CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

103362Orig1s5240

Trade Name:	LEUKINE, for injection, for subcutaneous or intravenous use
Generic or Proper Name:	sargramostim
Sponsor:	Sanofi-Aventis U.S. LLC
Approval Date:	March 29, 2018
Indication:	This supplement provides: (1) a PLR and PLLR conversion of the labeling (PI, PPI IFU); and, (2) a new indication to increase survival in adult and pediatric patients from birth to 17 years of age acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [H-ARS]).

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 103362/S-5240

sBLA APPROVAL –
ANIMAL EFFICACY

Sanofi-Aventis U.S. LLC
Attention: Cordula Schwarz, M.S.
Associate Director, Global Regulatory Affairs
500 Kendall Street
Cambridge, MA 01242

Dear Ms. Schwarz:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received September 29, 2017, and your amendments, submitted under section 351 of the Public Health Service Act for Leukine® (sargramostim) Injection, 250 mcg, 500 mcg.

This Prior Approval supplemental biologics application proposes:
(1) a PLR and PLLR conversion of the labeling (PI, PPI, IFU) and
(2) a new indication to increase survival in adult and pediatric patients from birth to 17 years of age acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [H-ARS]).

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.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling text for the prescribing information, text for the patient package insert, Instructions For Use and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.
The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

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 Leukine® (sargramostim) 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 Leukine® (sargramostim) meets the requirements for this subsection.

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 submission dated September 29, 2017, to conduct a field study to evaluate the safety and efficacy of Leukine (sargramostim) in the setting of Hematopoietic Syndrome (HS) following acute radiation exposure, when such studies are feasible and ethical in accordance with 21CFR 601.90.

This requirement, along with any agreed upon completion dates, is listed below.

3363-1 Conduct a Phase 4 observational study to evaluate the efficacy and safety of Leukine (sargramostim) in the setting of Hematopoietic Syndrome (HS) following acute radiation exposure

Draft Protocol Submission:	10/30/2018
Final Protocol Submission:	05/2019
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 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 prescribing information (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 Lisa Skarupa, Regulatory Project Manager, at (301) 796-2219

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(S):
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
03/29/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103362Orig1s5240

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LEUKINE safely and effectively. See full prescribing information for LEUKINE.

LEUKINE® (sargramostim) for injection, for subcutaneous or intravenous use

LEUKINE® (sargramostim) injection, for subcutaneous or intravenous use

Initial U S. Approval: 1991

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.5, 1.6)	03/2018
Dosage and Administration (2.6)	03/2018
Contraindications (4)	03/2018
Warnings and Precautions (5.2, 5 3, 5.4, 5.5, 5.6, 5.7, 5.9)	03/2018

----------INDICATIONS AND USAGE----------

LEUKINE is a leukocyte growth factor indicated:

- To shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death following induction chemotherapy in adult patients 55 years and older with acute myeloid leukemia (AML). (1 1)
- For the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis and autologous transplantation in adult patients. (1.2)
- For the acceleration of myeloid reconstitution following autologous bone marrow or peripheral blood progenitor cell transplantation in adult and pediatric patients 2 years of age and older. (1.3)
- For the acceleration of myeloid reconstitution following allogeneic bone marrow transplantation in adult and pediatric patients 2 years of age and older. (1.4)
- For treatment of delayed neutrophil recovery or graft failure after autologous or allogeneic bone marrow transplantation in adult and pediatric patients 2 years of age and older. (1 5)
- To increase survival in adult and pediatric patients from birth to 17 years of age acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [H-ARS]). (1.6)

----------DOSAGE AND ADMINISTRATION----------

See Full Prescribing Information for dosage adjustments and timing of administration (2.1-2.6).

- AML, Neutrophil recovery following chemotherapy:
  - 250 mcg/m^2/day administered intravenously over a 4-hour period. (2.1)
- Mobilization of peripheral blood progenitor cells:
  - 250 mcg/m^2/day administered intravenously over 24 hours or subcutaneous injection once daily. (2.2)
- Post peripheral blood progenitor cell transplantation:
  - 250 mcg/m^2/day administered intravenously over 24 hours or subcutaneous injection once. (2.3)
- Myeloid reconstitution after autologous or allogeneic BMT:
  - 250 mcg/m^2/day administered intravenously over a 2-hour period. (2.4)
- BMT failure or engraftment delayed:
  - 250 mcg/m^2/day for 14 days as a 2-hour intravenous infusion. (2.5)
- Patients acutely exposed to myelosuppressive doses of radiation, administer once daily as subcutaneous injection:
  - Adults and pediatric patients weighing >40 kg: 7 mcg/kg
  - Pediatric patients 15 kg to 40 kg: 10 mcg/kg
  - Pediatric patients <15 kg: 12 mcg/kg (2.6)

----------DOSAGE FORMS AND STRENGTHS----------

- For injection (lyophilized powder): 250 mcg of sargramostim in single-dose vial for reconstitution (3)
- Injection (solution): 500 mcg per mL sargramostim in multiple-dose vial (3)

----------CONTRAINDICATIONS----------

- Do not administer LEUKINE to patients with a history of serious allergic reactions, including anaphylaxis, to human granulocyte-macrophage colony stimulating factor such as sargramostim, yeast-derived products, or any component of the product. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity Reactions: Permanently discontinue LEUKINE in patients with serious allergic reactions. (5.1)
- Infusion Related Reactions: Manage using infusion rate reductions or discontinuations. (5.2)
- Effusions and Capillary Leak Syndrome: Manage with dose-reduction, discontinuation, or diuretics. Monitor body weight and hydration status during therapy. (5.4)
- Supraventricular Arrhythmias: Risk may be increased in patients with history of cardiac arrhythmias. Manage medically and discontinue LEUKINE. (5.5)

----------ADVERSE REACTIONS----------

The most common adverse reactions (incidence >30%) were (6 1):

- In recipients of autologous BMT: fever, nausea, diarrhea, vomiting, mucous membrane disorder, alopecia, asthenia, malaise, anorexia, rash, gastrointestinal disorder and edema.
- In recipients of allogeneic BMT: diarrhea, fever, nausea, rash, vomiting, stomatitis, anorexia, high glucose, alopecia, abdominal pain, low albumin, headache and hypertension.
- In patients with AML: fever, liver toxicity, skin reactions, infections, metabolic laboratory abnormalities, nausea, diarrhea, genitourinary abnormalities, pulmonary toxicity, vomiting, neurotoxicity, stomatitis, alopecia and weight loss.

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme Corporation at 1-888-4RX-LEUKINE or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Use with caution in patients receiving drugs that may potentiate LEUKINE's myeloproliferative effects, such as lithium and corticosteroids. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Benzyl alcohol–free formulation recommended. May cause fetal harm. (8 1)
- Pediatrics: In infants, avoid use of benzyl alcohol–containing solutions when feasible. (2.7, 5.9, 8.4)
- Lactation: Advise women not to breastfeed. (8.2)

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

Revised: 03/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Acute Myeloid Leukemia Following Induction Chemotherapy

LEUKINE is indicated to shorten time to neutrophil recovery and to reduce the incidence of severe, life-threatening, or fatal infections following induction chemotherapy in adult patients 55 years and older with acute myeloid leukemia (AML).

1.2 Autologous Peripheral Blood Progenitor Cell Mobilization and Collection

LEUKINE is indicated in adult patients with cancer undergoing autologous hematopoietic stem cell transplantation for the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis.

1.3 Autologous Peripheral Blood Progenitor Cell and Bone Marrow Transplantation

LEUKINE is indicated for the acceleration of myeloid reconstitution following autologous peripheral blood progenitor cell (PBPC) or bone marrow transplantation in adult and pediatric patients 2 years of age and older with non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) and Hodgkin's lymphoma (HL).

1.4 Allogeneic Bone Marrow Transplantation

LEUKINE is indicated for the acceleration of myeloid reconstitution in adult and pediatric patients 2 years of age and older undergoing allogeneic bone marrow transplantation from HLA-matched related donors.

1.5 Allogeneic or Autologous Bone Marrow Transplantation: Treatment of Delayed Neutrophil Recovery or Graft Failure

LEUKINE is indicated for the treatment of adult and pediatric patients 2 years and older who have undergone allogeneic or autologous bone marrow transplantation in whom neutrophil recovery is delayed or failed.

1.6 Acute Exposure to Myelosuppressive Doses of Radiation (H-ARS)

LEUKINE is indicated to increase survival in adult and pediatric patients from birth to 17 years of age acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [H-ARS]).

2 DOSAGE AND ADMINISTRATION

2.1 Neutrophil Recovery Following Induction Chemotherapy for Acute Myeloid Leukemia

The recommended dose is 250 mcg/m^2/day administered intravenously over a 4-hour period starting approximately on day 11 or four days following the completion of induction chemotherapy, if the day 10 bone marrow is hypoplastic with less than 5% blasts. If a second cycle of induction chemotherapy is necessary, administer LEUKINE approximately four days after the completion of chemotherapy if the bone marrow is hypoplastic with less than 5% blasts. Continue LEUKINE until an absolute neutrophil count (ANC) greater than 1500 cells/mm^3 for 3 consecutive days or a maximum of 42 days. Do not administer LEUKINE within 24 hours

preceding or following receipt of chemotherapy or radiotherapy *[see Warnings and Precautions (5.3)]*.

Dose Modifications

Obtain a CBC with differential twice per week during LEUKINE therapy and modify the dose for the following:

- Leukemic regrowth: Discontinue LEUKINE immediately
- Grade 3 or 4 adverse reactions: Reduce the dose of LEUKINE by 50% or interrupt dosing until the reaction abates
- ANC greater than 20,000 cells/mm^3: Interrupt LEUKINE treatment or reduce the dose by 50%

2.2 Autologous Peripheral Blood Progenitor Cell Mobilization and Collection

The recommended dose is 250 mcg/m^2/day administered intravenously over 24 hours or subcutaneously once daily. Continue at the same dose through the period of PBPC collection. The optimal schedule for PBPC collection has not been established. In clinical studies, collection of PBPC was usually begun after 5 days of LEUKINE and performed daily until protocol specified targets were achieved *[see Clinical Studies (14)]*.

If WBC greater than 50,000 cells/mm^3, reduce the LEUKINE dose by 50%. Consider other mobilization therapy if adequate numbers of progenitor cells are not collected.

2.3 Autologous Peripheral Blood Progenitor Cell and Bone Marrow Transplantation

Autologous Peripheral Blood Progenitor Cell Transplantation

The recommended dose is 250 mcg/m^2/day administered intravenously over 24 hours or subcutaneously once daily beginning immediately following infusion of progenitor cells and continuing until an ANC greater than 1500 cells/mm^3 for three consecutive days is attained. Do not administer LEUKINE within 24 hours preceding or following receipt of chemotherapy or radiotherapy.

Autologous Bone Marrow Transplantation

The recommended dose is 250 mcg/m^2/day administered intravenously over a 2-hour period beginning two to four hours after bone marrow infusion, and not less than 24 hours after the last dose of chemotherapy or radiotherapy. Do not administer LEUKINE until the post marrow infusion ANC is less than 500 cells/mm^3. Continue LEUKINE until an ANC greater than 1500 cells/mm^3 for three consecutive days is attained. Do not administer LEUKINE within 24 hours preceding or following receipt of chemotherapy or radiotherapy *[see Warnings and Precautions (5.3)]*.

2.4 Allogeneic Bone Marrow Transplantation

The recommended dose is 250 mcg/m^2/day administered intravenously over a 2-hour period beginning two to four hours after bone marrow infusion, and not less than 24 hours after the last dose of chemotherapy or radiotherapy. Do not administer LEUKINE until the post marrow infusion ANC is less than 500 cells/mm^3. Continue LEUKINE until an ANC greater than 1500 cells/mm^3 for three consecutive days is attained. Do not administer LEUKINE within 24 hours

preceding or following receipt of chemotherapy or radiotherapy *[see Warnings and Precautions (5.3)]*.

Dose Modifications

Obtain a CBC with differential twice per week during LEUKINE therapy and modify the dose as for the following:

- Disease progression or blast cell appearance: Discontinue LEUKINE immediately
- Grade 3 or 4 adverse reactions: Reduce the dose of LEUKINE by 50% or temporarily discontinue until the reaction abates
- WBC greater than 50,000 cells/mm^3 or ANC greater than 20,000 cells/mm^3: Interrupt LEUKINE treatment or reduce the dose by 50%

2.5 Allogeneic or Autologous Bone Marrow Transplantation: Treatment of Delayed Neutrophil Recovery or Graft Failure

The recommended dose is 250 mcg/m^2/day for 14 days as a 2-hour intravenous infusion. The dose can be repeated after 7 days off therapy if neutrophil recovery has not occurred. If neutrophil recovery still has not occurred, a third course of 500 mcg/m^2/day for 14 days may be tried after another 7 days off therapy. If there is still no improvement, it is unlikely that further dose escalation will be beneficial.

Dose Modifications

Obtain a CBC with differential twice per week during LEUKINE therapy and modify the dose as for the following:

- Disease progression or blast cell appearance: Discontinue LEUKINE immediately
- Grade 3 or 4 adverse reactions: Reduce the dose of LEUKINE by 50% or temporarily discontinue until the reaction abates
- WBC greater than 50,000 cells/mm^3 or ANC greater than 20,000 cells/mm^3: Interrupt LEUKINE treatment or reduce the dose by 50%

2.6 Acute Exposure to Myelosuppressive Doses of Radiation (H-ARS)

For patients with H-ARS, the recommended dose of LEUKINE is a subcutaneous injection administered once daily as follows:

- 7 mcg/kg in adult and pediatric patients weighing greater than 40 kg
- 10 mcg/kg in pediatric patients weighing 15 kg to 40 kg
- 12 mcg/kg in pediatric patients weighing less than 15 kg

Administer LEUKINE as soon as possible after suspected or confirmed exposure to radiation doses greater than 2 gray (Gy).

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 CBC with differential and then serial CBCs approximately every third day until the ANC remains greater than 1,000/mm^3 for three consecutive CBCs. Do not delay administration of LEUKINE if a CBC is not readily available.

Continue administration of LEUKINE until the ANC remains greater than 1,000/mm^3 for three consecutive CBCs or exceeds 10,000/mm^3 after a radiation-induced nadir.

2.7 Preparation and Administration of LEUKINE

- Do not administer LEUKINE simultaneously with or within 24 hours preceding cytotoxic chemotherapy or radiotherapy or within 24 hours following chemotherapy *[see Warnings and Precautions (5.3)]*.
- LEUKINE injection is formulated as a sterile solution preserved with 1.1% benzyl alcohol.
- LEUKINE for injection is a sterile, preservative-free lyophilized powder that requires reconstitution with 1 mL Sterile Water for Injection (without preservative), USP, to yield a clear, colorless single-dose solution or 1 mL Bacteriostatic Water for Injection, USP (with 0.9% benzyl alcohol as preservative) to yield a clear, colorless single-dose solution.

Use only LEUKINE for injection (lyophilized powder) reconstituted with Sterile Water for Injection without preservatives when administering LEUKINE to neonates or infants to avoid benzyl alcohol exposure *[see Warnings and Precautions (5.9)]*.

Do NOT use an in-line membrane filter for intravenous infusion of LEUKINE.

- Store LEUKINE solution and reconstituted lyophilized LEUKINE solutions under refrigeration at 2°C-8°C (36°F-46°F); DO NOT FREEZE.
- In the absence of compatibility and stability information, do not add other medication to infusion solutions containing LEUKINE. Use only 0.9% Sodium Chloride Injection, USP to prepare intravenous infusion solutions.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter is present or the solution is discolored, the vial should not be used.

LEUKINE for Injection (lyophilized powder) Preparation

Reconstitute LEUKINE for Injection aseptically with 1 mL of diluent. Do not mix the contents of vials reconstituted with different diluents together. Reconstitute with either Sterile Water for Injection, USP (without preservative) or Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol). Use reconstituted LEUKINE for injection (lyophilized powder) vials within 6 hours following constitution and/or dilution for intravenous infusion. Do not re-enter or reuse the vial. Discard any unused portions.

LEUKINE Injection (solution) Preparation

- For subcutaneous injection: Administer LEUKINE Injection without further dilution.
- For intravenous injection: Administer LEUKINE injection in 0.9% Sodium Chloride Injection, USP. Dilute LEUKINE for intravenous infusion in 0.9% Sodium Chloride Injection, USP. If the final concentration of LEUKINE is below 10 mcg/mL, add Albumin (Human) at a final concentration of 0.1% to the saline prior to addition of LEUKINE to

prevent adsorption to the components of the drug delivery system. To obtain a final concentration of 0.1% Albumin (Human), add 1 mg Albumin (Human) per 1 mL 0.9% Sodium Chloride Injection, USP (e.g., use 1 mL 5% Albumin [Human] in 50 mL 0.9% Sodium Chloride Injection, USP).

- Store LEUKINE injection for up to 20 days at 2°C-8°C once the vial has been entered. Discard any remaining solution after 20 days.

3 DOSAGE FORMS AND STRENGTHS

- For injection (lyophilized powder): 250 mcg of sargramostim, white powder in a single-dose vial for reconstitution
- Injection (solution): 500 mcg per mL clear, colorless solution of sargramostim in multiple-dose vials

4 CONTRAINDICATIONS

Do not administer LEUKINE to patients with a history of serious allergic reactions, including anaphylaxis, to human granulocyte-macrophage colony stimulating factor such as sargramostim, yeast-derived products, or any component of the product. Anaphylactic reactions have been reported with LEUKINE *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylactic reactions, have been reported with LEUKINE. Parenteral administration of LEUKINE should be attended by appropriate precautions in case an allergic or untoward reaction occurs. If any serious allergic or anaphylactic reaction occurs, immediately discontinue LEUKINE therapy and institute medical management. Discontinue LEUKINE permanently for patients with serious allergic reactions.

5.2 Infusion Related Reactions

LEUKINE can cause infusion-related reactions. Infusion-related reactions may be characterized by respiratory distress, hypoxia, flushing, hypotension, syncope, and/or tachycardia following the first administration of LEUKINE in a particular cycle. These signs have resolved with symptomatic treatment and usually do not recur with subsequent doses in the same cycle of treatment.

