10	14-22 days	8-15 days	22-32 days	NA

* Test Article: Neupogen 10 mcg/kg/day, SC; Control Article: 5% Dextrose in Water

Figure 16. Absolute Neutrophil Counts (ANC)



In summary, both the primary endpoint (increased survival) and key secondary endpoint (reduced duration of neutropenia) are met in this efficacy study.

AXG 22: A sixty-day efficacy study of subcutaneous delayed filgrastim (neupogen) administration to treat the hematopoietic syndrome of the acute radiation syndrome (ARS-HS) following an LD_{50/60} of total body irradiation (TBI) in Rhesus Macaques

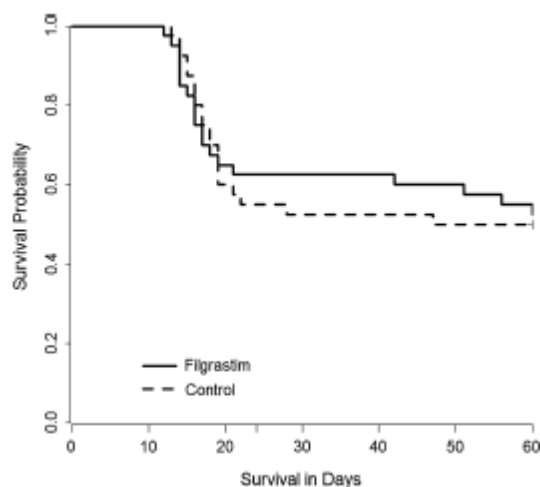
This study was conducted by the same lab conducting the study AXG15 and reviewed previously by the DMIP. This study is also published³. The key difference between this study and the study AXG15 was that neupogen was administered at 44 to 52 hr post TBI in this study instead of 20 to 26 hr in the study AXG15. The key information is summarized below.

Survival

The interim analysis revealed that neupogen, subcutaneously administered at 10 mcg/kg/day starting at 44 to 52 hr post LD_{50/60} TBI, did not significantly increase overall survival [52.5% (21/40) vs. 50.0% (20/40) in the control arm, $p = 0.82$, Figure 17]. The study was then terminated because of futility.

³ Farese, AM et al., 2014, The Ability of Filgrastim to Mitigate Mortality Following LD50/60 Total-Body Irradiation Is Administration Time-Dependent. Health Phys. 106:39

Figure 17. Kaplan-Meier Survival Curves*



* Survival curves in rhesus macaques administered Neupogen (n = 40) or D5W (control, n = 40) as a function of time post LD_{50/60} TBI.

Reviewer comment

In this study, neupogen, subcutaneously administered at 10 mcg/kg/day starting at 44-52 hr post LD_{50/60} TBI, did not significantly increase overall survival [52.5% (21/40) vs. 50.0% (20/40)]. However, neupogen, using same dose regimen but starting at 20-26 hr post LD_{50/60} TBI, significantly increased overall survival [79% (19/24) vs. 41% (9/22)] in the efficacy study aforementioned (AXG15). The study was conducted by the same lab using the similar protocol and in rhesus monkeys as well. As summarized in the AC briefing package, administration time post TBI is one of critical factors that can impact the efficacy of neupogen. Similarly, according to the publication by Farese et al³, the marginal database suggested that the more severe the insult, the more critical was the early administration of G-CSF and that G-CSF efficacy was diminished with longer delay in administration. The early administration of G-CSF in the lethal TBI models was necessary for optimal survival.

However, there were some issues, which could affect the study outcome, in this study. The issues are further discussed below.

Suspected or active Simian Varicella Virus (SVV) infection contributed to all 4 animals euthanized on SD 21 or later in the neupogen arm, either as sole basis (one animal) or contributed to euthanasia as additional criteria, which introduced a major imbalance between two arms. In addition, an animal (0806005) in the neupogen arm was found dead on SD 51, who also had clinical signs consistent with SVV infection. Only one animal in the control arm that was listed as early death had SVV infection.

There was no concurrent 24 hr neupogen administration control in this study. There are many variables that can affect the study outcome. For any convincing comparison study, a head-to-head, well controlled design is essential. Without a concurrent 24 hr neupogen administration control, the study outcome is challenging to interpret.

Taken together, the reviewer acknowledges that administration time post TBI is one of critical factors that can impact the efficacy of neupogen. Delayed neupogen administration post lethal TBI could diminish the survival benefit. Consistently, the neupogen labeling emphasized that neupogen should be administered as soon as possible and reflected the importance of neupogen administration time post radiation exposure. However, because of no concurrent 24 hr neupogen administration control, SVV infection, and imbalance between two arms over suspected or active SVV infection related early death, the data is inconclusive.

Key secondary endpoint

Neupogen mainly reduced the durations of ANC < 500/mcL (median: 13 vs. 16.5 days in the control arm, Table 25 and Figure 18). As a result, neupogen improved the ANC recovery as evidenced by reduced median time-to-recovery to ANC ≥ 1,000/mcL (19 vs. 23 days in the control arm). Neupogen did not significantly reduce the durations of ANC < 100/mcL (10 vs. 9 days in the control arm).

Table 25. Neutrophil-related parameters*

Treatment		First day (d) of Neutropenia		Duration (d) of Neutropenia		Recovery to ANC ≥ 1000 μL^{-1}	Nadir (ANC μL^{-1})
		Grade 3	Grade 4	Grade 3	Grade 4		
Control	Mean ± SE	5.0 ± 0.1 ^a	7.8 ± 0.3 ^a	16.4 ± 0.5 ^b	10.4 ± 0.6 ^b	23.5 ± 0.7 ^c	2.6 ± 1.0 ^a
	Median	5 ^a	7 ^a	16.5 ^b	9 ^b	23.0 ^c	0 ^a
	Range	d4–7	d5–11	d13–21	d6–17	d19–33	0–36
Filgrastim	Mean ± SE	4.9 ± 0.1 ^a	6.5 ± 0.1 ^a	13.1 ± 0.4 ^d	9.9 ± 0.3 ^d	18.9 ± 0.3 ^d	1.9 ± 0.5 ^a
	P	0.4802	0.0002	<0.0001	0.5504	<0.0001	0.9032
	Median	5 ^a	6 ^a	13.0 ^d	10 ^d	19.0 ^d	0 ^a
	Range	d3–6	d5–8	d11–18	d8–15	d16–22 ^f	0–12

* Adopted from Farese et al³. All animals (n = 40/arm) were included in analysis for first day of Grade 3 (ANC < 500/mcL) and Grade 4 (ANC < 100/mcL) neutropenia and ANC nadir. Survivors and the non-survivors that recovered to respective levels were included in duration of neutropenia and recovery to ANC ≥ 1,000/mcL analysis. P values were a result of the Wilcoxon rank-sum analysis for nadir and a two-sample t-test for all other analyses.

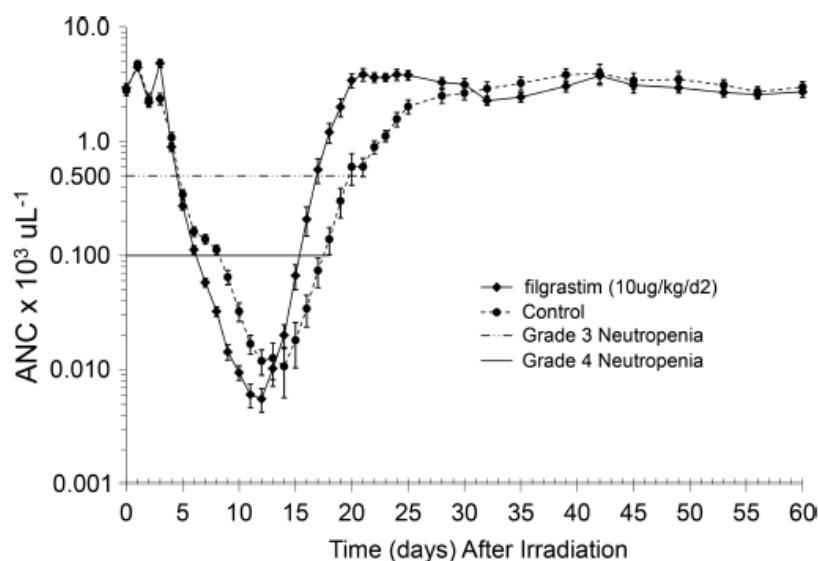
^an = 40.

^bn = 22.

^cn = 21.

^dn = 25.

Figure 18. ANC in Rhesus Macaques post TBI



Mean ($\pm$ SEM) ANC $\times 10^3/\text{mcL}$ in the peripheral blood of rhesus macaques administered D5W or Neupogen as a function of time post TBI.

Reviewer comment

Reduced duration of severe neutropenia is used as a primary endpoint for approval of neupogen. For example, according to the PI, neupogen (5 mcg/kg/day, SC) reduced the median duration of severe neutropenia ($\leq 500/\text{mm}^3$) by 5 days (14 days in the neupogen-treated arm vs. 19 days in the control arm, $p=0.0001$) in a phase 3 trial. As a result, neupogen reduced median time from initiation of chemotherapy to ANC recovery ($\text{ANC} \geq 500/\text{mm}^3$) by 5 days as well (20 days in the neupogen-treated arm vs. 25 days in the control arm, $p = 0.0001$).

Neupogen reduced the duration of severe neutropenia by 3.5 days (median: 13 vs. 16.5 days in the control arm) in this NHP study.

A Relevant Publication

A publication titled “Recombinant interleukin-12, but not granulocyte-colony stimulating factor, improves survival in lethally irradiated nonhuman primates in the absence of supportive care: Evidence for the development of a frontline radiation medical countermeasure⁴” was identified. In this publication, neupogen was used as a comparator. The relevant key information is summarized below based on this publication.

This study was a randomized, blinded GLP study in Rhesus monkeys. The study was conducted by CiToxLAB North America (Montreal, Quebec, Canada). Rhesus monkeys were obtained from the Yongfu County Xingui Wild Animals Raising, China. At the beginning of the treatment, animal age ranged from 2 years, 5 months to 3 years, 10 months and all animals weighed between 2.8 and 5.7 kg. Monkeys were exposed to 700 cGy TBI (60 cGy/min from a Theratron 1000 Co⁶⁰ source, a projected LD_{80/60} dose).

⁴ Gluzman-Poltorak, Z. et al., 2014, Am. J. Hematol. 89:868

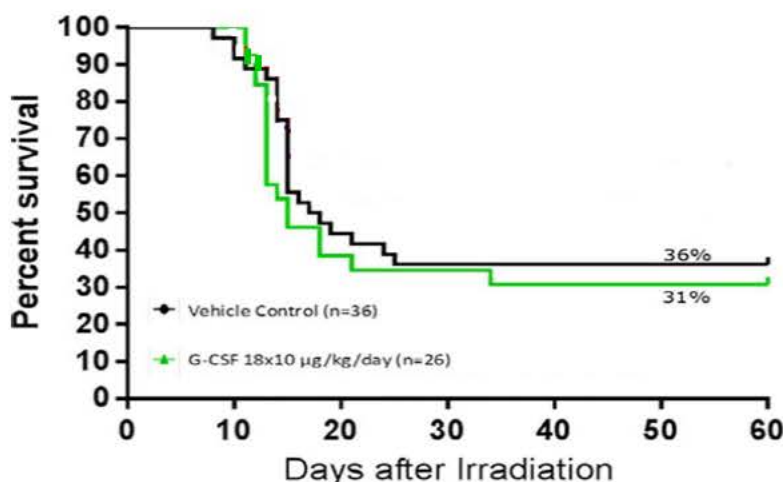
Neupogen at 10 mcg/kg/day was administered subcutaneously starting 24–25 hr post TBI through day 18 (n=26). The vehicle was not specified in the publication.

Unscheduled euthanasia were performed in a blinded manner if any of the following criteria were observed: respiratory distress; complete anorexia for 3 day; loss of > 20% of initial body weight over a 3 day period; severely decreased activity level (recumbent during an entire observation period or unresponsiveness to touch); acute loss of > 20% estimated blood volume; generalized seizure activity; abnormal appearance associated with abnormal vital signs; severe dehydration with hypothermia (rectal temperature < 34.6°C and severely decreased activity level); or hyperthermia (temperature >40.1°C and severely decreased activity level).

Symptomatic palliative care was provided for pain, mouth ulcers, diarrhea, wounds, and anorexia.

In this study, neupogen did not improve survival [31 vs. 36% in the control arm (n=36), $p = 0.6610$]. Mean survival times were 31.5 and 28.9 days in the vehicle and neupogen arms, respectively (Figure 19).

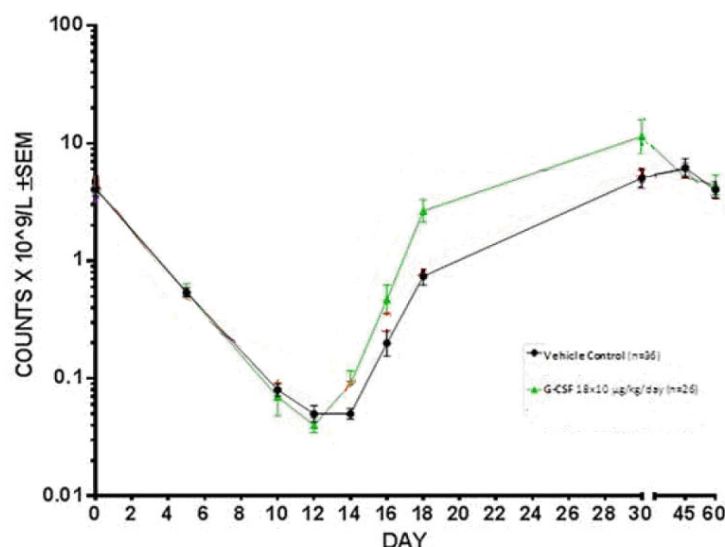
Figure 19. Kaplan–Meier Survival Curves



* The figure is modified based on the publication.

Severe decreases in neutrophils were noted in all animals between Days 10 and 18 with the lowest mean neutrophil counts on Days 12–14, which corresponded to the time of the highest mortality. Neupogen increased neutrophil counts starting on Day 14 (Figure 20).

Figure 20. Neutrophil Counts*



* The figure is modified based on the publication. Blood counts over time in rhesus monkeys exposed to lethal TBI and treated 24 hr post TBI with vehicle or neutropen. All data represent mean $\pm$ SEM. Normal ranges for neutrophils: $1.21\text{--}10.29 \times 10^9/\text{L}$.

Reviewer comment

There are the following differences in the study design and conduct, which could contribute to the outcome difference from the study AXG15 aforementioned.

Radiation source, dose, and rate

Radiation source was Theratron 1000 Co⁶⁰ and the dose was 700 cGy TBI (LD_{80/60}) at 60 cGy/min in this study. Radiation source was 6 MV linear accelerator and the dose was 750 cGy TBI (LD_{50/60}) at 80 cGy/min in the study AXG15.

Medical management

Only symptomatic palliative care was provided for pain, mouth ulcers, diarrhea, wounds, and anorexia in this study. No antibiotics, fluids, or blood products were provided. Extensive medical management and supportive care, including whole blood transfusion, prophylactic antibiotic treatment, and fluids, were provided according to the pre-specified criteria in the study AXG15.

According to the publication, the discrepancy between this study and the study AXG15 may be owing to the highly variable nature of intensive, trigger-based medical management. Early recovery of all blood cells lineages, preceded by bone marrow regeneration, is likely essential to increase the potential for survival.

Treatment duration

Neupogen was used starting on Day 1 (24–25 hr post TBI) through Day 18 in this study. Neupogen was used starting on Day 1 (20–26 hr post TBI) until ANC $\geq$ 1,000/mcL for 3 consecutive days or meeting other pre-specified ANC counts in the study AXG15. According to the clinical review of the study AXG15, neupogen was administered an average of 22 days ($\pm$ 1). Neupogen could be reinitiated in situations where the ANC returned to less than 500/mcL and one animal in the neupogen arm had neupogen reinitiated in the study AXG15.

Animal source

Rhesus monkeys were obtained from different sources. In this study, the animals were from Yongfu County Xingui Wild Animals Raising, China. At the beginning of the treatment, animal age ranged from 2 years, 5 months to 3 years, 10 months and all animals weighed between 2.8 and 5.7 kg. The animals in the study AXG15 were from 2 different vendors (Rhenollic and Three Springs Science). Animal age ranged from 3 to 6 years and all animals weighed between 4.0 and 6.5 kg.

Taken together, higher radiation exposure (projected LD_{80/60} in this study vs. LD_{50/60} in the study AXG15) and no supportive care such as whole blood transfusion, prophylactic antibiotic treatment, and fluids could contribute to the discrepancy between this study and the study AXG15. G-CSF is a lineage-specific CSF and regulates neutrophil production and function only. As aforementioned, excessive bleeding is also the main cause of death in HS-ARS. The medical management such as fluids, antibiotics, blood products increased the LD_{50/60} from 3.25–4.50 Gy to 6.0–7.0 Gy in humans. There was no detailed information regarding causes of mortality available in this publication. Therefore, the exact reason of discrepancy between this study and the study AXG15 cannot be determined.

The reviewer also has concern about the consistency of mortality in the control arms by this lab. There was 25% difference in mortality of control animals between two studies despite the radiation dose and source were same. The mortality was 64% in this study but was 89% (16/18) in a previous publication.⁵

4.2 Secondary Pharmacology

N/A

4.3 Safety Pharmacology

N/A

5 Pharmacokinetics/ADME/Toxicokinetics

N/A

⁵ Gluzman-Poltorak, Z. et al., Randomized comparison of single dose of recombinant human IL-12 versus placebo for restoration of hematopoiesis and improved survival in rhesus monkeys exposed to lethal radiation, Journal of Hematology & Oncology 2014, 7:31

5.1 PK/ADME**5.2 Toxicokinetics****6 General Toxicology**

N/A

7 Genetic Toxicology

N/A

8 Carcinogenicity

N/A

9 Reproductive and Developmental Toxicology

N/A

10 Special Toxicology Studies

N/A

11 Integrated Summary and Safety EvaluationIntroduction

Neulasta (pegfilgrastim) is a covalent conjugate of filgrastim and 20 kD monomethoxypolyethylene glycol with a longer half-life (ranged from 15 to 80 hours after subcutaneous injection vs. 210 minutes for filgrastim). Neulasta was initially approved in 2002. Neulasta is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. The recommended dosage of Neulasta is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle in adults.

Neupogen (filgrastim) is a recombinant human granulocyte colony-stimulating factor (rhG-CSF). The amino acid sequence of Neupogen is virtually identical to the natural sequence predicted from human DNA sequence analysis.

Neupogen was initially approved in 1991 under BLA 103353. Neupogen is approved for multiple indications including cancer patients receiving myelosuppressive chemotherapy (5 mcg/kg/day) and cancer patients receiving bone marrow transplant (10 mcg/kg/day). In addition, Neupogen is approved for increasing survival in patients acutely exposed to myelosuppressive doses of radiation (HS-ARS) recently. The approval is based on an efficacy sBLA under the animal rule. The recommended dose of Neupogen is 10 mcg/kg as a single daily subcutaneous injection. Neupogen should be administered as soon as possible after suspected or confirmed exposure to radiation doses greater than 2 Gy and should be continued until ANC remains greater than 1,000/mm³ for 3 consecutive days or CBC exceeds 10,000/mm³ after a radiation-induced nadir.

Under the current efficacy supplement, neulasta is indicated for increasing survival in patients acutely exposed to myelosuppressive doses of radiation. The recommended dose of neulasta is 6 mg for patients weighing at least 45 kg as two subcutaneous injections. The weight-tiered dosing is recommended for patients weighing less than 45 kg. The first dose should be administered as soon as possible after suspected or confirmed exposure to radiation doses greater than 2 Gy and the second dose should be administered one week after.

Mechanism of action of G-CSF

G-CSF regulates the production of neutrophils within the bone marrow by binding to specific cell surface receptors and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functions (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody-dependent killing, and the increased expression of some cell surface antigens). G-CSF is not species-specific and has been shown to have minimal direct in vivo or in vitro effects on the production or activity of hematopoietic cell types other than the neutrophil lineage.

Hematopoietic syndrome of the acute radiation syndrome (HS-ARS)

HS-ARS is a consequence of exposure to radiation dose greater than 1 Gy (The Medical Aspects of Radiation Incidents, <https://orise.orau.gov/files/reacts/medical-aspects-of-radiation-incidents.pdf>, FDA Advisory Committee Meeting briefing document, <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee/UCM350152.pdf>).

Radiation damages cells, generally most severe in rapidly reproducing cell types such as hematopoietic stem cells and progenitor cells. HS-ARS in humans is characterized by dose dependent bone marrow depression leading to neutropenia, thrombocytopenia, and anemia. The HS-ARS is dose- and time-dependent, with increasing mortality and morbidity as exposure doses increase. Clinical manifestations of HS-ARS can be seen following radiation exposures of 2 Gy to 10 Gy. Death due to HS-ARS from infection or excessive bleeding occurs within 2 to 3 weeks after exposure. Survival following HS-ARS is dependent on the recovery of the hematopoietic stem and progenitor cells so that production of mature, functional neutrophils and platelets can occur. Neutrophil recovery is inversely related to radiation exposure and can occur 3 to 4 weeks following radiation exposure. The rapid administration of CSFs including G-CSF to enhance hematopoietic recovery is recommended.

Efficacy Studies in Animals

The efficacy studies to support this efficacy supplement were conducted in animals under the animal rule (21 CFR 601.90) because human clinical trials cannot be ethically conducted.

Published reports of G-CSF use in animals

Based on FDA Advisory Committee Meeting briefing document

(<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee/UCM350151.pdf>), the survival benefit of rhG-CSF treatment was consistently demonstrated in a radiation dose- and rhG-CSF dose-related manner in dogs and mice. In addition, rhG-CSF enhanced neutrophil recovery in all animal species and strains studied. The effects were measured mainly as reduced duration of neutropenia (a few days) and reduced time to ANC recovery (a few days).

Pivotal efficacy studies in NHPs

The key endpoints of pivotal neulasta (Study AXG 21) and neupogen (Study AXG 15) NHP studies reviewed by FDA are summarized in

Table 26. The study AXG 21 is the pivotal efficacy study to support this efficacy supplement. Both neulasta and neupogen increased the survival. Both neulasta and neupogen also reduced duration of neutropenia and improved neutrophil recovery. Both primary and key secondary endpoints are met.

Table 26. Summary of Key Endpoints of Neulasta and Neupogen Studies in NHPs

Administration time post TBI*	24h (20-26 h)		24h (20-26 h)	
	D5W ^a	Neulasta ^b	D5W ^a	Neupogen ^c
Overall survival	47.8% (11/23)	91.3% (21/23) (p = 0.0014)	41% (9/22)	79% (19/24) (P<0.004)
Duration of ANC < 500/mcL (median, days)	18	14 (P<0.0001)	18	14 (P<0.0001)
Duration of ANC < 100/mcL (median, days)	12	8 (p=0.0002)	12	10 (p=0.009)
Time-to-recovery to ANC ≥1,000/mcL (median, days)	25	20 (p=0.0010)	24.5	20 (P<0.0001)
Durations of PLT < 20,000/mcL (median, days)	16	11	14	10
Time-to-recovery to PLT ≥ 20,000/mcL (median, days)	26	20	24	21
Number of transfusion per animal (mean)	3	2	2.4	1.8
Incidence of positive bacteria culture in both blood and tissue	24% (5/21)	4% (1/23)	32% (7/22)	17% (4/24)
Incidence of positive bacteria culture in blood	74% (18/23)	65 (15/23)	86% (19/22)	58% (14/24)
Incidence of febrile neutropenia	87% (20/23)	87% (20/23)	91% (20/22)	79% (19/24)

* Rhesus Macaques were exposed to LD_{50/60} TBI.

^a D5W (Dextrose 5% in Water) was used as a placebo.

^b Neulasta (Pegfilgrastim) at 300-319 mcg/kg/dose was subcutaneously administered on Days 1 (20-26 hr) and 8 post TBI.

^c Neupogen (Filgrastim) at 10 mcg/kg/day was subcutaneously administered 20-26 hr post TBI, then daily until ANC was ≥ 1,000/mcL for three consecutive days.

Efficacy studies in mice

The studies in (b)(4) and (b)(4) mice also demonstrated the survival benefit of neulasta. Neulasta increased survival by 32% or greater in these mouse studies over the controls. Of interest, in a (b)(4) mouse study, neulasta increased the survival in similar manner (40% or greater) either given one dose (22-28 hr post LD_{50/30} TBI) or two doses (Days 1 and 7) at 1 mg/kg or one dose (22-28 hr post LD_{90/30} TBI) at 0.1 mg/kg, 0.3 mg/kg, or 1.0 mg/kg. However, neulasta increased the survival in a neulasta dose dependent manner in another (b)(4) mouse study, in which mice were exposed to 13 Gy partial body irradiation with approximately 2.5% of the bone marrow shielded (PBI BM2.5). Thirty day survival rates were 80%, 50% or 20% in 1 mg/kg Neulasta (subcutaneously administered once at about 24 hours post 13 Gy PBI BM2.5), 0.1 mg/kg Neulasta, or vehicle control groups, respectively. Neulasta at either 1 mg/kg or 0.1 mg/kg did not increase the 30 day survival in (b)(4) mice post 13 or 14 Gy TBI, which caused 100% mortality within 13 days post TBI.

Marketing Approval Under the Animal Rule

Safety

Neulasta has been approved since 2002. Nonclinical and clinical safety information is available in the current label. Extensive safety profile has been established.

Efficacy

According to the FDA draft Guidance for Industry titled “Product Development Under the Animal Rule” published in May 2014

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM399217.pdf>), FDA may grant marketing approval based on adequate and well-controlled animal efficacy studies when the results of those studies establish that the drug is reasonably likely to produce clinical benefit in humans.

The Animal Rule states that FDA will rely on evidence from animal studies to provide substantial evidence of effectiveness only when all of the following four criteria, quoted below, are met:

1. There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product;
2. The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans;
3. The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity; and

4. The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans.

Regarding the first criteria, both the pathophysiological mechanism of radiation injury and mechanism of action of G-CSF are reasonably well understood as described above. Radiation of animals led to mortality and neutropenia, which is similar to human.

Regarding the second criteria, the survival benefit of neulasta is demonstrated in mice and NHPs. In a relatively well-characterized nonhuman primate model, Neulasta significantly increased the 60-day overall survival when administered at approximately 24 hr and on Day 8 post LD_{50/60} TBI as summarized in Table 26.

In addition, neulasta significantly reduced duration of neutropenia and improved neutrophil recovery in all animal species studied.

Recently (March 30, 2015), Neupogen was approved for increasing survival in patients acutely exposed to myelosuppressive doses of radiation (HS-ARS) under the animal rule.

Relevant to the setting of HS-ARS, both pegfilgrastim and filgrastim are approved to decrease the incidence of infection and reduce the duration of neutropenia and neutropenia-related clinical sequelae including cytotoxic chemotherapy induced myelosuppression, which is mechanistically similar to radiation-induced myelosuppression.

In summary, both primary and key secondary endpoints are met. The labeling emphasized the neulasta should be administered as soon as possible and reflected the importance of neulasta administration time post radiation exposure.

Regarding third criteria, the animal study endpoints: increased survival and neutrophil recovery, are clearly related to the desired benefit in humans.

Regarding fourth criteria, although limited pharmacokinetic (PK) data in irradiated animals are available, available PK and pharmacodynamics (PD) data in animals and in humans allows selection of an effective dose in humans. The dose selection will be reviewed under the pharmacometrics review.

Consistently, the AC meeting for LGF supports the approval of neulasta for HS-ARS under the animal rule

(<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee/UCM363898.pdf>).

Taken together, the data available for neulasta meet the criteria outlined by FDA for approval under the Animal Rule.

In conclusion, an approval is recommended based on the totality of available efficacy and safety data in animals and humans from a nonclinical perspective. In addition, neulasta dose regimen has practical advance over neupogen (two doses vs. daily dose with ANC monitoring).