Observe closely during infusion for symptoms, particularly in patients with pre-existing lung disease. If patients display dyspnea or other acute symptoms, reduce the rate of infusion by 50%. If symptoms persist or worsen despite rate reduction, discontinue the LEUKINE infusion. If patient experiences infusion-related reaction, subsequent intravenous infusions may be administered following the standard dose schedule with careful monitoring.

5.3 Risk of Severe Myelosuppression when LEUKINE Administered within 24 hours of Chemotherapy or Radiotherapy

Due to the potential sensitivity of rapidly dividing hematopoietic progenitor cells, LEUKINE should not be administered simultaneously with or within 24 hours preceding cytotoxic chemotherapy or radiotherapy or within 24 hours following chemotherapy. In one controlled

study, patients with small cell lung cancer received LEUKINE and concurrent thoracic radiotherapy and chemotherapy or the identical radiotherapy and chemotherapy without LEUKINE. The patients randomized to LEUKINE had significantly higher incidence of adverse reactions, including higher mortality and a higher incidence of grade 3 and 4 infections and grade 3 and 4 thrombocytopenia.

5.4 Effusions and Capillary Leak Syndrome

Edema, capillary leak syndrome, and pleural and/or pericardial effusion, have been reported in patients after LEUKINE administration. In 156 patients enrolled in placebo-controlled studies using LEUKINE at a dose of 250 mcg/m^2/day by 2-hour IV infusion, the reported incidences of fluid retention (LEUKINE vs. placebo) were as follows: peripheral edema, 11% vs. 7%; pleural effusion, 1% vs. 0%; and pericardial effusion, 4% vs. 1%. Capillary leak syndrome was not observed in this limited number of studies; based on other uncontrolled studies and reports from users of marketed LEUKINE, the incidence is estimated to be less than 1%. In patients with preexisting pleural and pericardial effusions, administration of LEUKINE may aggravate fluid retention; however, fluid retention associated with or worsened by LEUKINE has been reversible after interruption or dose reduction of LEUKINE with or without diuretic therapy. LEUKINE should be used with caution in patients with preexisting fluid retention, pulmonary infiltrates, or congestive heart failure. Body weight and hydration status should be carefully monitored during LEUKINE administration.

5.5 Supraventricular Arrhythmias

Supraventricular arrhythmia has been reported in uncontrolled studies during LEUKINE administration, particularly in patients with a previous history of cardiac arrhythmia. These arrhythmias have been reversible after discontinuation of LEUKINE. Use LEUKINE with caution in patients with preexisting cardiac disease.

5.6 Leukocytosis

White blood cell counts of $\geq$ 50,000/mm^3 were observed in patients receiving LEUKINE. Monitor complete blood counts (CBC) with differential twice per week. Base the decision whether to reduce the dose or interrupt treatment on the clinical condition of the patient *[see Dosage and Administration (2.1, 2.4, 2.5, 2.6)]*. Following cessation of LEUKINE therapy, excessive blood counts have returned to normal or baseline levels within 3 to 7 days.

5.7 Potential Effect on Malignant Cells

LEUKINE is a growth factor that primarily stimulates normal myeloid precursors. However, the possibility that LEUKINE can act as a growth factor for any tumor type, particularly myeloid malignancies, cannot be excluded. Because of the possibility of tumor growth potentiation, precaution should be exercised when using this drug in any malignancy with myeloid characteristics.

Discontinue LEUKINE therapy if disease progression is detected during LEUKINE treatment.

5.8 Immunogenicity

Treatment with LEUKINE may induce neutralizing anti-drug antibodies. The incidence of anti-sargramostim neutralizing antibodies may be related to duration of exposure to LEUKINE. In a study of patients with normal neutrophil count and a solid tumor in complete response (an unapproved use) treated with LEUKINE for up to 12 months, 82.9% of 41 evaluable patients

developed anti-sargramostim neutralizing antibodies and the myelostimulatory effect of LEUKINE was not sustained by day 155 as assessed by WBC count. Use LEUKINE for the shortest duration required *[see Adverse Reactions (6.2)]*.

5.9 Risk of Serious Adverse Reactions in Infants Due to Benzyl Alcohol Preservative

Serious and fatal adverse reactions including “gasping syndrome” can occur in neonates and low birth weight infants treated with benzyl alcohol-preserved drugs, including LEUKINE injection (solution) or LEUKINE for injection (lyophilized powder) reconstituted with Bacteriostatic Water. The “gasping syndrome" is characterized by central nervous system depression, metabolic acidosis and gasping respirations.

Avoid administration of solutions containing benzyl alcohol (including LEUKINE injection [solution] or LEUKINE for injection [lyophilized powder] reconstituted with Bacteriostatic Water for Injection, USP [0.9% benzyl alcohol]) to neonates and low birth weight infants. Instead, administer lyophilized LEUKINE reconstituted with Sterile Water for Injection, USP *[see Dosage and Administration (2.7)]*.

If LEUKINE injection (solution) or LEUKINE for injection (lyophilized powder) reconstituted with Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol) must be used in neonates and low birth weight infants, consider the combined daily metabolic load of benzyl alcohol from all sources including LEUKINE (LEUKINE injection and LEUKINE for injection reconstituted with Bacteriostatic Water contain 11 mg and 9 mg of benzyl alcohol per mL, respectively). The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known *[see Use in Specific Populations (8.4) and Dosage and Administration (2.7)]*.

6 ADVERSE REACTIONS

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

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
- Infusion Related Reactions *[see Warnings and Precautions (5.2)]*
- Risk of Severe Myelosuppression when LEUKINE Administered within 24 Hours of Chemotherapy or Radiotherapy *[see Warnings and Precautions (5.3)]*
- Effusions and Capillary Leak Syndrome *[see Warnings and Precautions (5.4)]*
- Supraventricular Arrhythmias *[see Warnings and Precautions (5.5)]*
- Leukocytosis *[see Warnings and Precautions (5.6)]*
- Potential Effect on Malignant Cells *[see Warnings and Precautions (5.7)]*
- Immunogenicity *[see Warnings and Precautions (5.8)]*
- Risk of Serious Adverse Reactions in Infants Due to Benzyl Alcohol Preservative *[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.

Autologous Peripheral Blood Progenitor Cell (PBPC) and Bone Marrow Transplantation

Studies 301, 302 and 303 enrolled a total of 156 patients after autologous or allogeneic marrow or PBPC transplantation. In these placebo-controlled studies, pediatric and adult patients received once-daily intravenous infusions of LEUKINE 250 mcg/m^2 or placebo for 21 days.

In Studies 301, 302, and 303, there was no difference in relapse rate between the LEUKINE and placebo-treated patients. Adverse reactions reported in at least 10% of patients who received intravenous LEUKINE or at a rate that was at least 5% higher than the placebo arm are shown in Table 1.

Table 1: Adverse Reactions after Autologous Marrow or PBPC Transplantation in at Least 10% of Patients Receiving Intravenous LEUKINE or at Least 5% Higher than the Placebo Arm

Adverse Reactions by Body System	**LEUKINE (n=79) %**	**Placebo (n=77) %**	**Adverse Reactions by Body System**	**LEUKINE (n=79) %**	**Placebo (n=77) %**
Body, General			**Metabolic, Nutritional Disorder**		
Fever	95	96	Edema	34	35
Mucous membrane disorder	75	78	Peripheral edema	11	7
Asthenia	66	51	**Respiratory System**		
Malaise	57	51	Dyspnea	28	31
Sepsis	11	14	Lung disorder	20	23
Digestive System			**Blood and Lymphatic System**		
Nausea	90	96	Blood dyscrasia	25	27
Diarrhea	89	82	**Cardiovascular Vascular System**		
Vomiting	85	90	Hemorrhage	23	30
Anorexia	54	58	**Urogenital System**		
GI disorder	37	47	Urinary tract disorder	14	13
GI hemorrhage	27	33	**Nervous System**		
Stomatitis	24	29	CNS disorder	11	16
Liver damage	13	14			
Skin and Appendages					

Adverse Reactions by Body System	LEUKINE (n=79) %	Placebo (n=77) %	Adverse Reactions by Body System	LEUKINE (n=79) %	Placebo (n=77) %
Alopecia	73	74			
Rash	44	38			

Additional Clinically Significant Adverse Reactions Occurring in Less than 10% Incidence

Investigations: Elevated creatinine, elevated bilirubin, elevate transaminases

Allogeneic Bone Marrow Transplantation

In the placebo-controlled trial of 109 patients after allogeneic BMT (Study 9002), acute graft-vs-host disease occurred in 55% on the LEUKINE arm and in 59% on the placebo arm. Adverse reactions reported in at least 10% of patients who received IV LEUKINE or at a rate at least 5% higher than the placebo arm are shown in **Table 2**.

Table 2: Adverse Reactions after Allogeneic Marrow Transplantation in at Least 10% of Patients Receiving Intravenous LEUKINE or at Least 5% Higher than the Placebo Arm

Adverse Reactions by Body System	LEUKINE (n=53) %	Placebo (n=56) %	Adverse Reactions by Body System	LEUKINE (n=53) %	Placebo (n=56) %
Body, General			Eye hemorrhage	11	0
Fever	77	80	**Cardiovascular System**		
Abdominal pain	38	23	Hypertension	34	32
Headache	36	36	Tachycardia	11	9
Chills	25	20	**Metabolic / Nutritional Disorders**		
Pain	17	36	Bilirubinemia	30	27
Asthenia	17	20	Hyperglycemia	25	23
Chest pain	15	9	Peripheral edema	15	21
Digestive System			Increased creatinine	15	14
Diarrhea	81	66	Hypomagnesemia	15	9
Nausea	70	66	Increased SGPT	13	16
Vomiting	70	57	Edema	13	11
Stomatitis	62	63	**Respiratory System**		
Anorexia	51	57	Pharyngitis	23	13
Dyspepsia	17	20	Epistaxis	17	16

Adverse Reactions by Body System	LEUKINE (n=53) %	Placebo (n=56) %	Adverse Reactions by Body System	LEUKINE (n=53) %	Placebo (n=56) %
Hematemesis	13	7	Dyspnea	15	14
Dysphagia	11	7	Rhinitis	11	14
GI hemorrhage	11	5	**Blood and Lymphatic System**		
Skin and Appendages			Thrombocytopenia	19	34
Rash	70	73	Leukopenia	17	29
Alopecia	45	45	**Nervous System**		
Pruritus	23	13	Paresthesia	11	13
Musculoskeletal System			Insomnia	11	9
Bone pain	21	5	Anxiety	11	2
Arthralgia	11	4	**Laboratory Abnormalities***		
Special Senses			High glucose	49	41
			Low albumin	36	27
			High BUN	17	23

* Grade 3 and 4 laboratory abnormalities only. Denominators may vary due to missing laboratory measures.

Acute Myeloid Leukemia Following Induction Chemotherapy

Nearly all patients in both arms developed leukopenia, thrombocytopenia, and anemia. Adverse reactions reported in at least 10% of patients who received LEUKINE or at least 5% higher than the placebo arm are reported in Table 3.

Table 3: Adverse Reactions after Treatment of AML in at Least 10% of Patients Receiving Intravenous LEUKINE or at Least 5% Higher than the Placebo Arm

Adverse Reactions by Body System	LEUKINE (n=52) %	Placebo (n=47) %	Adverse Reactions by Body System	LEUKINE (n=52) %	Placebo (n=47) %
Body, General			**Metabolic / Nutritional Disorder**		
Fever (no infection)	81	74	Metabolic Laboratory Abnormalities	58	49
Infection	65	68	Edema	25	23

Adverse Reactions by Body System	LEUKINE (n=52) %	Placebo (n=47) %	Adverse Reactions by Body System	LEUKINE (n=52) %	Placebo (n=47) %
Weight loss	37	28	**Respiratory System**		
Chills	19	26	Pulmonary toxicity	48	64
Allergy	12	15	**Blood and Lymphatic System**		
Digestive System			Coagulation	19	21
Nausea	58	55	**Cardiovascular System**		
Liver toxicity	77	83	Hemorrhage	29	43
Diarrhea	52	53	Hypertension	25	32
Vomiting	46	34	Cardiac	23	32
Stomatitis	42	43	Hypotension	13	26
Anorexia	13	11	**Urogenital System**		
Skin and Appendages			GU abnormalities	50	57
Skin Reactions	77	45	**Nervous System**		
Alopecia	37	51	Neuro-clinical	42	53
			Neuro-motor	25	26
			Neuro-psych	15	26

There was no significant difference between the arms in the proportion of patients achieving complete remission (CR; 69% in the LEUKINE group and 55% in the placebo group). There was also no significant difference in relapse rates; 12 of 36 patients who received LEUKINE and five of 26 patients who received placebo relapsed within 180 days of documented CR (p=0.26). The study was not sized to assess the impact of LEUKINE treatment on response.

Graft Failure

In a historically controlled study of 86 patients with AML, the LEUKINE treated group exhibited an increased incidence of weight gain (p=0.007), low serum proteins, and prolonged prothrombin time (p=0.02) when compared to the control group. Two LEUKINE treated patients had progressive increase in circulating monocytes and promonocytes and blasts in the marrow, which reversed when LEUKINE was discontinued. The historical control group exhibited an increased incidence of cardiac events (p=0.018), liver function abnormalities (p=0.008), and neurocortical hemorrhagic events (p=0.025). Headache (26%), pericardial effusion (25%), arthralgia (21%), and myalgia (18%) were also reported in patients treated with LEUKINE in the graft failure study.

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity with LEUKINE. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, duration of treatment, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to sargramostim in the studies described below with the incidence of antibodies in other studies or other products may be misleading.

In 214 patients with a variety of underlying diseases, neutralizing anti-sargramostim antibodies were detected in 5 patients (2.3%) after receiving LEUKINE by continuous IV infusion (3 patients) or SC injection (2 patients) for 28 to 84 days in multiple courses (as assessed by GM-CSF dependent human cell-line proliferation assay). All 5 patients had impaired hematopoiesis before the administration of LEUKINE, and consequently the effect of the development of anti-sargramostim antibodies on normal hematopoiesis could not be assessed.

Antibody studies of 75 patients with Crohn's disease (a disease for which LEUKINE is not indicated), with normal hematopoiesis and no other immunosuppressive drugs, receiving LEUKINE daily for 8 weeks by SC injection, showed 1 patient (1.3%) with detectable neutralizing anti-sargramostim antibodies (as assessed by GM-CSF dependent human cell-line proliferation assay).

In an experimental use trial where LEUKINE was given for an extended period, 53 patients with melanoma in complete remission (a disease for which LEUKINE is not indicated) received adjuvant therapy with LEUKINE 125 mcg/m^2 once daily (maximum dose 250 mcg) from day 1 to 14 every 28 days for 1 year. Serum samples from patients assessed at day 0, 2 weeks, 1 month, and 5 and/or 12 months were tested retrospectively for the presence of anti-sargramostim antibodies. Of 43 evaluable patients (having at least 3 timepoint samples post treatment), 42 (97.7%) developed anti-sargramostim binding antibody as assessed by ELISA and confirmed using an immunoprecipitation assay. Of these 42 patients, 41 had sufficient sample and were further tested: 34 patients (82.9%) developed anti-sargramostim neutralizing antibodies (as determined by a cell based luciferase reporter gene neutralizing antibody assay); 17 (50%) of these patients did not have a sustained pharmacodynamic effect of LEUKINE by day 155 as assessed by WBC counts. This study provided limited assessment of the impact of antibody formation on the safety and efficacy of LEUKINE.

Serious allergic and anaphylactoid reactions have been reported with LEUKINE, but the rate of occurrence of antibodies in such patients has not been assessed.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of LEUKINE in clinical trials and/or postmarketing surveillance. 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.

- Infusion related reactions including dyspnea, hypoxia, flushing, hypotension, syncope and/or tachycardia *[see Warnings and Precautions (5.1)]*

- Serious allergic reactions/hypersensitivity, including anaphylaxis, skin rash, urticaria, generalized erythema, and flushing *[see Warnings and Precautions (5.2)]*
- Effusions and capillary leak syndrome *[see Warnings and Precautions (5.3)]*
- Supraventricular arrhythmias *[see Warnings and Precautions (5.4)]*
- Leukocytosis including eosinophilia *[see Warnings and Precautions (5.6)]*
- Thromboembolic events
- Pain, including chest, abdominal, back, and joint pain
- Injection site reactions

7 DRUG INTERACTIONS

7.1 Concomitant Use with Products that Induce Myeloproliferation

Avoid the concomitant use of LEUKINE and products that induce myeloproliferation (such as lithium and corticosteroids). Such products may increase the myeloproliferative effects of LEUKINE. Monitor patients receiving both LEUKINE and products that induce myeloproliferation frequently for clinical and laboratory signs of excess myeloproliferative effects.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Both LEUKINE injection (solution) and LEUKINE for injection (lyophilized powder) reconstituted with Bacteriostatic Water for Injection, USP contain benzyl alcohol, which has been associated with gasping syndrome in neonates and infants. The preservative benzyl alcohol can cause serious adverse reactions and death when administered intravenously to neonates and infants. If LEUKINE is needed during pregnancy, use only LEUKINE for injection (lyophilized powder) reconstituted with Sterile Water for injection without preservatives *[see Dosage and Administration (2.7) and Use in Specific Populations (8.4)]*.

The limited available data on LEUKINE use in pregnant women are insufficient to inform the drug-associated risk of adverse developmental outcomes. Based on animal studies LEUKINE may cause embryofetal harm. In animal reproduction studies, administration of LEUKINE to pregnant rabbits during organogenesis resulted in adverse developmental outcomes including increased spontaneous abortion at systemic exposures ≥1.3 times the human exposure expected at the recommended human dose *[see Data]*. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2%-4% and 15%-20%, respectively.

Data

Animal data

In an embryofetal developmental study and a prenatal and postnatal study, pregnant rabbits were administered SC doses of LEUKINE during the period of gestation day (GD) 6 to GD19, GD19 to GD28, or GD19 to parturition at 25, 70, and 200 mcg/kg/day. An increase in spontaneous abortions, late resorptions, and postimplantation loss, and a reduction in viable fetuses, mean live litter size, and offspring body weight were evident in rabbits treated with LEUKINE at 200 mcg/kg/day. No adverse effects were observed at ≤70 mcg/kg/day.

After the first administration in rabbits, the dose of 200 mcg/kg/day corresponds to a systemic exposure (AUC) of approximately 11-25.3 times the exposures observed in patients treated with the clinical LEUKINE dose of 250 mcg/m^2; however, due to the production of anti-LEUKINE antibodies with repeat administration, the AUC in rabbits was reduced to 1.3-5.5 times the clinical exposure by the end of the dosing periods.

Similarly, after the first administration in rabbits, the dose of 70 mcg/kg/day corresponds to a systemic exposure (AUC) of approximately 7 to 11 times the exposures observed in patients treated with the clinical LEUKINE dose of 250 mcg/m^2; however, due to the production of anti-LEUKINE antibodies with repeat administration, the AUC in rabbits was reduced to 1.0-1.2 times the clinical exposure by the end of the dosing periods.

8.2 Lactation

Risk Summary

There is no information regarding the presence of LEUKINE in human milk, the effects on the breastfed child, or the effects on milk production. Administration of LEUKINE to rabbits during lactation resulted in reduction in postnatal offspring survival *[see Data]*. Because of the potential for serious adverse reactions advise a lactating woman not to breastfeed during treatment and for at least 2 weeks after the last dose.

Data

There are no data regarding the presence of LEUKINE in rabbit milk. However, in the prenatal and postnatal study, lactating rabbits were administered SC doses of LEUKINE during the period of lactation day (LD) 1 to LD14 at 25, 70, and 200 mcg/kg/day. At doses ≥25 mcg/kg/day a reduction in postnatal offspring survival was observed. Maternal toxicity was also observed at LEUKINE doses ≥25 mcg/kg/day.

After the first administration in rabbits, the dose of 25 mcg/kg/day corresponds to a systemic AUC of approximately 2.6 times the exposure observed in patients treated with the clinical LEUKINE dose of 250 mcg/m^2 however, due to the production of anti-LEUKINE antibodies with repeat administration, the exposure in rabbits decreased to 0.2 times the clinical exposure by the end of the dosing period.

8.4 Pediatric Use

The safety and effectiveness of LEUKINE have been established in pediatric patients 2 years of age and older for autologous peripheral blood progenitor cells and bone marrow transplantation, allogeneic bone marrow transplantation, and treatment of delayed neutrophil recovery or graft failure. Use of LEUKINE for these indications in this age group is based on adequate and well-controlled studies of LEUKINE in adults, in addition to clinical data in 12, 23, and 37 pediatric

patients, respectively *[See Clinical Studies (14.3, 14.4 and 14.5)]*. The pediatric adverse reactions were consistent with those reported in the adult population.

The safety and effectiveness of LEUKINE for pediatric patients less than 2 years of age for autologous peripheral blood progenitor cells and bone marrow transplantation, allogeneic bone marrow transplantation, and treatment of delayed neutrophil recovery or graft failure have not been established.

The use of LEUKINE to increase survival in pediatric patients acutely exposed to myelosuppressive doses of radiation (H-ARS) is based on efficacy studies conducted in animals and clinical data supporting the use of LEUKINE in patients undergoing autologous or allogeneic BMT following myelosuppressive chemotherapy with or without total body irradiation. Efficacy studies of LEUKINE could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Modeling and simulation was used to derive dosing regimens that are predicted to provide pediatric patients with exposure comparable to the observed exposure in adults receiving 7 mcg/kg *[see Clinical Pharmacology (12.3)]*. The dose for pediatric patients is based on weight *[see Dosage and Administration (2.2)]*.

Safety and effectiveness in pediatric patients have not been established in:

- Acute Myeloid Leukemia: Neutrophil Recovery Following Induction Chemotherapy
- Autologous Peripheral Blood Progenitor Cell Mobilization and Collection

Avoid administration of solutions containing benzyl alcohol [including LEUKINE injection (solution) or LEUKINE for injection (lyophilized powder) reconstituted with Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol)] to neonates and low birth weight infants. Instead, administer lyophilized LEUKINE reconstituted with Sterile Water for Injection, USP *[see Dosage and Administration (2.7)]*.

Serious adverse reactions including fatal reactions and the “gasping syndrome” occurred in premature infants in the neonatal intensive care unit who received drugs containing benzyl alcohol as a preservative. In these cases, benzyl alcohol dosages of 99 to 234 mg/kg/day produced high levels of benzyl alcohol and its metabolites in the blood and urine (blood levels of benzyl alcohol were 0.61 to 1.38 mmol/L). Additional adverse reactions included gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Preterm, low birth weight infants may be more likely to develop these reactions because they may be less able to metabolize benzyl alcohol.

If LEUKINE injection (solution) or LEUKINE for injection (lyophilized powder) reconstituted with Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol) must be used in neonates and low birth weight infants, consider the combined daily metabolic load of benzyl alcohol from all sources including LEUKINE (LEUKINE injection [solution] and LEUKINE for injection [lyophilized powder] reconstituted with Bacteriostatic Water for Injection, USP [0.9% benzyl alcohol] contain 11 mg and 9 mg of benzyl alcohol per mL, respectively). The minimum amount

of benzyl alcohol at which serious adverse reactions may occur is not known *[see Dosage and Administration (2.7)]*.

8.5 Geriatric Use

Clinical studies of LEUKINE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

10 OVERDOSAGE

Doses up to 100 mcg/kg/day (4,000 mcg/m^2/day or 16 times the recommended dose) were administered to four patients in a Phase 1 uncontrolled clinical study by continuous IV infusion for 7 to 18 days. Increases in WBC up to 200,000 cells/mm^3 were observed. Adverse events reported were dyspnea, malaise, nausea, fever, rash, sinus tachycardia, headache, and chills. All these events were reversible after discontinuation of LEUKINE.

In case of overdosage, discontinue LEUKINE therapy and monitor the patient for WBC increase and respiratory symptoms.

11 DESCRIPTION

LEUKINE (sargramostim) injection and LEUKINE (sargramostim) for injection for subcutaneous or intravenous use are recombinant human granulocyte-macrophage colony stimulating factor (rhu GM-CSF) produced by recombinant DNA technology in a yeast (*S. cerevisiae*) expression system. LEUKINE is a glycoprotein of 127 amino acids characterized by three primary molecular species having molecular masses of 19,500, 16,800 and 15,500 Daltons.

The amino acid sequence of LEUKINE differs from the natural human GM-CSF by a substitution of leucine at position 23, and the carbohydrate moiety may be different from the native protein. LEUKINE differs from human GM-CSF by one amino acid at position 23, where leucine is substituted for arginine.

LEUKINE (sargramostim) injection is a sterile, clear, colorless solution preserved with 1.1% benzyl alcohol in a multiple-dose vial. Each 1 mL vial contains 500 mcg sargramostim and has a pH range of 6.7 - 7.7. LEUKINE (sargramostim) for injection is supplied as a sterile, preservative-free, white lyophilized powder in a single-dose vial. Each single-dose vial delivers 250 mcg sargramostim. Inactive ingredients are mannitol (40 mg), sucrose (10 mg), and tromethamine (1.2 mg). Reconstitution with 1 mL of the appropriate diluent (sterile water for injection or bacteriostatic water for injection) yields a solution containing 250 mcg/mL sargramostim at a pH range of 7.1 - 7.7 with a deliverable volume of 1 mL (250 mcg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sargramostim (GM-CSF) belongs to a group of growth factors termed colony stimulating factors which support survival, clonal expansion, and differentiation of hematopoietic progenitor cells. GM-CSF induces partially committed progenitor cells to divide and differentiate in the granulocyte-macrophage pathways which include neutrophils, monocytes/macrophages and myeloid-derived dendritic cells.

GM-CSF is also capable of activating mature granulocytes and macrophages. GM-CSF is a multilineage factor and, in addition to dose-dependent effects on the myelomonocytic lineage, can promote the proliferation of megakaryocytic and erythroid progenitors. However, other factors are required to induce complete maturation in these two lineages. The various cellular responses (i.e., division, maturation, activation) are induced through GM-CSF binding to specific receptors expressed on the cell surface of target cells.

The biological activity of GM-CSF is species-specific. Consequently, *in vitro* studies have been performed on human cells to characterize the pharmacological activity of GM-CSF. *In vitro* exposure of human bone marrow cells to GM-CSF at concentrations ranging from 1-100 ng/mL results in the proliferation of hematopoietic progenitors and in the formation of pure granulocyte, pure macrophage and mixed granulocyte macrophage colonies. Chemotactic, anti-fungal, and anti-parasitic activities of granulocytes and monocytes are increased by exposure to GM-CSF *in vit*ro. GM-CSF increases the cytotoxicity of monocytes toward certain neoplastic cell lines and activates polymorphonuclear neutrophils to inhibit the growth of tumor cells.

12.2 Pharmacodynamics

LEUKINE stimulates hematopoietic precursor cells and increases neutrophil, eosinophil, megakaryocyte, macrophage, and dendritic cell production. In AML adult patients undergoing induction chemotherapy *[see Clinical Studies (14.1)]*, LEUKINE at daily doses of 250 mcg/m^2 significantly shortened the median duration of ANC <500/mm^3 by 4 days and <1000/mm^3 by 7 days following induction; 75% of patients receiving sargramostim achieved ANC greater than 500/mm^3 by day 16 compared to day 25 for patients receiving placebo. Animal data and clinical data in humans suggest a correlation between sargramostim exposure and the duration of severe neutropenia as a predictor of efficacy. At doses of 250 mcg/m^2 (approximately 7 mcg/kg in a 70 kg human with a body surface area of 1.96), daily LEUKINE treatment reduced the duration of severe neutropenia.

12.3 Pharmacokinetics

Intravenous Administration (IV)

Peak concentrations of sargramostim were observed in blood samples obtained during or immediately after completion of LEUKINE infusion. For LEUKINE injection, the mean maximum concentration (C_{max}) was 16.7 ng/mL and the mean area under the time-concentration curve $(AUC)_{0–inf}$ was 32.9 ng•h /mL. There is no accumulation of GM-CSF after repeat dosing and steady state conditions are met after a single dose.

Subcutaneous Administration (SC)

LEUKINE injection and LEUKINE for injection, at a dose of 6.5 mcg/kg (approximately 250 mcg/m^2) given by the SC route, have been determined to be bioequivalent. Based on a population pharmacokinetics analysis of lyophilized LEUKINE data, the mean C_{max} after a 7 mcg/kg SC dose (equivalent to a 250 mcg/m^2 dose in a 70 kg human with a body surface area of 1.96) was 3.03 ng/mL and mean AUC_{0-24} was 21.3 ng•h/mL (Table 4). There is no accumulation of GM-CSF after repeat SC dosing and steady state conditions are met after a single SC dose.

Table 4: Sargramostim serum C_{max} and AUC Exposure (CV%) in Humans after Subcutaneous Administration

Data type	Sargramostim dose	Formulation	Number of healthy subjects	AUC (CV%) (ng·h/mL)	C_{max} (CV%) (ng/mL)
Observed	250 mcg/m^2 [a]	LEUKINE injection	29 29	21.9 (28.1%) 20.3 (32.4%)	3.75 (45.5%) 3.24 (50.5%)
Observed	6.5 mcg/kg	Lyophilized LEUKINE	39	20.4 (28.7%)	3.15 (35.2%)
Population PK model simulation	7 mcg/kg	Lyophilized LEUKINE	500	21.3 (32.6)	3.03 (31.0)

[a] 250 mcg/m^2 is approximately 7 mcg/kg in 70 kg patient with a body surface area of 1.96 M^2

Absorption

After SC administration GM-CSF was detected in the serum early (15 min) and reached maximum serum concentrations between 2.5 and 4 h. The absolute bioavailability with the SC route, when compared to the IV route, was 75%.

Distribution

The observed volume of distribution after IV (Vz) administration was 96.8.

Elimination

When a 500 mcg dose of LEUKINE (injection) was administered IV over two hours to healthy volunteers, the mean terminal elimination half-life was approximately 3.84 h and the mean clearance rate was approximately 17.2 L/h. When LEUKINE (lyophilized product) was administered SC to healthy adult volunteers, GM-CSF and had a terminal elimination half-life of 1.4 h. The observed total body clearance/subcutaneous bioavailability (CL/F) was 23 L/h. Specific metabolism studies were not conducted, because LEUKINE is a protein and is expected to degrade to small peptides and individual amino acids.

Special Populations

Adult patients acutely exposed to myelosuppressive doses of radiation (H-ARS)

The pharmacokinetics of sargramostim are not available in adult patients acutely exposed to myelosuppressive doses of radiation. Pharmacokinetic data in irradiated and non-irradiated non-human primates and in healthy human adults were used to derive human doses for patients acutely exposed to myelosuppressive doses of radiation. Modeling and simulation of the healthy human adult pharmacokinetic data indicate that sargramostim C_{max} and AUC exposures at a LEUKINE dose of 7 mcg/kg in patients acutely exposed to myelosuppressive doses of radiation are expected to exceed sargramostim C_{max} (97.6% of patients) and AUC (100% of patients) exposures at a LEUKINE dose of 7 mcg/kg in non-human primates.

Pediatric patients acutely exposed to myelosuppressive doses of radiation (H-ARS)

The pharmacokinetics of sargramostim was not available in pediatric patients acutely exposed to myelosuppressive doses of radiation. The pharmacokinetics of sargramostim in pediatric patients after being exposed to myelosuppressive doses of radiation were estimated by scaling the adult population pharmacokinetic model to the pediatric population. The model-predicted mean AUC_{0-24} values at 7, 10, and 12 mcg/kg doses of LEUKINE in pediatric patients weighing greater than

40 kg (~adolescents), 15 to 40 kg (~young children), and 0 to less than 15 kg (~newborns to toddlers), respectively, were similar to AUC values in adults after a 7 mcg/kg dose.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Carcinogenicity and genetic toxicology studies have not been conducted with LEUKINE.

Impairment of Fertility

LEUKINE had no effect on fertility of female rabbits up to a dose of 200 mcg/kg/day.

The toxicology studies with up to 6 weeks of exposure to LEUKINE in sexually mature female and male cynomolgus monkeys did not reveal findings in male or female reproductive organs that would suggest impairment of fertility up to a dose of 200 mcg/kg/day. At 200 mcg/kg, the AUC exposure of LEUKINE was 8.8 to 11.4 times (monkeys) and 2.0 to 25.3 times (rabbits) the exposure in humans at the recommended clinical dose of 250 mcg/m^2.

After the first administration, a dose of 200 mcg/kg/day corresponds to an AUC of approximately 11.4 (monkeys) and 25.3 (rabbits) times the exposures observed in patients treated with the clinical LEUKINE dose of 250 mcg/m^2; however, due to the production of anti-LEUKINE antibodies with repeat administration, the AUC decreased to 8.8 (monkeys) and 2.0 (rabbits) times the clinical exposure by the end of the dosing periods.

14 CLINICAL STUDIES

14.1 Following Induction Chemotherapy for Acute Myelogenous Leukemia

The efficacy of LEUKINE in the treatment of AML was evaluated in a multicenter, randomized, double-blind placebo-controlled trial (study 305) of 99 newly-diagnosed adult patients, 55-70 years of age, receiving induction with or without consolidation. A combination of standard doses of daunorubicin (days 1-3) and ara-C (days 1-7) was administered during induction and high dose ara-C was administered days 1-6 as a single course of consolidation, if given. Bone marrow evaluation was performed on day 10 following induction chemotherapy. If hypoplasia with <5% blasts was not achieved, patients immediately received a second cycle of induction chemotherapy. If the bone marrow was hypoplastic with <5% blasts on day 10 or four days following the second cycle of induction chemotherapy, LEUKINE (250 mcg/m^2/day) or placebo was given intravenously over four hours each day, starting four days after the completion of chemotherapy. Study drug was continued until an ANC ≥1500 cells/mm^3 for three consecutive days was attained or a maximum of 42 days. LEUKINE or placebo was also administered after the single course of consolidation chemotherapy if delivered (ara-C 3-6 weeks after induction following neutrophil recovery). Study drug was discontinued immediately if leukemic regrowth occurred.

LEUKINE significantly shortened the median duration of ANC <500 cells/mm^3 by 4 days and <1000 cells/mm^3 by 7 days following induction (see Table 5). Of patients receiving LEUKINE, 75% achieved ANC >500 cells/mm^3 by day 16, compared to day 25 for patients receiving placebo. The proportion of patients receiving one cycle (70%) or two cycles (30%) of induction was similar in both treatment groups. LEUKINE significantly shortened the median times to

neutrophil recovery whether one cycle (12 vs. 15 days) or two cycles (14 vs. 23 days) of induction chemotherapy was administered. Median times to platelet (>20,000 cells/mm^3) and RBC transfusion independence were not significantly different between treatment groups.

Table 5: Hematological Recovery (in Days) in Patients with AML: Induction

Dataset	LEUKINE n=52[a] Median (25%, 75%)	Placebo n=47 Median (25%, 75%)	p-value[b]
ANC >500/mm^3 [c]	13 (11, 16)	17 (13, 25)	0.009
ANC >1000/mm^3 [d]	14 (12, 18)	21 (13, 34)	0.003
PLT >20,000/mm^3 [e]	11 (7, 14)	12 (9, >42)	0.10
RBC[f]	12 (9, 24)	14 (9, 42)	0.53

[a] Patients with missing data censored
[b] p = Generalized Wilcoxon
[c] 2 patients on LEUKINE and 4 patients on placebo had missing values
[d] 2 patients on LEUKINE and 3 patients on placebo had missing values
[e] 4 patients on placebo had missing values
[f] 3 patients on LEUKINE and 4 patients on placebo had missing values

During the consolidation phase of treatment, LEUKINE did not shorten the median time to recovery of ANC to 500 cells/mm^3 (13 days) or 1000 cells/mm^3 (14.5 days) compared to placebo. There were no significant differences in time to platelet and RBC transfusion independence.

The incidence of severe infections and deaths associated with infections was significantly reduced in patients who received LEUKINE. During induction or consolidation, 27 of 52 patients receiving LEUKINE and 35 of 47 patients receiving placebo had at least one grade 3, 4 or 5 infection (p=0.02). Twenty-five patients receiving LEUKINE and 30 patients receiving placebo experienced severe and fatal infections during induction only. There were significantly fewer deaths from infectious causes in the LEUKINE arm (3 vs. 11, p=0.02). The majority of deaths in the placebo group were associated with fungal infections with pneumonia as the primary infection.