12 Appendix/Attachments

AXG21: A Sixty-Day Neulasta Efficacy Study

Summary of Animal Identification, Source, Irradiation Date, and Randomization

Irradiation Date	Group	ID	Gender	Source	Treatment Arm
(b)(4)					

Tissues Collected at Necropsy

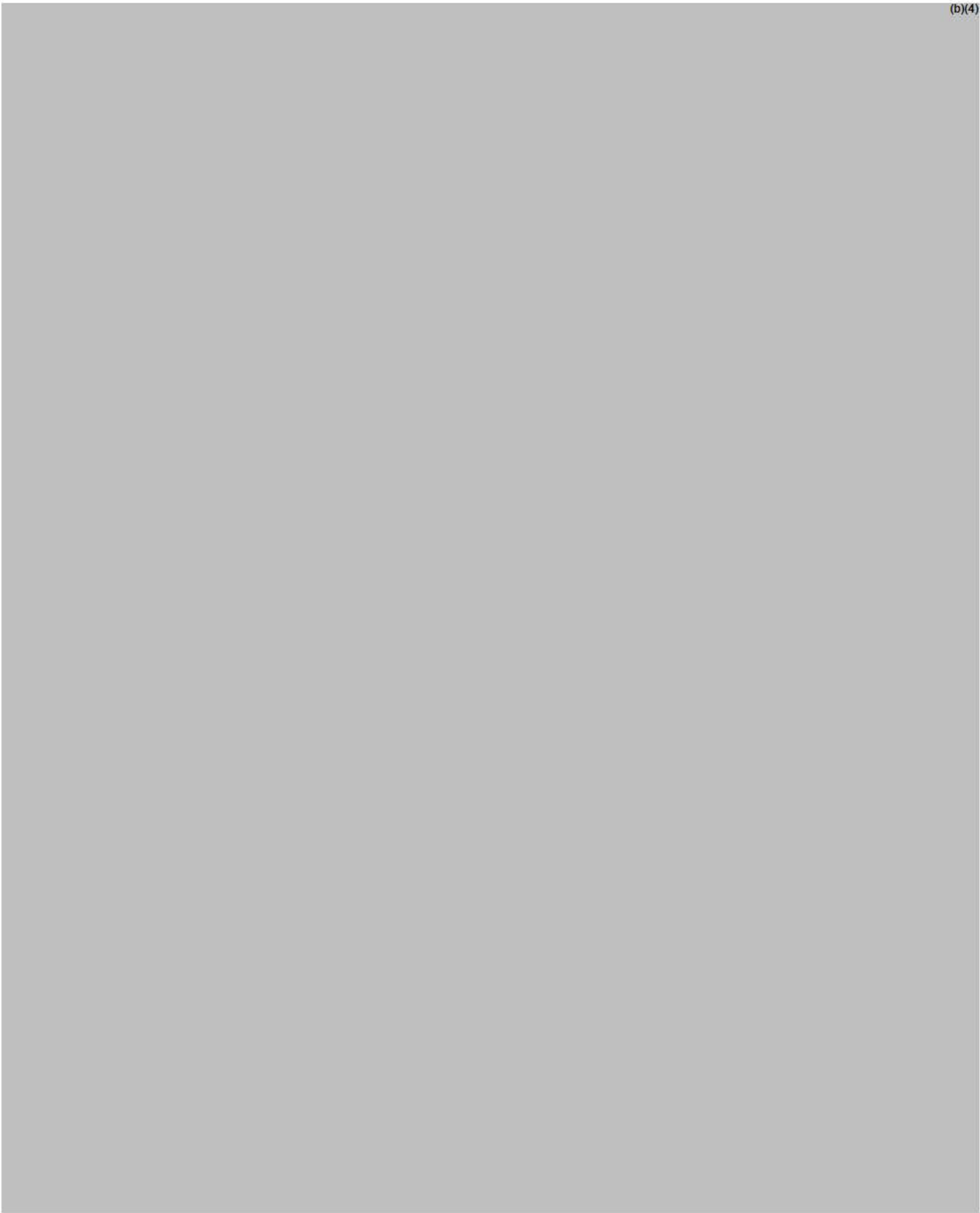
Tissue	Minimum Number of Samples
1. Heart	2 (from 2 different areas)
2. Lung	3 (from 3 different areas)
3. Liver	3 (from 3 different areas)
4. Spleen	2 (from 2 different areas)
5. Kidney (left and right)	4 (2 from different areas of each kidney)
6. Large Intestine	
Cecum	1
Proximal Colon	1
Distal Colon	1
7. Small Intestine	
Duodenum	1
Jejunum	1
Ileum	1
8. Thymus	1
9. Mesenteric lymph node	A minimum of 4 (from 3 different areas)
10. Skin	1 sample in addition to the tattoo
11. Sternum ^A	1 (approximately 2 cm transverse section)
12. Femur	1 (approximately 2-3 cm cross section)
13. Any lesions or abnormalities of the aforementioned tissues.	1 or 2 samples from a representative area

^A Decalcified prior to sectioning

AXG 15: Summary of animal fate in the neupogen study

Animal ID	Gender	Treatment	Study Day	Disposition
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(b)(4)



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YANLI OUYANG
10/21/2015

ADEBAYO A LANIYONU
10/21/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125031Orig1s180

STATISTICAL REVIEW



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number: BLA 125031/ efficacy supplement under animal rule, supplement 180, SD 1137, SN 0230

Drug Name: Pegfilgrastim (Neulasta)

Indication(s):

(b)(4)

Applicant: Amgen Inc.

Date(s): Received date: 2/13/2015

PDUFA due date: 11/15/2015

Review Priority: Priority

Biometrics Division: DBV

Statistical Reviewer: Lan Huang, Ph. D.

Concurring Reviewers: Jyoti Zalkikar, Ph. D. (Statistics Team Leader)
Thomas Gwise, Ph. D. (Deputy Division Director)

Medical Division: Division of Medical Imaging Products

Clinical Team: William Dickerson, M.D. (Clinical Reviewer)
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Project Manager: Frank Lutterodt

Keywords:

randomized two arm study, irradiation, survival, exact test, chi-square test, animal rule

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1. EXECUTIVE SUMMARY

Introduction

Pegfilgrastim is a PEGylated form of the recombinant human granulocyte colony-stimulating factor (GCSF) analog filgrastim. It serves to stimulate the level of white blood cells (neutrophils). Pegfilgrastim was approved in the United States in January 2002, and is indicated to decrease the incidence of infection, as presented by febrile neutropenia (FN), in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs that have been associated with a clinically significant incidence of FN.

Here, Amgen Inc. is submitting a supplemental Biologics License Application (sBLA) for the use of Neulasta® (pegfilgrastim) for increasing the survival of patients acutely exposed to myelosuppressive doses of radiation (b)(4). Efficacy studies of pegfilgrastim could not be conducted in humans with acutely exposed to myelosuppressive doses of radiation for ethical and feasibility reasons. Therefore, approval of this indication is to be based on efficacy studies conducted in animals. The dose for humans will be obtained using extrapolation of the animal dose.

Conclusion and recommendation

In conclusion (from the pivotal non-human primate study), Neulasta (300 mcg/kg administrated on day 1 and day 8 after irradiation) is shown to be efficacious in improving the 60-day survival rate of non-human primates having received a lethal total body irradiation (TBI). Neulasta is also effective in improving the recovery from events Absolute Neutrophil Count (ANC)<500/uL and ANC<1000/uL, in non-human primates having received lethal doses of TBI.

According to Pharmacometric review, the PD response with the regimen used in the animal study is similar to the 6 mg human dose given twice one week apart. The pharmacometric review team have found that the PK/PD relationship in pediatric appears to be consistent with that in adults. They proposed selecting a dose in pediatrics that produces similar PK to that of adults with 6 mg one week apart dosing regimen and recommended the dose for pediatric human population is 4 mg for 31-44 kg body weight; 2.5 mg for 21 – 30 kg; 1.5 mg for 10 - 20 kg; and 100 mcg per kg for those weighing less than 10 kg.

We recommend approval under the animal rule noting the following issues:

- The radiation doses in the studies may not reflect those in real situations. The radiation dose used in the pivotal animal study is LD 50/60 for the animals. The efficacy of Neulasta for other radiation doses is not clear from the information provided in this sBLA.
- Neulasta is shown to be efficacious when administering on day 1 and 8.

Statistical issues and concerns

The sponsor submitted the data for the animal **study AXG 21 (the pivotal study)** in this submission. The reviewer could reproduce the primary analysis using the data.

Variables for efficacy evaluation included death indicator, time to death, ANC, time of ANC, duration of neutropenia, day of ANC recovery, febrile neutropenia, number of transfusions, etc and baseline information (including Group, id, gender, etc) were included in the submitted electronic data sets. The partial supportive care, safety, and partial baseline information (including source, dose, etc) were submitted in pdf files.

Data including information on supportive care within each subject (degree of support) was not available.

Farese et al. 2012 (one animal study for exploring the effect of Neulasta with different doses vs. control) was not powered to show the effect of Neulasta vs. control or Neupogen. The sample size is not enough for understanding the performance. Therefore, this study is exploratory.

Only one center is included in the key studies (University of Maryland (UM)). The variation from centers cannot be evaluated.

All animals were male in the key studies, so one cannot evaluate the drug performance on females.

In addition, there is no information on the delayed administration of the Neulasta after TBI (1st injection after Day 1).

Extrapolation of animal dose to human dose

According to Pharmacometric review, simulations show that 6 mg dose of Neulasta might not be adequate to produce optimal benefit in humans exposed to radiation because it does not result in exposures exceeding the exposures associated with the NHP dose (300 mcg/kg) at which efficacy has been demonstrated. (b)(4)

. There is limited human safety experience with 18 mg dose level. There are only 4 subjects receiving 18 mg (300 mcg/kg) pegfilgrastim in study 970144 and 8 subjects with 18 mg (300 mcg/kg) pegfilgrastim in study 970230 in the submission. The information about both efficacy and safety for the administration of higher level dose of 18 mg is not enough for comment on its use. Therefore, considering the mechanism of action of pegfilgrastim and involving an inter-disciplinary discussion, the focus has shifted to the pharmacodynamic (PD) endpoint, absolute neutrophil count (ANC), as the target for dose selection. The PD response with the regimen used in the animal study is similar to the 6 mg human dose given twice one week apart.

The pharmacometric review team have found that the PK/PD relationship in pediatric appears to be consistent with that in adults. They proposed selecting a dose in pediatrics that produces similar PK to that of adults with 6 mg one week apart dosing regimen and recommended the dose for pediatric human population is 4 mg for 31-44 kg body weight; 2.5 mg for 21 – 30 kg; 1.5 mg for 10 - 20 kg; and 100 mcg per kg for those weighing less than 10 kg.

Efficacy overview from the pivotal NHP study

The efficacy of Neulasta for the acute radiation syndrome setting was studied in a randomized, placebo-controlled non-human primate model of radiation injury. The planned sample size was

78 animals, but the study was stopped at the interim analysis with 46 animals because of efficacy. Rhesus macaques were randomized to either a control (n=23) or treated (n=23) cohort. On study day 0, animals (n = 6 to 8 per irradiation day) were exposed to total body irradiation (TBI) of 750 ± 15 cGy delivered at 80 ± 3.0 cGy/min, representing an LD50 dose after 60 days follow-up. Animals were administered subcutaneous injections of a blinded treatment (control article [5% dextrose in water] or pegfilgrastim [300-319 mcg/kg/day]) on study day 1 and on study day 8. The primary endpoint was survival at Day 60. Animals received medical management consisting of intravenous fluids, antibiotics, blood transfusions, nutrition and other support as required, according to pre-determined criteria for use.

Pegfilgrastim significantly (p-value from exact chi-square test of $0.0031 < \text{the alpha level}$ allocated for the interim analysis 0.0107) reduced 60-day mortality in the irradiated non-human primates: 91% survival rate (21/23) in the pegfilgrastim group compared to 48% survival rate (12/23) in the control group.

The Logrank test for the two Kaplan Meier (KM) survival curves (Neulasta vs. Control) had a nominal p-value of 0.011, in favor of Neulasta. The Neulasta group had Hazard ratio (HR) 0.13 (95% CI as [0.03, 0.56]) compared with Control group, from Cox model with only treatment as the covariate.

During the 60 day study period, 13/23 (56.5%) of animals in control group and 22/23 (95.6%) animals in the Neulasta group recovered from $\text{ANC} < 500/\mu\text{L}$ and $\text{ANC} < 1000/\mu\text{L}$. The Neulasta group had shorter time to recovery from $\text{ANC} < 500/\mu\text{L}$ and $\text{ANC} < 1000/\mu\text{L}$ for the exrecovered animals (13 in control and 22 in Neulasta group). For time to recovery to $\text{ANC} \geq 500/\mu\text{L}$ for all animals (median recovery time 27 days for control group, and 18 days for Neulasta group) and to $\text{ANC} \geq 1000/\mu\text{L}$ for all animals (median recovery time 35 for control and 20 for Neulasta group), the logrank test had nominal p-value < 0.001 for testing the difference of the two time to recovery curves (Neulasta vs. control).

The Neulasta group had fewer transfusions. The number of transfusions range from 1 to 7 for the control arm (average of 3), and from 1 to 5 for the Neulasta arm (average of 2).

2. INTRODUCTION

2.1 Overview

3.1.2. Class and Indication

Pegfilgrastim is a covalent conjugant of recombinant methionyl human granulocyte colony-stimulating factor (r-metHuG-CSF, filgrastim). To produce pegfilgrastim, a 20 kD monomethoxy polyethylene glycol (PEG) molecule is covalently bound to the N-terminal methionyl residue of filgrastim. Similar to endogenous G-CSF, pegfilgrastim selectively stimulates granulopoietic cells of the neutrophil lineage. It acts at all stages of neutrophil development, increasing the

proliferation and differentiation of neutrophils from committed progenitor cells. Pegfilgrastim also enhances the survival and function of mature neutrophils.

The current approved indications for pegfilgrastim in the Neulasta United States Prescribing Information (USPI) include:

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

Neulasta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

New indication proposed by the sponsor:

Neulasta® (pegfilgrastim)

(b)(4)

3.1.3. History of Program Development

Pegfilgrastim was approved in the United States in January 2002, and is indicated to decrease the incidence of infection, as presented by febrile neutropenia (FN), in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs that have been associated with a clinically significant incidence of FN.

On 5/23/05, there was a preIND meeting between FDA/Division of Biologic Products (DBOP) & NIAID-Amgen-U of MD for the treatment of individuals exposed to lethal TBI in the event of a nuclear terrorist attack is of paramount concern to health professionals. In that meeting,

- *NIAID outlined plan for a “pivotal” NHP & murine study*
- *Studies are intended to support g-CSF licensure under Animal Rule*

On 7/11/12, NIAID submitted the final study reports for AXG15: “A sixty-day efficacy study of subcutaneous filgrastim (Neupogen) to treat the hematopoietic syndrome of the acute radiation syndrome (ARS-HS) following a Lethal Dose (LD) 50/60 of total body irradiation (TBI) in rhesus macaques.” The results from the animal study AXG 15 is published in Farese et al, 2013, which demonstrated that filgrastim improves survival in a well-characterized NHP model of radiation-induced myelosuppression.

On 5/3/2013, Joint Meeting of the Medical Imaging Drugs Advisory Committee (MIDAC) and the Oncologic Drugs Advisory Committee (ODAC) discussed the results from the NHP study (Farese et al. 2013) and the published literature on use of the Leukocyte Growth Factors (LGFs). The committee concluded that filgrastim therapy is reasonably likely to produce clinical benefits in humans exposed to radiation that is likely to induce myelosuppression during or following a radiological/nuclear incident.

In 2014, NIAID study AXG-21 (Hankey 2014) showed survival advantage of Neulasta for ARS-HS. The title of AXG-21 is “A sixty-day efficacy study of subcutaneous pegfilgrastim (Neulasta®) to treat the hematopoietic syndrome of the Acute Radiation Syndrome (ARS-HS) following an LD50/60 of Total-body Irradiation (TBI) in rhesus macaques”.

In September 2014, Amgen submitted, in electronic Common Technical Document (eCTD) format, a supplemental Biologics License Application (sBLA) for the use of Neupogen® (filgrastim) for (b)(4)

Since human clinical trials cannot be ethically conducted to study treatment of myelosuppression from radiation exposure resulting in the hematopoietic syndrome of Acute Radiation Syndrome (HS-ARS). Neupogen was approved for treatment of adults and children with H-ARS on 3/30/2015.

In February 2015, Amgen submitted, in electronic Common Technical Document (eCTD) format, a supplemental Biologics License Application (sBLA) for the use of Neulasta® (pegfilgrastim) for the (b)(4)

. Since human clinical trials cannot be ethically conducted to study treatment of myelosuppression from radiation exposure resulting in the hematopoietic syndrome of Acute Radiation Syndrome (HS-ARS), approval is being sought using data from efficacy studies in well-characterized animal models.

3.1.4. Specific Studies Reviewed

There is no new clinical study included in this submission. The NHP studies explored in this review are all from previously submitted INDs and shown in the Table 1.

Pivotal study (AXG 21, Hankey et al. 2014) in (b)(4) is a sixty-day efficacy study of subcutaneous pegfilgrastim (Neulasta®) to treat the hematopoietic syndrome of the Acute Radiation Syndrome (ARS-HS) following an LD50/60 of Total-body Irradiation (TBI) in rhesus macaques

Farese et al. 2012 is a blinded four arm study of pegfilgrastim and filgrastim for improvement of neutrophil recovery after high-dose radiation-induced myelosuppression in rhesus macaques.

Only AXG 21 is considered as the pivotal study to support the proposed indication.

Farese et al. 2012 explored the effect of Neulasta on neutrophil recovery, with different administrations. The Neulasta arms with different administration schedule were compared with Neupogen and control arms. However, the sample sizes in the four arms in Farese et al. 2012 are small, and not powered to show the efficacy of Neulasta on survival benefit.

Table 1: List of studies explored in the review

Study number	Phase and Design	Treatment period	Follow-up period	# subjects per arm	Study population
AXG 21	Animal study Double blinded, randomized two arm study	Up to 60 days	60 days	23 for Neulasta arm and 23 for control arm	Non-human primate (NHP) with Total Body Irradiation (TBI)
Farese 2012	Animal study, blinded, four arm study	Up to 60 days	60 days	9 in pegfilgram with one injection, 9 in pegfilgrastim with two injection, 4 in filgrastim, 10 in control	Non-human primate (NHP) with Total Body Irradiation (TBI)

3.1.5. Major Statistical Issues

The sponsor submitted the data for the animal **study AXG 21 (the pivotal study)** in this submission. The reviewer could reproduce the primary analysis using the data.

Variables for efficacy evaluation included death indicator, time to death, ANC, time of ANC, duration of neutropenia, day of ANC recovery, febrile neutropenia, number of transfusions, etc and baseline information (including Group, id, gender, etc) were included in the submitted electronic data sets. The partial supportive care, safety, and partial baseline information (including source, dose, etc) were submitted in pdf files.

Data including information on supportive care within each subject (degree of support) was not available.

Farese et al. 2012 (one animal study for exploring the effect of Neulasta with different doses vs. control) was not powered to show the effect of Neulasta vs. control or Neupogen. The sample size is not enough for understanding the performance. Therefore, this study is exploratory.

Only one center is included in the key studies (University of Maryland (UM)). The variation from centers cannot be evaluated.

All animals were male in the key studies, so one cannot evaluate the drug performance on females.

In addition, there is no information on the delayed administration of the Neulasta after TBI (1st injection after Day 1).

2.2 Data Sources

The application reports are provided electronically. The full electronic path of the documents is \\CDSESUB1\evsprod\BLA125031\0230

The application study reports submitted by the sponsor include introduction, non-clinical overview, and clinical overview in M2.

There was no new study conducted in this submission. This application cross references some animal studies and human studies from different INDs. The study reports and data sets are located in M4 and M5.

The AXG 21 study (pivotal study) reports are provided by scanned pdf files of the hard copy submission at \\CDSESUB1\evsprod\BLA125031\0230\m4\42-stud-rep\. The sas data sets and key programs are located at \\CDSESUB1\evsprod\BLA125031\0230\m4\datasets.

The paper of Farese et al. 2012 can be found at RADIATION RESEARCH 178, 403--413 (2012)
The sas data sets for Farese et al. 2012 are located at <\\CDSESUB1\evsprod\BLA125031\0230\m4\datasets>.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The results from some main studies are obtained from other INDs and literature publications. The sponsor obtained the information from the authors of the studies. However, it is difficult to locate the data sets and files. Some files are available in good format, some are not (in excel sheets, and report tables in pdf files). Since the sponsor did not conduct those key animal studies, not all variables have the individual level data.

The following information requests related to data were conveyed to the sponsor during the review.

- Provide the define files for the data sets in Study AXG21, AXG15, Farese-2012 folders (included in M4).

The sponsor provided the define files based on the request.

- Provide a sas data including radiation dose information for each subject in Study AXG21 (with unique id).

From the sponsor, the individual radiation dose data is included in a report table (pdf file).

- Provide Age and transfusion information for each animal (included in sas data) if it is available. If the information is included the submitted data sets, please identify the location of the information.

From the sponsor, age information at animal level is not available. Individual transfusion information is provided in a sas data.

- Provide Data sets (sas data) for the Safety parameters (activity, hemorrhage, histopathology-- bone marrow, lung, liver, small intestine, large intestine) if they are available. If the information is included the submitted data sets, please identify the location of the information.

From the sponsor, the summary information were included in the appendix for the AXG-21 study report pdf file in the table format, which cannot be read directly into sas or other software.

3.2 Evaluation of Efficacy

Two studies on animals (Non-Human Primates) using Neulasta were reviewed by the reviewer. The study design and efficacy are summarized in Table 2.

Table 2: Summary of the study and efficacy in three NHP studies with Neupogen

	AXG 21	Farese et al. 2012
Design	Randomized, two arm, blinded, single center	Randomized, 4 arm, blinded, single center
Center	University of Maryland (UM)	UM
Radiation dose	LD50/60 Target dose 750cGy	LD10/30 with care (LD 70/30 without care) 600cGy (6Gy)
Treatment drug	Neulasta in trt arm Vehicle in control arm	2 pegfilgrastim groups 1 filgrastim group 1 vehicle control group
Dose and treatment period	Start on day 1 (20-26hr after TBI) and day 8 300-319 ug/gk/day	See *
Supportive care	Level 1 IV fluids, blood products, nutrition, antibiotics	Level 0 Antibiotics, blood and fluids as needed
Animals	Rhesus Macaques	Rhesus Macaques

Sample size	Actual (all male) 23 in control, 23 in treatment	All male 9 group1 (pegfilgrastim) 9 group2 (pegfilgrastim) 4 group3 (filgrastim) 10 group4 (control)
Interim analysis on mortality rate	Lan-Demets version of the O'Brien-Fleming boundary was met (p-value < 0.0107) Study Stopped 46 out of 78 animal were enrolled	no
Analysis on survival on Day 60	91% vs. 48% for trt vs. con P=0.0014 (pearson) P=0.0031 (exact) Primary analysis All males, no female information	Not available
Exploratory analyses		
Logrank test for the two survival curves	Nominal p=0.011	Not available
Hazard ratio (HR) from Cox model with treatment only	0.31 (0.028, 0.56) Neulasta vs. control	Not available
HR from Cox model with treatment and other variables	0.25 (0.015, 0.46) Neulasta vs. control	Not available
Other endpoints	Transfusion ANC 100 (<100/1000) ANC500 (<500/1000) ANC1000(<1000/1000) Duration from event to recovery Febrile neutropenia Animal activities	ANC and PLT related parameters Pegfilgrastim vs. control ANC nadir, duration of ANC<100, <500, time to recovery, all with p<0.01 (Bonferroni adjusted for the 3 comparison, Peg vs. con, Fil vs. con, Peg vs. Fil)

		Same for PLT related parameters No difference in transfusion
Conclusion	Neulasta is efficacious in improving survival for NHP with TBI	Neulasta is efficacious in improving neutrophil recovery in NHP. Administration of pegfilgrastim at day 1 and 7 was more effective than a single injection on day 1 after TBI.
Data	Available in sas data or pdf files. Not in standard format. Primary results verified by reviewer	Partial data available in excel format. No define files. Not in standard format

*group 1: single dose pegfilgrastim (300 ug/kg) on day 1 (n=9) two doses

Group 2: 2 doses of pegfilgrastim (300 ug/kg) on day 1 and 7 (n=9)

Group 3: filgrastim (10 ug/kg/d) n=4 until the absolute neutrophil count $\geq 1000/\mu\text{L}$ for 3 consecutive days

Group 4: control (n=10) with 0.1% autologous serum (AS) for 18 consecutive days

From Table 2, both Studies AXG 21 and Farese et al. 2012 show that Neulasta is efficacious in improving the recovery after TBI. However, Farese et al. 2012 had lower dose compared with the AXG 21 study, and it explored the effect of pegfilgrastim and filgrastim on the neutrophil recovery instead of survival with small sample sizes. In the following, we focus on some details of pivotal study AXG 21 (mainly on the study design and the primary analysis).

Efficacy evaluation of Study AXG 21 by the reviewer:

Study Design and Endpoints

Study AXG 21 was designed to determine whether Neulasta (Amgen, Thousand Oaks, CA) administered as 300-319 mcg/kg/d on SD 1 (20-28 hrs) and on SD 8 (between 0800 hr and 1200hr) following a lethal total-body irradiation (TBI) exposure to a 6 megavolt (MV) computerized linear accelerator (LINAC) photon source (at $750 \text{ cGy} \pm 15 \text{ cGy}$ which represent approximate LD50) and administered to effect based on absolute neutrophil count, will improve survival in Rhesus macaques receiving medical management compared to control animals receiving vehicle (Dextrose 5% in water) and medical management.

Following TBI, animals were administered SC injections of either the control article (Dextrose 5% in Water [D5W] at 0.031 ± 0.001 mL/kg/d) or Neulasta at 300-319 mcg/kg/d on SD 1 (20-28 hrs) and on SD 8 (between 0800 hr and 1200 hr). All animals were monitored for complete blood count (CBC), body weight (BW), core body temperature (CBT) and hydration status for 60 days. Animals received medical management consisting of intravenous (IV) fluids, antibiotics, blood transfusions, nutrition and other support as required.

The planned sample size was 78 animals, but the study was stopped at the interim analysis with 46 animals. Prior to irradiation, animals were randomized to either a control (n=23) or treated (n=23) cohort. On study day (SD) 0, rhesus macaques (n=6 to 10 per “Group”, and each “Group” received the irradiation in one day) were exposed to a TBI of 750 cGy delivered at 80 ± 10 xGy/min, using a 2 MV (average) photon beam from a clinical linear accelerator at 153 cm source to surface distance.

A specific set of criteria for **euthanasia** were applied by all veterinarians caring for the animals. Any NHP which was recumbent in the cage or had decreased or absent responsiveness to touch or experienced hemorrhage from the GI tract to be in excess of 20% of the estimated blood volume in any 24 hour period or it experienced unrelieved pain **was euthanized**. Any NHP which experienced any combination of the following observations such as respiratory distress, decreased food and water intake, reluctance to move for >2 hours, and severe dehydration classified an animal to **be euthanized**.

Animals survived to the end of the experiment (≥ 60 days) had necropsy (sacrificed for a pathologic examination).

Primary Endpoint:

Overall survival measured at 60-days post randomization (Specified in study protocol).

Secondary endpoints:

- Survival time of the decedents
- Cage side observations per day (morning and afternoon): activity, posture, stool consistency, vomit, hemorrhage, respiratory, alopecia.
- Hematopoietic recovery parameters:
 - ANC nadir
 - Duration of neutropenia ($ANC < 500/uL$ and $< 100/uL$),
 - Day of ANC recovery ($ANC > 500/uL$ and $1000/uL$)
 - Incidence of Febrile Neutropenia (FN) ($ANC < 500/uL$ and core body temperature $\geq 103F$)
 - Time to recovery to an $ANC > 500/mcL$ and $ANC > 1,000/mcL$ after the ANC nadir has occurred.
 - Duration of thrombocytopenia
 - Platelet-related parameters (day of PLT recovery)
 - Number of transfusions
 - Body weights and temperatures

Reviewer's comment:

*The focus of this review is on the primary endpoint.
The PLT is confounded with blood transfusion, and will not be evaluated in this review.*

Blinding

All personnel involved in the study except the statistician(s), Quality Assurance Unit personnel, archivist, and the Drug Managers (personnel preparing the TA or CA doses) were blinded until the end of the in-life phase of the study.

The veterinary pathologist was initially blinded to treatment arm (TA or CA) and provided a written histopathology analysis for each individual animal without correlation to treatment group. The veterinary pathologist was unblinded after this initial evaluation and then provided a written evaluation and conclusion based on treatment group.

Randomization

NHP were randomized in cohorts of six (6) to eight (8) to the target treatment arms prior to each irradiation. The study statistician created the randomization for NHP in each treatment arm. The code was provided to a designated unblinded member of the testing facility who was responsible for maintaining the randomization schedule and overseeing the dosing of NHP in accordance with their assigned treatment arm. Following experimental termination of the study, the randomization schedule was made available to the Study Director

Subject Disposition, Demographic and Baseline Characteristics

As shown in Tables 3 and 4, in this study, all animals are male. Most of the animals were from (b)(4). There are similar number of animals in control and Neulasta groups by cohort group (animals in one cohort received TBI in one day). Because of the small sample size, it will be difficult to investigate the effect of the group factors.

Table 3: Number of animals by gender and source in Neulasta and control arms

	Gender	Source	(b)(4)	
	Male			total
Control(D5W)	23	21	2	23
Neulasta	23	22	1	23

Table 4: Number of animals by cohort in Neulasta and control arms

cohort	control	Neulasta
1	3	3
2	4	4
3	5	3
4	3	5
5	4	4
6	4	4

There are some medical measures taken on Day 0 (the day of irradiation) for each animal (Table 5). The baseline measures are similar in the two groups.

There is no individual age information. From the study report, the age range for the animal at the time of irradiation was approximately 3-7 years.