14.2 Autologous Peripheral Blood Progenitor Cell Mobilization and Collection

A retrospective review was conducted of data from adult patients with cancer undergoing collection of peripheral blood progenitor cells (PBPC) at a single transplant center. Mobilization of PBPC and myeloid reconstitution post transplant were compared between four groups of patients (n=196) receiving LEUKINE for mobilization and a historical control group who did not receive any mobilization treatment [progenitor cells collected by leukapheresis without mobilization (n=100)]. Sequential cohorts received LEUKINE. The cohorts differed by dose (125 or 250 mcg/m^2/day), route (IV over 24 hours or SC) and use of LEUKINE post transplant. Leukaphereses were initiated for all mobilization groups after the WBC reached 10,000 cells/mm^3. Leukaphereses continued until both a minimum number of mononucleated cells (MNC) were collected (6.5 or 8.0 × 10^8/kg body weight) and a minimum number of aphereses (5-8) were performed. Both minimum requirements varied by treatment cohort and planned

conditioning regimen. If subjects failed to reach a WBC of 10,000 cells/mm^3 by day 5, another cytokine was substituted for LEUKINE.

Marked mobilization effects were seen in patients administered the higher dose of LEUKINE (250 mcg/m^2) either IV (n=63) or SC (n=41). PBPCs from patients treated at the 250 mcg/m^2/day dose had a significantly higher number of granulocyte-macrophage colony-forming units (CFU-GM) than those collected without mobilization. The mean value after thawing was 11.41×10^4 CFU-GM/kg for all LEUKINE-mobilized patients, compared to 0.96×10^4/kg for the non-mobilized group. A similar difference was observed in the mean number of erythrocyte burst-forming units (BFU-E) collected (23.96×10^4/kg for patients mobilized with 250 mcg/m^2 doses of LEUKINE administered SC vs. 1.63×10^4/kg for non-mobilized patients).

A second retrospective review of data from patients undergoing PBPC at another single transplant center was also conducted. LEUKINE was given SC at 250 mcg/m^2/day once a day (n=10) or twice a day (n=21) until completion of apheresis. Apheresis was begun on day 5 of LEUKINE administration and continued until the targeted MNC count of 9×10^8/kg or CD34+ cell count of 1×10^6/kg was reached. There was no difference in CD34+ cell count in patients receiving LEUKINE once or twice a day.

14.3 Autologous Peripheral Blood Progenitor Cell and Bone Marrow Transplantation

The efficacy of LEUKINE to accelerate myeloid reconstitution following autologous PBPC was established in the retrospective review above. After transplantation, mobilized subjects had shorter times to neutrophil recovery and fewer days between transplantation and the last platelet transfusion compared to non-mobilized subjects. Neutrophil recovery (ANC >500 cells/mm^3) was more rapid in patients administered LEUKINE following PBPC transplantation with LEUKINE-mobilized cells (see Table 6). Mobilized patients also had fewer days to the last platelet transfusion and last RBC transfusion, and a shorter duration of hospitalization than did non-mobilized subjects.

Table 6: ANC and Platelet Recovery after PBPC Transplantation

	LEUKINE Route for Mobilization	**Post transplant LEUKINE**	**Median Day ANC >500 cells/mm^3**	**Median Day of Last platelet transfusion**
No Mobilization	–	No	29	28
LEUKINE 250 mcg/m^2	IV	No	21	24
	IV	Yes	12	19
	SC	Yes	12	17

The efficacy of LEUKINE on time to myeloid reconstitution following autologous BMT was established by three single-center, randomized, placebo-controlled and double-blinded studies (studies 301, 302, and 303) in adult and pediatric patients undergoing autologous BMT for lymphoid malignancies. A total of 128 patients (65 LEUKINE, 63 placebo) were enrolled in these three studies. The median age was 38 years (range 3-62 years), and 12 patients were younger than 18 years of age. The majority of the patients had lymphoid malignancy (87 NHL, 17 ALL), 23 patients had Hodgkin lymphoma, and one patient had AML. In 72 patients with

NHL or ALL, the bone marrow harvest was purged with one of several monoclonal antibodies prior to storage. No chemical agent was used for *in vitro* treatment of the bone marrow. Preparative regimens in the three studies included cyclophosphamide (total dose 120-150 mg/kg) and total body irradiation (total dose 1,200-1,575 rads). Other regimens used in patients with Hodgkin's disease and NHL without radiotherapy consisted of three or more of the following in combination (expressed as total dose): cytosine arabinoside (400 mg/m^2) and carmustine (300 mg/m^2), cyclophosphamide (140-150 mg/kg), hydroxyurea (4.5 grams/m^2), and etoposide (375-450 mg/m^2).

Compared to placebo, administration of LEUKINE in two studies (study 301: 44 patients, 23 patients treated with LEUKINE, and study 303: 47 patients, 24 treated with LEUKINE) significantly improved the following hematologic and clinical endpoints: time to neutrophil recovery, duration of hospitalization and infection experience or antibacterial usage. In the third study (study 302: 37 patients who underwent autologous BMT, 18 treated with LEUKINE) there was a positive trend toward earlier myeloid engraftment in favor of LEUKINE. This latter study differed from the other two in having enrolled a large number of patients with Hodgkin lymphoma who had also received extensive radiation and chemotherapy prior to harvest of autologous bone marrow. In the following combined analysis of the three studies, these two subgroups (NHL and ALL vs. Hodgkin lymphoma) are presented separately.

Patients with Lymphoid Malignancy (Non-Hodgkin's Lymphoma and Acute Lymphoblastic Leukemia)

Neutrophil recovery (ANC ≥500 cells/mm^3) in 54 patients with NHL or ALL receiving LEUKINE on Studies 301, 302 and 303 was observed on day 18, and on day 24 in 50 patients treated with placebo (see Table 7). The median duration of hospitalization was six days shorter for the LEUKINE group than for the placebo group. Median duration of infectious episodes (defined as fever and neutropenia; or two positive cultures of the same organism; or fever >38°C and one positive blood culture; or clinical evidence of infection) was three days less in the group treated with LEUKINE. The median duration of antibacterial administration in the post transplantation period was four days shorter for the patients treated with LEUKINE than for placebo-treated patients.

Table 7: Autologous BMT: Combined Analysis from Placebo-Controlled Clinical Trials of Responses in Patients with NHL and ALL Median Values (days)

	ANC ≥500 cells /mm^3	**ANC ≥1000 cells/mm^3**	**Duration of Hospitalization**	**Duration of Infection**	**Duration of Antibacterial Therapy**
LEUKINE n=54	18[a,b]	24 [a, b]	25 [a]	1 [a]	21 [a]
Placebo n=50	24	32	31	4	25

[a] p <0.05 Wilcoxon or Cochran-Mantel-Haenszel RIDIT chi-squared

[b] p <0.05 Log rank

14.4 Allogeneic Bone Marrow Transplantation

A multicenter, randomized, placebo-controlled, and double-blinded study (study 9002) was conducted to evaluate the safety and efficacy of LEUKINE for promoting hematopoietic reconstitution following allogeneic BMT. A total of 109 adult and pediatric patients (53 LEUKINE, 56 placebo) were enrolled in the study. The median age was 34.7 years (range 2.2-65.1 years). Twenty-three patients (11 LEUKINE, 12 placebo) were 18 years old or younger. Sixty-seven patients had myeloid malignancies (33 AML, 34 CML), 17 had lymphoid malignancies (12 ALL, 5 NHL), three patients had Hodgkin's disease, six had multiple myeloma, nine had myelodysplastic disease, and seven patients had aplastic anemia. In 22 patients at one of the seven study sites, bone marrow harvests were depleted of T cells. Preparative regimens included cyclophosphamide, busulfan, cytosine arabinoside, etoposide, methotrexate, corticosteroids, and asparaginase. Some patients also received total body, splenic, or testicular irradiation. Primary GVHD prophylaxis was cyclosporine and a corticosteroid.

Accelerated myeloid engraftment was associated with significant laboratory and clinical benefits. Compared to placebo, administration of LEUKINE significantly improved the following: time to neutrophil engraftment, duration of hospitalization, number of patients with bacteremia, and overall incidence of infection (see Table 8).

Table 8: Allogeneic BMT: Analysis of Data from Placebo-Controlled Clinical Trial Median Values (days or number of patients)

	ANC ≥500/mm^3	**ANC ≥1000/mm^3**	**Number of Patients with Infections**	**Number of Patients with Bacteremia**	**Days of Hospitalization**
LEUKINE n=53	13[a]	14 [a]	30 [a]	9[b]	25 [a]
Placebo n=56	17	19	42	19	26

[a] p <0.05 generalized Wilcoxon test
[b] p <0.05 simple chi-square test

Median time to myeloid recovery (ANC ≥500 cells/mm^3) in 53 patients receiving LEUKINE was 4 four days less than in 56 patients treated with placebo (see Table 8). The numbers of patients with bacteremia and infection were significantly lower in the LEUKINE group compared to the placebo group (9/53 versus 19/56 and 30/53 versus 42/56, respectively). There were a number of secondary laboratory and clinical endpoints. Of these, only the incidence of severe (grade 3/4) mucositis was significantly improved in the LEUKINE group (4/53) compared to the placebo group (16/56) at p<0.05. LEUKINE-treated patients also had a shorter median duration of post transplant IV antibiotic infusions, and a shorter median number of days to last platelet and RBC transfusions compared to placebo patients, but none of these differences reached statistical significance.

14.5 Treatment of Delayed Neutrophil Recovery or Graft Failure After Allogeneic or Autologous Bone Marrow Transplantation

A historically-controlled study (study 501) was conducted in patients experiencing graft failure following allogeneic or autologous BMT to determine whether LEUKINE improved survival after BMT failure.

Three categories of patients were eligible for this study:

1. patients displaying a delay in neutrophil recovery (ANC $\leq$100 cells/mm^3 by day 28 post transplantation);
2. patients displaying a delay in neutrophil recovery (ANC $\leq$100 cells/mm^3 by day 21 post transplantation) and who had evidence of an active infection; and
3. patients who lost their marrow graft after a transient neutrophil recovery (manifested by an average of ANC $\geq$500 cells/mm^3 for at least one week followed by loss of engraftment with ANC <500 cells/mm^3 for at least one week beyond day 21 post transplantation).

A total of 140 eligible adult and pediatric patients from 35 institutions were treated with LEUKINE and evaluated in comparison to 103 historical control patients from a single institution. One hundred sixty-three patients had lymphoid or myeloid leukemia, 24 patients had NHL, 19 patients had Hodgkin's disease and 37 patients had other diseases, such as aplastic anemia, myelodysplasia or non-hematologic malignancy. The majority of patients (223 out of 243) had received prior chemotherapy with or without radiotherapy and/or immunotherapy prior to preparation for transplantation. The median age of enrolled patients was 27 years (range 1-66 years). Thirty-seven patients were younger than 18 years of age.

One hundred-day survival was improved in favor of the patients treated with LEUKINE for graft failure following either autologous or allogeneic BMT. In addition, the median survival was improved by greater than two-fold. The median survival of patients treated with LEUKINE after autologous failure was 474 days versus 161 days for the historical patients. Similarly, after allogeneic failure, the median survival was 97 days with LEUKINE treatment and 35 days for the historical controls. Improvement in survival was better in patients with fewer impaired organs. The Multiple Organ Failure (MOF) score is a clinical and laboratory assessment of seven major organ systems: cardiovascular, respiratory, gastrointestinal, hematologic, renal, hepatic and neurologic. Median survival by MOF category is presented in Table 9.

Table 9: Median Survival by Multiple Organ Failure (MOF) Category Median Survival (days)

	MOF $\leq$2 Organs	**MOF >2 Organs**	**MOF (Composite of both groups)**
Autologous BMT			
LEUKINE	474 (n=58)	78.5 (n=10)	474 (n=68)
Historical	165 (n=14)	39 (n=3)	161 (n=17)
Allogeneic BMT			
LEUKINE	174 (n=50)	27 (n=22)	97 (n=72)
Historical	52.5 (n=60)	15.5 (n=26)	35 (n=86)

14.6 Acute Exposure to Myelosuppressive Doses of Radiation (H-ARS)

Efficacy studies of LEUKINE could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. The use of LEUKINE in the H-ARS indication was based on efficacy studies conducted in animals and data supporting LEUKINE's effect on severe neutropenia in patients undergoing autologous or allogeneic BMT following myelosuppressive chemotherapy with or without total body irradiation, and in patients with acute myelogenous leukemia following myelosuppressive chemotherapy *[see Dosage and Administration (2.1 to 2.6)]*.

The recommended dose of LEUKINE for adults exposed to myelosuppressive doses of radiation is 7 mcg/kg as a single daily SC injection *[see Dosage and Administration (2.6)]*. The 7 mcg/kg dosing regimen is based on population modeling and simulation analyses. The sargramostim exposure associated with the 7 mcg/kg adult dose is expected to be higher than sargramostim exposure in the nonclinical efficacy study and therefore are expected to provide sufficient pharmacodynamic activity to treat humans exposed to myelosuppressive doses of radiation *[see Clinical Pharmacology (12.3)]*. The safety of LEUKINE at a dose of 250 mcg/m^2/day (approximately 7 mcg/kg) has been assessed on the basis of clinical experience in myeloid reconstitution in patients after autologous or allogeneic BMT, and in patients with AML *[see Adverse Reactions (6.1)]*.

The efficacy of LEUKINE was studied in a randomized, blinded, placebo-controlled study in a nonhuman primate model of radiation injury. Rhesus macaques (50% male) were randomized to a control (n = 36) or treated (n = 36) group. Animals were exposed to total body irradiation at a dose that would be lethal in 50% to 60% of animals (655 cGy) by day 60 post irradiation (lethal dose $[LD]_{50\text{-}60/60)}$. Starting 48 ± 1 hour after irradiation, animals received daily SC injections of placebo (sterile water for injection, USP) or LEUKINE (7 mcg/kg/day). Blinded treatment was stopped when one of the following criteria was met: ANC ≥1,000 cells/mm^3 for 3 consecutive days or if the ANC ≥10,000 cells/mm^3. Animals received minimal supportive care that included a prophylactic antibiotic, antiemetic, analgesics and parenteral fluids. No whole blood, blood products or individualized antibiotics were provided.

LEUKINE significantly (p=0.0018) increased survival at day 60 in irradiated nonhuman primates: 78% survival (28/36) in the LEUKINE group compared to 42% survival (15/36) in the control group.

In the same study, an exploratory cohort of 36 rhesus macaques randomized to control (n=18) or treated (n=18) was exposed to total body irradiation at a dose that would be lethal in 70-80% of animals (713 cGY) by day 60 post irradiation. LEUKINE increased survival at day 60 in irradiated nonhuman primates: 61% survival (11/18) in the LEUKINE group compared to 17% survival (3/18) in the control group.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

LEUKINE (sargramostim) for injection is a sterile, preservative-free, white lyophilized powder supplied in a carton containing five 250 mcg single-dose vials. (NDC 0024-5843-05).

LEUKINE (sargramostim) injection is a sterile, clear, colorless solution preserved with 1.1% benzyl alcohol supplied in a carton containing one 500 mcg/mL multiple-dose vial (NDC 0024-

5844-01) and a carton containing five 500 mcg/mL multiple-dose vials (NDC 0024-5844-05).

Storage and Handling

Store LEUKINE vials refrigerated at 2°C-8°C (36°F-46°F) in the original carton to protect from light. Do not freeze or shake. Do not use beyond the expiration date printed on the vial.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

LEUKINE should be used under the guidance and supervision of a health care professional. However, if the physician determines that LEUKINE may be used outside of the hospital or office setting, persons who will be administering LEUKINE should be instructed as to the proper dose, and the method of reconstituting and administering LEUKINE *[see Dosage and Administration (2.7)]*. If home use is prescribed, patients should be instructed in the importance of proper disposal and cautioned against the reuse of needles, syringes, drug product, and diluent. A puncture resistant container should be used by the patient for the disposal of used needles.

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

- Serious allergic reactions *[see Warnings and Precautions (5.1)]*
- Infusion related reactions *[see Warnings and Precautions (5.2)]*
- Risk of severe myelosuppression when LEUKINE administered within 24 hours of chemotherapy or radiotherapy *[see Warnings and Precautions (5.3)]*
- Effusions and capillary leak syndrome *[see Warnings and Precautions (5.4)]*
- Supraventricular arrhythmias *[see Warnings and Precautions (5.5)]*
- Leukocytosis including eosinophilia *[see Warnings and Precautions (5.6)]*
- Potential effect on malignant cells *[see Warnings and Precautions (5.7)]*
- Pain including chest, abdominal, back, and joint pain *[see Adverse Reactions (6.1)]*
- Thromboembolic events *[see Adverse Reactions (6.3)]*
- Embryofetal Toxicity: Advise females of reproductive potential that LEUKINE may cause fetal harm and to inform their prescriber of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*
- Lactation: Advise lactating woman not to breastfeed during treatment and for at least 2 weeks after the last dose *[see Use in Specific Populations (8.2)]*
- Advise patients acutely exposed to myelosuppressive doses of radiation (H-ARS) that efficacy studies of LEUKINE 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 (14.6)]*

Instruct patients who self-administer LEUKINE:

- Follow the Instructions for Use

- Do not reuse needles, syringes, or unused portions of vials
- Follow local requirements for proper disposal of used syringes, needles, and unused vials

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Manufactured by:
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807
A SANOFI COMPANY

US License No. 1752

Phone: 1-888-4RX-LEUKINE

Patient Information

LEUKINE® (loo-kine) (sargramostim) injection	LEUKINE® (loo-kine) (sargramostim) for injection

What is LEUKINE?

LEUKINE is a man-made form of granulocyte-macrophage colony-stimulating factor (GM-CSF). GM-CSF is a substance produced by the body. It stimulates the growth of certain white blood cells that are important in the body's fight against infection.

Acute Radiation Syndrome: The effectiveness of LEUKINE for this use was only studied in animals because it could not be studied in people.

Do not take LEUKINE if you have had a serious allergic reaction to human GM-CSF, such as sargramostim, products that are made from yeast, or any of the ingredients in LEUKINE. See the end of this leaflet for a complete list of ingredients in LEUKINE.

Before receiving LEUKINE, tell your healthcare provider about all your medical conditions, including if you:

- have heart or lung disease
- are allergic to benzyl alcohol
- are pregnant or plan to become pregnant. It is not known if LEUKINE will harm your unborn baby. See **"What are the possible side effects of LEUKINE?"** Talk to your healthcare provider about the type of LEUKINE that is right for you.
- are breastfeeding or plan to breastfeed. It is not known if LEUKINE passes into your breast milk. Do not breast feed during treatment and for at least 2 weeks after your last dose of LEUKINE.

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 LEUKINE?

- LEUKINE comes in two ways: as a solution or as a powder to be mixed for injection.
- LEUKINE is given as an injection under your skin (subcutaneous injection) by a healthcare provider.
- **If your healthcare provider decides that the subcutaneous injections can be given at home by you or your caregiver, see the detailed "Instructions for Use" that comes with your LEUKINE for information on how to draw up and inject a dose of LEUKINE**.
- **If your healthcare provider gives you LEUKINE for injection (powder) to be mixed, carefully follow your healthcare provider's instructions on how to store, mix, draw up and inject the medicine**.
- You and your caregiver should be shown how to prepare and inject LEUKINE before you use it, by your healthcare provider.
- Your healthcare provider will tell you how much LEUKINE to inject and when to inject it. Do not change your dose or stop LEUKINE unless your healthcare provider tells you to.
- If you are also receiving chemotherapy or radiation therapy, your dose of LEUKINE should be injected **at least 24 hours before or 24 hours after** your dose of chemotherapy and **at least 24 hours before** your dose of radiation therapy. Your healthcare provider will do blood tests to monitor your white blood cell count and, if necessary, adjust your LEUKINE dose.
- If you are receiving LEUKINE because you have been suddenly (acutely) exposed to an amount of radiation that can affect your bone marrow (Acute Radiation Syndrome), you will need to have blood tests about every 3 days during treatment with LEUKINE to check your white blood cell count until it returns to normal.
- If your child needs to receive LEUKINE for Acute Radiation Syndrome, follow your healthcare provider's instructions. LEUKINE injection contains the preservative benzyl alcohol.
- If you miss a dose of LEUKINE, talk to your healthcare provider about when you should give your next dose.

What are the possible side effects of LEUKINE?

LEUKINE may cause serious side effects, including:

- **Serious allergic reactions.** LEUKINE can cause serious allergic reactions that can be severe. Get medical help right away if you get any of the following signs or symptoms of a serious allergic reaction with LEUKINE, including: skin rash over your entire body, hives, trouble breathing, wheezing, swelling around your mouth or eyes, a fast heartbeat, sweating, and dizziness or feeling faint.
- **Infusion related reactions.** When LEUKINE is given as an infusion, it can cause reactions during or soon after an infusion. Tell your healthcare provider or nurse right away if you develop trouble breathing, skin flushing, a fast pulse, dizziness or you feel faint during or soon after your infusion.
- **Too much body fluid (fluid retention) and Capillary Leak Syndrome.** LEUKINE can cause you to have too much fluid in your body, and fluid may leak from blood vessels into your body's tissues. This can happen anywhere in your body, including around your heart and lungs. 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 of your feet or ankles, and are urinating less than usual
- swelling of your stomach area (abdomen) and feeling of fullness
- sudden weight gain
- swollen legs or feet
- trouble breathing
- dizziness or feeling faint
- a general feeling of tiredness

- **Abnormal heart rhythm.** An abnormal heart rhythm may happen during treatment with LEUKINE, especially in people with a history of an abnormal heart rhythm.
- **Increased white blood cell count .** LEUKINE can cause your white blood cell count to increase too high (leukocytosis). Your healthcare provider will check your blood during treatment with LEUKINE.
- **Risks of using LEUKINE in newborns, babies born with a low birth weight, and in pregnant women.** Some forms of LEUKINE may contain the preservative benzyl alcohol. Medicines that contain benzyl alcohol, including LEUKINE, can cause serious side effects that can lead to death in newborns and babies born with a low birth weight. Avoid using LEUKINE containing benzyl alcohol in newborns, babies born with a low birth weight, and in pregnant women. If LEUKINE needs to be given to your newborn or baby with a low birth weight, or in pregnant women, talk to your healthcare provider about this risk and which form of LEUKINE to use.

The most common side effects of LEUKINE in people who receive an autologous bone marrow transplant include: fever, nausea, diarrhea, vomiting, mouth sores, weakness and lack of energy, generally do not feel well, decreased appetite, rash, stomach and intestine problems, fluid buildup.

The most common side effects of LEUKINE in people who receive an allogeneic bone marrow transplant include: diarrhea, fever, nausea, rash, vomiting, mouth sores, decreased appetite, hair loss, stomach-area (abdomen) pain, headache and high blood pressure.

The most common side effects of LEUKINE in people with AML include: fever, liver problems, skin reactions, infections, abnormal amount of salts and other minerals in the blood, nausea, diarrhea, urinary tract problems, lung problems, vomiting, nervous system problems, mouth sores, hair loss and weight loss.

These are not all the possible side effects of LEUKINE.

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

How should I store LEUKINE injection (solution)?

- Store LEUKINE in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Do not freeze LEUKINE.
- Do not shake.
- Store LEUKINE vials in the original carton to protect from light.
- Do not use LEUKINE beyond the expiration date printed on the vial label.
- Used vials with remaining LEUKINE should be stored in the refrigerator and used within 20 days (be sure to mark down the date you first used the vial).
- Throw away (dispose of) any remaining LEUKINE after 20 days.

Keep LEUKINE out of the reach of children.

General information about the safe and effective use of LEUKINE.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use LEUKINE for a condition for which it was not prescribed. Do not give LEUKINE to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about LEUKINE that is written for health professionals.

What are the ingredients in LEUKINE?

Active ingredient: sargramostim

Inactive ingredients:

LEUKINE injection: benzyl alcohol

LEUKINE for injection: mannitol, sucrose, tromethamine

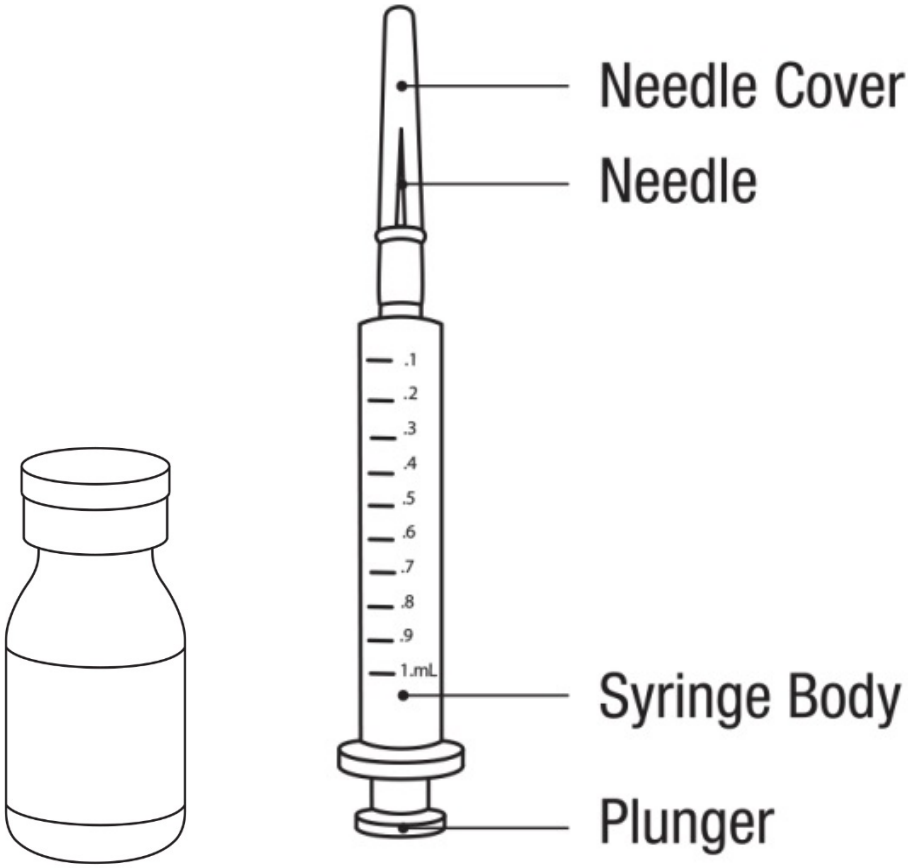
Manufactured by: sanofi-aventis U.S. LLC Bridgewater, NJ 08807 A SANOFI COMPANY

LEUKINE® is a registered trademark licensed to Genzyme Corporation.

For more information go to www.leukine.com, or call 1-888-4RX-LEUKINE

This Patient Information has been approved by the U.S. Food and Drug Administration Revised: 03/2018

Instructions for Use
LEUKINE® (loo'-kine)
(sargramostim)
Injection, for subcutaneous use
Multiple-dose vial



Important:

Read the Patient Information for important information you need to know about LEUKINE before using these Instructions for Use.

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Storing the LEUKINE vial

- Store LEUKINE in the refrigerator between 36°F to 46°F (2°C to 8°C).
- **Do not** freeze LEUKINE
- **Do not** shake LEUKINE.
- Keep the LEUKINE vial in the original carton to protect from light.

- **Do not** use LEUKINE beyond the expiration date printed on the vial label.
- Once the vial has been used, any remaining LEUKINE should be stored in the refrigerator and used within 20 days (be sure to mark down the date you first used the vial).
- Throw away (dispose of) any remaining LEUKINE in a used vial after 20 days. Throw away empty LEUKINE vials in the trash, unless otherwise instructed.

Keep LEUKINE, needles and syringes out of the reach of children.

Using LEUKINE vials

- **It is important that you do not try to give the injection unless you or your caregiver have received training from your healthcare provider about how to draw up and inject LEUKINE, and how often to inject it.** LEUKINE is given as an injection under the skin (subcutaneous injection). If you have any questions about your dose of LEUKINE, or how to draw up and inject a dose, talk to your healthcare provider.
- Use only the syringe and needle that your healthcare provider tells you to use to inject LEUKINE.
- Generally, a 1 mL syringe with a 25 to 30 gauge 5/8-inch needle is used. Your healthcare provider will either supply you with the correct syringes and needles, or will write you a prescription so you can get the correct syringes and needles from your pharmacy. The dose for LEUKINE will usually be measured in milliliters (mL). (For example: 0.8 mL). It is important that you use a syringe that is marked in tenths of a milliliter so that you are able to measure the correct dose prescribed by your healthcare provider. See the figure at the beginning of this leaflet.
- Make sure the name LEUKINE appears on the carton and vial label.
- Check the carton and vial label to make sure the dose strength is 500 mcg/mL.
- Look at the LEUKINE vial. LEUKINE should be clear and colorless. Do not use the vial of LEUKINE if the medicine is cloudy or discolored or contain flakes or particles. Contact your healthcare provider or pharmacist.
- **Do not** shake the vial.
- **Do not** use the vial if the carton is open or damaged.
- A skin reaction may occur at the injection site. Your skin may become red, painful, or swollen. If you develop a skin reaction, call your healthcare provider.
- **Do not** change your dose of LEUKINE unless your healthcare provider tells you to.
- Call your healthcare provider if you have any questions.

Step 1: Draw up the dose

A. Remove a LEUKINE vial from the refrigerator.
   - Put original carton with any unused vials back in the refrigerator.
   - Place the vial on a clean, flat, well-lit surface.

B. Inspect the LEUKINE vial.

   Make sure the medicine in the vial is clear and colorless.

   - **Do not** use the vial if:
     - The medicine is cloudy, discolored or contains lumps, flakes, or particles.

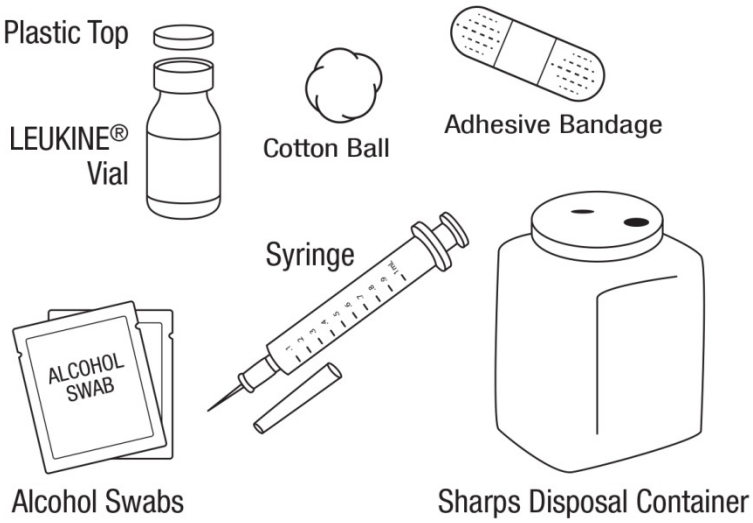
- The expiration date printed on the label has passed.

C. **Gather supplies needed for an injection.**

Wash your hands well with soap and water.

Place the following supplies on your clean, flat, well-lit surface:

- 1 vial of LEUKINE
- 1 sterile disposable syringe and needle
- 2 sterile alcohol swabs
- 1 cotton ball or gauze pad
- 1 adhesive bandage
- sharps disposal container. See Step 5.



- Only use the disposable syringes and needles that your healthcare provider prescribes.
- Only use the syringes and needles 1 time. Discard (throw away) any used syringes and needles. See Step 5.

Step 2: **Get ready**

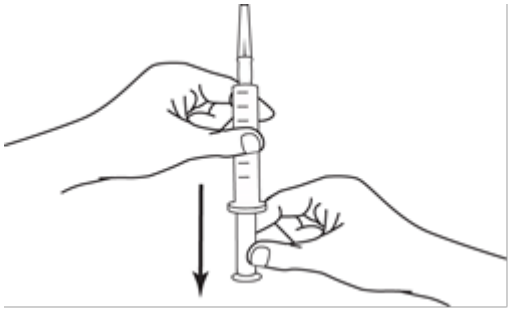
D. Take the cap off of the LEUKINE vial. **Do not** remove the gray rubber stopper.

- Wipe the top of the rubber stopper with a new alcohol swab.
- **Do not** touch the rubber stopper with your hands or fingers. If you do touch the stopper, clean it again with a new alcohol swab.

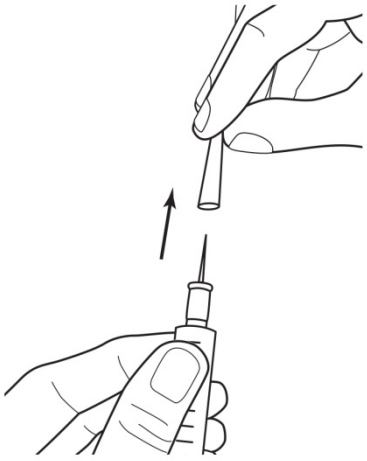
E. Check the syringe packaging. If the packaging is opened or damaged, do not use that syringe. Dispose of (throw away) that syringe in the sharps disposal container. See Step 5.

- Remove the syringe and needle from its packaging.

F. Hold the syringe by the barrel with the needle cover pointing up. With the needle cover still on the needle, draw air into the syringe by pulling back on the plunger. The amount of air (mLs) you draw into the syringe should be equal to your prescribed LEUKINE dose.



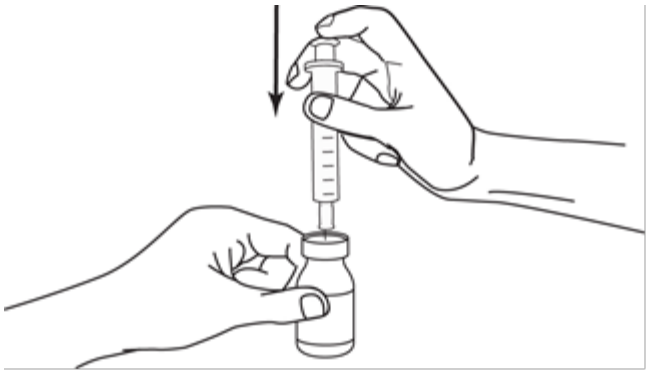
- Carefully remove the needle cover by pulling straight off and away from your body. Throw the needle cover into the sharps disposal container.



- **Do not** lay down the syringe or allow the needle to touch anything. If the needle touches any surface, including your hands, throw away the needle and syringe in your sharps disposal container and start over with a new syringe and needle.

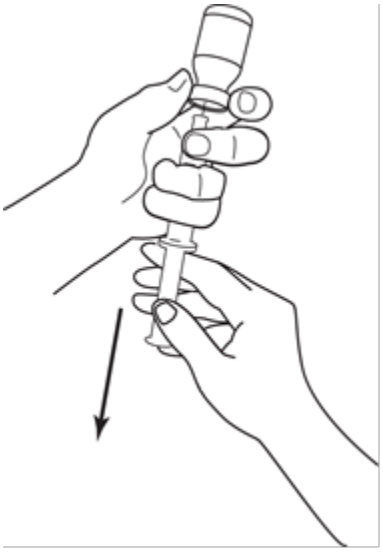
G. Keep the vial on your flat work surface and insert the needle downward, through the center of the rubber stopper.

H. Push the plunger down all the way to inject the air into the vial. Make sure the needle is above the LEUKINE liquid. Leave the needle in the rubber stopper.



I. Keep the needle in the vial and turn the vial upside down. Make sure that the LEUKINE liquid is covering the needle tip.

J. Keep the vial upside down and slowly pull back on the plunger to fill the syringe barrel with LEUKINE until the plunger lines up with the amount (mL) that matches your prescribed dose.



K. Keep the needle in the vial and check for air bubbles in the syringe. If there are air bubbles, gently tap the syringe barrel with your finger until the air bubbles rise to the top of the syringe. Slowly push the plunger up to push the air bubbles out of the syringe.

L. Keep the tip of the needle in the LEUKINE liquid and again pull the plunger back to the number on the syringe barrel that matches your prescribed dose. Check again for bubbles. The air in the syringe will not hurt you, but too large of an air bubble can reduce the amount of LEUKINE you inject. If there are still air bubbles, repeat the above steps to remove them.