The mean (std) for total irradiation dose is 744.5 cGy (19.6) for Neulasta group, and 739.3 cGy (20.2) for Control group. The range of the radiation dose is (710, 775) for Neulasta group and (696, 772) for the control group. Therefore, the irradiation doses are similar in Neulasta and control arms (slightly higher dose in Neulasta group).

Table 5: Baseline information for the Neulasta and control groups

Baseline variable	Treatment (pegfilgrastim) group		Control (D5W) group	
	Mean (std)	Range	Mean (std)	range
Temperature (in F)	102(1.1)	(99.5, 103.3)	102 (0.9)	(99.7, 103.5)
Weight in kg	6.2 (1)	(5.0, 7.9)	6.4 (1)	(4.6, 8.4)
Absolute neutrophil count (ANC)	2.6 (1.9)	(1, 8.7)	2.2 (1.2)	(0.8, 5.9)
Platelets (PLT)	321 (66.6)	(238, 442)	329 (63.1)	(218, 455)
White Blood Cell	7.7 (2.1)	(4.0, 11.9)	6.9 (2.2)	(2.8, 10.7)
Absolute lymphocyte count	4.8 (1.6)	(1.9, 8.3)	4.5 (1.7)	(1.5, 7.5)
Mononuclear cells	4.9 (1.6)	(1.9, 8.5)	4.6 (1.7)	(1.6, 7.6)
Red Blood Cell	5.2 (0.2)	(4.7, 5.7)	5.2 (0.4)	(4.6, 6.2)
Hemoglobin	12.4 (0.5)	(11.2, 13.1)	12.5 (0.8)	(11.4, 14.3)
Hematocrit	38 (1.2)	(35, 40)	39 (2.4)	(35, 44)
Segmented neutrophils	33 (16)	(14, 55)	32 (12)	(16, 55)
Lymphocytes	63 (16)	(26, 82)	65 (12)	(45, 82)

Statistical Methodologies

Primary analysis:

According to the sponsor, the primary analysis will be conducted on the ITT population using a Chi-square test of a two-tailed null hypothesis using an overall 5% significance level, to compare the overall survival measured at 60-days post randomization, i.e., mortality rate at 60 days between the treatment and the control groups

Reviewer's comment:

*Because of the small sample size, exact Chi-square test will also be used for evaluating the independence assumption in the 2*2 table in addition to chi-square test.*

Sample Size

A maximum sample size of 78 animals was proposed for this study. The sample size was based on a two group design (D5W and Neulasta) with 80% power to detect a 30% difference in 60-day survival (50% control, 80% treated) using a two-tailed 5% significance level.

Interim analysis:

Interim analyses for efficacy or futility on the basis of survival will be performed to determine if the study may be terminated early, prior to the experimental termination. Analyses will be conducted after the cohort associated with at least 60% of the animals has completed the in-life phase of the study by means of the following statistical analyses. Formal efficacy analyses will be based on the Lan-Demets version of the O'Brien-Fleming boundary to provide an overall two-sided $P = 0.05$ test.

Futility will be assessed informally based on conditional power. For example, termination due to futility may be considered if conditional power is very low (e.g., less than 0.10), under the assumption that the hypothesized treatment difference is correct. In addition, if the interim analysis indicates that the current study design needs significant modification, the study may be discontinued. The efficacy interim analyses will be performed on unblinded animal fate data.

Additional data that will be included in the interim analyses are: Kaplan-Meier survival curves and a log rank test comparing the survival curves, and mean, StDev, SEM, median, minimum, maximum, and range of survival time of decedents.

Reviewer's comments:

The sponsor conducted an interim analysis with 46 animals, and claimed that for an interim analysis with a fraction of 0.58 (a cohort of 46/78 animals) information, the spending alpha is 0.0107. Thus, analyses of the primary outcome are considered significant if the resulting p-value is less than 0.0107.

Efficacy results from AXG 21

Mortality comparison

The sponsor used the Chi-square test for evaluating the overall survival measured at 60-days post randomization as the primary analysis. At the interim analysis, a Chi-square test indicates there is

a significant association between mortality (survival) and treatment (p-value =0.0014<0.0107). Therefore, the sponsor terminated the study with 46 animals instead of 78 animals.

An exact chi-square test (non-parametric) is more conservative for evaluating the independence in the 2*2 table. And a two-sided p-value of 0.0031 (<0.0107) is obtained from the exact test.

There are 52% of death (48% survived) in Control group and 9% death (91% survived) in Neulasta group.

Table 6: Summary of count by treatment and outcome (Death or not on Day 60)

	Not death (survivor)	Death (euthanized)	Total
Control	11 (48%)	12	23
Neulasta	21 (91%)	2	23
Total	28	18	46

The following analyses are exploratory analyses. The results are consistent with NIH NIAID's findings.

Euthanized animals

There are 14 animals euthanized according to the pre-specified protocol (12 in control group, 2 in Neulasta group) within 60 days

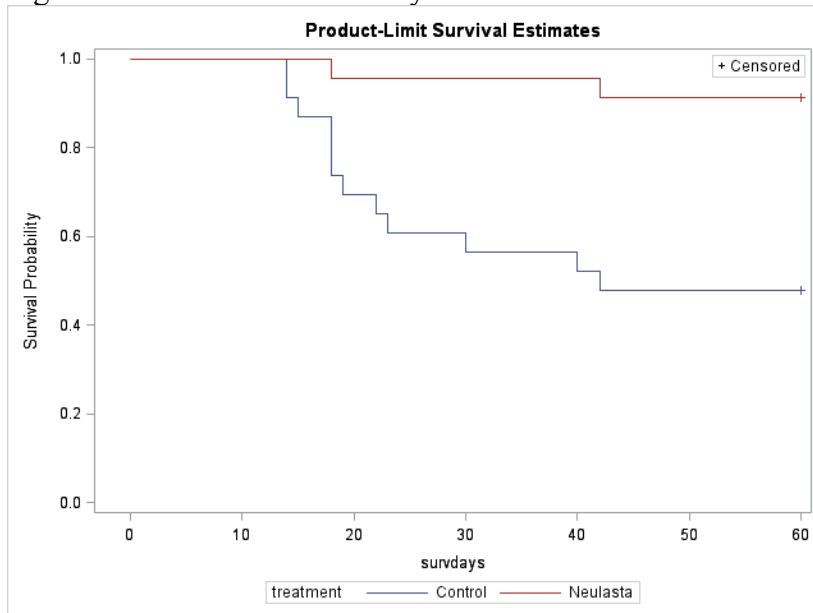
There are 32 (=46-14) euthanized with SD >60 for necropsy.

Survival analyses

First, we explored the survival pattern in the following figure (Figure 1). Kaplan Meier method (KM) is used to estimate the survival rates by treatment over time. No animal died before Day 14. After Day 14, two animals in Neulasta group were euthanized on Day 18 and Day 42, and twelve animals in control group were euthanized from Day 14 to Day 42.

Log-rank test for comparing the two survival curves resulted in a nominal p-value of 0.0011 in favor of Neulasta group. Median survival time is 42 day for the control group, and not estimable for the Neulasta group.

Figure 1: KM survival curves by treatment



Cox models with and without adjustment baseline information

Without adjusting for any baseline information, Cox model with only treatment has Hazard Ratio (HR) (Neulasta vs. Control) as 0.125 (95% CI as [0.028, 0.56]).

In Cox model with treatment, source, baseline weight, ANC, PLT, and temperature, the HR (Neulasta vs. Control) is 0.08 with 95% CI as (0.02, 0.46).

Recovery from events ANC<500/uL and ANC<1000/uL

The duration of ANC recovery is defined to be the time from events ANC <500/uL, or <1000/uL, to ANC $\geq$ 500/uL, or $\geq$ 1000/uL for three consecutive days.

For all the 46 animals, the Neulasta group had a higher rate of recovery from events ANC<500/uL and ANC<1000/uL, compared with the Control group.

During the 60 day study period, there are 13/23 (56.5%) of animals in control group and 22/23 (95.6%) animals in the Neulasta group recovered from ANC<500/uL and ANC<1000/uL.

Duration of recovery for recovered animals

The Neulasta group had shorter time to recovery from ANC<500/uL and ANC<1000/uL for the recovered animals (13 in control group and 22 in Neulasta group). The mean recovery duration was 18 days (95% CI as (14, 22)) in the Neulasta group vs. 23 days (95% CI as (17, 29)) in the Control group for ANC<500/uL; and 20 days (95% CI as (14, 27)) in the Neulasta group vs. 27 days (95% CI as (16, 39)) in the Control group for ANC<1000/uL.

Time to recovery from events ANC<500/uL and ANC<1000/uL

If one animal is not recovered from the event, we treat this animal as censored case with censoring time 60 day. Logrank test is used to test the difference of the two curves (one for treatment group and one for control group).

For time to recovery to ANC $\geq 1000/\mu\text{L}$, the median recovery time is 27 days for control group, and 18 days for Neulasta group. The logrank test had nominal p-value <0.001 for testing the difference of the two time to recovery curves.

For time to recovery to ANC $\geq 1000/\mu\text{L}$, the median recovery time is 35 days for control group, and 20 days for Neulasta group. The logrank test had nominal p-value <0.001 for testing the difference of the two time to recovery curves.

Febrile neutropenia (FN)

Febrile Neutropenia (FN), defined as an ANC $< 500/\text{mcL}$ concurrent with core body temperature (CBT) $\geq 103.0^\circ\text{F}$. Majority of the animals in both treatment groups (20/23) had FN during the 60 day study period. The occurrence of FN is not associated with the treatment

Transfusion

Animals could have transfusions several times during the study. Most of the observed volume values per transfusion are 54mL for the study animals. Two animals (both in control arm) had 81mL.

The number of transfusion ranges from 1 to 7 for the control arm (average of 3), and from 1 to 5 for the Neulasta arm (average of 2). The difference in the mean number of transfusions between the two cohorts was different (Wilcoxon rank sum, nominal $p = 0.0013$).

Efficacy conclusion from the sponsor:

From Study AXG 21, pegfilgrastim significantly improved survival (91% [21/23]) as compared to the controls (47.8% [11/23], $p = 0.0014$). Pegfilgrastim significantly decreased the duration of grade 3 and grade 4 neutropenia, improved the speed of recovery of ANC and increased neutrophil counts at the ANC nadir relative to the control group. Febrile neutropenia was the same in both treatment arms (87.0% [20/23]). Pegfilgrastim significantly reduced the mean percent of days on study that an animal experienced febrile neutropenia or required antibiotics.

3.3 Evaluation of Safety

There is no major safety issue for this product (For more details please see clinical review).

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Because of the small sample size (23 Neulasta + 23 Control) in the AXG 21 study, we did not evaluate the survival pattern by subgroups.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Statistical issues

The sponsor submitted the data for the animal **study AXG 21 (the pivotal study)** in this submission. The reviewer could reproduce the primary analysis using the data.

Variables for efficacy evaluation included death indicator, time to death, ANC, time of ANC, duration of neutropenia, day of ANC recovery, febrile neutropenia, number of transfusions, etc and baseline information (including Group, id, gender, etc) were included in the submitted electronic data sets. The partial supportive care, safety, and partial baseline information (including source, dose, etc) were submitted in pdf files.

Data including information on supportive care within each subject (degree of support) was not available.

Farese et al. 2012 (one animal study for exploring the effect of Neulasta with different doses vs. control) was not powered to show the effect of Neulasta vs. control or Neupogen. The sample size is not enough for understanding the performance. Therefore, this study is exploratory.

Only one center is included in the key studies (University of Maryland (UM)). The variation from centers cannot be evaluated.

All animals were male in the key studies, so one cannot evaluate the drug performance on females.

In addition, there is no information on the delayed administration of the Neulasta after TBI (1st injection after Day 1).

Collective evidence

The efficacy of filgrastim for the acute radiation setting was studied in a randomized, placebo-controlled NHP model of radiation injury (study AXG 21, Hankey et al, 2014) designed to demonstrate the ability of pegfilgrastim to improve survival of lethally irradiated rhesus macaques

As shown in AXG 21, Filgrastim significantly (p-value from exact chi-square test of 0.0031 < the alpha level allocated for the interim analysis 0.0107) reduced 60-day mortality in treated animals (9% [2/23]) as compared to the controls (52% [12/23]).

During the 60 day study period, there are 13/23 (56.5%) of animals in control group and 22/23 (95.6%) animals in the Neulasta group recovered from ANC<500/uL and ANC<1000/uL. The Neulasta group had shorter time to recovery from ANC<500/uL and ANC<1000/uL for the recovered animals (13 in control and 22 in Neulasta group). For time to recovery to ANC >=500/uL for all animals (median recovery time 27 days for control group, and 18 days for Neulasta group) and to ANC>=1000/uL for all animals (median recovery time 35 for control and

20 for Neulasta group), the logrank test had nominal p-value <0.001 for testing the difference of the two time to recovery curves (Neulasta vs. control).

The number of transfusion ranges from 1 to 7 for the control arm (average of 3), and from 1 to 5 for the Neulasta arm (average of 2).

The efficacy of pegfilgrastim on neutrophil recovery is also shown in another NHP study (Farese et al. 2012) with different administration time of the treatment product and radiation dose.

Extrapolation of animal dose to human dose

According to Pharmacometric review, simulations show that 6 mg dose of Neulasta might not be adequate to produce optimal benefit in humans exposed to radiation because it does not result in exposures exceeding the exposures associated with the NHP dose (300 mcg/kg) at which efficacy has been demonstrated (b)(4)

There is limited human safety experience with 18 mg dose level. There are only 4 subjects receiving 18 mg (300 mcg/kg) pegfilgrastim in study 970144 and 8 subjects with 18 mg (300 mcg/kg) pegfilgrastim in study 970230 in the submission. The information about both efficacy and safety for the administration of higher level dose of 18 mg is not enough for comment on its use. Therefore, considering the mechanism of action of pegfilgrastim and involving an inter-disciplinary discussion, the focus has shifted to the pharmacodynamic (PD) endpoint, absolute neutrophil count (ANC), as the target for dose selection. The PD response with the regimen used in the animal study is similar to the 6 mg human dose given twice one week apart.

The pharmacometric review team have found that the PK/PD relationship in pediatric appears to be consistent with that in adults. They proposed selecting a dose in pediatrics that produces similar PK to that of adults with 6 mg one week apart dosing regimen and recommended the dose for pediatric human population is 4 mg for 31-44 kg body weight; 2.5 mg for 21 – 30 kg; 1.5 mg for 10 - 20 kg; and 100 mcg per kg for those weighing less than 10 kg.

5.2 Conclusions and Recommendations

In conclusion (from the pivotal non-human primate study), Neulasta (administrated on day 1 and day 8 after irradiation) is shown to be efficacious in improving the 60-day survival of non-human primates having received a lethal total body irradiation (TBI). Neulasta is also effective in improving the recovery from events Absolute Neutrophil Count (ANC)<500/uL and ANC<1000/uL, in non-human primates having received lethal doses of TBI. According to the Clinical Pharmacology review, the recommended dose for adult is 6 mg human dose given twice one week apart; and for pediatric human population is 4 mg for 31-44 kg body weight; 2.5 mg for 21 – 30 kg; 1.5 mg for 10 - 20 kg; and 100 mcg per kg for those weighing less than 10 kg.

We recommend approval under the animal rule noting the following issues:

- The radiation doses in the studies may not reflect those in real situations. The radiation dose used in the pivotal animal study is LD 50/60 for the animals. The efficacy of Neulasta for other radiation doses is not clear from the information provided in this sBLA.
- Neulasta is shown to be efficacious when administering on day 1 and 8.

5.3 Labeling Recommendations

We recommend the following changes in Section 14.2 for revised indication of increase of survival in patients acutely exposed to myelosuppressive doses of radiation in the label.

The efficacy of Neulasta for the acute radiation syndrome setting was studied in a randomized, placebo-controlled non-human primate model of radiation injury. The planned sample size was 78 animals, but the study was stopped at the interim analysis with 46 animals because of efficacy. Rhesus macaques were randomized to either a control (n=23) or treated (n=23) cohort. On study day 0, animals (n = 6 to 8 per irradiation day) were exposed to total body irradiation (TBI) of 750 ± 15 cGy delivered at 80 ± 3.0 cGy/min, representing an LD50 dose after 60 days follow-up. Animals were administered subcutaneous injections of a blinded treatment (control article [5% dextrose in water] or pegfilgrastim [300-319 mcg/kg/day]) on study day 1 and on study day 8. The primary endpoint was survival at Day 60. Animals received medical management consisting of intravenous fluids, antibiotics, blood transfusions, nutrition and other support as required, according to pre-determined criteria for use.

Pegfilgrastim significantly (p-value from exact chi-square test of $0.0031 < \text{the alpha level}$ allocated for the interim analysis 0.0107) reduced 60-day mortality in the irradiated non-human primates: 91% survival rate (21/23) in the pegfilgrastim group compared to 48% survival rate (12/23) in the control group.

References

Farese AM, Cohen MV, Stead RB, Jackson III W, and MacVittie TJ. Pegfilgrastim administered in an abbreviated schedule significantly improved neutrophil recovery after high dose, radiation-induced myelosuppression in rhesus macaques. *Radiat Res.* 2012;178:403-413.

Kim G. Hankey, Ann M. Farese, Erica C. Blaauw, Allison M. Gibbs, Cassandra P. Smith, Barry P. Katz, Yan Tong, Karl L. Prado, and Thomas J. MacVittie (2015) Pegfilgrastim Improves Survival of Lethally Irradiated Nonhuman Primates. *Radiation Research*: June 2015, Vol. 183, No. 6, pp. 643-655.

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/s/

LAN HUANG
11/02/2015

JYOTI ZALKIKAR
11/02/2015
I concur with the primary statistical reviewer.

THOMAS E GWISE
11/03/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125031Orig1s180

CLINICAL PHARMACOLOGY REVIEW

CLINICAL PHARMACOLOGY REVIEW

BLA	125031
Supplement Number	180; SDN1137
Submission Date	February 13, 2015
Brand Name	Neulasta®
Generic Name	Pegfilgrastim
Pharmacometrics Reviewer	Lian Ma, Ph.D.
Pharmacometrics Team Leader	Nitin Mehrotra, Ph.D.
Clinical Pharmacology Team Leader	Gene Williams, Ph.D.
OCP Division	DCP-V and DPM
OND Division	ODEIV/DMIP
Sponsor	Amgen
Submission Type	Efficacy Supplement
Formulation; Strength(s)	6 mg/0.6 mL solution in a single use prefilled syringe for manual use only; or 6 mg/0.6 mL solution in a single prefilled syringe co-packaged with the On-body Injector for Neulasta
Proposed Indication	(b)(4)
Proposed Dosage and Administration	(b)(4)

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology, Division of Pharmacometrics (OCP/DPM) and Division of Clinical Pharmacology V (OCP/DCP-V) have reviewed this efficacy supplement for BLA 125031 for Neulasta® (pegfilgrastim) and found it acceptable for approval from a Clinical Pharmacology perspective.

Based on the totality of evidence from clinical and non-clinical data, and dose selection considerations from the animal rule guidance, the reviewers recommend approval of a dosing regimen of two 6 mg doses administered one-week apart in patients ≥ 45 kg for the proposed indication. In addition, the reviewers also recommend a weight-based dosing for patients weighing less than 45 kg (see table below). A 100 $\mu\text{g/kg}$ dose is recommended for patients weighing < 10 kg while a weight-tiered based dosing is recommended for patients weighing 10 to < 45 kg. This pediatric dosing regimen is proposed for both HS-ARS and the CIN (chemotherapy-induced neutropenia) indication.

Body Weight	Pegfilgrastim Dose
< 10 kg	100 $\mu\text{g/kg}$
10 - 20 kg	1.5 mg
21 - 30 kg	2.5 mg
31 - 44 kg	4 mg

1.2 Post-marketing Commitments/Requirements

None.

Signatures:

Lian Ma, Ph.D.

Reviewer

Division of Pharmacometrics

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Team Leader

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Gene Williams, Ph.D.

Team Leader

Division of Clinical Pharmacology V

Cc: DHP: CSO – **F Lutterodt**; MTL – **A Gorovets**, MO – **W Dickerson**
DCP-V: TL – **G Williams**; DD - **A Rahman**; DCP-4: TL – **K Bergman**; DPM:
Reviewer – **L Ma**; PMTL – **N Mehrotra**; DD – **V Sinha**

1.3 Summary of Clinical Pharmacology Findings

Pegfilgrastim is a covalent conjugate of recombinant methionyl human G-CSF (filgrastim) and monomethoxy polyethylene glycol (PEG). Similar to endogenous G-CSF, pegfilgrastim selectively stimulates granulopoietic cells of the neutrophil lineage. It acts at all stages of neutrophil development, increasing the proliferation and differentiation of neutrophils from committed progenitor cells. Pegfilgrastim also enhances the survival and function of mature neutrophils.

Neulasta® (pegfilgrastim) was approved in the United States in January 2002, indicated to decrease the incidence of infection, as presented by febrile neutropenia (FN), in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs.

(b)(4)

The current submission is an efficacy supplement for Neulasta®

(b)(4)

Since human clinical trials cannot be ethically conducted to study treatment of myelosuppression from radiation exposure resulting in the HS-ARS, approval is being sought using data from efficacy studies in animal models (21 CFR 601.90). The pivotal efficacy study was a GLP-compliant study designed to demonstrate the ability of pegfilgrastim to improve survival of lethally irradiated non-human primates (NHP) in a previously validated radiation plus medical management model. Pegfilgrastim (two doses of 300 µg/kg given one week apart) significantly improved survival (91.3% [21/23]) as compared to the controls (47.8% [11/23], $p = 0.0014$).

Based on the totality of the evidence, the 6 mg one-week apart dosing regimen is recommended for patients weighing ≥ 45 kg as it is expected to be an appropriate choice to ensure an acceptable benefit/risk profile.

According to the dose selection considerations from the “Animal Rule”, because of the uncertainty associated with extrapolating animal efficacy data to humans, human dose should provide exposures that exceed those observed in animal efficacy studies with fully effective dose. Upon FDA’s request, pharmacokinetic (PK) simulations were conducted by the sponsor that indicated that 6 mg dose may not be adequate to produce optimal benefit in humans exposed to radiation because it did not exceed the exposures associated with the effective dose (300 µg/kg) evaluated in NHPs. Based on the simulation results, even a higher dose (18 mg) would not fully exceed the exposures observed in the NHP studies. In addition, there is limited safety experience with 18 mg dose level in adults. Upon carefully considering the mechanism of action of pegfilgrastim and discussion with the clinical and non-clinical review team, it was decided to focus on the pharmacodynamic (PD) endpoint, absolute neutrophil count (ANC), as the target for dose selection.

1. From a benefit perspective, the reviewers’ independent simulation results indicate that the 18 mg dose and 6 mg one-week apart regimen will likely lead to faster ANC recovery post-nadir (b)(4) For the clinically relevant ANC endpoints (duration of grade 3 neutropenia, duration

of grade 4 neutropenia, etc.)

(b)(4)

2. From a safety perspective, the 6 mg dose is considered safe in both adult patients and healthy subjects since it has been approved for clinical use in cancer patients for more than 10 years. However, as stated earlier, there is only limited clinical experience with the 18 mg dose of pegfilgrastim, and the 18 mg dose maybe associated with potential risk of leukocytosis in relatively healthy subjects, according to the clinical review team.

Given the PK/PD relationship in pediatric appears consistent with that in adults, the proposed weight-tiered based dosing in pediatrics for HS-ARS is based on selecting a dose in pediatrics that produces similar PK to that of adults with 6 mg one week apart dosing regimen.

In addition, this weight-tiered based dosing regimen is also proposed for the CIN indication. For CIN indication, observed pediatric PK data is available at 100 µg/kg dose. Based on pharmacokinetic simulations, it was seen that the exposures achieved with the weight-tiered based dosing are similar to those of 100 µg/kg dose in pediatrics.

2 Question Based Review

2.1 *What are the proposed dosage(s) and route(s) of administration?*

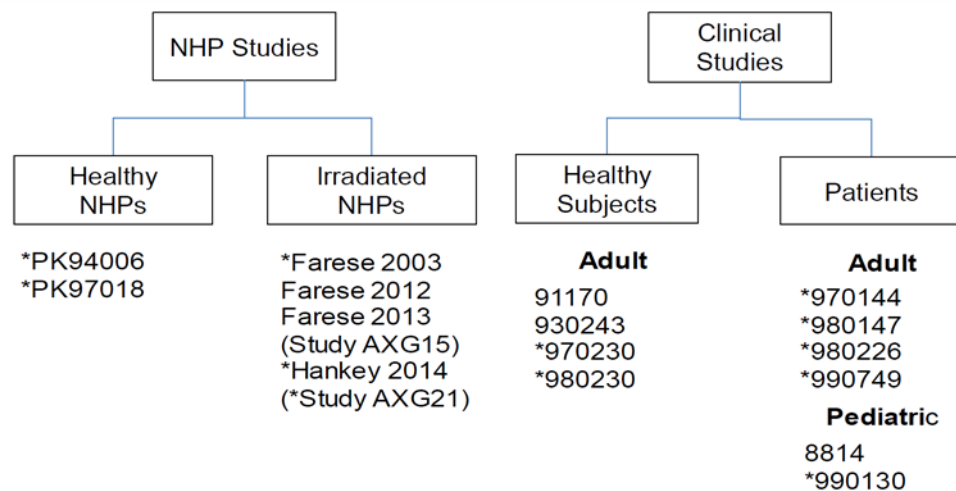
The sponsor proposes a dosing regimen of

(b)(4)

2.2 *What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?*

For ethical and feasibility reasons, no clinical efficacy studies of pegfilgrastim were conducted. Approval of this indication is to be based on efficacy studies conducted in animals. Data from 4 non-clinical studies in nonhuman primates (NHPs) and 7 clinical studies of filgrastim and/or pegfilgrastim in approved indications are used to support this proposed ARS indication. Summary of these studies are shown in Figure 1 and Table 1.

Figure 1. Filgrastim and Pegfilgrastim studies in nonhuman primates and humans



* = pegfilgrastim studies; NHP = non-human primate

(Source: sponsor's Summary of Clinical Pharmacology, Figure 1)

Table 1. Filgrastim and Pegfilgrastim Studies in Nonhuman Primates and Humans

Study	G-CSF	Regimen	Radiation (cGy)	No. of Subjects	Subject	Data
Non-Clinical Studies in NHPs						
PK94006	Peg-F	10 & 300 mcg/kg IV/SC, SD	NA	12	Healthy NHPs	PK, ANC
PK97018	Fil	10, 100 µg/kg SC QD	NA	7	Healthy NHPs	PK, ANC
	Peg-F	100, 300 and 1000 µg/kg SC QD	NA	9		
Farese et al. 2012b	Fil	10 µg/kg SC QD	600	11	Irradiated NHPs	PK (2), ANC(9)
	Peg-F	300 µg/kg SC SD/MD	600 or none	3 (none); 2 (600cGy)		PK
	Fil	10 µg/kg SC QD	750	9 (600cGy)		ANC
AXG21	Peg-F	300 mcg/kg SD/MD	750	23	Irradiated NHPs	ANC, OS
Clinical studies in Healthy Volunteers						
Study	G-CSF	Regimen	Route	No. of Subjects	Time Point (PK)	Sampling Duration

						(PD)
980230	Fil	5 µg/kg QD	SC	8	Intensive	14 days
	Peg-F	30 µg/kg SD	IV	6		
		60 µg/kg SD		8		
		30 µg/kg SD	SC	8		
		60 µg/kg SD		8		
970243	Fil	375 µg SD	SC	16	Intensive	72 hours
		750 µg SD		16		
		375 µg SD	IV	16		
		750 µg SD		16		
Clinical studies in Adults with Chemotherapy						
Study	G-CSF	Regimen	Type of Patients	No. of Patients	Time Point (PK)	Sampling Duration (PD)
970144	Fil	5 µg/kg QD	NSCLC	4	Intensive (Cycle 1 and Cycle 2)	36 days
	Peg-F	30 µg/kg Day 0, 16		3		
		100 µg/kg Day 0, 16		3		
		300 µg/kg Day 0, 16		4		
		60 µg/kg Q3W		7	Intensive	84 days
		100 µg/kg Q3W		3		
980147	Fil	5 µg/kg QD	Breast Cancer	25	Intensive	84 days
	Peg-F	30 µg/kg Q3W		18		
		60 µg/kg Q3W		59		
		100 µg/kg Q3W		44		
980226	Fil	5 µg/kg QD	Breast Cancer	149	Sparse (pre and day 7)	84 days
	Peg-F	100 µg/kg Q3W		147		
990749	Fil	5 µg/kg QD	Breast Cancer	76	Intensive 21 days	84 days
	Peg-F	6000 µg Q3W		76		
Clinical studies in Pediatric with Chemotherapy						
990130	Fil	5 µg/kg QD (4 cycles)	Sarcoma	6	Intensive (Cycle 1 and Cycle 3)	72 days
	Peg-F	100 µg/kg SD (4 cycles)		38		

PK: Pharmacokinetics; ANC: Absolute Neutrophil Counts; OS: Overall Survival; NSCLC: Non-small cell lung cancer

The pivotal efficacy study was a GLP-compliant study designed to demonstrate the ability of pegfilgrastim to improve survival of lethally irradiated non-human primates

(NHP) in a previously validated radiation plus medical management model. Pegfilgrastim (two doses of 300 µg/kg given one week apart) significantly improved survival (91.3% [21/23]) as compared to the controls (47.8% [11/23], Chi-square test, $p = 0.0014$). The duration of grade 3 and grade 4 neutropenia were significantly decreased, the speed of recovery of ANC was improved, and neutrophil counts were increased at the ANC nadir in the pegfilgrastim group compared to the control group. For more details on the pivotal non-clinical study, please refer to non-clinical review by Dr. Yanli Ouyang in DAARTs dated 10/21/2015.