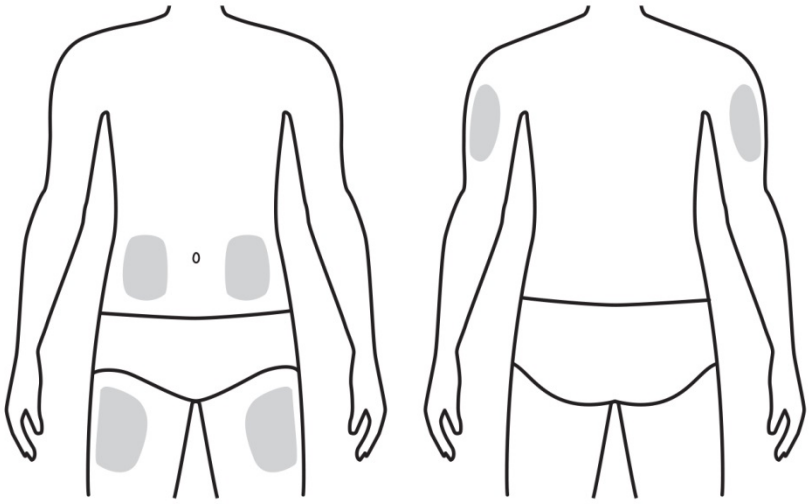
M. Check again that you have the correct dose of LEUKINE in the syringe. It is important that you use the correct dose as prescribed by your healthcare provider.

- **Do not** remove the needle from the vial. Place the vial down on its side on your flat work surface with the needle still in the vial.

Step 3: Choose and prepare the injection site

You can use

- Thigh
- Stomach-area (abdomen), except for a 2-inch area right around your navel area (belly button) or waistline.
- Outer area of upper arm (only if someone else is giving you the injection).
  - Choose a different site with each injection. Injection sites should be at least one inch apart.
  - **Do not** inject into an area where the skin is tender, bruised, red, or hard. Avoid injecting into areas with scars or stretch marks.



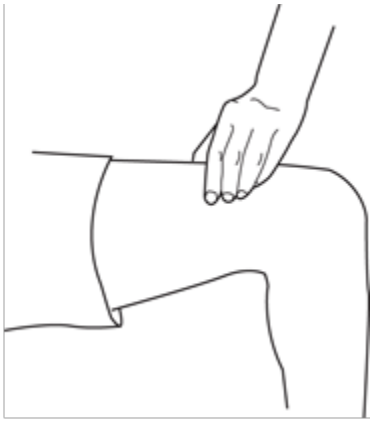
N. Clean the injection site

- Clean the injection site with an alcohol swab. Throw the alcohol swab away.
- Let the skin dry for 10 seconds.
- **Do not** touch this area again before injecting.

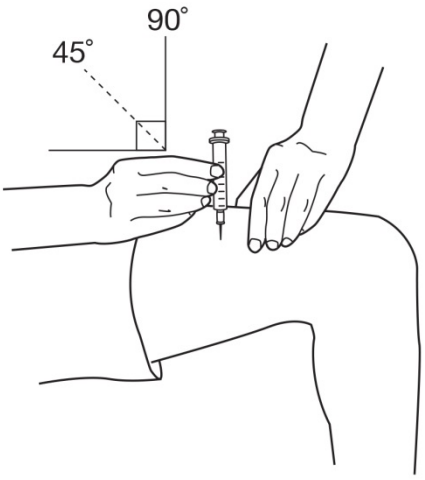
Step 4: Subcutaneous (under the skin) injection

O. Withdraw the needle from the LEUKINE vial by pulling the syringe back through the rubber stopper.

P. Pinch your injection site to create a firm surface. **Keep skin pinched while injecting.**



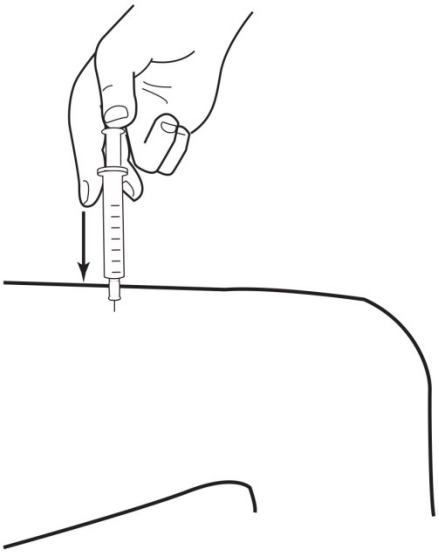
Q. Hold the pinch. Insert the needle into the skin at a 45 to 90-degree angle.



R. Release your grasp on the skin. Gently pull back on the plunger just a little bit (about 1/8 of an inch).

- **If you see blood in the syringe, do not inject LEUKINE**. Withdraw the needle at the same angle it was inserted. Dispose of the syringe in your sharps disposal container. **See Step 5.**
  Repeat Steps 1 through 4 to prepare a new syringe of LEUKINE.

- **If you do not see blood in the syringe**, slowly inject all of the LEUKINE by pushing the plunger until it reaches the bottom.



S. When finished injecting LEUKINE, remove the needle at the same angle as it was inserted. **Do not** try to re-cap the needle.

Step 5: Dispose of (throw away) needles and syringes

- **Do not** reuse syringes or needles. Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and syringes in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your sharps disposal container.

Important: Always keep the sharps disposal container out of the reach of children.

Step 6: Examine the injection site

- If there is blood at the injection site, press a cotton ball or gauze pad on the injection site. **Do not** rub the injection site. Apply an adhesive bandage if needed.

IMPORTANT NOTES

- Try to give yourself LEUKINE at the same time each day.
- Call your healthcare provider or pharmacist if you:
  - miss a dose of LEUKINE
  - notice anything unusual about your condition while you are taking LEUKINE

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by: Sanofi-aventis U.S. LLC
Bridgewater, NJ 08807
US License No. 1752

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Revised: 03/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103362Orig1s5240

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: BLA 103362 Supplement 5240

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

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103362Orig1s5240

MULTI-DISCIPLINE REVIEW

Clinical Review
Nonclinical Review
Clinical Pharmacology
Statistical Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Supplemental Biologics License Application (sBLA)
Application Number(s)	BLA 103362, s5240
Priority or Standard	Priority
Submit Date(s)	September 29, 2017
Received Date(s)	September 29, 2017
PDUFA Goal Date	March 29, 2018
Division/Office	Division of Medical Imaging Products/ODE IV
Review Completion Date	March 28, 2018
Established Name	Sargramostim
Established Trade Name	Leukine
Pharmacologic Class	Biologic
Applicant	Sanofi-Aventis, LLC
Formulation(s)	• Lyophilized powder: 250 mcg (1.4 x 10^6 IU/vial) sargramostim in vials • Solution: 500 mcg/mL (2.8 x 10^6 IU/mL) sargramostim in vials
Dosing Regimen	For patients with Hematopoietic Syndrome of Acute Radiation Syndrome (H-ARS), the recommended dose of LEUKINE is a subcutaneous (SC) injection administered once daily as follows: • 7 mcg/kg in adults and children weighing >40 kg; • 10 mcg/kg in children weighing 15 kg to 40 kg; • 12 mcg/kg in children weighing <15 kg. Administer LEUKINE as soon as possible after suspected or confirmed exposure to radiation doses greater than 2 gray (Gy). 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 cell count (CBC) with differential and then serial CBCs approximately every third day until the absolute neutrophil count (ANC) remains greater than >1,000/mm^3 for three consecutive CBCs. Do not delay administration of LEUKINE if a CBC is not readily available. Continue administration of LEUKINE until the ANC remains greater than 1,000/mm^3 for three consecutive CBCs or exceeds 10,000/mm^3 after a radiation-induced nadir.
Applicant Proposed Indication(s)/Population(s)	(b)(4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	To increase survival in adult and pediatric patients from birth to 17 years of age acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [H-ARS])

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Reviewers Team and Signature Approval Section

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORIZED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Cindy Welsh, MD	ODE IV/ DMIP	Sections 1, Risk Benefit table 2, 3, 4.1, a few paragraphs in 5, sections 8.2, 10,11, 12, and 13	Select one: _X__ Authored ___ Approved
	Signature: Cynthia A. Welsh -S Digitally signed by Cynthia A. Welsh -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300385504, cn=Cynthia A. Welsh -S Date: 2018.03.29 15:08:45 -04'00'			
Clinical Team Leader/ CDTL	Nushin Todd, MD, PhD	ODE IV/ DMIP	Sections all	Select one: ___ Authored _X_ Approved
	Signature: FDA Nushin Todd -S 2018.03.29 15:36:35 -04'00'			
Nonclinical Reviewer	Ron Honchel, PhD	ODE IV/ DMIP	Sections 5.3 and 5.4	Select one: _X__ Authored ___ Approved
	Signature: Ronald Honchel -S Digitally signed by Ronald Honchel -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ronald Honchel -S, 0.9.2342.19200300.100.1.1=1300124657 Date: 2018.03.29 14:51:27 -04'00'			
Nonclinical Reviewer	Olayinka Dina, PhD	ODE IV/ DMIP	Section 5.5	Select one: _X_ Authored ___ Approved
	Signature: Olayinka Dina -S Digitally signed by Olayinka Dina -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olayinka Dina -S, 0.9.2342.19200300.100.1.1=2000594003 Date: 2018.03.29 14:34:47 -04'00'			
Nonclinical Supervisor	Adebayo Laniyonu, PhD	ODE IV/ DMIP	Section 5	Select one: X_ Authored ___ Approved
	Signature: Adebayo A. Laniyonu -S Digitally signed by Adebayo A. Laniyonu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300127170, cn=Adebayo A. Laniyonu -S Date: 2018.03.29 14:59:22 -04'00'			
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Statistical Primary Reviewer	Xiangmin Zhang, PhD	OTS/OB/DB1	Sections 8.1 and 8.3	Select one: _X_ Authored ___ Approved
	Signature: Xiangmin Zhang -S (Affiliate) Digitally signed by Xiangmin Zhang -S (Affiliate) Date: 2018.03.29 15:28:43 -04'00'			
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Division Director	Libero Marzella, MD, PhD	ODE IV/DMIP	Sections all	Select one: ___ Authored __X_ Approved
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Nonclinical Team Leader	Adebayo Laniyonu, PhD
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Statistical Acting Deputy Division Director	Sue Jane Wang, PhD
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Cross-Disciplinary Team Leader	Nushin Todd, MD, PhD
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NonClinical OSIS	Zhou Chen, MD, PhD CDER Pharmacologist Gopa Biswas, PhD, CDER Pharmacologist
Other	

OBP= Office of Biotechnology Products
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSIS=Office of Study Integrity and Surveillance
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DHP = Division of Hematology Products
DMEPA=Division of Medication Error Prevention and Analysis
DPMH= Division of Pediatric and Maternal Health
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALL	acute lymphoblastic leukemia
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
ARS	acute radiation syndrome
BLA	biologics license application
BMT	bone marrow transplant
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
cGy	centigray
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
D	day
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
DMIP	Division of Medical Imaging Products
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GCSF	granulocyte colony stimulating factor(s)
GD	gestation day
GMCSF	granulocyte macrophage colony stimulating factor(s)

GRMP	good review management practice
H-ARS	hematopoietic acute radiation syndrome
HLA	human leukocyte antigen
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISR(s)	injection site reaction(s)
ISS	integrated summary of safety
ITT	intent to treat
Kg	kilogram
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MSC	minimal supportive care
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NHL	non-Hodgkin's lymphoma
NHP	non-human primate
NME	new molecular entity
OCS	Office of Computational Science
OHOP	Office of Hematology and Oncology Products
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PLR	physician labeling rule
PLLR	pregnancy and lactation labeling rule
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
rhuGM-CSF	recombinant human granulocyte-macrophage colony stimulating factor
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneously
SGE	special government employee
SOC	standard of care

TBI	total body irradiation
TEAE	treatment emergent adverse event
ug	microgram

1 Executive Summary

1.1. Product Introduction

Leukine (sargramostim) is a recombinant granulocyte macrophage colony-stimulating factor (GM-CSF) that functions as a hematopoietic growth factor and immunostimulator. Leukine was originally approved in 1991 to shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death following induction chemotherapy in adult patients with acute myeloid leukemia. Leukine was subsequently approved for four other oncology-related indications.

On September 29, 2017, Sanofi-Genzyme (the Applicant) submitted a supplemental Biologic License Application (sBLA) for Leukine for consideration for approval under the Animal Efficacy Rule (21 CFR 601.90). Leukine is proposed for (b)(4) . For patients with H-ARS, the recommended dose of Leukine is a subcutaneous injection administered once daily as follows: 7 mcg/kg in adults and children weighing >40 kg; 10 mcg/kg in children weighing 15 kg to 40 kg; and 12 mcg/kg in children weighing <15 kg.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The approval of Leukine (b)(4)) is based on the results of two efficacy studies in non-human primates (NHP) in conjunction with the clinical safety and efficacy of Leukine in myelosuppression induced by chemotherapy or total body irradiation (TBI). Pharmacokinetic (PK) studies in healthy and irradiated NHP, and PK studies in healthy adult humans were used for the selection of a Leukine dose to provide exposures in humans that exceed those observed in the animal efficacy studies.

The efficacy study providing primary support was a randomized, blinded, vehicle-controlled study in 72 NHP exposed to a dose of TBI (~655 centigray [cGy]) expected to be lethal in 50% of exposed animals in 60 days ($LD_{50/60}$ dose). The animals received minimal supportive care (fluids, antimicrobials) and were treated with Leukine or vehicle control beginning 48 hours after exposure to irradiation. A statistically significant improvement in survival was shown in the Leukine group compared to the vehicle group. Exploration of higher TBI doses (713 cGy) in NHP showed higher survival in the Leukine group compared to vehicle control group. Pediatric use for the H-ARS indication was determined based upon a population PK study, pediatric experience, and extrapolation from adult data.

The Applicant has met the burden of proof for demonstrating both safety and effectiveness under the prevailing statutory and regulatory standards. The safety of Leukine has been established from the trials conducted during clinical development and from post marketing experience and is summarized in the Leukine prescribing information. The requirements of 21 CFR 601.90 have been met based on adequate and well controlled animal efficacy and PK studies. These studies establish that Leukine is reasonably likely to produce a clinical benefit in humans. The totality of the data from animal and clinical studies provides substantial evidence of safety and effectiveness of Leukine for use in adult and pediatric patients for H-ARS.

Leukine provides patients exposed to myelosuppressive doses of radiation a treatment option shown to be effective in increasing survival with a delay in start of treatment of up to 48 hours and in the setting of minimal supportive care that mimics the limited resource environment in a radionuclear mass casualty event.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Leukine is a leukocyte growth factor (LGF) approved for use to shorten the duration of neutropenia due to myelosuppression from marrow injury induced by chemotherapy or total body irradiation. The Hematopoietic Syndrome of Acute Radiation Syndrome (H-ARS) occurs after whole-body or partial-body irradiation >1 Gray (Gy) causing damage to rapidly dividing tissues, including bone-marrow, resulting in neutropenia and thrombocytopenia that may lead to infection, bleeding, and death. The risk of injury and death from irradiation is dose dependent and may be affected by comorbidity and concomitant injury. FDA-approved therapies for treatment of ARS are the LGFs filgrastim (Neupogen) and pegfilgrastim (Neulasta) added to supportive care.

The efficacy and safety of Leukine as therapy for H-ARS was established based on animal efficacy studies under the Animal Rule as well as on clinical evidence of Leukine for use in other approved indications affecting the marrow. The primary evidence of efficacy was based upon the NHP study TSK0144 a randomized, double blinded, vehicle-controlled study conducted under Good Laboratory Practice (GLP). The study compared Leukine vs. vehicle as an add-on to supportive care in 72 NHP irradiated at an LD50/60 dose. The primary endpoint was mortality rate at Day 60. Mortality in the Leukine group was 22% compared to mortality in the vehicle group of 58%.

The H-ARS indication of Leukine for the pediatric population was based upon extrapolation from adult data, a population PK study, and clinical experience in the pediatric population. Based on experience with other approved indications, the safety of Leukine in the pediatric population does not differ from safety in adults. Preparation of the Leukine using benzyl alcohol should be avoided in neonates and low birth weight infants due to the benzyl alcohol toxicity (gasping syndrome) in this age group.

The risks of Leukine in the proposed population of use are as summarized in the safety profile described in the Leukine labeling. The survival benefit of Leukine in ARS outweighs the risks posed by adverse reactions to the drug.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• H-ARS occurs at doses > 1 Gy total or partial body irradiation damaging the bone marrow in a dose dependent fashion resulting in neutropenia and thrombocytopenia that may lead to death • The extent of the myelosuppression and mortality is related to radiation dose, volume of body irradiated, comorbidities, and concomitant injury. Age and gender are factors influencing susceptibility to H-ARS.	H-ARS is a serious and life threatening condition. Lethality is dependent upon the absorbed radiation dose. Development of treatments for the hematopoietic and other systemic manifestations of ARS is critical for national preparedness for radiological or nuclear emergencies.
Current Treatment Options	• The current standard of care for neutropenia secondary to H-ARS is administration of leukocyte growth factors in addition to supportive care. • FDA approved therapies for H-ARS are Neupogen and Neulasta. • The availability of the two products may be limited in a mass casualty situation.	Treatment of myelosuppression induced by H-ARS is supportive care and growth factors to stimulate bone-marrow recovery. Leukine provides an additional treatment option.
Benefit	• Study TSK0144 in 72 NHP compared Leukine subcutaneously 7 ug/kg/day to vehicle as an add-on to supportive care beginning 48 hours after 655 cGy TBI ($LD_{50/60}$) until the ANC reached ≥1000 uL for 3 consecutive days. • The primary endpoint was mortality rate at Day 60. Mortality in the treated group was 22% compared to 58% in the vehicle group. • Exploration of higher TBI doses (713 cGy, $LD_{70\text{-}80}$) showed higher survival at Day 60 in the Leukine group (61% ,11/18) compared to vehicle group (17%, 3/18). • Pediatric use and dosing for H-ARS indication was determined based upon a population PK study, extrapolation from adult	Leukine is recommended for all age groups. In the standard NHP TBI model Leukine increased survival when started up to 48 hrs after irradiation, at up to $LD_{70\text{-}80}$ radiation doses, and in the presence of minimal supportive care.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	data, and clinical experience in the pediatric age group. • Efficacy evidence from approved uses of Leukine in myelosuppression induced by chemotherapy and TBI supported the animal efficacy data. • Leukine treatment was shown to be effective in NHP when started at up to 48 hours after TBI and as an add-on to minimal supportive care consisting of fluids and antimicrobials. A Leukine treatment effect was also observed at LD_{70-80} TBI doses.	
Risk and Risk Management	• The adverse reactions to Leukine are known from the clinical trials for the approved uses and from the postmarketing experience in approximately (b)(4) patients and are summarized in the prescribing information. • Risk management steps include: 1) ANC measurements to determine when to discontinue administration of Leukine 2) Avoidance of benzyl alcohol preparation in neonates or low birth weight infants.	The survival benefit of Leukine in ARS outweighs the known risks of Leukine.