2.3 Is the proposed dose (b)(4) adequate to produce clinical benefit in humans acutely exposed to myelosuppressive doses of radiation? Should an alternative dosing regimen be approved?

No, considering the totality of evidence and considerations of dose selection when extrapolating animal efficacy data to humans, the reviewers recommend approval of a (b)(4) two 6 mg doses administered one week apart for patients weighing ≥ 45 kg, as it is expected to be an appropriate choice to ensure an acceptable benefit/risk profile:

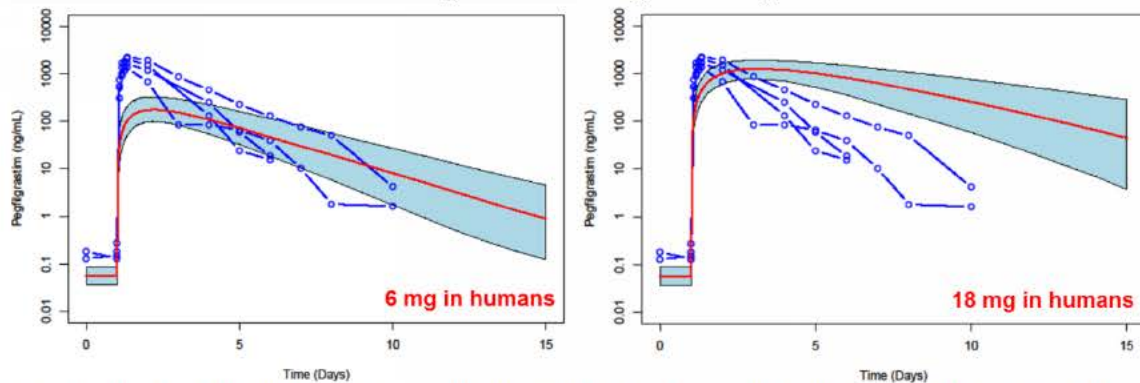
- 1 From a benefit perspective, the reviewers' independent simulation results indicate that 6 mg one-week apart regimen is likely to expedite ANC recovery (b)(4). Furthermore, in general, for the clinically relevant ANC endpoints (duration of grade 3 neutropenia, duration of grade 4 neutropenia, etc.) (b)(4).
- 2 From a safety perspective, the safety profile of 6 mg pegfilgrastim has been well characterized in the approved patient population through its clinical development program and more than 10 years of post-marketing experience.

Animal Rule Perspective

According to the dose selection considerations from the "Animal Rule", because of the uncertainty associated with extrapolating animal efficacy data to humans, human dose should provide exposures that exceed those observed in animal efficacy studies with fully effective dose.

The PK information of pegfilgrastim is not available in patients with the proposed indication. Upon FDA's request, the sponsor conducted simulations using their population PK model to predict the PK profiles in adult patients exposed to radiation. As shown in **Figure 2**, the results indicate that 6 mg dose may not be adequate to produce optimal benefit in humans exposed to radiation because it did not exceed the exposures associated with the effective dose (300 µg/kg) in NHPs. Based on the simulation results, even a higher dose (18 mg) would not fully exceed the exposures observed in the NHP studies.

Figure 2. Observed (open circles) pegfilgrastim serum concentrations in NHPs at a single dose of 300 µg/kg versus simulated (shaded area) pegfilgrastim serum concentrations in adults at a single dose of 6mg or 18 mg



Key: Predicted pegfilgrastim serum concentrations in humans exposed to radiation - red line: mean; blue shaded region: 90% prediction interval.

(Source: Sponsor's Response to 30 March 2015 FDA Information Request, Figure 1)

In addition, there is limited clinical experience with the 18 mg dose level of pegfilgrastim, and the 18 mg dose maybe associated with potential risk of leukocytosis in relatively healthy subjects, according to the clinical review team. Upon carefully considering the mechanism of action of pegfilgrastim and discussion with the Clinical and Non-Clinical review team, it was decided to focus on the PD endpoint, ANC, as the target for dose selection. Furthermore, it was contemplated that the approval of doses higher than 6 mg is an unlikely option because of lack of safety experience and focus should be to evaluate

(b)(4)

Dose Justification with ANC as the Target Pharmacodynamic Biomarker

The sponsor developed a comprehensive population model that integrated the ANC and overall survival (OS) data for NHPs treated with pegfilgrastim, as well as the PK and ANC data from adult and pediatric patients, and some data from healthy subjects receiving pegfilgrastim. A summary of the included data is shown in **Table 1**. Using the developed model, simulations were conducted with multiple scenarios to predict the effect of radiation exposure and pegfilgrastim treatment on ANC profiles and OS in humans.

Results of these simulations suggest that doses higher than 6 mg or different dosing frequencies are unlikely to increase the 60-day survival rate.

(b)(4)

(b)(4) The main driver of the predicted survival benefit is assumed to be whole time-course of ANC profile. Based on discussion with the clinical review team, the duration of grade 3/4 neutropenia is considered to be the most relevant endpoint for clinical efficacy evaluation. In addition, it should be noted that there is only limited information of the higher dose (4 NSCLC patients at 300 µg/kg dose from study 970144).

The reviewer made minor modifications to sponsor's PK/PD model, to make the prediction consistent with the observed data of pegfilgrastim treatment and placebo in the

non-clinical study (see section 4 for more details). Using the revised PK/PD model, the reviewer further conducted independent simulations on several scenarios in ARS patients,

(b)(4)

However, the results indicate that a more frequent regimen of two 6 mg doses one-week apart is likely to expedite ANC recovery post-nadir

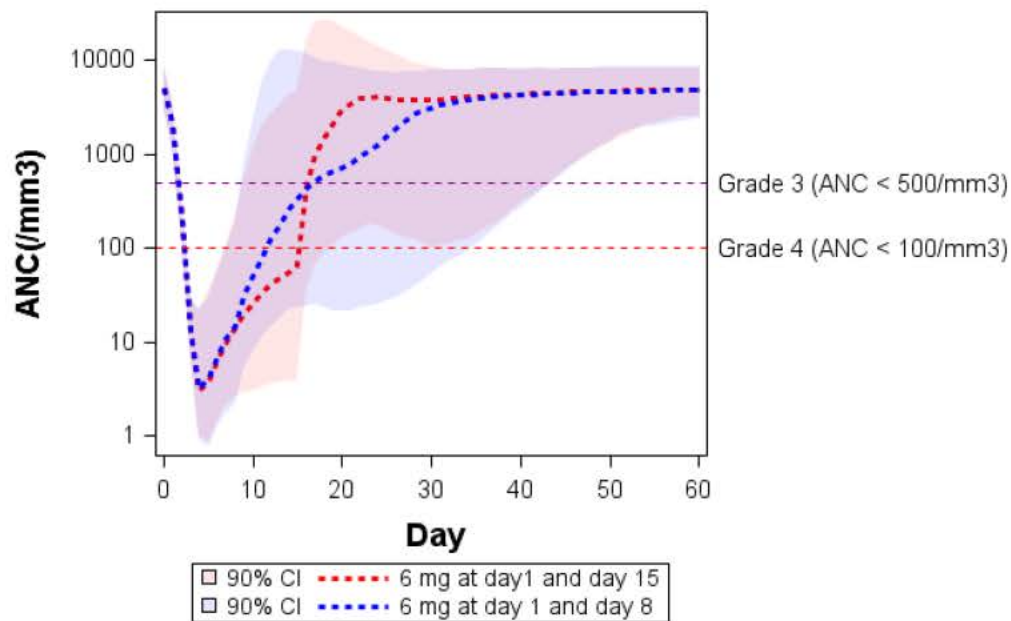
(b)(4)

(b)(4)

(b)(4)

(Figure 3). Summary statistics of the clinically relevant ANC endpoints, duration of grade 3 neutropenia, and duration of grade 4 neutropenia are derived from the simulation results and presented in Figure 4. The results indicate that while duration of grade 3 neutropenia are similar, higher proportion of patients are expected to have shorter duration of grade 4 neutropenia with one week apart dosing regimen.

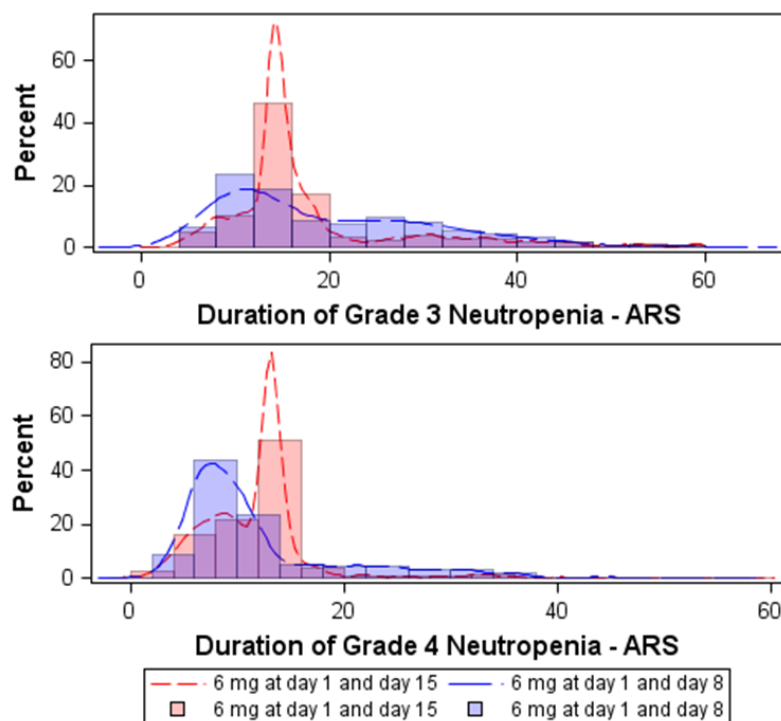
Figure 3. Comparison of simulated ANC profiles following two dosing regimens: two 6 mg doses given 2-weeks apart (red) and two 6 mg doses given one-week apart (blue), in adults patients (≥ 45 kg) exposed to LD50 radiation dose (3 Gy at 1 Gy/hr)



Sensitivity analyses were further conducted to simulate scenarios with varying radiation levels (1 Gy – 7 Gy), and varying starting time of the first dose (day 2 to day 4). The results support that, in general, one week apart dosing regimen performs similar or better relative to 2 week apart dosing regimen for clinically relevant ANC parameters (duration of grade 3 neutropenia, duration of grade 4 neutropenia). See section 4.2 (Reviewer's analysis) for detailed results.

With the predicted benefit in efficacy in terms of ANC and well-established safety profile, the overall results support that 6 mg given at day 1 and day 8 would be the preferable regimen for the ARS patients weighing ≥ 45 kg.

Figure 4. Distribution of Duration of Grade 3 Neutropenia and Duration of Grade 4 Neutropenia based on simulated ANC profiles following two dosing regimens: two 6 mg doses given 2-weeks apart (red) and two 6 mg doses given one-week apart (blue), in adults patients (≥ 45 kg) exposed to LD50 radiation dose



2.4 What dosing regimen should be recommended for patients weighing < 45 kg?

We propose a weight-tiered dosing for patients weighing less than 45 kg (**Table 2**). A dose of 100 $\mu\text{g/kg}$ is proposed for patients weighing < 10 kg while a fixed dosing regimen for different weight tiers is proposed for patients between 10 and 45 kg. The proposed weight-tiered based dosing in pediatrics is selected based on similarity of PK to those of adults with 6 mg one week apart dosing regimen. In addition, the exposures achieved with this weight-tiered based dosing regimen are similar to that observed with the 100 $\mu\text{g/kg}$ dose in pediatrics, a dose that has been studied in sarcoma pediatric patients. This weight tiered based pediatric dosing regimen is therefore proposed for both, HS-ARS and the CIN indication.

Table 2. Proposed weight-tiered dosing for patients weighing less than 45 kg

Body Weight	Pegfilgrastim Dose
< 10 kg	100 $\mu\text{g/kg}$
10 - 20 kg	1.5 mg
21 - 30 kg	2.5 mg
31 - 44 kg	4 mg

(b)(4)

in evaluating the use of pegfilgrastim for the ARS indication, the review team considers it essential from a public health standpoint to provide information on its use in the pediatric population. (b)(4)

Given there is only one strength (6 mg/0.6 mL solution) in the currently available presentations of Neulasta, the 100 µg/kg dose for children (<45 kg) may cause potential difficulty in emergency situations. For convenience in administration, the reviewers proposed a simplified body weight-tiered dosing and conducted independent simulations. Since the PK/PD relationship of pegfilgrastim in pediatrics appear to be consistent with that in adults, the simulation results support the recommended dosing by demonstrating that:

1. The exposure in pediatrics with the weight-tiered dosing are similar to that in adults with 6 mg one week apart dosing regimen.
2. The exposure in pediatrics with the weight-tiered dosing are similar to that with the 100 µg/kg dose in pediatrics.

The simulated PK time-profiles following the proposed weight-tiered dosing in pediatrics patients (2 to < 45 kg) are overlaid with those in adults patients (≥ 45 kg) following the two 6 mg doses 1-week apart dose. As shown in **Figure 5**, the profiles are generally overlapping. Based on the simulated profiles, AUC and $C_{\max}$ were also derived and compared to those in adults patients. The results show that for both exposure metrics', more than 90% of pediatric patients receiving the weight-tiered dosing are associated with exposure within the 90% CI of exposure range in adult patients (**Figure 6**). To propose a consistent and simpler dosing strategy, a simulation with fixed dosing in pediatrics < 10 kg was also conducted. But, it was not considered optimal due to potential of overshooting of AUC and $C_{\max}$ in very low weight pediatrics and potential of under-dosing pediatrics with higher body weight in the 2-10 kg weight group. Therefore, a 100 µg/kg dose is proposed for 2-10 kg pediatric patients.

Similar simulations were further performed to compare the weight-tiered dosing and 100 µg/kg dosing regimen. The results show comparable PK exposures in pediatric patients with these two regimens supporting the recommended weight-tiered based dosing for CIN patients (**Figure 7** and **Figure 8**).

Figure 5. Simulated PK profiles following the body weight-tiered dosing (two doses 1-week apart) in pediatric patients (2 to < 45kg), compared to those following two 6 mg doses 1-week apart dose in adults patients (≥ 45 kg), after exposure to a LD50 radiation dose

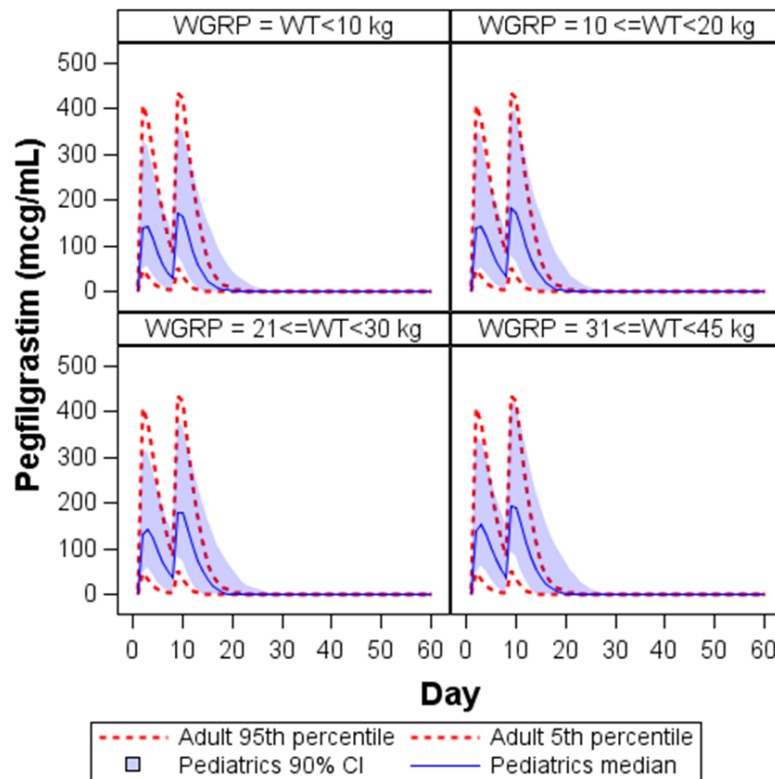
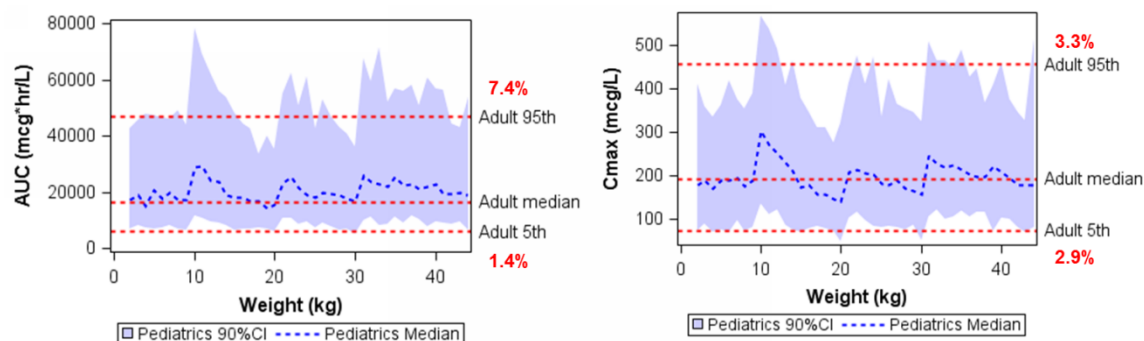


Figure 6. Simulated AUC and Cmax of pegfilgrastim following the body weight-tiered dosing (two doses 1-week apart) in pediatric patients (2 to < 45 kg), compared to that following two 6 mg doses 1-week apart dose in adults patients (≥ 45 kg), after exposure to a LD50 radiation dose



Note: the red numbers represent percentage of pediatric subjects with exposure above the 95th and below the 5th percentile of adult exposure.

Figure 7. Simulated PK profiles following the body weight-tiered dosing (two doses 1-week apart), compared to that following two 100 µg/kg doses 1-week apart dose in pediatric patients (2 to < 45 kg), after exposed to a LD50 radiation dose

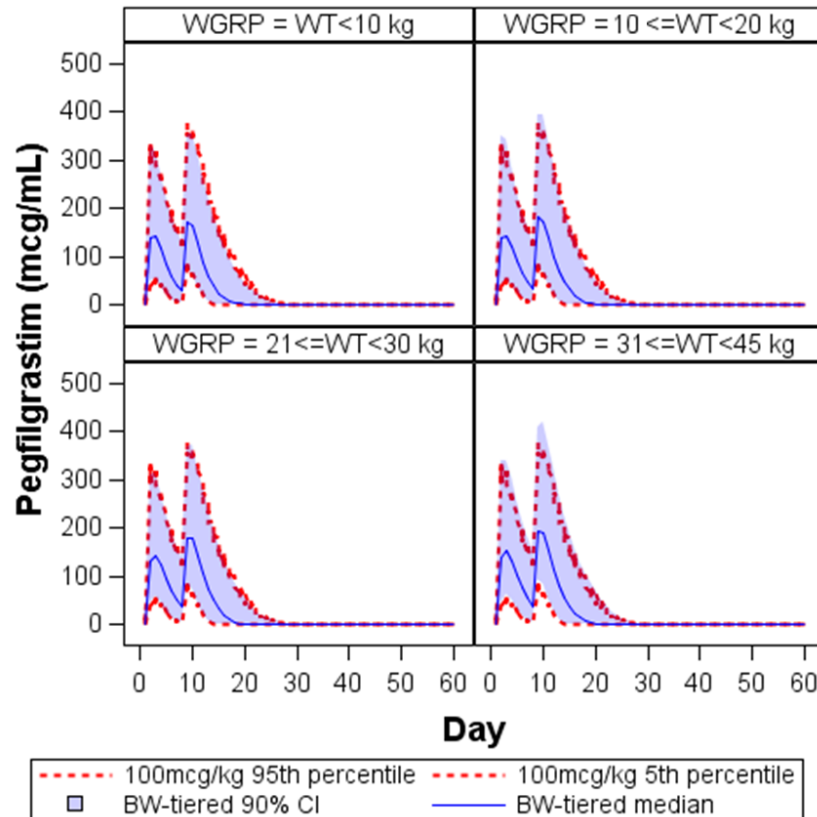
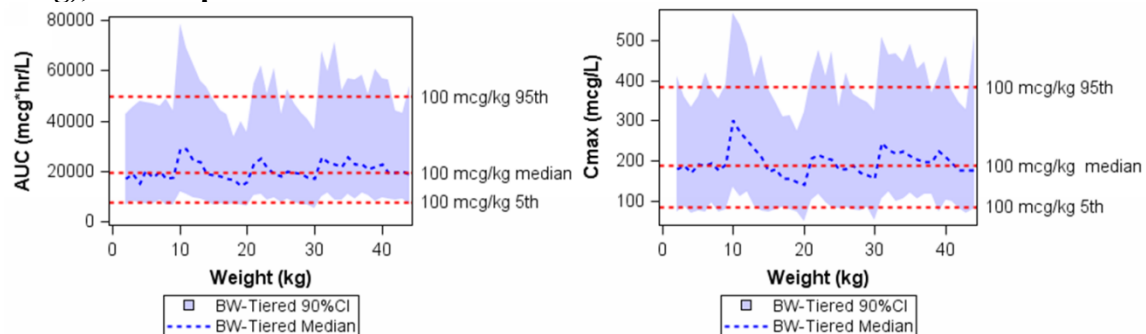


Figure 8. Simulated AUC and Cmax of pegfilgrastim following the body-weight tiered dosing (two doses 1-week apart) in pediatric patients (2 to < 45 kg), compared to that following two 100 µg/kg doses 1-week apart dose in pediatric patients (2-45kg), after exposed to a LD50 radiation dose



3 Labeling Recommendations

Below are the labeling recommendations pertaining to the current indication:

Section 2 (Dosage and Administration)

2.2 Patients with Hematopoietic Syndrome of Acute Radiation Syndrome

The recommended dose of Neulasta is 6 mg administered subcutaneously as two doses one week apart. Administer the first dose as soon as possible after suspected or confirmed exposure to radiation levels greater than 2 gray (Gy). Administer the second dose one week after the first dose.

2.3 Administration

Neulasta is administered subcutaneously via a single prefilled syringe for manual use or for use with the On-body Injector for Neulasta which is co-packaged with a single prefilled syringe.

Patients weighing less than 45 kg

Do not use the prefilled syringe for direct administration of Neulasta in patients weighing less than 45 kg. The Neulasta prefilled syringe is not designed to allow for direct administration of doses less than 6 mg. For dosing in < 45 kg patients, refer to Table 1.

Table 1. Dosing for patients weighing less than 45 kg

Body Weight	Pegfilgrastim Dose
< 10 kg	100 µg/kg
10 - 20 kg	1.5 mg
21 - 30 kg	2.5 mg
31 - 44 kg	4 mg

Section 8.4 (pediatrics)

The use of Neulasta to increase survival in pediatric patients acutely exposed to myelosuppressive doses of radiation is based on efficacy studies conducted in animals and clinical data supporting the use of Neulasta in patients with cancer receiving myelosuppressive chemotherapy. Efficacy studies of Neulasta could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Results from population modeling and simulation indicate that two doses of Neulasta administered one week apart provide pediatric patients with exposures comparable to that in adults receiving two 6 mg doses one week apart [see *Dosage and Administration* (2.3), *Clinical Pharmacology* (12.3) and *Clinical Studies* (14.2)].

Section 12.3 (Pharmacokinetics)

Patients Acutely Exposed to Myelosuppressive Doses of Radiation

The pharmacokinetics of pegfilgrastim is not available in patients acutely exposed to myelosuppressive doses of radiation. Based on limited pharmacokinetic data in irradiated non-human primates, the area under the concentration-time curve (AUC), reflecting the exposure to pegfilgrastim in non-human primates following a 300 mcg/kg dose of Neulasta, appears to be greater than in adults receiving a 6 mg dose.

Results from population modeling and simulation indicate that two doses of Neulasta administered one week apart in adults results in clinically relevant effects of duration of grade 3 and 4 neutropenia. In addition, the proposed weight based dosing in pediatrics [*see Dosing and Administration, Section 2.3, Table 1*] provide pediatric patients with exposures that are comparable to that in adults receiving two 6 mg doses one week apart.

Section 14.2

Efficacy studies of Neulasta could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Approval of this indication was based on efficacy studies conducted in animals and data supporting Neulasta's effect on severe neutropenia in patients with cancer receiving myelosuppressive chemotherapy [*see Dosage and Administration (2.1)*].

The dosing regimen with two 6 mg doses one week apart is selected for humans exposed to myelosuppressive doses of radiation because the exposure associated with such a dose is expected to provide sufficient pharmacodynamic activity based upon population modeling and simulation [*see Clinical Pharmacology (12)*]. The safety of Neulasta at a dose of 6 mg has been assessed on the basis of clinical experience in patients with cancer receiving myelosuppressive chemotherapy.

4 Appendices

4.1 Sponsor's analysis

The objectives of the sponsor's population modeling were as follows:

- Characterize the granulopoietic system in NHPs and in adult and pediatric patients in response to chemotherapy and treatment (in humans) and radiation (in NHPs) using a mechanism-based PK-PD model.
- Quantify the relationship between ANC profiles and OS after pegfilgrastim administration in NHPs in the HS-ARS setting.
- Predict the effect of radiation exposure and pegfilgrastim treatment on ANC profiles and OS in humans (adults and pediatric patients) in the HS-ARS setting.

A schematic representation of the structural PK/PD model describing the injury due to chemotherapy/radiation and response to pegfilgrastim treatment on the granulopoiesis system is shown in **Figure 9**. The structural model consisted of 4 main components: a) an ANC dynamics component, b) a filgrastim and pegfilgrastim component, c) a chemotherapy/radiation component; d) a corticoid component. The structural components of granulopoiesis described in **Figure 9** are the same for NHPs and humans. In the bone marrow, progenitor stem cells (SM) are produced at a nominal rate (k_p), and these progenitor cells mature into mitotic cells (MT) at a rate (k_{tr}). This same rate (k_{tr}) describes the maturation of mitotic cells through precursor compartments (PM1 and PM2) and the rate in which ANC becomes systemically observable. The granulopoiesis model used here tracks the turnover of neutrophils in terms of the target receptor (G-CSFR) by assuming that the number of receptors per cell is constant through the different stages of granulocyte production and maturation. The total receptors concentrations (R_{tot}) in the systemic circulation are proportional to the measured ANC values through the parameter SR. The effects of different interventions, are accounted for by either removing cells from the system due to the killing effects of radiation (**Figure 10**) or chemotherapy (Figure 9) or stimulating the rate of production and maturation through the stimulatory functions S1 and S2 as seen with G-CSF and corticosteroid treatment.

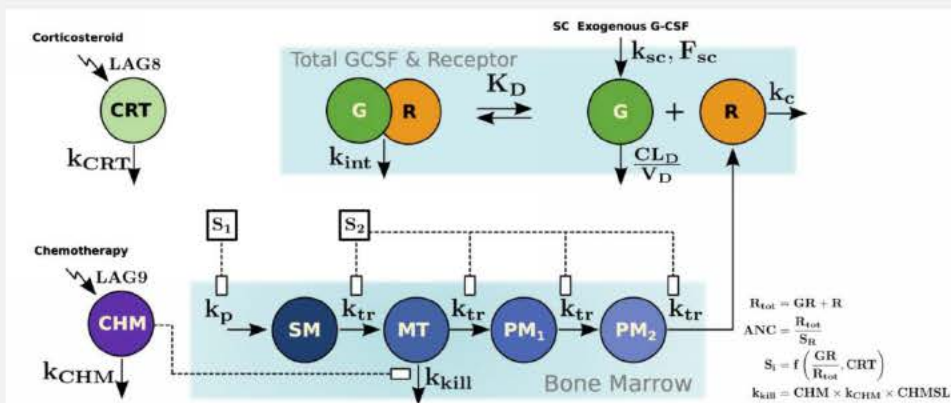
Data originated from 7 clinical studies and 4 non-clinical NHPs studies was utilized in the model development (Table 1). The final estimates of the Healthy Volunteer and Adult Patient (First Chemotherapy Cycle) are presented in **Table 3**.

The overall survival was best described by a time-to-event model with a time-varying hazard, which was driven by the ANC time-course data through an effect compartment (ANCe). With this parameterization, at steady-state ANCe equals the observed baseline ANC. Before modeling the survival data, the observed ANCe values were transformed by Box-Cox transformation to ensure normal distribution.