1.4. Patient Experience Data

No new clinical or other patient experience data were submitted nor was any considered necessary for the clinical review.

2 Therapeutic Context

2.1. Analysis of Condition

ARS occurs after whole-body or significant partial-body irradiation of greater than 1 Gy over a relatively short time usually within minutes. H-ARS is the result of radiation-induced myelosuppression that manifests primarily with neutropenia and thrombocytopenia. Measures aimed at shortening the duration of neutropenia and thrombocytopenia are a critical aspect of medical management. The survival rate of patients with H-ARS decreases with increasing radiation absorbed dose. The primary causes of death in H-ARS are infection and hemorrhage. Estimates of the lethal dose of radiation, 50% (LD50) have ranged from 1.4 Gy among atomic bomb casualties in Japan to 4.5 Gy following uniform total-body exposure to external photons. Other manifestations of ARS include gastrointestinal (GI) and central nervous system (CNS) syndromes that are associated with higher radiation absorbed doses than H-ARS and are outside the scope of this review.

The signs and symptoms of H-ARS vary based upon the radiation absorbed dose, the dose rate, the volume of the body exposed (e.g., partial body vs. total body), the type of the radiation (e.g., photon, beta, alpha, neutron) as well as the individual sensitivity to radiation. The signs and symptoms in a population presenting for care after a radiation incident may be minimal in those with <1 Gy exposure. Nausea, vomiting, headache, fatigue, fever, and perhaps skin reddening manifest in those with >1 Gy exposure. At this time, there is no FDA cleared biodosimeter for use in radiation emergencies. A combination of the presenting signs and symptoms as well as lymphocyte depletion kinetics or dicentric chromosome formation are useful to determine the extent of radiation exposure. Unfortunately, those diagnostic tests are not expected to be widely available in the initial stages of assessment in a mass casualty situation.

The development of products for ARS is conducted under the Animal Rule (21 CFR 314 Subpart I for drugs or 21 CFR 601 Subpart H for biological products) as human efficacy studies are not ethical or feasible. For more detailed information see the FDA guidance for industry titled: Product Development Under the Animal Rule
https://www.fda.gov/downloads/drugs/guidances/ucm399217.pdf

Chemotherapy induced bone marrow injury is considered to have similar pathophysiology as that of radiation induced injury. Colony stimulating factors (CSF) are useful for the myelosuppression induced by radiation because they enhance the proliferation, differentiation, and function of hematopoietic precursor cells. G-CSF regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and certain end-cell functions. Two G-CSF products, filgrastim (Neupogen) and pegfilgrastim (Neulasta) have been approved for H-ARS under the Animal Rule. The evidence of efficacy was based on studies in an NHP model of lethal total body irradiation and on established clinical evidence of benefit in patients with myelosuppression induced by chemotherapy or TBI. This same regulatory paradigm has been used for the development of the GM-CSF product sargramostim (Leukine). The animal efficacy studies for the three CSFs have utilized the same NHP model of myelosuppression induced by TBI (LD_{50-60}) and evaluated survival benefit of CSF treatment beginning at 24 hours following TBI. The two G-CSF were studied as add-on to standard veterinary care that included fresh NHP blood transfusions to provide for additional hematologic support.

In the GM-CSF animal studies, a number of important additional treatment variables were examined. The GM-CSF treatment effect did not require concomitant hematologic support in the form of fresh blood transfusions and the effect was retained when the start of sargramostim treatment was delayed for up 48 hrs after TBI. Moreover, exploratory evidence of treatment effect of sargramostim after more severe radiation exposure (i.e. $LD_{70/80-60}$) was obtained.

Several professional organizations and agencies recommend the use of CSF 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), and the Strategic National Stockpile Radiation Working Group. Additionally, Leukine is noted as a treatment option on the REMM website https://www.remm.nlm.gov/cytokines.htm

2.2. Analysis of Current Treatment Options

Treatment options for H-ARS consists of supportive care based upon severity of the radiation exposure and resource availability (e.g. antimicrobials, IV fluids, transfusions, anti-emetics) and CSF. As shown in the table below, Neupogen and Neulasta have been approved for H-ARS in adult and pediatric patients. The principal evidence for approval for this indication is improved survival at 60 days in adequate and well controlled animal efficacy studies of myelosuppression induced by TBI. Neupogen, Neulasta, and Leukine are included in the national strategic stockpile with vendor controlled rotation of the supply. Biosimilars of these CSF, while not approved for the H- ARS indication, would likely be utilized in radionuclear incidents resulting in

mass casualties. Procedures and guidelines for triage and treatment with limited resources have been instituted for preparedness for a mass casualty event.

Approved products for indication

Product Name	H-ARS Indication	Year of Approval	Dosing/Administration
Neupogen	To increase survival in patients acutely exposed to myelosuppressive doses of radiation	2015	Adults 10 ug/kg/day SC until ANC > 1000/mm3 for 3 consecutive CBCs or >10,000/mm3 after nadir Pediatric Same as adults
Neulasta	To increase survival in patients acutely exposed to myelosuppressive doses of radiation	2015	Adults Two doses (6 mg each SC) 1 week apart Pediatric – two weight based doses SC 1 week apart 31-44 Kg: 4 mg 21-30 kg: 2.5 mg 10-20 kg: 1.5 mg <10 kg: 0.1 mg/kg

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Leukine Initial Approval
3/5/1991, BLA 103362

Leukine Approved Indications

- Use following induction chemotherapy in older adult patients with acute myelogenous leukemia (AML) to shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death
- Mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis
- Acceleration of myeloid recovery in patients with non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL), and Hodgkin's disease undergoing autologous bone marrow transplantation (BMT)
- Acceleration of myeloid recovery in patients undergoing allogeneic BMT from HLA matched

related donors

- Patients who have undergone allogeneic or autologous BMT in whom engraftment is delayed or has failed

Formulation

The formulations are solution and lyophilized.

Labeling

The prescribing information submitted with this efficacy supplement was revised to conform with the content and format requirements described in the regulations commonly referred as the Physician Labeling rule (PLR). In addition, the labeling submitted was revised to address requirements for Pregnancy and Lactation Labeling Rule (PLLR).

Postmarketing Commitments

2/10/2017: Fulfillment of Postmarketing Commitments
PMC 2391-2 (immunogenicity) and PMC 2391-7 (revised labeling) have been fulfilled (Reference ID: 4054752). There are no outstanding PMCs.

Postmarketing Requirements

Studies to demonstrate safety and efficacy in humans must be conducted at the time of use of products approved under the Animal Efficacy Rule. The Applicant, in the event of a radionuclear emergency, will conduct a Phase 4 observational study (PMR 3362-1) to evaluate the efficacy and safety of Leukine in the setting of hematopoietic syndrome (HS) following acute radiation exposure (H-ARS).

3.2. Summary of Presubmission/Submission Regulatory Activity

Pre-EUA

The Emergency Use Authorization (EUA) authority allows FDA to help strengthen the nation's preparedness for public health emergencies such as radionuclear events. Under section 564 of the FD&C Act, FDA may allow unapproved uses of approved medical products to be used for life-threatening conditions caused by threat agents. Pre-emergency activities are designed to address regulatory issues before an emergency occurs, enabling access to medical countermeasures to the public during an emergency.

March 2013: Pre-EUA #17 submission by Biomedical Advanced Research and Development Authority (BARDA) and Centers for Disease Control and Prevention (CDC). During the Pre-EUA process the Executive Summary, Fact Sheet for Health Care Providers, Fact Sheet for Recipients were developed.

IND (b)(4)

11/14/12 Pre-IND Type B Meeting:
FDA provided recommendations regarding non-clinical study compliance with GLP, primary endpoint of survival, and dose conversion approaches. The Applicant postponed further development until after a public Advisory Committee meeting (see below).

5/3/13 Joint Meeting of the Medical Imaging Drugs and Oncologic Drugs Advisory Committees:
The committees discussed the safety and efficacy of the currently approved LGFs as potential treatments for radiation-induced myelosuppression associated with a radiological/nuclear incident. The committees considered the approved LGFs licensed under biological license applications (BLAs): 103353, Neupogen (filgrastim), 125031, Neulasta (pegfilgrastim), 103362, Leukine, (sargramostim), and 125294, TBO-FILGRASTIM (tbo-filgrastim). The committees considered safety and other supportive information described in the labeling for LGFs and efficacy data submitted by the National Institute of Allergy and Infectious Diseases (NIAID) for filgrastim in an animal model of radiation-induced myelosuppression.

The committees voted 17:1 that filgrastim therapy was reasonably likely to produce clinical benefits in humans exposed to radiation following a radiological/nuclear incident. One of the questions discussed was: "To what extent, if any, could filgrastim safety and efficacy in the radiological/nuclear incident setting be generalized to the use of other LGFs in this setting? Consider whether definitive animal model studies are necessary for other LGFs." Overall, the committees 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. However, the committees noted that there may be safety differences between the LGFs and additional efficacy questions for LGFs needed to be taken into consideration e.g. response to LGF treatment following exposure to various radiation doses, delay in start of treatment and treatment in the presence of comorbidities.

The committees supported the use of the NHP animal model to establish the efficacy of each LGF in the H-ARS indication. Additionally, the committees supported using mortality rate measured at Day 60 after radiation exposure as the primary endpoint for NHP efficacy studies in the H-ARS indication as the most persuasive evidence of benefit in humans. Committee members also believed that shortening the ANC recovery time is a useful supportive endpoint. Transcripts of the committee's discussions are available at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee/ucm334176.htm)

8/27/2013 Communication:
FDA agreed to use of existing safety data for adults and pediatric populations, and survival at 60 days as the primary endpoint in the same NHP study model used for the approval of Neupogen and Neulasta for the same indication. FDA recommended that the Applicant develop a plan for supportive care in their efficacy study.

4/28/2016 Communication:
FDA recommended a population PK study to determine the adequacy of the dose (converting from 250 ug/m^2 to 7 ug/kg for ease of administration in an emergency setting). FDA agreed to the design of the planned confirmatory efficacy study as well as use of a BARDA sponsored animal study as supportive. FDA agreed that one study may be sufficient provided it is adequate and well controlled and the endpoints have been met.

6/1/2017 Pre-sBLA meeting:
FDA agreed with the content of the submission with respect to the nonclinical studies, use of data for supportive human safety and efficacy evidence for both adults and pediatric populations, plan for dose conversion, and dataset format.

Orphan Designation
On 11/9/16, orphan drug designation (#16-5418) was granted for Leukine treatment of individuals acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)

Pediatric studies are not required for products with orphan designation. Nevertheless, the Applicant submitted a summary of literature studies on the use of their product in the pediatric population as well as previously conducted clinical trials for non-H-ARS related indications assessed during their development program. The Applicant also included the pediatric population in the population PK study that was conducted to determine dose conversion from animals to humans for the H-ARS indication. FDA had agreed to this approach.

Priority Review
Priority review was granted due to the evidence that Leukine increased survival in the setting of minimal supportive care consisting of fluids and antimicrobials and with start of treatment delayed up to 48 hours post irradiation. On the other hand, filgrastim and pegfilgrastim had been studied in the setting of intensive supportive care that included fresh blood transfusions and with start of treatment at 24 hours post irradiation.

Animal Rule
FDA's regulations concerning the approval of new drugs when human efficacy studies are not feasible are codified in 21 CFR 314.600 through 314.650 for drugs and 21 CFR 601.90 through 601.95 for biological products. Approval under the Animal Rule may be pursued only if human efficacy studies cannot be conducted because the conduct of such trials is unethical and field trials after an accidental or deliberate exposure are not feasible.

The design of the efficacy studies for Leukine was similar to the design of studies conducted for Neupogen and Neulasta with respect to the NHP model (TBI, LD_{50}) and primary efficacy endpoint of survival at 60 days. However, in the Leukine studies, blood transfusions were not given, and the administration of Leukine was delayed until 48 hours after radiation exposure to

mimic a mass casualty situation with limited health care resources. Additionally the efficacy of Leukine at a higher $LD_{70/80}$ TBI doses was also evaluated.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Study Integrity and Surveillance (OSIS)

One efficacy study (TSK0144) and two PK studies (DDK0110 and DDK0111) were audited. An important aspect of the study site inspection was the assessment of the adequacy of the blinding and the accuracy of the irradiation dose. The inspection confirmed that the study personnel making decisions regarding supportive care and euthanasia were adequately blinded. The irradiation was conducted in batches with dosing cohorts intermixed. The Agency determined that the data was reliable. The inspection did not identify any issues related to the integrity of the data or the study conduct. No Form FDA 483 was issued. The final classification of the inspection is No Action Indicated (NAI).

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Animal Efficacy Studies

In one exploratory study (FY14-045) Rhesus macaques (n = 35 males/group) were irradiated with 680 cGy total body irradiation (TBI) on Day 0. Dosing for the vehicle and one 7 µg/kg/day Leukine group began on Day 1 (24 hrs after TBI) while dosing for the other 7 µg/kg/day Leukine group began on Day 2 (48 hrs after TBI). Animals were irradiated in 10 sequential cohorts. Each cohort contained 3-4 animals from the control and treated groups. Animals were subcutaneously administered vehicle or Leukine once daily for 18 days or until the most recent neutrophil count increased to above 1000 cells/µL. Survival was 29% (10/34 animals) on Day 60 in the 680 cGy TBI vehicle control group compared to 49% survival in the Day 1 Leukine group (17/35 animals; p = 0.11 log rank test and p = 0.14 for the Fisher exact test compared to vehicle control). Survival was 60% in the Day 2 Leukine group (21/35 animals; p = 0.03 log rank test and p = 0.02 for the Fisher exact test compared to control). Radiation exposure did not produce the expected mortality. In the vehicle control group; 680 cGy TBI under study conditions was expected to produce approximately 50% mortality. The causes of lower than expected survival were not established, and might include the variability in the susceptibility of the experimental

animals and the steep radiation dose-response curve. Limitations identified in study FY14-045 included use of only male NHPs, and lack of blinding. Nevertheless, the study is valuable in that it shows evidence of treatment effect of Leukine.

In the confirmatory study TSK0144, rhesus macaques were irradiated with 655 cGy TBI (18/sex/group) or 713 cGy TBI (9/sex/group) on Day 0. Dosing (subcutaneous) for vehicle or 7 µg/kg/day Leukine groups began at 48 hours. Dosing was continued daily until the absolute neutrophil count was ≥ 1000/µL for 3 consecutive days. Survival was 42% (15/36 animals) on Day 60 in the 655 cGy TBI vehicle control group compared to 78% survival in the 655 cGy Leukine group (28/36 animals; p = 0.002 for both the Fisher exact test and the log-rank test compared to control). Survival was 17% (3/18 animals) on Day 60 in the 713 cGy TBI vehicle control group compared to 61% survival in the 713 cGy Leukine group (11/18 animals; p = 0.008 for the Fisher exact test and p = 0.004 for the log-rank test compared to control). The strengths of study TSK0144 include the use of male and female animals, blinding laboratory personnel who conducted the clinical care and observations, the use of two control arms and two doses of radiation exposure.

For this supplemental BLA application, study TSK0144 was considered the adequate and well controlled confirmatory study and study FY14-045 was considered supportive. Overall, the data show that Leukine provides a survival benefit when administered starting up to 48 hours after acute lethal radiation exposure.

Toxicology Studies
In a 6-week toxicity study, Cynomolgus monkeys received daily subcutaneous injection 0, 20, 63, or 200 µg/kg/day sargramostim. Three of 14 high dose animals were euthanized due to moribundity between Days 14 and 18. Drug-related effects observed at all dose levels were pharmacology-related. These effects included injection site inflammation, increased WBC and platelet counts, spleen and lymph node enlargement, and inflammation in various organs and tissues such as liver, heart, lung, epididymides, skin, cerebrum, and trachea. The elevation in platelet counts is consistent with the multi-lineage hematopoietic effects of GM-CSF.

Reproductive and Developmental Toxicity Studies
In a fertility and early embryonic development study, female rabbits received subcutaneous injections (0 , 25, 70 or 200 µg/kg/day) of sargramostim once daily beginning 6 days prior to artificial insemination and continuing through gestation day (GD) 7, for a total of 14 injections. Sargramostim did not affect fertility at any of the doses tested. However, at the 200 µg/kg/day dose, lower embryonic survival (primarily due to preimplantation loss) was observed compared to the control group. Based on this finding, 70 µg/kg/day was considered the NOAEL for female early embryonic toxicity.

In an embryo-fetal developmental study and a pre- and post-natal study, female rabbits received subcutaneous injections (0, 25, 70 or 200 µg/kg/day) of sargramostim once daily during the periods of GD 6 to GD 19 or GD 19 to GD 28 (embryo-fetal study) or GD 19 to

parturition and lactation day (LD) 1 to LD 14 (pre- and post-natal study). An increase in spontaneous abortions, late resorptions, post-implantation loss and a reduction in viable fetuses, mean live litter size, and offspring body weights was observed in both studies at the 200 µg/kg/day sargramostim dose level. The NOAEL for fetal toxicity in these studies was 70 µg/kg/day sargramostim.

5.2. Referenced NDAs, BLAs, DMFs

No references were needed or provided.

5.3. Pharmacology

Sargramostim binds to receptors on the surface of progenitor hematopoietic cells of granulocyte, monocyte, megakaryocyte, and erythroid lineages resulting in the proliferation, differentiation, and activation of these cells. The mechanism of action for sargramostim for the mitigation of H-ARS is likely due to improved neutrophil and platelet recovery following radiation-induced myelosuppression. The amino-acid sequence of GM-CSF is homologous in human and monkey and the biological activity of sargramostim is similar in both species. The Applicant submitted two NHP efficacy study reports performed at two different animal facilities. The study reports are reviewed below.

Supportive Efficacy Study FY14-045

Study Title: A Non-Clinical Study Evaluating the Survival Benefit of Leukine as a Medical Countermeasure (MCM) Relative to Control Groups in an Established Hematopoietic Acute Radiation Syndrome (H-ARS) Model in Male Rhesus macaques.