To project the effects of HS-ARS in humans and the potential benefits of pegfilgrastim treatment, the PK/ANC model shown in **Figure 10** was used. This model is structurally similar to that used to model the NHP HS-ARS data; however, it has been parameterized to represent HS-ARS in humans. Granulopoietic homeostasis and regulation by G-CSF as

well as the parameters controlling the disposition of G-CSF were assumed to be independent of injury (chemotherapy vs radiation). Consequently, the parameters associated with these processes (green region of **Figure 10**) were fixed to the estimates derived from analyzing the human healthy and CIN (adult and pediatric) patient data. Parameters characterizing the impact of HS-ARS on granulopoiesis and the relationship between ANC levels and overall survival (orange regions of **Figure 10**) were scaled from NHPs. Consequently, model scaling was accomplished by modifying only the radiation effect parameters, and keeping the λ_{ANC} , λ_{BC} , and $ke0$ as estimated from NHP.

Figure 9. ANC Response model structure describing the relationship between pegfilgrastim exposure and neutrophil turnover in the presence of chemotherapy and corticosteroids

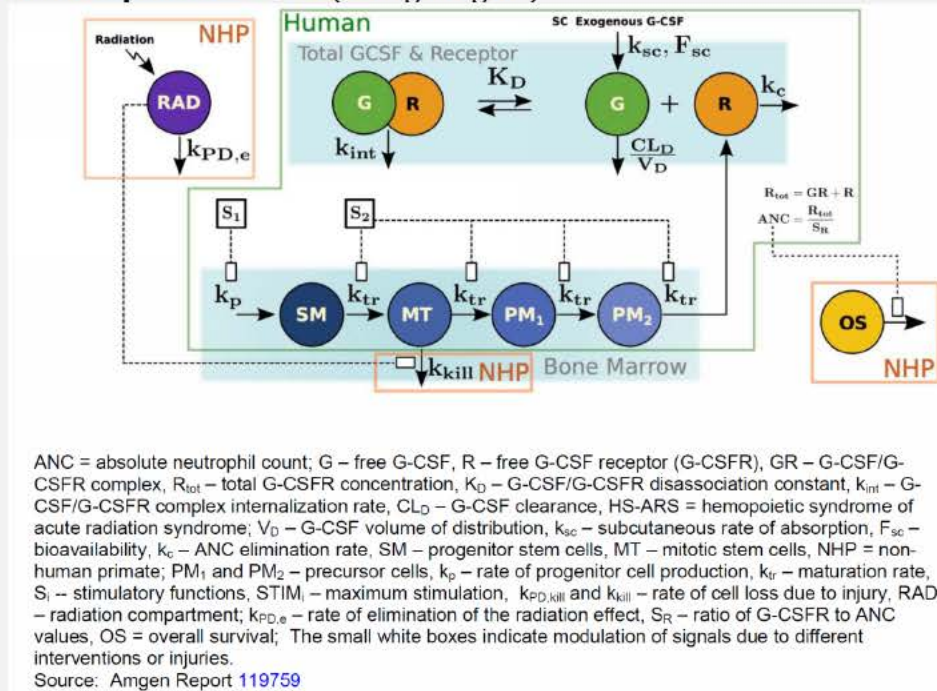


ANC = absolute neutrophil count; G – free G-CSF, R – free G-CSF receptor (G-CSFR), GR – G-CSF/G-CSFR complex, R_{tot} – total G-CSFR concentration, K_D – G-CSF/G-CSFR disassociation constant, k_{int} – G-CSF/G-CSFR complex internalization rate, CL_D – G-CSF clearance, V_D – G-CSF volume of distribution, k_{sc} – subcutaneous rate of absorption, F_{sc} – bioavailability, k_c – ANC elimination rate, SM – progenitor stem cells, MT – mitotic stem cells, PM_1 and PM_2 – precursor cells, k_p – rate of progenitor cell production, k_r – maturation rate, S_1 – stimulatory functions, $STIM_i$ – maximum stimulation, $k_{PD,kill}$ and k_{kill} – rate of cell loss due to injury, CRT – corticosteroid compartment, LAG8 – lag time for corticosteroids; k_{CRT} – rate of elimination of corticosteroid effect, CHM – chemotherapy compartment, LAG9 – lag time for chemotherapy; k_{CHM} – rate of elimination of chemotherapeutic effect, S_R – ratio of G-CSFR to ANC values. The small white boxes indicate modulation of signals due to different interventions or injuries.

Source: Amgen Report [119698](#)

(Source: Sponsor's Summary of Clinical Pharmacology, Figure 12-1)

Figure 10. Model structure used for predicting survival in humans with HS-ARS, combining parameters from the human model (green region) with those scaled from the non-human primate model (orange region)



(Source: Sponsor's Summary of Clinical Pharmacology, Figure 12-1)

After calibration of the model, simulations were performed. As a base case, patients would receive 3 Gy of radiation given at a rate of 1 Gy/hr at time zero, and patients would be given 6 mg of pegfilgrastim SC on days 1 and 15 post irradiation with survival evaluated on day 60. Subsequently, the impact by several factors were evaluated: (1) the start of pegfilgrastim treatment in relation to radiation exposure (beginning on days: 1 to 4, 7, 10, 14, 17, and 21), (2) 12 mg of pegfilgrastim on day 1 or 6 mg of pegfilgrastim on day 1 and delaying the second 6 mg pegfilgrastim dose by 1, 2, 3, 4 and 5 weeks (3) applying a single 12 mg pegfilgrastim dose on either days 1, 2, 3, 5, 7, 10, 14, 17, or 21; (4) altering the radiation dose rate (LD50 over a range of dose rates); and (5) pediatric patients (3 weight categories 10-25 kg, 25-45 kg, and 45-55 kg) with pegfilgrastim dosing on days 1 and 15 post irradiation of 6 mg for subjects with a body weight ≥ 45 kg and weight based pegfilgrastim dosing of 100 μ g/kg for subjects with a body weight < 45 kg.

Table 3. Model Parameters of the Filgrastim and Pegfilgrastim Pharmacokinetic and ANC Model (RUN1325F) Developed on Healthy Volunteer and Adult Patient (First Chemotherapy Cycle) Data

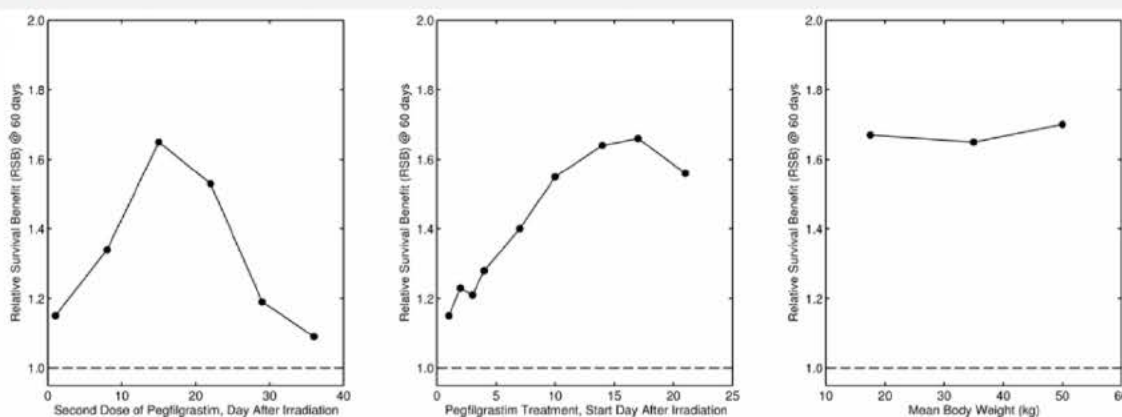
Parameter	(units)	Mean	s.e. (s.a.)	r.s.e.(%)	p-value
F _{SC} _FIL	-	1	-	-	-
F _{SC} _PEG	-	0.646	0.023	4	7.50E-05
K _{SC} _FIL	(hr ⁻¹)	0.123	0.0036	3	-
K _{SC} _PEG	(hr ⁻¹)	0.0188	0.00028	2	< 1E-010
V _D _FIL	(L)	3.12	0.13	4	-
V _D _PEG	(L)	5.76	0.19	3	4.9E-07
beta_V _D (WT/70)	-	0.943	0.10	11	< 1e-010
CL _D _FIL	(L/hr)	0.833	0.031	4	-
CL _D _PEG	(L/hr)	0.362	0.013	4	< 1e-010
beta_CL _D (WT/70)	-	0.641	0.10	16	2.8E-07
CL _D _PEG300mg	(L/h)	0.107	0.016	15	2E-10
KP	(nM/h)	0.0276	0.00041	1	-
KTR	(hr ⁻¹)	0.0330	-	-	-
K _C	(hr ⁻¹)	0.120	-	-	-
K _D _FIL	(nM)	0.0237	0.0018	8	-
K _D _PEG	(nM)	0.0959	0.0052	5	< 1e-010
STIM ₁	-	7.53	0.16	2	-
STIM ₂ _HV	-	5.21	0.19	4	-
STIM ₂ _PT	-	3.89	0.064	2	< 1e-010
S _R	(recep. 6x10 ³ /Cell)	0.0590	-	-	-
K _{int} _HV	(hr ⁻¹)	0.197	0.013	7	-
K _{int} _PT	(hr ⁻¹)	0.113	0.0041	4	< 1e-010
BSLD	(nM)	0.00299	9.70E-05	3	-
LAG8	(hr)	16.3	1.4	9	-
LAG9	(hr)	66.2	0.4	1	-
K _{CHM}	(hr ⁻¹)	0.0724	0.00087	1	-
KCRT	(hr ⁻¹)	0.200	-	-	-
CHMSL	(mg·hr ⁻¹)	668	64	10	-
CRT50	(mg·hr ⁻¹)	0.00151	0.00022	15	-

Parameter (units)	Mean	s.e. (lin)	r.s.e.(%)	
omega_F _{SC}	0.440	0.021	5	-
omega_K _{SC}	0.225	0.011	5	-
omega_V _D	0.282	0.02	7	-
omega_CL _D	0.370	0.021	6	-
omega_KP	0.265	0.012	5	-
omega_KTR	0	-	-	-
omega_K _C	0	-	-	-
omega_K _D	0.726	0.039	5	-
omega_STIM ₁	0.315	0.017	5	-
omega_STIM ₂	0.273	0.013	5	-
omega_S _R	0	-	-	-
omega_K _{INT}	0.570	0.027	5	-
omega_B _{SLD}	0.260	0.031	12	-
omega_LAG8	0.698	0.083	12	-
omega_LAG9	0.110	0.0045	4	-
omega_K _{CHM}	0.259	0.0094	4	-
omega_KCRT	0	-	-	-
omega_CHMSL	2.28	0.070	3	-
omega_CRT50	1.18	0.17	15	-
corr(KCHM,CHMSL)	0.731	0.023	3	-
a_1	0.537	0.0057	1	-
a_2	0.298	0.0029	1	-

(Source: Sponsor's Summary of Clinical Pharmacology, Appendix Table 1-2)

To quantify the treatment efficacy predictions, the relative survival benefit (RSB) was used as the quantitative metric. RSB is defined as the fraction patients surviving for the pegfilgrastim-treated cohort relative to the placebo cohort at 60 days after radiation exposure. During the analysis process it was found that more than one dose was required in order to potentially maximize the RSB. The left panel of **Figure 11** shows that a drug holiday between 7 and 21 days is expected to optimize the RSB, and an RSB of 1.7 is predicted by dosing 6 mg on days 1 and 15. The ability to treat subjects using a single 12 mg dose was also explored, by varying the treatment time relative to radiation exposure (center panel of **Figure 11**). This figure indicates that a single dose may be sufficient if administered between day 10 and day 17 post-irradiation (RSB = 1.6). Pediatric patients, treated on days 1 and 15 following irradiation, were considered in two different categories: weight based dosing of 100 mg/kg for weight < 45kg or a fixed dose of 6mg for patients $\geq$ 45kg. The model predicts a similar RSB (right panel of **Figure 11**) in pediatric patients across a range of body weights. The positive impact of pegfilgrastim on OS can be seen over a range of potential radiation exposure rates, and the RSB is predicted to increase as the severity of radiation decreases.

Figure 11. (Left) Effect of altering drug interval: A total of 12 mg is administered to the treatment group either as a single 12 mg dose on day 1 or as two 6 mg doses with the first dose on day 1 and the second dose administered as indicated; (Center) Effect of delaying treatment with a single 12 mg dose of pegfilgrastim; (Right) Pediatrics administered either 6 mg (body weight $\geq$ 45 kg) or 100 μ g/kg (body Weight < 45 kg) subcutaneous of pegfilgrastim on days 1 and 15 after radiation exposure

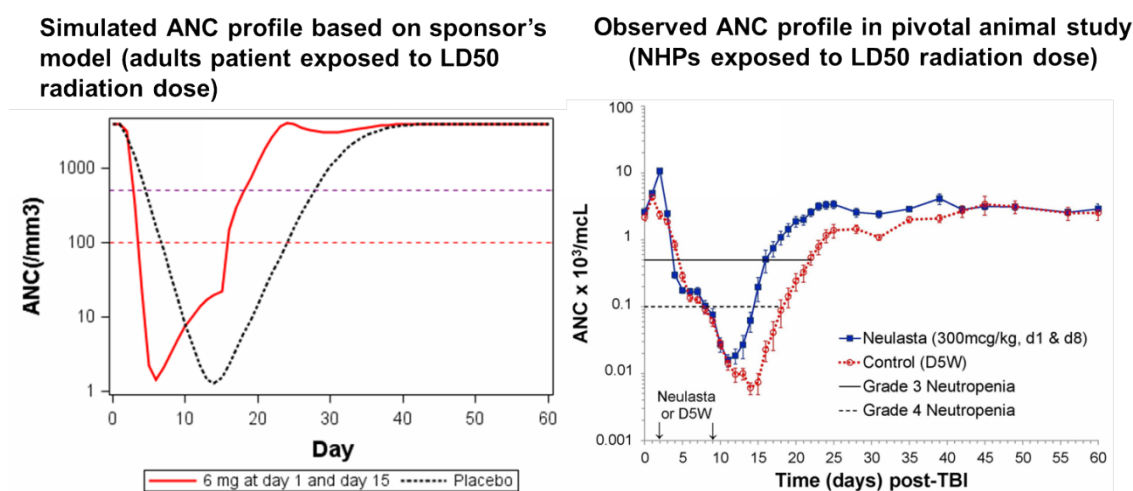


Source: Amgen Report [119893](#)

Reviewer's Comments: The comprehensive PK/PD model developed by the sponsor generally well characterizes the PK and ANC profiles in subjects receiving pegfilgrastim. The model qualification indicated that the model could be used for simulating the time-course of ANC in the absence or the presence of chemotherapy. For detailed modeling results please refer to the sponsors' Reports 119698 and 119893. Of note, for the 300

$\mu\text{g/kg}$ dose, data was only available in 4 NSCLC patients from study 970144. This small sample size may limit the predictability of survival benefit at higher doses. In addition, based on sponsor's model, the predicted initial declines of ANC appear to be steeper with the pegfilgrastim treatment than that with the placebo (**Figure 12, left**). The depths of the nadir also seem to be deeper with the treatment. These differences, however, were not observed in the pivotal efficacy study in NHPs (AXG21) (**Figure 12, right**). To account for this, the reviewer made modifications to the model and was able to refit the model and correct this discrepancy. Reviewer's revised model was further used for simulation of alternative regimens. See section 4.2 for details.

Figure 12. Differences in the initial decline and nadir of ANC, between sponsor's model prediction (left) and the observation in the pivotal non-clinical study (right)



4.2 Reviewer's analysis

4.2.1 Introduction

Based on sponsor's PK/PD model, the initial decline in ANC was steeper with the treatment arm compared to placebo while this observation was not evident in the pivotal animal efficacy study. To account for this, the reviewer made modification to sponsor's model to correct this discrepancy. Further, simulations were conducted based on this revised model, to explore potential benefits of alternative dosing regimens in the proposed patient population.

4.2.2 Objectives

Analysis objectives are:

- To correct the discrepancy identified between predictions from sponsor's PK/PD model and the observed data in animals.

- To evaluate the potential benefits of alternative dosing regimens in terms of ANC recovery and duration of grade 3/4 neutropenia, based on the simulation results.
- To propose a dosing recommendation in patients < 45 kg by PK comparison to recommended dose in adults.

4.2.3 Data Sets

Data sets used are summarized in Table 4.

Table 4. Analysis Data Sets

Study Number	Name	Link to EDR
Pooled adults data	hvptpegfilscfadc1.csv	\\cdsesub1\evsprod\bla103353\0173\m5\datasets\19623\analysis\legacy\datasets\hvptpegfilscfadc1.csv
Pooled adults/children data	hvptpegfilscfallc1.csv	\\cdsesub1\evsprod\bla103353\0173\m5\datasets\19623\analysis\legacy\datasets\hvptpegfilscfallc1.csv

4.2.4 Software

Population PK/PD modeling and simulation were performed with NONMEM (version 7.2) and graphical, statistical analysis and simulation were performed with SAS (version 9.3).

4.2.5 Methods

On the basis of sponsor's PK/PD model, four "ST2"s were removed from two transit processes (compartment 3 to 4, and 5 to 6). The same datasets in adult and pediatric patients were utilized for re-fitting the model as shown in **Table 1**. The final estimates of the PK/PD parameters from the revised model were used in the simulation. As a base case, patients would receive a calibrated human LD50 radiation dose (3 Gy given at a rate of 1 Gy/hr) at time zero, and 6 mg of pegfilgrastim on days 1 and 15 post irradiation with PK and ANC profiles simulated over 60 days. For the parameters characterizing the duration and effect of radiation (KPD,e, KPD,kill, γ) on ANC, sponsor's scaled estimates from NHPs to humans were used for the simulation. Each dosing scenario was simulated for 1000 subjects, including inter-subject variability of both PKPD and radiation parameters. The simulation with varying radiation dose (1-7 Gy) was based on assumption that the duration and effect of radiation are similar at different radiation level.

4.2.6 Results

The revised model adequately described the time-courses of PK and ANC for the 5 dose levels of pegfilgrastim studied in adults and pediatrics. The parameter estimates from the revised model for adults patients are presented in **Table 5**. The parameter estimates from the revised model for pediatric patients are generally comparable to that for adults and not shown. The goodness-of-fit plots and VPC results of the final model are shown in **Figure 13** and **Figure 14**, respectively.

Based on revised model, the simulated ANC profiles are now consistent with the observation in the non-clinical study, with no separation in the initial decline phase between pegfilgrastim treatment and placebo. The simulated ANC profiles comparing the original model and revised model are shown in **Figure 16**.

Upon FDA's request, the sponsor conducted simulations for 7 alternative regimens and concluded (b)(4) these regimens are not superior in terms of duration of grade 3 and 4 neutropenia and ANC recovery in the ARS patients. Based on the revised model, the reviewer conducted independent simulations for the same regimens to verify sponsor's results. Two alternative regimens were identified from the simulation results with potential benefit in early ANC recovery: a higher single dose 18 mg given at day 1, (b)(4) regimen of two 6 mg doses given at day 1 and day 8 (one-week interval). The simulated ANC profiles in **Figure 17**, indicate that both alternative regimens will likely to expedite ANC recovery post-nadir (b)(4) dosing regimen in adults patients (≥ 45 kg) exposed to LD50 radiation dose (3 Gy at 1 Gy/hr). Summary statistics of the clinically relevant ANC endpoints, duration of grade 3 neutropenia, duration of grade 4 neutropenia, are calculated based on the simulation results and are presented in **Figure 4** (similar for the 18 mg dose). The distribution plots show that higher proportion of patients are expected to have shorter duration of grade 4 neutropenia with 6 mg one week apart dosing regimen, or with 18 mg single dose given at day 1.

Figure 13. Goodness-of-Fit plots for the revised model in adults and pediatric patients

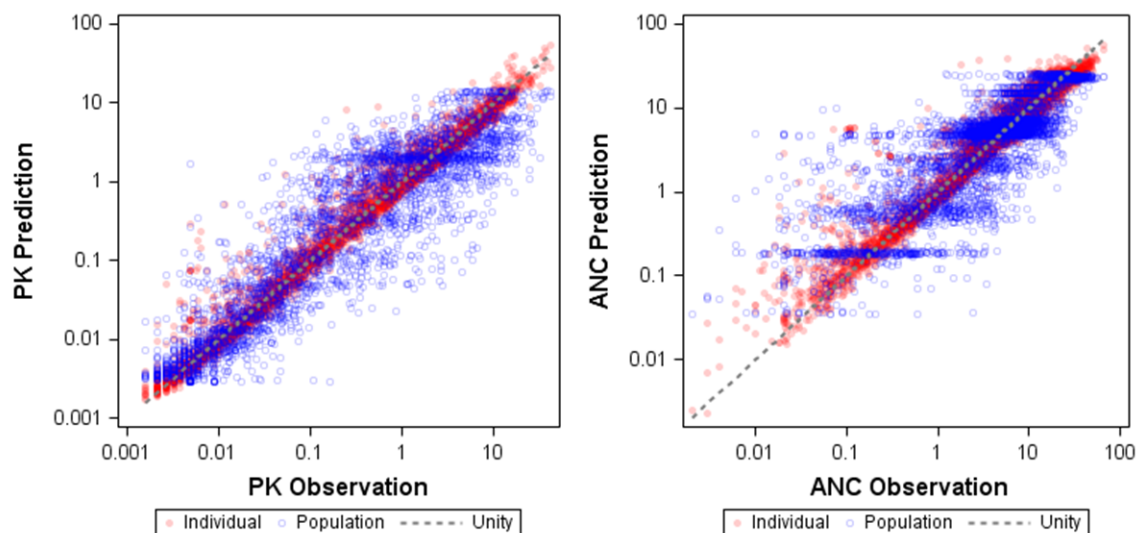


Figure 14. Visual Predictive Check plots for the revised model in adult patients

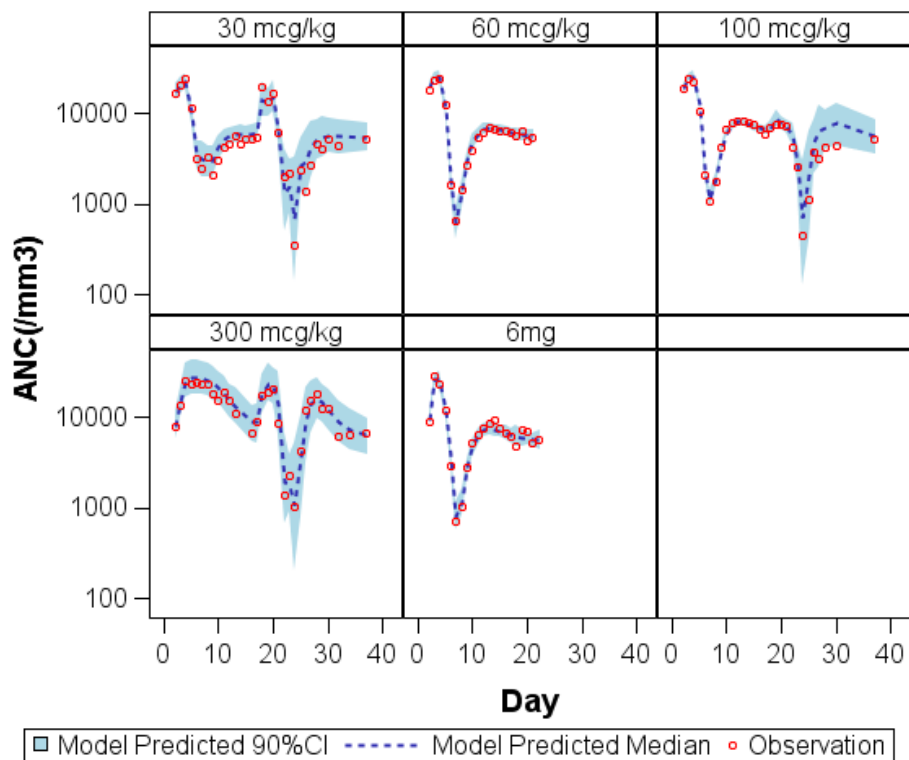
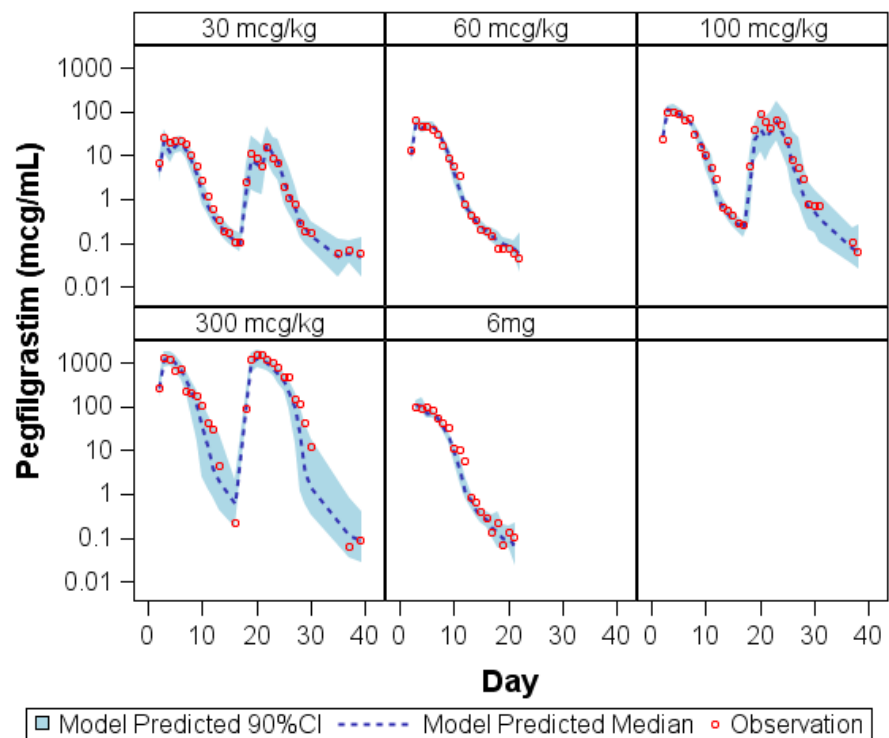


Figure 15. Representative individual plots for pediatric patients with the revised model

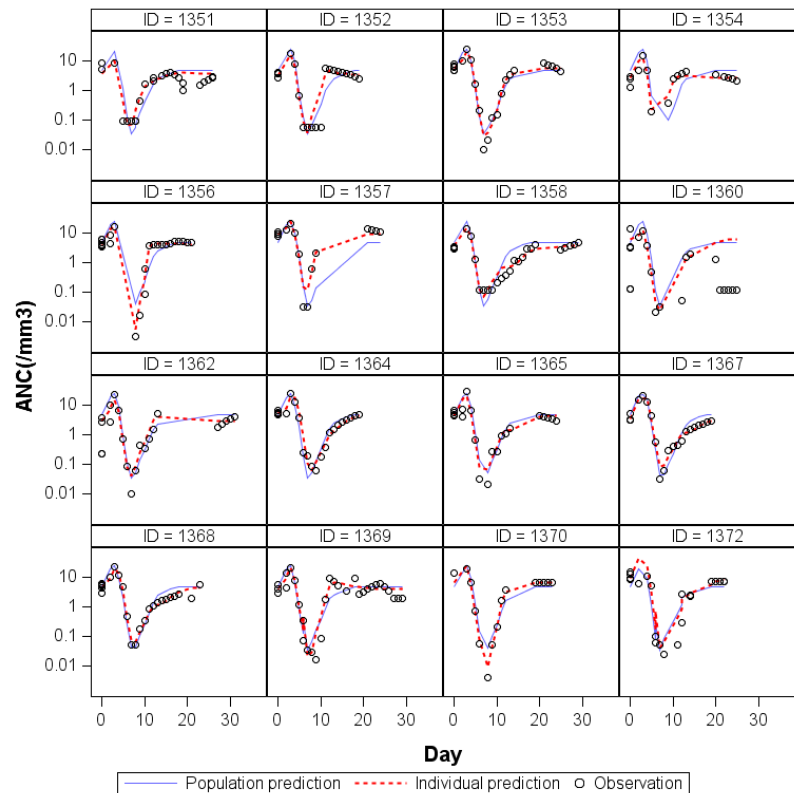
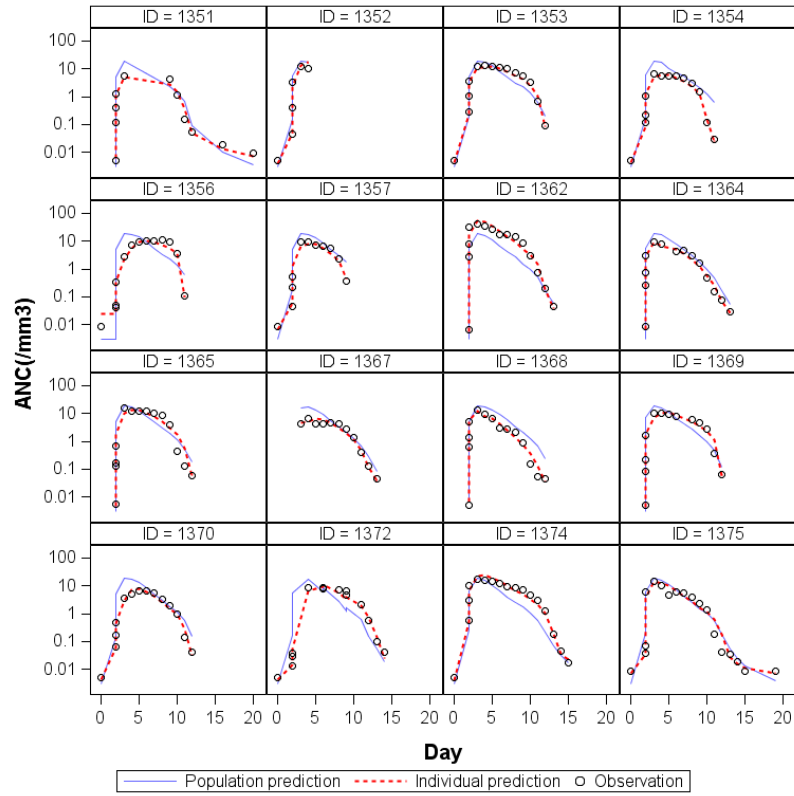


Table 5. Parameter estimates for the revised PK/ANC model in adult cancer patient following first chemotherapy cycle

Parameter	Units	Estimate	RSE, %	Estimate	RSE, %
		Fixed Effect		Random Effect	
FSC		0.646	16	4.67	8
KSC	h ⁻¹	0.0189	3	0.0562	5
Vd	L	3.9	2	0.227	10
beta_Vd (WT/70)	-	0.943	15	-	-
CLd	L/h	0.433	3	0.566	6
beta_CLd (WT/70)	-	0.641	12	-	-
CLD_PEG300mg	L/h	0.115	13	-	-
Kp	nM/h	0.156	2	0.114	4
Ktr	h ⁻¹	0.128	-	-	-
Kc	h ⁻¹	0.128	-	-	-
Kd	nM	0.165	4	0.436	8
STM1	-	4.04	3	0.141	5
STM2	-	4.55	5	0.279	8
SR	-	0.247	-	-	-
KINT	h ⁻¹	0.0758	5	0.237	5
BSLD	nM	0.00244	4	0.230	18
LAG8	h	19.4	8	0.296	9
LAG9	h	75	3	0.143	4
KCHM	h ⁻¹	0.0642	6	0.0613	3
KCRT	h ⁻¹	0.152	-	-	-
CHMSL	mg ⁻¹	587	8	3.60	4
CRT50	mg* h ⁻¹	0.0328	21	0.427	8
Corr (KCHM, CHMSL)	-	-	-	0.326	5
Exponential Error					
ERR1	-	0.13	2	-	-
ERR2	-	0.0862	1	-	-

Figure 16. Differences in the initial decline and nadir of ANC, between sponsor's model prediction (left) and revised model by the reviewer (right)

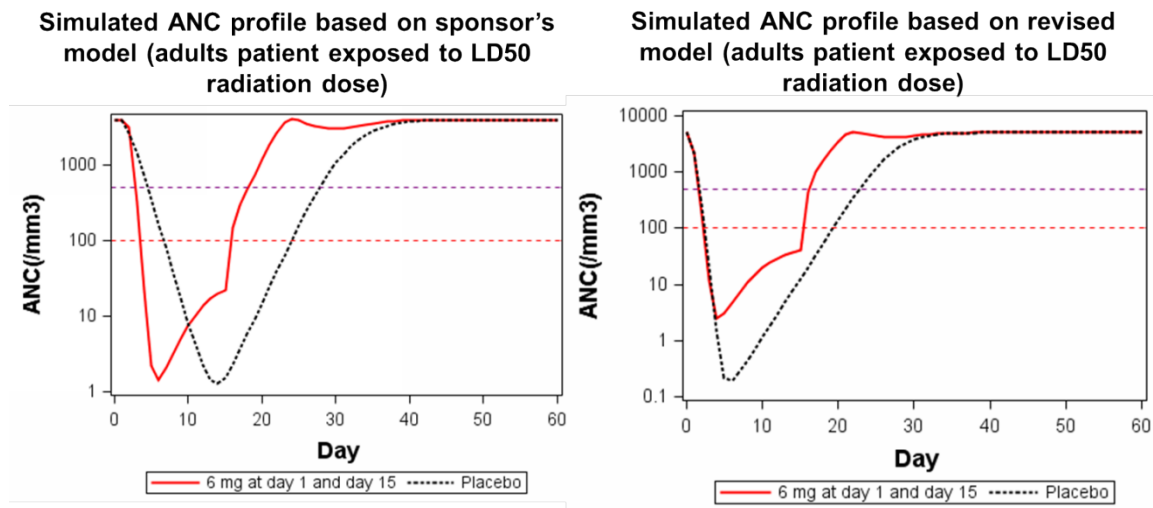
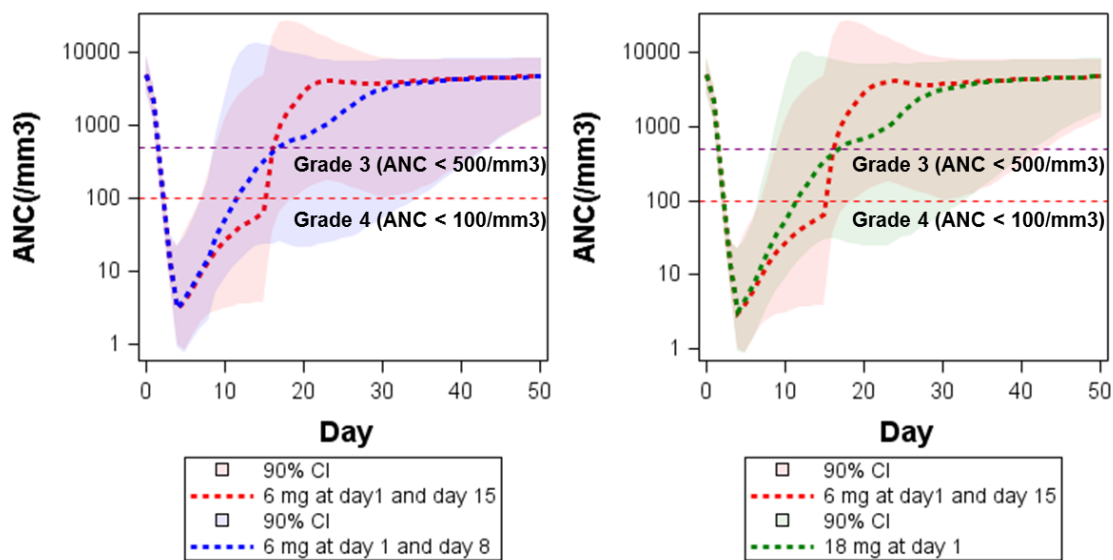


Figure 17. Simulated ANC profiles comparing the 6 mg doses 2-weeks apart dosing (red) versus two alternative regimens: 6 mg doses one-week apart (blue), and 18 mg single dose, in adults patients (≥ 45 kg) exposed to LD50 radiation dose (3 Gy at 1 Gy/hr)



Sensitivity analyses were further conducted to simulate scenarios with varying radiation dose levels (1 Gy – 7 Gy), and varying starting time of the first dose (day 2 to day 4). As shown in **Figure 18** and **Figure 19**, in most scenarios, one week apart dosing regimen performs similar or better than 2 weeks apart dosing regimen in early ANC recovery from nadir, and clinical relevant ANC endpoint (duration of grade 3 neutropenia, duration of grade 4 neutropenia). At high radiation dose 7 Gy, the two weeks apart dosing seems to be better in terms of duration of grade 3 neutropenia. The reviewer acknowledges that the

simulation with varying radiation dose was limited by assumption that the duration and effect of radiation will not change at different radiation level.

To predict potential risk of leukocytosis in relatively healthy subjects that are not exposed to or only exposed to minimal radiation, sensitivity analyses were also performed to simulate scenarios where no radiation dose was given. The simulated ANC profiles following three dosing regimens are shown in **Figure 20**. Based on simulated results, the proportion of subjects with ANC level exceeding an ANC of 100,000/mm³ (clinically relevant target for the risk of leukocytosis) was estimated to be lower than 2% in either one of the dosing groups.

Figure 18. Simulated ANC profiles comparing the 6 mg doses 2-weeks apart dosing (red) versus 6 mg doses one-week apart dosing (blue) in adults patients (≥ 45 kg) exposed to varying radiation doses; First dose given at 1 day after radiation exposure

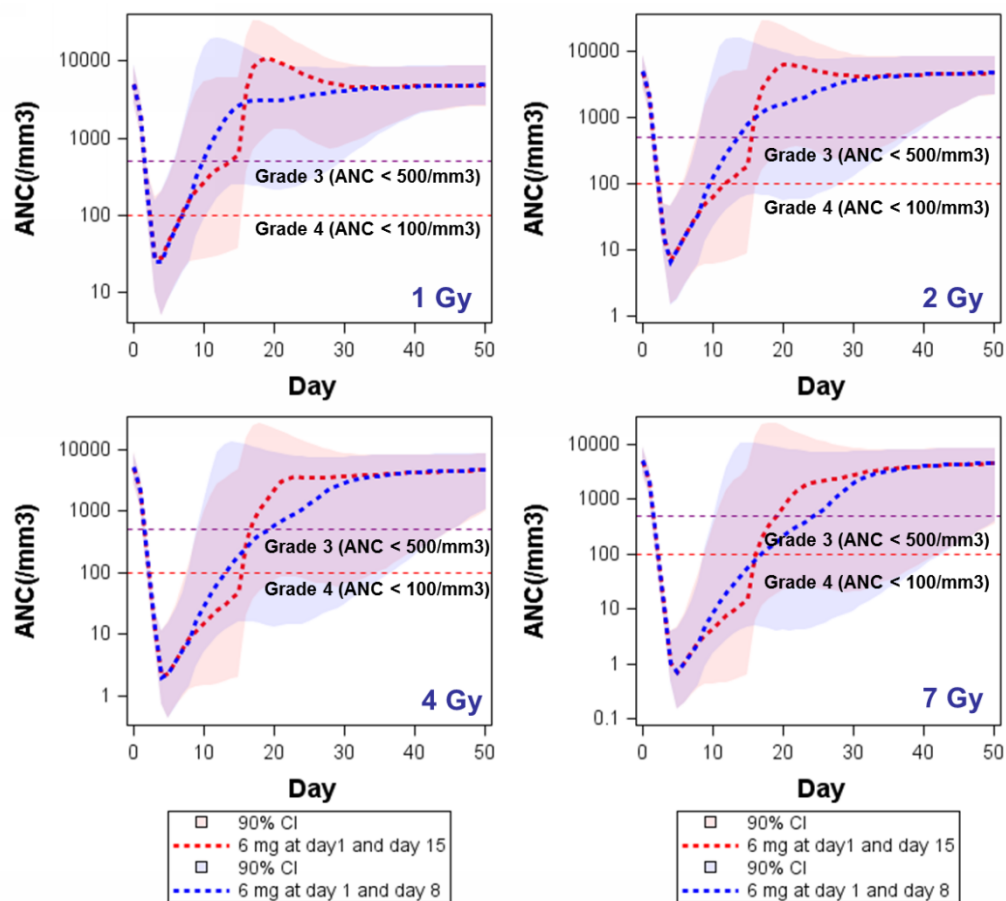


Figure 19. Simulated ANC profiles comparing the 6 mg doses 2-weeks apart dosing (red) versus 6 mg doses one-week apart dosing (blue) in adults patients (≥ 45 kg) exposed to varying radiation doses; First dose given at 3 days after radiation exposure

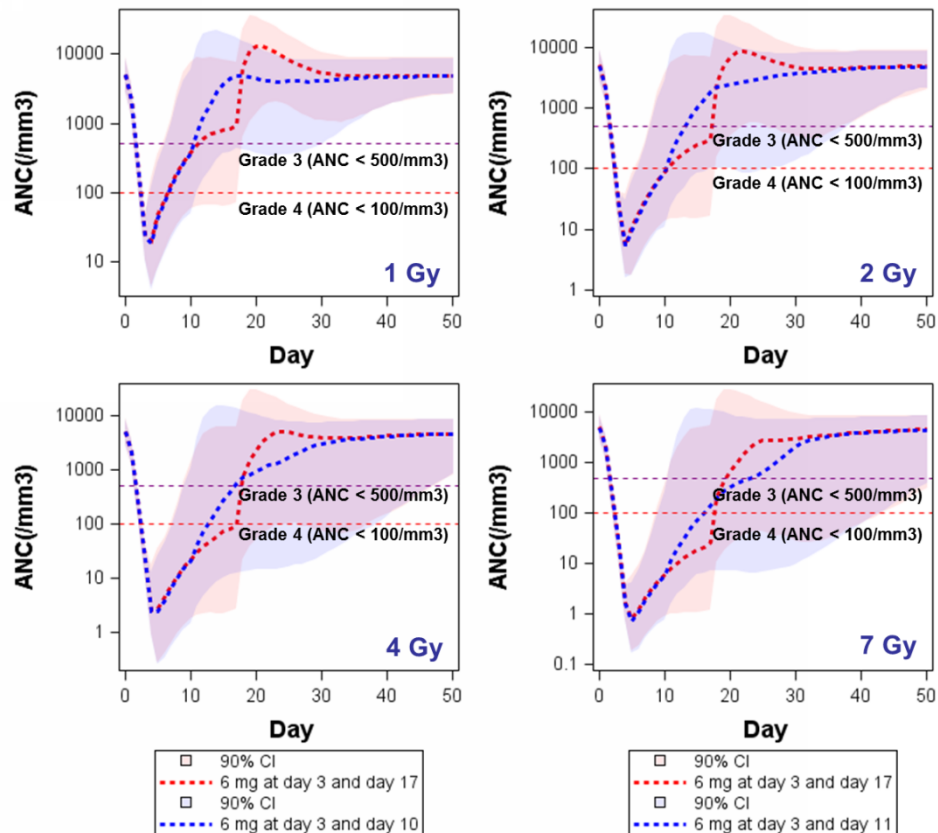
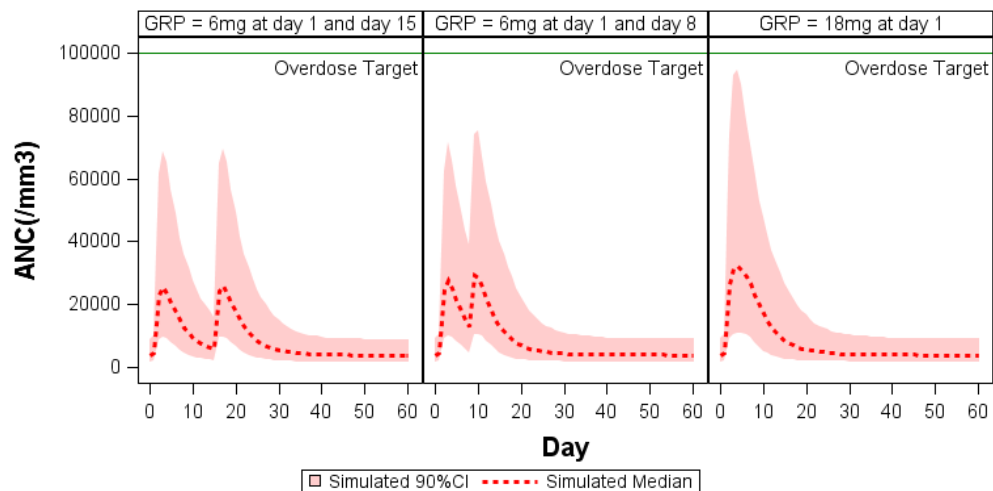


Figure 20. Simulated ANC profiles in healthy subjects (≥ 45 kg) with no radiation exposure



4.2.7 Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
pegchemo_adc1.ctl pegchemo_adc1.csv pegchemo_allc1.ctl pegchemo_allc1.csv	Revised PKPD model files	Reviews\Ongoing PM Reviews\PegFilgrastim_sBLA125031_LM\PKPD model
rad_ad.ctl rad_ad.csv	Simulation files for adults	Reviews\Ongoing PM Reviews\PegFilgrastim_sBLA125031_LM\PKPD model\Simulation
rad_ped.ctl rad_ped.csv	Simulation files for pediatrics	Reviews\Ongoing PM Reviews\PegFilgrastim_sBLA125031_LM\PKPD model\Simulation

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LIAN MA
10/26/2015

GENE M WILLIAMS
10/26/2015
I concur with the recommendations

NITIN MEHROTRA
10/26/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125031Orig1s180

OTHER REVIEWS

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: November 9, 2015

To: Frank Lutterodt
Regulatory Project Manager
Division of Medical Imaging Products (DMIP)

From: Adam George, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Amy Toscano, Pharm.D, RAC, CPA
Team Leader
Office of Prescription Drug Promotion (OPDP)

Subject: **BLA 125031 supplement 180, Neulasta (pegfilgrastim)
injection, for subcutaneous use**

In response to your consult dated April 14, 2015, we have reviewed the draft prescribing information (PI) for Neulasta (pegfilgrastim) injection, for subcutaneous use. OPDP has reviewed the substantially complete version of the PI titled "S-NLS-US-PI-v16 2-ARS-R-2015-1030" which was accessed via the following link (<http://my.fda.gov/personal/lutterodtf/Products%20MCM/November%20Neulasta%20Labeling>) on November 9, 2015 and does not have any comments at this time.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Adam George at 301-796-7607 or adam.george@fda.hhs.gov.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ADAM N GEORGE
11/09/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs/
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

From: Erica Radden, M.D., Medical Officer
Division of Pediatric and Maternal Health (DPMH),
Office of New Drugs

Through: Lynne Yao, M.D., Director
Division of Pediatric and Maternal Health (DPMH),
Office of New Drugs

To: Division of Medical Imaging Products (DMIP)

Drug: Neulasta (pegfilgrastim)

Application number: BLA 125031

Sponsor: Amgen, Inc.

Approved Indication: To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia in adults.

Approved Dosage Form & Route of Administration: 6 mg per 0.6 mL in single use prefilled syringe administered subcutaneously

Approved Dosing Regimen: Administer 6 mg once per chemotherapy cycle

Proposed Indication: [REDACTED] (b)(4)

(b)(4)

Proposed Dosage Form &

Route of Administration: same as Approved Dosage Form and Route of Administration

Proposed Dosing Regimen:

(b)(4)

Consult request:

DMIP requests Division of Pediatric and Maternal Health (DPMH) participation in the labeling discussions.

Materials Reviewed:

- Consult Request
- Current Neulasta (pegfilgrastim) labeling (May 25, 2012)
- Current Neupogen (filgrastim) labeling (September 13, 2013)
- Office of Clinical Pharmacology review (November 4, 2008) and Executive Summary of the Pediatric Assessment for PMC 3-4 (November 2, 2008) for Neulasta (pegfilgrastim), BLA 125031
- Draft Neulasta (pegfilgrastim) labeling (February 13, 2015)
- Pharmacovigilance review on pediatric adverse events for Neulasta (pegfilgrastim) (October 21, 2014 and August 28, 2015)
- Division of Hematology review of Neulasta (August 6, 2015)
- Amgen's response to FDA's Information Request (July 7, 2015 and July 17, 2015)
- DPMH prior consult review on Neulasta (pegfilgrastim) (December 22, 2013)

Background:

Pegfilgrastim is a pegylated form of filgrastim, a human granulocyte colony-stimulating factor (G-CSF) that is produced by recombinant DNA technology. Similar to filgrastim, pegfilgrastim acts on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end cell functional

activation. However, pegfilgrastim has sustained duration of action relative to filgrastim as evidenced by the longer half-life.

Regulatory Background:

Pegfilgrastim was approved in January, 2002, to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. Upon approval, two Post Marketing Commitments (PMCs) were issued under the Pediatric Rule. Amgen was required to (1) submit the results of a pharmacokinetic (PK), safety and efficacy study in pediatric sarcoma patients, and (2) develop a pediatric dosage form based on the results of that study.

Due to slow patient accrual and low interest on the part of investigators, the PK, safety and efficacy study was terminated prematurely, and Amgen submitted the data from the study in August, 2007. (b)(4)

Reviewer comment: DPMH and the division currently agree that extrapolation of efficacy for the febrile neutropenia indication is acceptable. (See the Discussion on Labeling Recommendations section below.)

Upon review, the Agency determined that substantial evidence of effectiveness was not established because of the small numbers of subjects; however, descriptive pharmacokinetic (PK) data for pegfilgrastim were provided. The division acknowledged Amgen's due diligence in completing the requirement and the difficulties in pediatric patient accrual. The division agreed that similar challenges with patient accrual were likely to occur with any future pediatric clinical studies. In addition, there was a marketed alternative therapy (filgrastim [Neupogen]) which was approved for the same indication as pegfilgrastim. (b)(4)

Ultimately, data on the pharmacokinetics of pegfilgrastim and the adverse reaction profile on 37 pediatric sarcoma patients age 0-21 years was included in subsection 8.4 of labeling. Labeling also included a statement that safety and effectiveness was not established in pediatric patients.

On February 13, 2015, Amgen submitted a supplemental BLA (BLA 125031/S0180) for pegfilgrastim under the Animal Rule (21 CFR 601.90) for the treatment (b)(4)

In addition to published literature, the application relies on data from a nonhuman primate model of radiation-induced myelosuppression because human clinical trials cannot be ethically conducted to study treatment of myelosuppression from radiation exposure resulting in the hematopoietic syndrome of ARS. Pegfilgrastim was granted orphan designation for

this proposed indication; therefore, this application is exempt from requirements under Pediatric Equity Research Act.

The Division of Medical Imaging Products (DMIP) consulted the Division of Pediatric and Maternal Health Staff (DPMH) to provide input on the sponsor's proposed labeling related to pediatrics.

DPMH Review of labeling:

The DPMH labeling review will focus on section 2 (Dosing and Administration) and subsection 8.4 (Pediatric Use).

Pediatric Use Labeling:

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population. (Also see draft Guidance for Industry and Review Staff Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling, February, 2013)

Discussion on Labeling Recommendations:

Pegfilgrastim labeling in subsection 8.4 currently states the following:

(b)(4)



The sponsor initially proposed (b)(4) and the proposed presentation for the product is the currently approved pre-filled syringe. Note that this prefilled syringe does not support accurate direct administration of the product to patients weighing < 45 kg. Therefore, the sponsor proposed the following paragraph in the Pediatric Use section of labeling:

(b)(4)



(b)(4)

Neither DPMH nor DMIP agree with the sponsor's proposed labeling provided above. Furthermore, DPMH agrees with the division that the mechanism of action and course of disease are sufficiently similar to allow extrapolation of efficacy from adequate and well-controlled studies in adults. Moreover, the dose used in the study of the 37 pediatric patients (100 mcg/kg) was the same dose used in one of the two trials in adult patients with cancer which supported the approval of pegfilgrastim in 2001. Additionally, although the currently marketed pre-filled syringe does not provide an option for direct administration to patients weighing < 45 kg, the Division of Hematology Products' review (BLA 125031 dated July 7, 2015) confirms that based on literature review and Children's Oncology Group protocols, this product is widely used off-label in pediatric cancer patients. Most often, the contents of the pre-filled syringe are emptied into a separate container and the appropriate amount is drawn into a separate syringe for administration to a pediatric patient. Thus, both DHP and DPMH have concluded that there was sufficient evidence in the literature that:

- Available data supported a safe and effective dose down to birth for the indication of febrile neutropenia. Because Neulasta can be dosed less frequently than Neupogen (filgrastim¹), there is wide-spread "off-label" use of this product in febrile neutropenia.
- The dose proposed for the treatment of ARS in adults is the same as the dose approved for febrile neutropenia.
- Pediatric dosing for ARS is supported by data in adult and pediatric patients for febrile neutropenia.
- Review of the available published literature, FAERS reports, and pharmacovigilance failed to identify unexpected, more severe, or more frequent adverse events in children compared to adults.

Thus, DMIP, DHP, and DPMH all agreed that there was sufficient safety and efficacy information from use of Neulasta in febrile neutropenia to support the safety and efficacy of the product in ARS. Moreover, the single dose (as compared to multiple doses required for Neupogen) is a particular advantage in a pediatric population, as injections are frequently perceived as noxious in this population.

(b)(4)

(b)(4)

¹ Note that Neupogen, also manufactured by Amgen, was approved in March, 2015, for ARS. Neupogen is fully labeled for pediatric patients for all indications including febrile neutropenia and ARS.

DMIP requested in an information request dated June 4, 2015,

(b)(4)

After internal discussions with DMIP, DHP, and DPMH, DMIP agreed that Amgen had not provided any data identifying a significant difference in the safety profile of pegfilgrastim between pediatric and adult patients. Furthermore, DMIP, DHP, and DPMH all agreed that the availability of Neulasta for a radiological/nuclear disaster would provide a clear advantage over Neupogen; however,

(b)(4)

(b)(4)

informed Amgen that DMIP would be conducting an independent review of the literature. The division also stated that in evaluating the use of pegfilgrastim for the ARS indication, “we consider it essential from a public health standpoint to provide information on its use in the pediatric population.”

Although, DMIP, DHP, and DPMH agreed

(b)(4)

DPMH defers to Clinical Pharmacology regarding the appropriate dosing based on current data for febrile neutropenia in addition to modeling and simulation.

Because the ARS and febrile neutropenia indications will include all pediatric patients, information regarding pediatric use should be placed throughout labeling. Accordingly, the Dosage and Administration section should include dosing for patients < 45 kg. The Pediatric Use subsection (8.4) must describe the data used to establish safety and effectiveness (21 CFR 201.57(c)(9)(iv)). Therefore, labeling for the febrile neutropenia indication should state that use is based on adequate and well controlled adult studies, in addition to safety and PK data in pediatric sarcoma patients. Labeling for the ARS indication should state that use is based on studies conducted in animals in addition to dosing and safety data supporting Neupogen's effect on severe neutropenia with cross-references to the Dosing and Administration and Clinical Studies sections.

DPMH Actions and Labeling Recommendations:

DPMH reviewed the sponsor's draft labeling and participated in the internal meetings from May to November, 2015. Recommended labeling for the pediatric population is provided below per 21 CFR 201.57(c)(9)(iv). The following recommendations were provided to DMIP based on labeling discussions between DHP, DMIP and DPMH. DPMH's input will be reflected in the final labeling and the approval letter. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here. (Proposed changes are underlined.)

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----DOSAGE AND ADMINISTRATION-----

- Patients with cancer receiving myelosuppressive chemotherapy
 - 6 mg administered subcutaneously once per chemotherapy cycle. (2.1)
 - Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy. (2.1)
- Patients acutely exposed to myelosuppressive doses of radiation
 - Two doses, 6 mg each, administered subcutaneously one week apart. Administer the first dose as soon as possible after suspected or confirmed exposure to myelosuppressive doses of radiation, and a second dose one week after. (2.2)
- Patients with cancer receiving myelosuppressive chemotherapy or acutely exposed to myelosuppressive doses of radiation weighing less than 45 kg
 - Do not use the prefilled syringe for direct administration of Neulasta in patients weighing less than 45 kg. (2.3)

Body Weight	Pegfilgrastim Dose	Volume
< 10 kg	100 mcg/kg	0.05 mL
10 - 20 kg	1.5 mg	0.15 mL
21 - 30 kg	2.5 mg	0.25 mL
31 - 44 kg	4 mg	0.40 mL

2 DOSAGE AND ADMINISTRATION

2.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy

The recommended dosage of Neulasta is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle. For patients weighing less than 45 kg, refer to Table 1 for ease of dosing. Do not administer Neulasta between 14 days before and 24 hours after administration of cytotoxic chemotherapy.

2.2 Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome

The recommended dose of Neulasta is two doses, 6 mg each, administered subcutaneously one week apart. For patients weighing less than 45 kg, refer to Table 1 for ease of dosing. Administer the first dose as soon as possible after suspected or confirmed exposure to radiation levels greater than 2 gray (Gy). Administer the second dose one week after the first dose.

Estimate a patient's absorbed radiation dose (i.e., level of radiation exposure) based on information from public health authorities, biodosimetry if available, or clinical findings such as time to onset of vomiting or lymphocyte depletion kinetics.

Obtain a baseline complete blood count (CBC). Do not delay administration of Neulasta if a CBC is not readily available.

Do not readminister Neulasta if the ANC is greater than 1,000/mm³.

2.3 Administration

Neulasta is administered subcutaneously via a single prefilled syringe for manual use or for use with the On-body Injector for Neulasta which is co-packaged with a single prefilled syringe. Use of the On-body Injector for Neulasta has not been studied in pediatric patients.

Patients weighing less than 45 kg

The Neulasta prefilled syringe is not designed to allow for direct administration of doses less than 0.6 mL (6 mg). The syringe does not bear graduation marks which are necessary to accurately measure doses of Neulasta less than 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of less than 0.6 mL (6 mg) is not recommended due to the potential for dosing errors. For ease of dosing, refer to Table 1.

Table 1. Dosing for patients weighing less than 45 kg

<u>Body Weight</u>	<u>Pegfilgrastim Dose</u>	<u>Volume</u>
<u>< 10 kg</u>	<u>100 mcg/kg</u>	<u>0.05 mL</u>

<u>10 - 20 kg</u>	<u>1.5 mg</u>	<u>0.15 mL</u>
<u>21 - 30 kg</u>	<u>2.5 mg</u>	<u>0.25 mL</u>
<u>31 - 44 kg</u>	<u>4 mg</u>	<u>0.40 mL</u>

Visually inspect parenteral drug products (prefilled syringe) for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer Neulasta if discoloration or particulates are observed.

The needle cap on the prefilled syringes contains dry natural rubber (derived from latex); persons with latex allergies should not administer these products.

8.4 Pediatric Use

The safety and effectiveness of Neulasta have been established in pediatric patients. No overall differences in safety were identified between adult and pediatric patients based on postmarketing surveillance and review of the scientific literature.

Use of Neulasta in pediatric patients for chemotherapy-induced neutropenia is based on adequate and well controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients with sarcoma [see Clinical Pharmacology (12.3) and Clinical Studies (14.1)].

The use of Neulasta to increase survival in pediatric patients acutely exposed to myelosuppressive doses of radiation is based on efficacy studies conducted in animals and clinical data supporting the use of Neulasta in patients with cancer receiving myelosuppressive chemotherapy. Efficacy studies of Neulasta could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Results from population modeling and simulation based on two doses of Neulasta, each 100 mcg/kg, administered one week apart provide pediatric patients with exposure and pharmacodynamics comparable to that in adults receiving two 6 mg doses one week apart [see Dosage and Administration (2.3), Clinical Pharmacology (12.3) and Clinical Studies (14.2)].

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/s/

ERICA D RADDEN
11/04/2015

LYNNE P YAO
11/06/2015

FILE MEMORANDUM

Submission: 125031 s180
Submission Date: 2/13/15
Submitted by: Amgen
Date Review Completed: 11/6/15

FROM: Patricia Dinndorf, MD, Medical Officer; Division of
Hematology Products (DHP), OHOP; CDER

SUBJECT: Review of Label Changes

EXECUTIVE SUMMARY:

The DHP team agrees with the changes to the Neulasta label, specifically safety and effectiveness has been established in pediatric patients based on postmarketing surveillance and review of the scientific literature, and the dosing recommendations for patients less than 45 kg as determined by the clinical pharmacology review team.

REVIEW:

This supplement supporting use of Neulasta (pegfilgrastim) in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic subsyndrome of Acute Radiation Syndrome) was supported by efficacy studies conducted in animals and data supporting Neulasta's effect on severe neutropenia in patients with cancer receiving myelosuppressive chemotherapy. Section 8.4 of the Neulasta label stated "Safety and effectiveness of Neulasta in pediatric patients have not been established." (b)(4)

An evaluation of the literature, and drug usage information confirmed that pegfilgrastim has been used extensively in children. No unique safety signals were identified with use of pegfilgrastim. Based on this evidence the statement concerning safety and effectiveness was removed from Section 8.4.

Dosing recommendations were made based on the clinical pharmacology simulation.

Body Weight	Pegfilgrastim Dose	Volume
10 - 20 kg	1.5 mg	0.15 mL
21 - 30 kg	2.5 mg	0.25 mL
31 - 44 kg	4 mg	0.40 mL

Patients less than 10 Kg 100 mcg/kg.

The results of the pediatric study in pediatric and young adult patients with sarcoma were moved from Section 8.4 to Section 14 as Study 4.

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/s/

PATRICIA A DINNDORF
11/06/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 23, 2015
Requesting Office or Division:	Division of Medical Imaging Products (DMIP)
Application Type and Number:	BLA 125031/S-180
Product Name and Strength:	Neulasta (Pegfilgrastim) Injection 6mg/0.6mL
Product Type:	Single-Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Amgen
Submission Date:	February 13, 2015
OSE RCM #:	2015-1012
DMEPA Primary Reviewer:	Ebony Ayres, PharmD
DMEPA Team Leader:	Yelena Maslov, PharmD
DMEPA Deputy Director:	Lubna Merchant, PharmD, MS
OMEPRM Deputy Director:	Kellie Taylor, PharmD, MPH

1 REASON FOR REVIEW

Amgen submitted an efficacy supplement for Neulasta (BLA 125031/S-180). This supplement proposes a new indication (b)(4)

The Division of Medical Imaging Products (DMIP) requested that the Division of Medication Error and Prevention Analysis (DMEPA) review the Prescribing Information (PI) to identify areas vulnerable to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA evaluated the proposed Prescribing Information (PI) for Neulasta, BLA 125031/S-180. The Applicant proposes a new indication for (b)(4)

Amgen initially proposed to (b)(4)

Neulasta is supplied as a single-use prefilled syringe containing 6 mg/0.6 mL, and the syringe label does not bear graduation marks that would allow for the accurate measurement and

direct administration of doses less than 0.6 mL (6 mg). The pediatric dose of Neulasta for ARS is 100 mcg/kg; therefore, doses for patients weighing less than 45 kg are less than 0.45 mL (4.5 mg). Preparation and dispensing of Neulasta for the indirect administration to pediatric patients weighing less than 45 kg would require manipulation of the prefilled syringe or dose approximation, both of which may lead to medication errors.

In fact, our review of FDA's spontaneous adverse event reports finds that the lack of graduation markings on Neulasta PFS is already causing some inaccurate dosing of pegfilgrastim. Specifically, we have analyzed medication error reports stemming from off-label use of pegfilgrastim in the pediatric oncology population and found reports where children received the incorrect dose, which in three cases led to dosing errors. One of these cases reported a patient outcome of bone pain. In the other two cases, patient outcomes were not reported (see Appendix E for additional details). Two reporters noted that the "lack of calibration" on the PFS as a factor that contributed to the dosing errors, and we agree with the reporters' assessment. The addition of pediatric dosing without corresponding labeling changes to add graduation marks to the PFS may allow the errors in the off-label use of this product to persist.

In the September 2015 teleconference, both OND and the Applicant acknowledged that the current Neulasta prefilled syringes lack graduations to enable direct administration of pegfilgrastim in accurate doses for the proposed ARS indication. (b)(4)

From the medication error perspective, we reviewed the labeling with OND's advice to Amgen (b)(4)

We note that the labeling statements clearly advise that the prefilled syringe is not designed for direct administration of the drug for the doses less than 6 mg and provides information in Section 2, (b)(4) 11, and 16 of the labeling to describe the appropriate use of the PFS and physical presentation of the product for healthcare providers. Similar statements and language appear in the Zarxio (filgrastim-SNDZ) label approved in March 2015.

Based on our analysis, we believe these statements should help to reduce the risk of error in circumstances where the label is read and attended to by providers. However, prefilled syringes are generally designed for direct patient administration. Syringes are also among the most commonly used devices to deliver drugs, and, as a general matter, they tend to have calibrated graduation marks that allow for accurate measurement of variable quantities of fluid. Collectively, these factors will likely predispose some practitioners who are ordering, dispensing or administering a prefilled syringe of Neulasta for ARS to not consult the label for this administration aspect. Thus, there is some likelihood that practitioners will mistakenly assume

that the PFS can accurately measure a variable range of doses to be directly administered to a patient. For these reasons, our analysis suggests that even with the dosing information and statements against direct administration in the label, there is some residual risk for error due to the fact that the labeling of the Neulasta PFS is not consistent with the design features of syringes that healthcare providers are familiar with and because it is not designed to measure a variable amount of liquid that corresponds to the labelled doses for ARS.

4 CONCLUSION & RECOMMENDATIONS

Our review of the proposed Prescribing Information (PI) modifications for Neulasta (BLA 125031/S-180) identified medication error concerns regarding use in pediatric patients. Neulasta is currently available as a prefilled syringe containing 6 mg/0.6 mL, the recommended adult dose to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs. (b)(4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

We provide specific recommendations on the proposed labeling below. Overall, we do not believe that changes to the prescribing information alone will completely eliminate the risk of medication errors. The best approach to facilitate the accurate dosing of pegfilgrastim for ARS would be to require Amgen to label the PFS with calibrated graduation marks to accommodate the full range of pediatric dosages or develop an alternative presentation to facilitate the safe use of pegfilgrastim for ARS. Such changes would take time for Amgen to implement since manufacturing changes may be needed to add the graduation marks to their syringe and data may need to be gathered to support the accurate measurement of the marks, both of which would further delay this supplement that is essential to the public health. And, we have identified some alternative labeling approaches that can be implemented immediately to offer some reduction in the risk of error and that would not delay action on a supplement that is essential to the public health. Thus, in the interest of an efficient implementation of this labeling that is intended to address an essential public health need, we do not recommend that DMIP require Amgen to add graduation marks to the PFS labeling at this time. (b)(4)

[REDACTED]

[REDACTED]

Given that we have concern regarding the potential residual risk of dosing errors with Neulasta, we will monitor post-marketing errors to gauge whether the statements are sufficient and recommend any appropriate regulatory action for DMIP's consideration if and when we identify safety issues related to this issue.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

- a. Section 2 Dosage and Administration, 2.1 Cancer Patient Receiving Myelosuppressive Chemotherapy
 - i. We do not concur with the revision to this section in which “in adults” was deleted. This information should remain in the PI to specify that this indication is only approved in the adult population
- b. Section 2 Dosage and Administration, 2.2 (b)(4) with Hematopoietic Syndrome of Acute Radiation Syndrome
 - i. We do not concur with the revision to this section in which (b)(4) was deleted. The aforementioned phrase is a necessary clarification to inform prescribers that the pediatric dosing is weight based.
- c. Section 2 Dosage and Administration, 2.3 Administration
 - i. Include the following statement to alert users to the use limitations of the Neulasta prefilled syringe, particularly as it relates to pediatric doses:
 1. Neulasta prefilled syringe is not designed to allow for direct administration of doses less than 0.6 mL (6 mg). The syringe does not bear graduation marks which are necessary to accurately measure doses of Neulasta less than 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of less than 0.6 mL (6 mg) is not recommended due to the potential for dosing errors.
 - ii. Revise the subheading (b)(4) to read “Patients weighing less than 45 kg with Hematopoietic Subsyndrome of Acute Radiation Syndrome”. This revision will help to indicate that this dosing should only be utilized in patients with ARS and will help mitigate the risk of prescribers using the dosing table for patients with other indications.
- d. Section 3 Dosage Forms and Strengths
 - i. Revise the statement “Injection: 6 mg/0.6 mL solution in a single-use prefilled syringe for manual use only” to read “Injection: 6 mg/0.6 mL solution in a single-use prefilled syringe that does not bear graduation marks and is for manual use only”. We recommend this revision to indicate to readers that the prefilled syringe cannot accommodate doses less than 6 mg (0.6 mL).
- e. Section 11 Description
 - i. Revise the two bullet points listed under “Neulasta (b)(4) two presentations” to read:

1. Neulasta for manual subcutaneous injection is supplied in 0.6 mL prefilled syringes. The prefilled syringe does not bear graduation markings and is designed to deliver the entire contents of the syringe (6 mg/0.6 mL).
 2. On-body Injector for Neulasta is supplied with a prefilled syringe containing 0.64 mL of Neulasta in solution that delivers 0.6 mL of Neulasta in solution. The syringe does not bear graduation marks and is only to be used with the On-body Injector for Neulasta.
- f. Section 16 How Supplied/Storage and Handling
- i. Revise this section to include the following statement:
 1. Neulasta prefilled syringe does not bear graduation markings and is intended only to deliver the entire contents of the syringe (6 mg/0.6 mL) for direct administration. Use of the prefilled syringe is not recommended for direct administration for patients weighing less than 45 kg who require doses that are less than the full contents of the syringe.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Neulasta that Amgen submitted on February 13, 2015.

Table 2. Relevant Product Information for Neulasta (pegfilgrastim)	
Initial Approval Date	January 31, 2002
Active Ingredient	Pegfilgrastim
Indication	- Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia (b)(4)
Route of Administration	Subcutaneous
Dosage Form	Pre-filled syringe
Strength	6 mg/0.6 mL
Dose and Frequency	<i>Cancer patients receiving myelosuppressive chemotherapy</i> - 6 mg administered subcutaneously once per chemotherapy cycle (b)(4)
How Supplied	- 6 mg/0.6 mL solution in a single use prefilled syringe for manual use only - 6 mg/0.6 mL solution in a single prefilled syringe co-packaged with the On-body Injector for Neulasta
Storage	Store refrigerated between 36° to 46°F (2° to 8°C) (b)(4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On October 2, 2015, we searched the L:drive and AIMS using the terms, Neulasta and pegfilgrastim, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two previous reviews relevant to this review.^{1,2} The 2010 labeling review recommended the development of a pediatric specific dosing device; this recommendation was not implemented.

¹ Abate, Richard. Medication Error Review for Neulasta BLA 125031. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2010 OCT 18. RCM No.: 2010-1804.

² Rahimi, Leeza. Label and Labeling Review Memo for Neulasta BLA 125031/S-180. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 MAY 18. RCM No.: 2015-973.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On September 30, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Joint Commission QAA Community PA Patient Safety Canada Safety Bulletin Nursing Community Acute Care
Search Strategy and Terms	Boolean Query: Neulasta OR pegfilgrastim

D.2 Results

Our search did not identify any relevant Neulasta medication errors.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on October 2, 2015 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.³

Table 3: FAERS Search Strategy	
Date Range	FDA Received Date To: 20151001
Product	Pegfilgrastim [active ingredient] Neulasta [product name]
Event (MedDRA Terms)	DMEPA Official FBIS Search Terms Event List: Contraindicated Drug Administered (PT) Drug Administered to Patient of Inappropriate Age (PT) Inadequate Aseptic Technique in Use of Product (PT) Medication Errors (HLGT) Overdose (PT) Prescribed Overdose (PT) Prescribed Underdose (PT) Product Adhesion Issue (PT) Product Compounding Quality Issue (PT) Product Formulation Issue (PT) Product Label Issues (HLT) Product Packaging Issues (HLT) Product Use Issue (PT) Underdose (PT)
Country	USA

E.2 Results

Our search identified 118 cases, of which four cases described medication errors relevant to this review.

³ The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

Physical product label issue (n = 3)

- Two cases (FAERS Case No. 10521961 and 10640649) described the same medication error case; the initial report was from the healthcare facility and the second report was from ISMP. The reports noted that Neulasta is commonly used off-label in pediatric oncology patients and that Neulasta's outer packaging does not note that the prefilled syringes are not calibrated. The reports also stated that pharmacy staff was hesitant to open the packaging prior to dispensing due to product cost. Inadvertently, Neulasta prefilled syringes were dispensed to pediatric patients on several occasions, including cases in which the dose was less than 6 mg.
- One case (FAERS Case No. 9256083) reported that due to lack of calibration of the Neulasta prefilled syringe, inaccurate doses of Neulasta were administered. The intended doses were 0.2 mL and 0.4 mL.
- A review of the carton labeling for Neulasta indicates that the labeling does not mention that the prefilled syringes are not calibrated. A review of Section 2 of the Prescribing Information notes that Neulasta is not indicated for use in pediatric oncology patients, and therefore, the indication is considered off label. However, because the proposed indication for this supplement includes pediatric patients, revisions to Prescribing Information are warranted.

Wrong dose (n = 1)

- One case (FAERS Case No. 6944061) described a medication error in which a 19 month old patient was prescribed Neulasta 1 mg and received an overdose of 6 mg. The patient was on Neulasta for chemotherapy-induced neutropenia. The physician stated that the patient experienced bone pain and elevated WBCs in response to the overdose; however, the patient did not experience additional clinical sequelae and recovered well.
- A review of Section 2 of the Prescribing Information notes Neulasta is not indicated for chemotherapy-induced neutropenia in pediatric patients, and therefore, the indication considered off label. However, because the proposed indication for this supplement includes pediatric patients, revisions to Prescribing Information are warranted.

We excluded 114 cases describing the following errors which were not relevant to this review: wrong drug (n = 24), Neulasta OBI device issue (n = 22), improper timing of administration (n = 18), wrong site of administration/wrong route (n = 13), improper storage/expired product (n = 9), unrelated literature reports (n = 5), dose omission (n = 4), wrong patient (n = 2), wrong dose (n = 2), accidental exposure (n = 1), off label use (n = 1), and other medication errors (n = 13).

E.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

FAERS Case	Version	Manufacturer Control Number
------------	---------	-----------------------------

Number		
10521961	1	Not reported
6944061	1	(b)(4)
10640649	1	Not reported
9256083	1	(b)(4)

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁴ along with postmarket medication error data, we reviewed the following Neulasta labels and labeling submitted by Amgen on February 13, 2015.

- Prescribing Information

⁴ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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10/23/2015

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Drug Utilization Review

Date: October 7, 2015

Reviewer: Kusum Mistry, PharmD
Drug Utilization Analyst
Division of Epidemiology II

Team Leader: Mohamed Mohamoud, PharmD, MPH, BCPS
Drug Utilization Team Leader
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Deputy Director: Grace Chai, LCDR, Pharm.D.
Deputy Director for Drug Utilization
Division of Epidemiology II

Subject: Neulasta[®] (Pegfilgrastim) Drug Utilization

Drug Names: Neulasta[®] (Pegfilgrastim)

Application Type/Number: BLA 125031

Applicant/sponsor: Amgen Inc.

OSE RCM #: 2015-1541

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EXECUTIVE SUMMARY

The Division of Medical Imaging Products (DMIP) requested drug utilization data on Neulasta® (pegfilgrastim) to assess the extent of use in pediatric patients. This consult request was prompted by an efficacy supplement submitted by the Sponsor to seek a new indication for Neulasta® for the treatment of adult and pediatric victims who are at risk of developing myelosuppression after a radiological/nuclear incident. Pegfilgrastim is not currently approved in the U.S. for use in pediatrics. In support of this assessment, the Division of Epidemiology (DEPI II) examined utilization of pegfilgrastim in pediatric patients based on U.S. non-federal hospital data and health plan claims data projected to the U.S. commercially insured population from 2010 through 2014.

Our analyses of U.S. non-federal hospital data showed that (b)(4) pediatric patients aged 0-17 years ((b)(4)) had a hospital discharge billing for pegfilgrastim in 2014. During the five year period, the use of pegfilgrastim in the pediatric population (b)(4) from (b)(4) patients in 2010 to (b)(4) patients in 2014. Patients aged 7-12 accounted for the largest proportion of pediatric use (b)(4) followed by patients aged 13-17 years at (b)(4) of pediatric patients. However, the overall use of pegfilgrastim in pediatric patients in the hospital data may be underestimated as standalone pediatric and other specialty hospitals are not available in the hospital database.

Our analyses of U.S. health plan claims data projected to the U.S. commercially insured population showed that approximately (b)(4) pediatric patients aged 0-17 years had a prescription and/or procedure claim for pegfilgrastim in 2014. During the defined study period, the pediatric use of pegfilgrastim increased (b)(4) patients in 2010 to (b)(4) patients in 2014. Patients aged 13-17 years accounted for the largest proportion of use at (b)(4), followed by patients aged 3-6 years at (b)(4). Based on the claims data, (b)(4) pediatric patients had a prescription and/or procedure claim for pegfilgrastim AND a claim for the selected diagnoses codes for radiotherapy in 2014.

The overall findings from these analyses show use of pegfilgrastim in the pediatric population during the examined time period although current labeling states that the safety and effectiveness in pediatric patients have not been established.

1 INTRODUCTION

The Division of Medical Imaging Products (DMIP) requested drug utilization data on Neulasta® (pegfilgrastim) to assess the extent of use in pediatric patients. DMIP is evaluating an efficacy supplement submitted by the Sponsor to seek a new indication for Neulasta® (b)(4)

(b)(4) Since pegfilgrastim is not currently approved in the U.S. for use in pediatrics, these data will assist DMIP in evaluating this efficacy supplement. In support of this assessment, the Division of Epidemiology (DEPI II) examined utilization of pegfilgrastim in pediatric patients based on U.S. non-federal hospital data and health plan claims data projected to the U.S. commercially insured population from 2010 through 2014.

1.1 BACKGROUND

On February 13, 2015, the sponsor, Amgen, submitted an efficacy supplemental BLA (sBLA-180) for the use of Neulasta[®] (b)(4)

Since human clinical trials cannot be ethically conducted to study treatment of myelosuppression from radiation exposure resulting in the hematopoietic syndrome of acute radiation syndrome, the sponsor is seeking approval using data from efficacy studies in well-characterized animal models under the FDA Animal Rule (21 CFR 601.90).

In order to evaluate the supplemental application, on June 4, 2015 DMIP requested information on all available safety information on the use of Neulasta[®] in the pediatric population from Amgen sponsored studies, literature reviews and all safety databases available to Amgen.² (b)(4)

In response to this information, DMIP is seeking drug utilization to evaluate the extent of use of pegfilgrastim in the pediatric population.

1.2 PRODUCT INFORMATION³

Neulasta[®] (pegfilgrastim) is a leukocyte growth factor approved under BLA 125031 on January 31, 2002. Pegfilgrastim is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Pegfilgrastim is available in a 6 mg/0.6 mL strength solution and supplied in a single use prefilled syringe for manual use and a delivery kit containing a single prefilled syringe co-packaged with an On-body Injector. The recommended dose of pegfilgrastim is 6 mg administered subcutaneously once per chemotherapy cycle in adults.

The *Prescribing Information* for pegfilgrastim currently states that the safety and effectiveness in pediatric patients have not been established.

2 METHODS AND MATERIALS

2.1 DETERMINING SETTING OF CARE

¹ Neulasta[®], BLA 125031. DARRTS: Cover Letter for Efficacy Supplement 180. eCTD Sequence Number 0230, Supporting Document 1137. Amgen, Thousand Oaks, CA. Submitted on February 13, 2015.

² Neulasta[®], BLA 125031. DARRTS: Response to Information Request of 4 June 2015 (Supplement 180). eCTD Sequence Number 0247, Supporting Document 1235. Amgen, Thousand Oaks, CA. Submitted on July 7, 2015.

³ Neulasta[®] (pegfilgrastim) prescribing information. Amgen Inc. Thousand Oaks, CA. December 2014.

The IMS Health, IMS National Sales Perspectives™ (NSP) database (see **Appendix B** for database description) was used to determine the settings of distribution for pegfilgrastim. From 2010 through 2014, sales data for pegfilgrastim by the number of bottles/packages sold from the manufacturer to all U.S. channels of distribution showed that approximately (b)(4) sales were to non-retail settings (primarily clinics and non-federal hospitals), (b)(4) mail-order/specialty pharmacies, (b)(4) to retail settings.⁴

As a result, this analysis focuses on pegfilgrastim use from non-federal hospital data and health plan claims data for care provided in a clinics, hospitals, physician offices, and retail and mail-order/specialty pharmacies.

2.2 DATA SOURCES

Proprietary drug utilization databases available to the Agency were used to conduct this analysis. Detailed descriptions of the databases are included in Appendix B.

2.2.1 U.S. Non-Federal Hospital Data

The IMS Inpatient Healthcare Utilization System (IHCareUS) database was used to obtain the nationally estimated number of patients with a hospital discharge billing for pegfilgrastim from inpatient and outpatient settings of U.S. non-federal hospitals, stratified by patient age groups (0-2, 3-6, 7-12, 13-17, and 18 years and older) from 2010 through 2014 by calendar year. This database only includes non-federal hospital data and does not include data from Federal hospitals (including VA facilities) and other specialty hospitals (including children's hospitals and other standalone specialty oncology hospitals).

2.2.2 U.S. Health Plan Claims Data⁵

IMS Health conducted a health plan claims analysis from their IMS Pharmetrics Plus Health Plan Claims Database to obtain the number of patients with one or more pharmacy prescription and/or procedure claim(s) for pegfilgrastim stratified by patient age groups (0-2, 3-6, 7-12, 13-17, and 18 years and older) from 2010 through 2014 by calendar year. Healthcare claims data from a closed sample of more than (b)(4) covered lives with both medical and pharmacy benefits were then projected nationally to the U.S. commercially insured population. The health plan claims were captured from all settings of care including outpatient retail pharmacy and non-retail facilities (i.e. physician's offices or clinics). Only patients insured through an employer-sponsored plan or a self-purchased commercial plan were included in the data analysis if they had a pharmacy prescription/ procedure claim for pegfilgrastim in any calendar year from 2010 through 2014.

⁴ IMS Health, IMS National Sales Perspectives™ Database. Years 2010-2014. Extracted September 2015. File: NSP 2015-1541 Neulasta by Sup Ch Y2010-2014, 9-9-2015

⁵ IMS Health, IMS Pharmetrics Plus Health Plan Claims Neulasta Ad Hoc Study Requirements and Project Plan. Dan Bradford and Silvia Valkova. Submitted via email on August 25, 2015.

Patient selection was based on the presence of a pharmacy prescription claim using National Drug Codes for pegfilgrastim and/or the presence of a procedure claim using the Health Care Common Procedure Coding System.

- National Drug Codes (NDC): 55513-0190-01, 55513-0192-01, 54868-5229-00
- Health Care Common Procedure Coding System (HCPS): J2505

Patients with a health plan claim (prescription and/or procedure) for pegfilgrastim were also further stratified by selected diagnoses codes of interest for radiotherapy using the International Classification of Diseases, Ninth Revision System (ICD-9-CM). The diagnoses codes of interest were captured only in patients with a diagnosis claim made within 365 days prior to the first pegfilgrastim claim during the index time frame for each cohort (years 2010 through 2014). The selected diagnoses codes of interest included the following ICD-9 codes for radiotherapy:

- Irradiation: ICD-9 V15.3
- Radiotherapy: ICD-9 V58.0
- Convalescence following radiotherapy: ICD-9 V.66.1
- Follow up exam following radiotherapy: ICD-9 V67.1
- Overdose of radiation in therapy: ICD-9 E873.2
- Radiological procedure and radiotherapy: ICD-9 E879.2
- Effects of radiation, unspecified: ICD-9 990

These health plan claims data were then projected to the **U.S. commercially insured population** using U.S. Census data by IMS Health for each calendar year from 2010 through 2014. Patient weights were established by using the total eligible population for each year as the denominator and the total number of people in the commercially insured population from census data as the numerator. The projection weights were created for each age group independently and are developed based on the timeframe of the data being studied so that the results will reflect the size of the population at that time. The total eligible population consisted of all patients meeting the continuous enrollment requirement (current calendar year plus prior calendar year) as well as having good demographic data quality. Thus, the patients selected were a subset of the total eligible population.

3 RESULTS

3.1 U.S NON-FEDERAL HOSPITAL PATIENT DATA

Table 1 in Appendix A provides the nationally estimated number of patients with a hospital discharge billing for pegfilgrastim from U.S. non-federal hospitals, stratified by patient age groups, from 2010 through 2014 by calendar year. In 2014, approximately (b)(4) patients had a hospital discharge billing for pegfilgrastim during an inpatient or outpatient hospital visit. The adult population aged 18 years and older accounted for the vast majority of hospital utilization (b)(4) of total patients, while the pediatric population aged 0-17 years accounted for (b)(4) patients) of total patients. Among the pediatric population, patients aged 7-12 years accounted for the largest proportion of use at (b)(4) followed

by patients aged 13-17 years (b)(4) and patients aged 3-6 years (b)(4) (b)(4) of pediatric patients. Patients aged 0-2 years accounted (b)(4) patients) of pediatric patients in 2014.

Figure 1 in Appendix A shows the total number of pediatric patients aged 0-17 years with a hospital discharge billing for pegfilgrastim from U.S. non-federal hospitals, stratified by pediatric patient age groups, from 2010 through 2014 by calendar year. Although the proportion remained the same (b)(4) throughout the examined time period, the absolute number of pediatric patients (b)(4) in 2010 (b)(4) in 2014.

3.2 U.S. HEALTH PLAN CLAIMS PATIENT DATA

Table 2 in Appendix A provides the nationally estimated number of patients with a pharmacy prescription and/or procedure claim for pegfilgrastim in the U.S. commercially insured population, stratified by patient age groups, from 2010 through 2014 by calendar year. In 2014, (b)(4) patients had a prescription and/or procedure claim for pegfilgrastim. The adult population aged 18 years and older accounted for the vast majority of patient use (b)(4) of total patients, while the pediatric population aged 0-17 years accounted (b)(4) total patients. Among the pediatric population, patients aged 13-17 years accounted for the largest proportion of use (b)(4) followed by patients aged 3-6 years (b)(4) and patients aged 7-12 years (b)(4) of pediatric patients. Patients aged 0-2 years accounted (b)(4) pediatric patients in 2014.

Figure 2 in Appendix A shows the total number of pediatric patients aged 0-17 years with a prescription and/or procedure claim for pegfilgrastim in the U.S. commercially insured population, stratified by patient age groups, from 2010 through 2014 by calendar year. Similar to the hospital utilization, the proportion remained the same (b)(4) throughout during the defined time period, the absolute number of pediatric patients (b)(4) in 2010 to (b)(4) in 2014.

3.3 U.S. HEALTH PLAN CLAIMS DIAGNOSES DATA

Table 3 in Appendix A provides the nationally estimated number of patients with a prescription and/or procedure claim for pegfilgrastim AND a claim for the selected diagnoses codes of interest for radiotherapy in the U.S. commercially insured population, stratified by patient age groups, from 2010 through 2014 by calendar year. In 2014, out (b)(4) with a claim for pegfilgrastim (b)(4) patients had a prescription and/or procedure claim for pegfilgrastim AND a claim for the selected diagnoses codes for radiotherapy. During the defined time period, the total number of pediatric patients aged 0-17 years with a claim for pegfilgrastim AND a diagnosis claim for radiotherapy (b)(4) in 2010 (b)(4) in 2014.

4 DISCUSSION

Pegfilgrastim is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs; however, the safety and efficacy for pediatric use have not been established. Therefore, an analysis of pediatric drug utilization patterns for pegfilgrastim are provided in this review to assist DMIP in evaluating the Sponsor's efficacy supplement to seek a new indication for Neulasta® (b)(4)

Our findings from both U.S non-federal hospital data and health plan claims data show that the vast majority of pegfilgrastim use was in the adult population aged 18 years and older. According to U.S. non-federal hospital data, the pediatric population aged 0-17 years accounted (b)(4) with a hospital discharge billing for pegfilgrastim throughout the examined time period. However, over the five year study period, the total number of pediatric patients did increase (b)(4) in 2010 to (b)(4) 2014. It is also important to note that the IMS IHCARUS database used to estimate the use of pegfilgrastim in hospitals only includes non-federal hospital data and does not include data from Federal hospitals (including VA facilities) and other specialty hospitals (including children's hospitals and other standalone specialty oncology hospitals). Therefore, the overall use of pegfilgrastim in pediatric patients in our hospital data may be underestimated as we suspect that most pediatric patients using pegfilgrastim are treated in standalone pediatric and specialty hospitals.

Based on U.S. health plan claims data, our findings show that the pediatric population accounted (b)(4) patients with a claim for pegfilgrastim. Our health plan claims analysis also examined which pediatric patients with a claim for pegfilgrastim also had a diagnoses claim for radiotherapy; our results suggest that only a small proportion of pediatric patients were captured with a claim for pegfilgrastim and the selected diagnoses claims for radiotherapy.

Although the claims data analysis suggests that there may be some use of pegfilgrastim in the pediatric population for myelosuppression due to radiotherapy, many limitations prohibit the use of claims based analyses solely to determine the prevalence or extent of off-label use. First, diagnosis codes used in claims data analysis are generated for billing purposes - not for clinical care or research- and thus may reflect billing practices and not true disease prevalence. Second, the claims data used in our analyses were not validated by medical records to make sure that the coded diagnoses are truly reflective of the patients' clinical conditions. Therefore, the estimates provided may be overestimates of the true number because provisional or rule-out diagnoses may have been included. Third, there is also no direct linkage in the claims data between drug and diagnosis, meaning that we cannot assume that these diagnoses represent actual indications for the drug treatment. Finally, it is also important to note that diagnoses were captured if a claim with the selected ICD-9 diagnoses codes was made within 365 days prior to the first pegfilgrastim claim. The exact time correlation between when diagnosis claims were billed in relation to pegfilgrastim claims was not examined in this study. Therefore, any diagnosis claims billed outside the observed time periods were not captured.

The IMS Pharmetrics Plus Health Plan Claims data presented in this review were obtained claims from a sample of (b)(4) covered lives with both medical and pharmacy benefits in the commercially insured U.S. population, including a small subset of patients insured through both a private plan and a government plan such as Medicare and Medicaid. Of note, these analyses may underestimate the utilization of pegfilgrastim therapy in the pediatric population as it does not capture patients covered by Medicaid. These claims data were then projected by IMS to the commercially insured population to provide national estimates to this population. Therefore, this analysis likely underestimates the utilization of pegfilgrastim therapy in the elderly population, and the overall fee for service Medicare and Medicaid populations. As a result, patients aged 65 years and older might be underestimated due to Medicare coverage in this population. For patients aged 0-2 years old, patients were captured by including those with a year of birth during the cohort data time frame and continuously enrolled from their first enrollment date through the end of the cohort data time frame. The assumption is made that the patient's first enrollment date corresponds to their date of birth. Also, data on uninsured or cash-paying patients are not available; however, due to the substantial high cost of pegfilgrastim, it is less likely that un-insured or cash-paying patients use pegfilgrastim.

The estimates provided are national estimates, but no statistical tests were performed to determine statistically significant changes over time. Therefore, all changes over time should be considered approximate, and may be due to random error.

5 CONCLUSIONS

Utilization of pegfilgrastim from U.S. non-federal data and U.S. health plan claims data were examined to assist DMIP in evaluating the extent of use in pediatric patients. Based on an analysis of non-federal hospital data, (b)(4) patients had a hospital discharge billing for pegfilgrastim, of which the pediatric population aged 0-17 years accounted for (b)(4) in 2014. Patients aged 7-12 years accounted for the largest proportion of use (b)(4), followed by patients aged 13-17 years (b)(4).

Based on an analysis of health plan claims data in the U.S. commercially insured population, (b)(4) patients had a prescription and/or procedure claim for pegfilgrastim in 2014. Similar to hospital utilization, the pediatric population accounted (b)(4). Patients aged 13-17 years accounted for the largest proportion (b)(4) followed by patients aged 3-6 years (b)(4) patients. The overall findings from these analyses show use of pegfilgrastim in the pediatric population during the examined 5-year study period although current labeling states that the safety and effectiveness in pediatric patients have not been established.

6 APPENDICES

6.1 APPENDIX A: TABLES AND FIGURES

Table 1:

**Nationally estimated number of patients with an inpatient or outpatient hospital discharge billing for
neogfilgrastim from U.S. non-federal hospitals[†] stratified by patient age 2010 through 2014**

(b)(4)

Figure 1:

Nationally estimated number of pediatric patients (0-17 years) with an inpatient or outpatient hospital discharge billing for pegfilgrastim from U.S. non-federal hospitals*, 2010 through 2014

(b)(4)

Table 2:

Nationally estimated number of patients with a prescription and/or procedure claim for pegfilgrastim in the U.S. commercially insured population, stratified by patient age, 2010 through 2014

(b)(4)

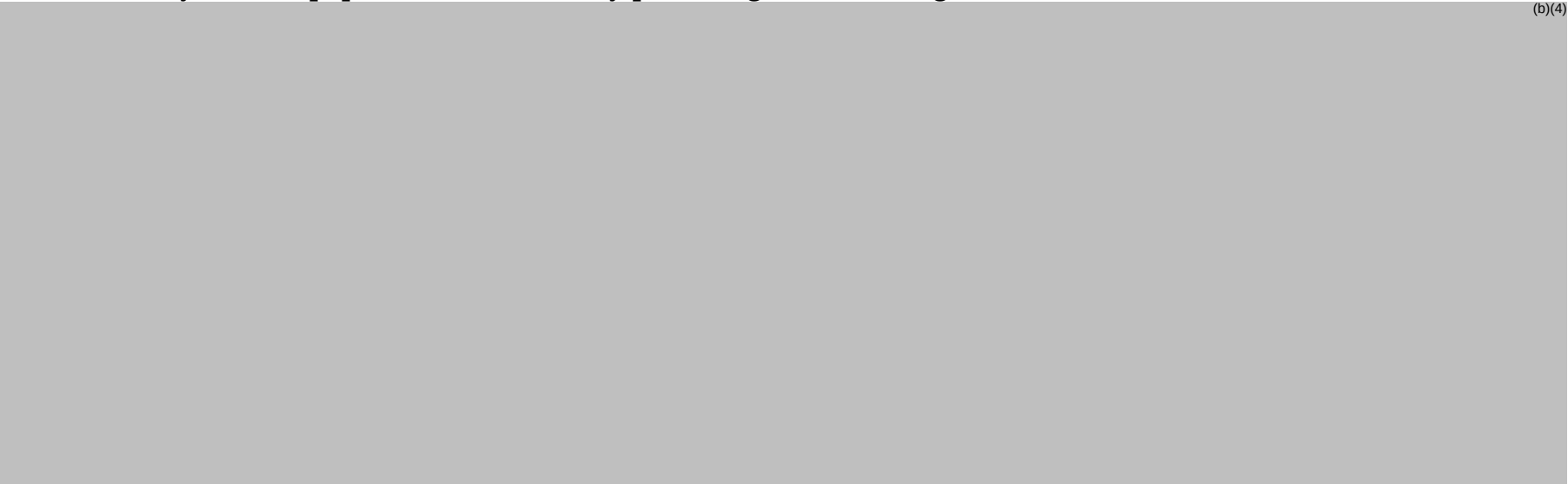


Figure 2:

Nationally estimated number of pediatric patients with a prescription and/or procedure claim for pegfilgrastim in the U.S. commercially insured population, 2010 through 2014

(b)(4)

Table 3:

Nationally estimated number of patients with a prescription and/or procedure claim for pegfilgrastim AND a claim for selected ICD-9 diagnoses codes for radiotherapy in the U.S. commercially insured population, stratified by patient age, 2010 through 2014

(b)(4)

6.2 APPENDIX B: DRUG USE DATABASE DESCRIPTIONS/LIMITATIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS, Inpatient HealthCare Utilization System (IHCareUS)

The IMS, Inpatient HealthCare Utilization System (IHCareUS) provides hospital inpatient and outpatient emergency department encounter transactions and patient level data drawn from hospital operational files and other reference sources. Encounter information is available from mid-2001, are collected weekly and monthly and are available 25-30 days after the end of each monthly period. This robust data set includes (b)(4) hospitals with hospital inpatient and outpatient encounter data linked to each appropriate patient as well as to select individual hospital departments by anonymized, consistent, longitudinal patient identifiers. These data include (b)(4) annual hospital encounters (including ED visits) representing acute care, short-term hospital inpatient sites, and their associated hospital emergency departments in order to measure and track the near term health care utilization of hospitalized patients. Each hospital patient encounter includes detailed drug, procedure, device, diagnosis, and applied charges data as well as location of initiation of each service within the hospital setting of care (e.g. Pediatric, ICU) by day for each patient's entire stay, as well as patient demographics and admission/discharge characteristics. IMS' datasets are geographically representative, and include claims across all third-party payer types, including commercial insurers, Medicare, Medicare Part D, Medicaid and other payer types.

The IMS Hospital CDM sample does not include Federal hospitals, including VA facilities, and some other specialty hospitals (including children's hospitals and other standalone specialty hospitals), and does not necessarily represent all acute care hospitals in the U.S. in all markets. Caveats of the IMS CDM data source are common to this type of hospital charge information, but are mostly limited to limitations of charge descriptions and what is actually entered by the sample hospitals. However, validations of IMS' Hospital CDM data using both the National Hospital Discharge Survey (NHDS) and the AHRQ HCUP data have shown IMS' patient level data to be representative and accurate across multiple therapeutic areas.

IMS, PharMetrics Plus Claims Database

The PharMetrics Plus database, a healthcare claims database, contains more (b)(4) covered lives with both medical and pharmacy benefits. PharMetrics Plus contains claims data from January 1, 2006 onwards. The information is continuously updated and available with a 4-6 month lag due to claims adjudication. In terms of geographic span, PharMetrics Plus covers the four United States census regions and has patient representation in all states. The data is similar to the US Commercially Insured population in age and gender for those 65 years of age and under.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KUSUM S MISTRY

10/07/2015

The drug use data has been cleared by the database vendors.

MOHAMED A MOHAMOUD

10/07/2015

GRACE CHAI

10/08/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology**

Pharmacovigilance Review

Date: August 27, 2015

Reviewer: Kathleen M. Phelan, RPh
Division of Pharmacovigilance II

Team Leader: Sara Camilli, PharmD, BCPS
Division of Pharmacovigilance II

Deputy Division Director: S. Christopher Jones, PharmD, MS, MPH
Division of Pharmacovigilance II

Product Name: Neulasta (pegfilgrastim)

Subject: Adverse events in pediatric patients

Application Type/Number: BLA 125031

Submission Number: sBLA-180

Applicant/Sponsor: Amgen Inc.

OSE RCM #: 2015-1696

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EXECUTIVE SUMMARY

As requested by the Division of Medical Imaging Products (DMIP), this review evaluates all FDA Adverse Event Reporting System (FAERS) reports of adverse events with Neulasta (pegfilgrastim) in pediatric patients received since the October 2014 Pharmacovigilance Memo in which DPV summarized all adverse events with Neulasta in pediatric patients. Also, this review provides the adverse event reports by pediatric age group in the October 2014 Pharmacovigilance Memo.

FDA received seven new adverse event cases with Neulasta (pegfilgrastim) since the 2014 memo. The new cases included one potential dosing error report. The 2014 memo included two dosing error reports.

DPV will refer the medication error cases to the Division of Medication Error Prevention and Analysis (DMEPA) to determine if further review is needed.

If a dose less than 6 mg is approved for pediatric patients, DPV recommends DMIP consult DMEPA to determine if carton- or container-labeling changes are needed to minimize dosing errors in this patient population.

1 INTRODUCTION

This review evaluates all FDA Adverse Event Reporting System (FAERS) reports of adverse events with Neulasta (pegfilgrastim) in pediatric patients received since the October 2014 Pharmacovigilance Memo, authored by Jenna Lyndly and available in DARRTS, in which DPV summarized all adverse events with Neulasta in pediatric patients. Also, this review provides the break-down by age group (0<2, 2<6, 6<12, and 12≤17 years) of the adverse event reports in the October 2014 Pharmacovigilance Memo. This review was requested by the Division of Medical Imaging Products (DMIP) as part of the evaluation of sBLA-180, which proposes an additional indication: (b)(4)

(b)(4) DMIP is considering approval (b)(4) “increase survival in patients acutely exposed to myelosuppressive doses of radiation.”

1.1 BACKGROUND

Neulasta is PEGylated filgrastim (recombinant methionyl human C-GSF) that acts on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end cell functional activation. Neulasta is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients receiving myelosuppressive anti-cancer drugs. A single 6 mg dose is administered once per treatment cycle, 24 hours after the administration of cytotoxic chemotherapy.^a The product is supplied in a dispensing pack containing one sterile 6 mg/0.6 mL prefilled syringe.

On October 21, 2014, at the request of the Division of Hematology Products (DHP), the Division of Pharmacovigilance II (DPV II) completed a memo providing an overview of the pediatric cases for Neulasta (pegfilgrastim) in FAERS.^b The memo was written to support discussion at an FDA Center Director briefing on November 19, 2014, to discuss the laws regarding biosimilars and the Pediatric Research Equity Act (PREA).

The October 2014 DPV II Pharmacovigilance Memo concluded that there were no new significant safety concerns for Neulasta in the pediatric cases.

The October 2014 memo summarizes 55^c cases comprising 21 reports of labeled events (9 allergic reactions, 7 exposures during pregnancy, 3 leukocytosis/increased white blood cell counts, 2 injection site reactions) and 34 reports of unlabeled events (20 hematologic events, 8 miscellaneous adverse events, 3 medication errors, and 3 cases of interest). Except for the cases of interest and the medication errors, the memo points out that the cases are confounded by disease and concomitant medications, making causal association with a specific drug difficult to determine. The medication errors included overdosing of two patients, aged 1.5 and 2 years, who each received the full syringe containing 6 mg Neulasta followed by white blood cell counts

^a Neulasta product labeling. Thousand Oaks, California: Amgen Inc. December 2014. In COR-SBLAACTION-05 (Approval) for BLA 125031 Supplement-175 (Manufacturing (CMC)). December 23, 2014. DARRTS

^b Lyndly JM. Consult Rev-Safety-03 (Post-Market Safety Review). BLA 125031 Supplement-170 (Labeling) October 21, 2014. DARRTS.

^c The memo provides a total count of included cases of 56; this was a mathematical error.

above 50,000/mcL in both cases but no adverse clinical events. The prescribed doses were 1 mg and 100 mcg/kg for the 1.5-year-old and 2-year-old, respectively. According to the published case report, the dose of 6 mg was equivalent to 937 mcg/kg for the 2-year-old (FAERS case 7376708).^d In the third medication error, the physician suspected intramuscular rather than subcutaneous administration. The cases of interest were a possible interaction with vincristine causing neurotoxicity, a case of febrile neutropenia, and a case of thrombocytosis.

Neulasta may have contributed to the adverse events in the cases of interest but none are conclusive. In the case of possible interaction with vincristine, the reporter said the neurological adverse events were more severe than expected and postulated an interaction that increased vincristine exposure. The adverse events, though severe in this case, are consistent with vincristine labeling. In the case of febrile neutropenia, the patient had a recurrence, leading the reporting physician to consider that Neulasta may have been causally related, but the physician then increased the dose of Neulasta. In the case of thrombocytosis, the physician reported that the patient “had presented with thrombocytosis at several Neulasta administrations,” along with leukocytosis, but provides no specific temporal information.

1.2 REGULATORY HISTORY

Neulasta was approved by the FDA under BLA 125031 in January 2002 for use in adults, “to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.”

In February 2015, the sponsor submitted an efficacy supplement (s-180) seeking, “approval under the Animal Rule (21 CFR 601.90) for pegfilgrastim (b)(4)

The efficacy supplement is under review by DMIP.

In March 2015, DMIP requested that the sponsor, (b)(4) DMIP is considering approval of Neulasta (b)(4) “increase survival in patients acutely exposed to myelosuppressive doses of radiation.”

^d Dufour C, Cappelli B, Calvillo M, et al. Similar favorable outcome of pegfilgrastim over-dose in patients with different age and underlying disease [Letter]. *Haematologica* 2010; 95(4): 684-685.

^e Supporting Document Number 1137, eCTD Sequence Number 0230. New/Supplement BLA 125031 Supplement-180 (Efficacy Supplement) February 13, 2105. DARRTS.

^f Lutterodt FA. COR-SBLAIR-01 (Pending BLA Information Request). BLA 125031. March 27, 2015. DARRTS.

1.3 PRODUCT LABELING

Highlights of Prescribing Information from labeling^g approved in December 2014 include

-----WARNINGS AND PRECAUTIONS-----

- Fatal splenic rupture can occur. Evaluate for splenomegaly or splenic rupture in patients with left upper abdominal or shoulder pain. (5.1)
- Acute respiratory distress syndrome (ARDS) can occur. Evaluate for ARDS in patients who develop fever, lung infiltrates, or respiratory distress. Discontinue Neulasta in patients with ARDS. (5.2)
- Serious allergic reactions, including anaphylaxis, can occur. Permanently discontinue Neulasta in patients with serious allergic reactions. (5.3)
- The On-body Injector for Neulasta uses acrylic adhesive. For patients who have reactions to acrylic adhesives, use of this product may result in a significant reaction. (5.4)
- Severe and sometimes fatal sickle cell crises can occur. (5.5)

-----ADVERSE REACTIONS-----

Most common adverse reactions ($\geq 5\%$ difference in incidence) in placebo controlled clinical trials are bone pain and pain in extremity. (6)

-----USE IN SPECIFIC POPULATIONS-----

- Pediatric Use: The safety and effectiveness of Neulasta have not been established. (8.4)

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

All cases of adverse events with Neulasta in patients 17 years of age or younger are included in this review.

2.2 FAERS SEARCH STRATEGY

The FAERS database was searched with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of search	July 29, 2015
Time period of search	September 8, 2014 [†] - July 29, 2015
Search type	FBIS Quick Query
Product Terms	Product name: Neulasta Active ingredient: pegfilgrastim
Age	0 - 17.99 years
* See Appendix A for a description of the FAERS database.	
[†] The end date for the search in DPV's October 21, 2014 Pharmacovigilance Memo for pediatric cases with Neulasta was October 8, 2014. September 8, 2014 was chosen for this review to capture any cases that were received before October 8, 2014 but not yet entered into FAERS.	

^g Neulasta product labeling. Thousand Oaks, California: Amgen Inc. December 2014. In COR-SBLAACTION-05 (Approval) for BLA 125031 Supplement-175 (Manufacturing (CMC)). December 23, 2014. DARRTS

3 RESULTS

3.1 FAERS CASE SELECTION

The FAERS search retrieved eight reports, representing eight unique cases, seven of which were not in the October 2014 OSE Pharmacovigilance Memo and one of which updates a case in that document. In the updated case (FAERS case 10451023), the adverse event “chest pain” in the original report was updated to “musculoskeletal chest pain” in version 2; no other changes were made.

Table 2 provides the age ranges in the cases described in the October 2014 Pharmacovigilance Memo by adverse event category.

Table 2. FAERS Cases of Pediatric Patients Treated with Neulasta, by Event Type and Age Category for Cases Included in the October 2014 Pharmacovigilance Memo (N=54*)					
		Patient age in years			
Adverse event category	Total	0 < 2	2 < 6	6 < 12	12 ≤ 17
Allergic reactions	9	0	0	3	6
Exposure during pregnancy	7	6	1	0	0
Injection site reactions	2	0	1	0	1
Leukocytosis/increased white blood cell count	2*	0	0	0	2
Other hematologic events	20	1	4	3	12
Medication errors	3	1	1	0	1
Miscellaneous adverse events	8	0	0	4	4
Cases of interest	3	0	0	1	2
Total	54*	8	7	11	28
* The October 2014 Pharmacovigilance Memo included one report that was found to be a duplicate when reconsidered for this review, therefore these counts are reduced by one.					

The seven new cases received by FDA since September 8, 2014, are summarized in Table 3.

Table 3. FAERS Cases of Pediatric Patients Treated with Neulasta Initially Received by FDA from September 8, 2014 to July 29, 2015 (N=7)

FAERS case number* Manufacturer Control number Adverse event category	Age Sex	Summary
11173412 (b)(4) Miscellaneous adverse events	4 month male	Patient (weight not reported) received Neulasta at an unspecified dose for an unspecified time. He developed a rhabdoid tumor localized to the axilla at an unspecified time. The reporter requested information on how to draw up the required dose for the patient's Neulasta regimen at "700 mcg/0.075 mL." No other information was reported.
10778000 (b)(4) Medication errors	4 yr male	Patient received Neulasta 6 mg to treat post-chemotherapy neutropenia beginning on an unknown date. One dose of Neulasta in original packaging was left in a car in the sun for 72 hours before administration. No adverse events were reported.
10521961 Direct report Medication errors	5 yr male	Prefilled syringe without markings containing 6 mg was dispensed for a prescribed dose of 1.7 mg for a child weighing 16.5 kg (100 mcg/kg). The home-health nurse noted the full contents and measured the dose with a separate syringe. The child's WBC count was 6.4 (no units) on the day of the injection and 3 days later was 108.5 (no units). The reporter, a pharmacist, suggested that, "excessive therapeutic response...indicates that dosing error was possible." The reporter cited the lack of markings on the pre-filled syringe as a potential source of medication errors and described measures their pharmacy has instituted to prevent these errors.
10890528 (b)(4) Miscellaneous adverse events	7 yr male	Patient with reduced platelet count, perinatally-transmitted HIV, and polio since receiving a polio vaccine, began receiving Neulasta at age 7 years to increase platelet count whenever it was reduced significantly. At an unspecified time, he developed pneumonia and systemic mycosis. He died at age 12 years of systemic mycosis, 6 months after his last dose of Neulasta.

Table 3. FAERS Cases of Pediatric Patients Treated with Neulasta Initially Received by FDA from September 8, 2014 to July 29, 2015 (N=7)		
10598285 (b)(4) Other hematologic events	10 yr female	Patient receiving oral dasatinib since (b)(6) to treat acute lymphoblastic leukemia was hospitalized on (b)(6) with febrile neutropenia, decreased WBC and platelet counts, and left shoulder pain. The patient had received Neulasta but no dates or doses were reported. Shoulder ultrasound showed pleural effusion. Three days after admission, pneumonia was confirmed by X-ray. The patient recovered from febrile neutropenia, decreased WBC count, and bone pain. Decreased platelet count, pneumonia, and pleural effusion continued 6 days after admission. Treatment included RBC and platelet transfusions and antibiotics.
10778076 (b)(4) Allergic reactions	11 yr female	Patient started bevacizumab, doxorubicin, and Neulasta for an unknown indication on an unknown date. Reported adverse events were unspecified "allergy" to Neulasta, unspecified "reaction" to doxorubicin, sensation of foreign body in throat, and blood in sputum. The outcomes of the adverse events and whether Neulasta and doxorubicin were continued were not reported.
10712553 (b)(4) Other hematologic events	16 yr female	Patient received Neulasta at unspecified times and doses to treat pineoblastoma. She experienced a lack of effect and febrile neutropenia. No other information was reported.
* All cases are version 1.		

4 DISCUSSION

This review identified one case in which a prefilled syringe containing 6 mg Neulasta was dispensed to fill a prescription for a 1.7-mg dose. The administered dose was an unknown dose less than 6 mg, but the child's WBC count was 108.5 (no units) 3 days later. The October 2014 memo identified two cases in which the 6 mg dose was administered to patients ≤ 2 years old causing WBC counts above 50,000/mL but no reported clinical effects. The prescribed doses were 1 mg and 100 mcg/kg (weight not reported). These medication errors occurred with off-label use in pediatric patients; Neulasta is currently approved only for use in adults.

We did not identify any new safety concerns in the remaining cases.

Causal relationships between Neulasta and rhabdoid tumor localized to the axilla in one case and death from systemic mycosis 6 months after the last dose of Neulasta in another case are unlikely. The report of rhabdoid tumor in a 4-month-old male contains very little information and the reporter asked for advice on drawing up the prescribed dose. The rhabdoid tumor is likely the indication rather than an adverse event. The death from systemic mycosis occurred in a 12-year-old male who had HIV infection since birth, received Neulasta sporadically since the age of 7 years, and had not received Neulasta in 6 months at the time of death. A causal

association for Neulasta and systemic mycosis and death is unlikely because of the 5-year history of Neulasta use, lack of use for the 6 months preceding the adverse event, and the underlying disease.

Two of the three FAERS cases that provide no information about the timing of Neulasta use report hematological adverse events. The first case reports lack of drug effect and febrile neutropenia. Lack of drug effect is a possibility with any drug; febrile neutropenia could reflect a lack of effect of Neulasta. In the second case, platelet count decreased, white blood cell count decreased, and febrile neutropenia were temporal to dasatinib use; dasatinib is labeled for these adverse events. As in the first case, febrile neutropenia could reflect a lack of effect of Neulasta. In addition, the second case reported shoulder pain, pleural effusion, and pneumonia. Pleural effusion and pneumonia may be consequences of reduced WBC counts and resultant infection. Bone pain and pain in the extremity were the most common adverse reactions in clinical trials of Neulasta, according to current labeling. However, Neulasta labeling also states that patients who report shoulder pain should be evaluated for enlarged spleen or splenic rupture. In this case, shoulder pain was evaluated with imaging and no adverse event involving the spleen was mentioned.

The third case with no information on the timing of Neulasta use reports an unspecified allergy to Neulasta, blood in sputum, and sensation of a foreign body in the throat. This case does not provide enough information to understand the nature of the possible allergic reaction or to assess the causal relationship of these events to Neulasta.

5 CONCLUSION

DPV identified several cases of dosing errors or potential dosing errors in pediatric patients receiving Neulasta off label.

6 RECOMMENDATIONS

DPV will refer the medication error cases to the Division of Medication Error Prevention and Analysis (DMEPA) to determine if further review is needed.

If a dose less than 6 mg is approved for pediatric patients, DPV recommends DMIP consult DMEPA to determine if carton- or container-labeling changes are needed to minimize dosing errors in this patient population.

7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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/s/

KATHLEEN M PHELAN
08/27/2015

SARA L CAMILLI
08/28/2015

STEVEN C JONES
08/28/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: May 18th, 2015
Requesting Office or Division: Division of Medical Imaging Products (DMIP)
Application Type and Number: BLA # 12503/S-180
Product Name and Strength: Neulasta (Pegfilgrastim)
Injection
6mg/0.6mL
Submission Date: February 20th, 2015
Applicant/Sponsor Name: Amgen
OSE RCM #: 2015-973
DMEPA Primary Reviewer: Leeza Rahimi, Pharm.D.
DMEPA Team Leader: Yelena Maslov, Pharm.D.

1 PURPOSE OF MEMO

The Division of Medical Imaging Products (DMIP) is currently reviewing an Efficacy supplement (S-180) from Amgen. This supplement provides for a new indication for the treatment (b)(4)

(b)(4) DMIP requested the Division of Medication Error and Prevention Analysis (DMEPA) to review the Prescribing Information (PI) with respect to potential medication errors, specifically for additions pertaining to the new indication.

2 CONCLUSIONS

Upon review of the proposed indication for treatment (b)(4) (b)(4) e, we note the recommended dose is 6 mg, which is the same dose as currently approved indications. However, in this indication, the patients are to receive two doses (b)(4) The first dose is administered as soon as possible after suspected or confirmed exposure to radiation

levels > 2 Gy, and the second dose of Neulasta administered [REDACTED] (b)(4). Although the frequency of administration is different from the currently approved indications, the information is presented in a manner that is clear. Thus, the revised package insert is acceptable from a medication error perspective.

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/s/

LEEZA RAHIMI

05/20/2015

YELENA L MASLOV

05/20/2015