Study number:	FY14-045
Study report location:	(b)(4)
Conducting laboratory:	(b)(4)
Date of study initiation:	April 25, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug:	Leukine (sargramostim, rhGM-CSF)

METHODS

Study Design

The overall study design is outlined in the study report, see Table 1 below. Animals were randomized by body weight into the 3 groups listed below. Animals were irradiated on Day 0.

Table 1 Study Design for FY14-045

Group	Animals per Group	Dose of Drug	1st Drug Administration Time Point Post Irradiation
Water Control	35[a]	0.028 mL/kg/day	Day 1
Leukine®	35	7[b] µg/kg/day	Day 1
Leukine®	35	7 µg/kg/day	Day 2

[a] Group sizes were determined based on a power function estimating that 35 animals/group are needed to see a 25% difference in survival with an alpha = 0.05 (power of 0.7).
[b] 7 µg/kg was chosen based on the human Leukine® dose of 425 µg/dose and the standard human weight of 60 kg, therefore the µg/kg dose was 7.
[Source: page 15 of the Applicant's study report]

Radiation Source: (b)(4) (6-MV X-ray)

Radiation Procedure: The (b)(4) was calibrated to ± 2% absolute accuracy using a NIST-traceable ionization chamber. Prior to each day of use, the instrumentation output was verified using a lucite block physical phantom with an ionization chamber. A diode detector system was used to monitor individual delivered doses. A diode was also placed in the center of a second phantom and monitored with each day animals were irradiated (measured values were consistently within 1% of the targeted dose). Animal size, thickness, and radiation source distance to the center of animal were calculated and a 680 cGy dose of radiation was delivered to each animal. Unanesthetized animals were transported to the (b)(4), fasted overnight and sedated with 10 mg/kg (b)(4) Just prior to irradiation, animals were anesthetized (b)(4) positioned into a sling, and received half of the targeted radiation dose to one lateral surface followed the other half of the other targeted dose to the opposite lateral surface. Diode detectors were placed on the shoulders and hips of animals to measure sum entrance and exit radiation doses. Animals were returned to holding cages and allowed to recover from anesthesia prior to transport back to their housing facility.

Frequency of Drug Dosing: Dosing for the vehicle and one 7 µg/kg/day Leukine group began on Day 1. Dosing for the other 7 µg/kg/day Leukine group began on Day 2. Animals were administered vehicle or Leukine once daily for 18 days or until the most recent neutrophil count increased to above 1000 cells/µL.

Route of Administration: Subcutaneous

Formulation/Vehicle:	Solution/Bacteriostatic water for injection
Species/Strain:	macaques/rhesus single source
Age:	2-4 years-old
Weight:	3.1-5.5 kg when body weights for all animals was first recorded prior to acclimation.
Sex:	Male only
Protocol Deviations:	There were no protocol deviations that affected the overall quality of the study.

Blinding

The study was not blinded.

Supportive Care

The supportive care used in the study was orally administered (b)(4) enrofloxacin from Days 3-30 and parenteral fluids. The study protocol did include the standard criteria for administration of fluids and the use of the fluids was not recorded. In addition, the animals received humane supportive care as directed by the veterinarian care taker. The timing and the extent of this care was not documented in the protocol.

Euthanasia Criteria

Animals were monitored at least 3 times daily between 6 am and 8 pm for the following euthanasia criteria.

1. Abnormal activity: difficulty with ambulation, decreased food intake, self-mutilation, reluctance to move for > 24 hr.
2. Behavior indicating the animal is in clinical need of pain medication.
3. Clinical conditions (combination criteria requirement):
    i. Frank bleeding or hemorrhage. Frank bleeding or hemorrhage from the nasal or oral cavity that persists for greater than one hour, or compromises the animal's airway patency. Lower gastrointestinal bleeding supported by frank bleeding or hemorrhage from the rectum quantified for a minimum of two hours to obtain an estimated 24-hour blood loss volume. Blood loss greater than or equal to 20% of the estimated circulating blood volume for an animal over a 24-hour period, or persistent frank bleeding or hemorrhage for over 24 hours.
    ii. Severe dehydration (> 3% increase in hematocrit from a blood collection sample measured within the past 7 days), sunken eyes, dry mucous, skin tenting of > 3 seconds.
    iii. Respiratory distress (i.e. open mouth shallow - thoracic, gasping and jerky – abdominal).
    iv. Evidence of eye or upper respiratory infections.
4. Loss of body weight >20% of baseline body weight for greater than 72 hr.

5. Abnormal appearance: rough coat, head down, tucked abdomen, pallor, exudates around eyes and/or nose.

No animal was euthanized based on a single criterion, but rather the entirety of the clinical picture was assessed in terms of the animal's overall well-being.

Statistical Analyses

See Section 8.1.1.

Observations and Results

Dosimetry

The radiation exposure was performed in 10 cohorts. Each cohort contained 3-4 animals from the control and treated groups. The time of day animals were irradiated was not specified. Mean Group irradiation doses were 99.3 to 99.6% the nominal irradiation dose. Mean standard deviation of 1.1-1.3% for radiation exposure was similar between groups. Individual animal radiation dose (the mean from 4 diode detectors/animal) ranged from 653-694 cGy in the control group, 661-693 cGy in the Day 1 Leukine group, and 662-693 cGy in the Day 2 Leukine group. Overall, radiation administered dose was similar between groups as determined by the diode detectors. Therefore, even though the TBI protocol did not meet its $LD_{50/60}$ mortality rate, the study results are interpretable.

Dosing Solution Analysis

The concentration of Leukine in dosing solutions were shown to be not more than (b)(4)% different than the nominal dose. Dosing solutions were shown to be stable under condition of use.

Primary Efficacy Outcome

See section 8.1.1.

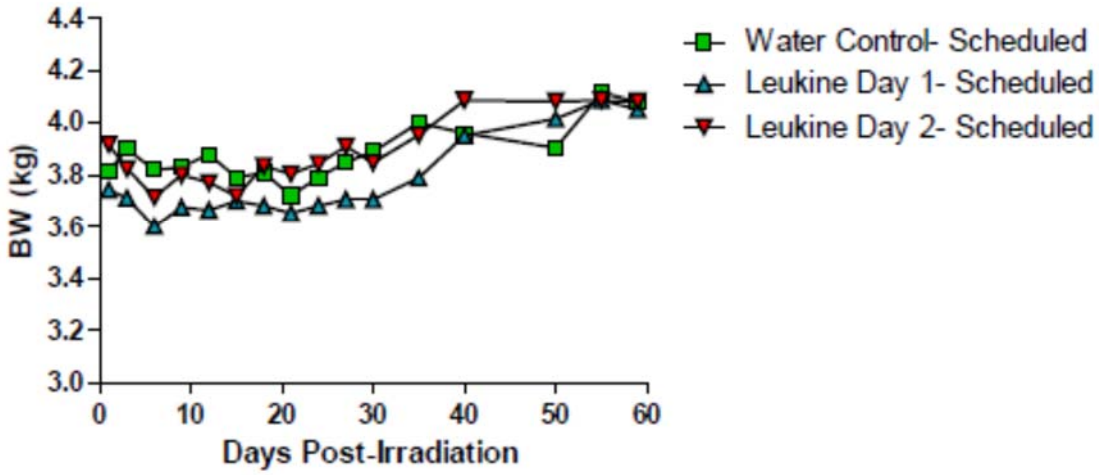
Clinical Signs

Animals were observed for clinical signs at least 3 times daily between 6 am and 8 pm. The most common clinical signs were GI related, bruising, and hair loss. Decreased oral intake was observed in the majority of animals in all groups following irradiation. The oral intake was greatly diminished between Days 12 and 18. The highest incidence of bruising was observed between Day 11 and Day 25 and affected most animals. Hair loss was experienced by almost all animals by the end of the study. Other radiation-related manifestations included skin swelling, skin redness, rough hair coat and lack of grooming.

Body Weights

Mean body weight results are shown in the study report Figure 1. Mean body weight decreased in all groups up to 3 to 5% during the first six days post irradiation. Mean body weights then generally stabilized in all groups through Day 21 and tended to slightly increase thereafter.

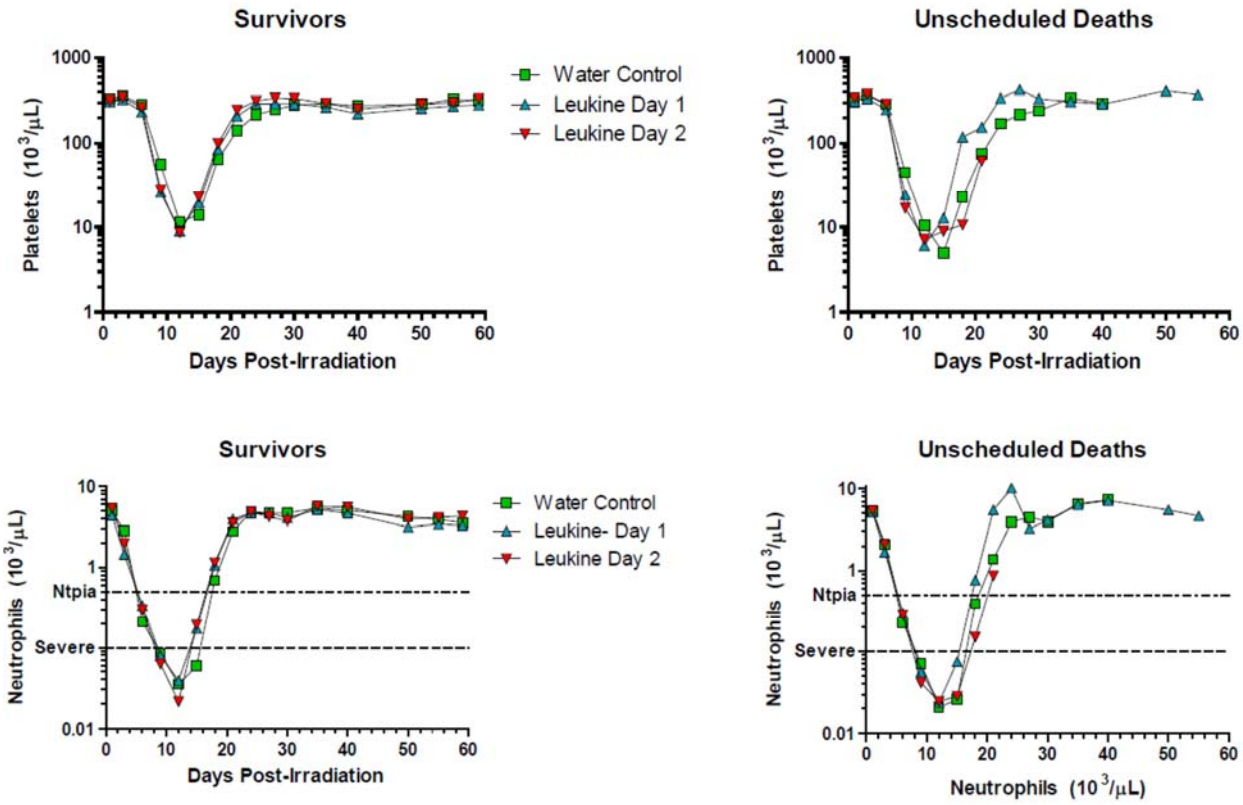
Figure 1 Mean Body Weight Results for Study FY14-045



Hematology

The mean values for hematology parameters for the animals surviving by Day 60 and for unscheduled death animals are shown in
Figure 2 .

Figure 2 Mean Values for Hematology Parameters of Survivors Until Day 60 for Study FY14-045



Mean WBC and ANC showed steep decreases following irradiation. The WBC nadir was observed on Day 12 with mean WBC similar between groups. Mean WBC returned to baseline values by Day 24.

Lymphocytes

Mean lymphocyte counts also decreased following irradiation. The lowest mean lymphocyte counts were observed between Days 9 and 15 with mean lymphocyte values similar between groups (0.17-0.22 x 10^3/µL compared to 0.49-0.54 x 10^3/µL mean Day 1 values). Mean lymphocyte counts returned to baseline values by Day 18 in Groups 2 and 3 and by Day 21 in Group 1 animals.

Platelets

Mean platelet counts were slightly decreased compared to Day 1 values on Day 6. Mean platelet counts dramatically decreased thereafter. Group 2 and 3 mean platelet counts returned to Day 1 values by Day 24. Group 1 mean platelet values returned to near Day 1 values on Day 30.

Erythrocytes

Mean RBC, HGB, and HCT decreased following irradiation beginning at Day 9 and the mean lowest values (approximately 40% below Day 1 values) were observed between Days 15 and 24. Group 2 and 3 mean values returned to near Day 1 values by Day 35. Group 1 mean values returned to near Day 1 values by Day 40.

Blood Cultures and Bacteriology

Blood samples for blood cultures were collected at baseline, Day 12, and at euthanasia (scheduled or moribund). Samples for culture were collected from moribund or scheduled euthanasia animals from the liver and kidney. Blood culture and bacteriology results are summarized in the study report table below ( ). Positive blood culture, tissue culture and/or bacteria demonstrable on histopathology was observed in all animals that succumbed to radiation (unscheduled death animals). A variety of organisms were identified, but consisted predominantly of staphylococcus and streptococcus species.

Table 2 Blood culture and bacteriology results

Exposure	*6.8 Gy*	*6.8 Gy*	*6.8 Gy*
Dose Group	**Water Ctrl**	**Leukine Day 1**	**Leukine Day 2**
(Provantis Group ID)	**(1)**	**(2)**	**(3)**
Number on Study	**35**	**35**	**35**
Scheduled Euthanasia (SE)	10	17	21
Moribund Euthanasia (ME)	19	17	12
Found Dead (FD)[a]	6	1	2
Baseline- Blood Culture Positive[b]	2[c]/ 35[d] (5.7%)[e]	2/ 35 (5.7 %)	0/ 35 (0%)
Day 12- Blood Culture Positive	10/ 35 (28.6%)	13/ 33 (39.4%)	18/ 35 (51.4%)
Terminal Blood Culture Positive			
Scheduled Euthanasia[f]	0/ 10 (0%)	1/ 17 (5.9%)	7/ 21 (33.3%)
Moribund Euthanasia	11/ 13 (84.7%)	9/ 15 (60.0%)	8/ 11 (72.7%)
Liver and/or Kidney Culture Positive[b]			
Scheduled Euthanasia	1/ 10 (0.1%)	3/ 17 (17.7%)	4/ 21 (19.1%)
Moribund Euthanasia	17/ 19 (89.5%)	13/ 17 (76.5%)	11/ 12 (91.7%)
Summary of Culture and Histopathology Positive Results (ME animals only)			
ME animals with positive blood and/or liver and/or kidney culture	17/ 19 (89.5%)	14/ 17 (82.4%)	11/ 12 (91.7%)
ME animals with bacteria demonstrable on histopathology[g]	11/ 19 (57.9%)	8/ 17 (47.1%)	8/ 12 (66.7%)
ME animals with bacteria demonstrable on histopathology which were culture positive	(100%)	(100%)	(100%)

[a]Cultures were not collected on FD animals.
[b]Positive results for any bacterial genus/species.
[c]Number of animals positive.
[d]Number of animals from which samples were obtained.
[e]Percentage of animals positive of those for which samples were obtained.
[f]Positive cultures on baseline and scheduled euthanasia animals are probable contaminants.
[g]Animals with invasive bacteria demonstrable on histopathology in tissues other than skin.

Simian Varicella-Zoster Virus (SVV)

One animal presented SVV-like observations and lesions while on study. Baseline and terminal samples were collected for SVV analysis using PCR and/or ELISA. PCR results showed no active SVV infection in baseline samples, and only the animal presenting symptoms showed active infection in terminal samples. ELISA results showed the presence of SVV antibodies in 16 baseline samples. Only samples from the same 16 animals showed presence of SVV antibodies in terminal samples. The overall conclusion was that SVV did not impact study results.

Macroscopic Findings

Detailed gross necropsies were performed on all animals. Special attention was paid to the gastrointestinal tract, lungs, lymph nodes, kidneys and bladder. All gross findings, bone marrow, and representative samples from the spleen, gastrointestinal tract, lungs, kidney, liver, heart, brain and adrenal glands were collected, placed in neutral buffered formalin, and prepared for microscopic examination. Most animals found dead or moribund within 30 days of irradiation exhibited discolored red areas on the skin that was likely the result of irradiation-induced decreases in platelet counts. Common necropsy findings included patchy or diffuse discoloration of heart, lungs, stomach, intestines and urinary bladder. There were fewer, less severe necropsy findings in animals that survived to scheduled death compared to unscheduled death animals.

Microscopic Findings

Bone marrow smears in unscheduled death animals typically had marked hypocellularity whereas smears from animals that survived to scheduled sacrifice typically were generally unremarkable and consistent with marrow recovery.

The microscopic findings noted in this study were findings commonly observed following irradiation and were consistent with coagulopathy and septicemia. It is difficult to determine any possible treatment effect on microscopic findings because animals were euthanized at different timepoints. Select microscopic observations as summarized in the study report are shown in Table 3

Table 3 Microscopic Observations

Exposure		*6.8 Gy*	*6.8 Gy*	*6.8 Gy*
Dose Group		**Water Ctrl**	**Leukine Day 1**	**Leukine Day 2**
(Provantis Group ID)		**(1)**	**(2)**	**(3)**
Total Number Examined[a]		**35**	**35**	**35**
Scheduled Euthanasia (SE)		10	17	21
Moribund Euthanasia (ME)		19	17	12
Found Dead (FD)		6	1	2
LUNG				
Alveolus, Hemorrhage	SE	1[b] (10%)[c] 1.0[d]	1 (5.9%) 1.0	0 (0.0%) -
	ME	8 (42.1%) 1.8	5 (29.4%) 1.8	5 (41.7%) 2.0
	FD	4 (66.7%) 1.5	0 (0.0%) -	1 (50.0%) 2.0
Necrosis, Focal/ Multifocal	SE	0 (0.0%) -	0 (0.0%) -	0 (0.0%) -
	ME	3 (15.8%) 2.7	4 (23.5%) 2.0	5 (41.7%) 2.4
	FD	1 (16.7%) 3.0	0 (0.0%) -	0 (0.0%) -
Bacteria, Cocci (Intravascular)	SE	0 (0.0%) -	0 (0.0%) -	0 (0.0%) -
	ME	5 (26.3%) 2.2	1 (5.9%) 3.0	1 (8.3%) 1.0
	FD	4 (66.7%) 2.5	0 (0.0%) -	0 (0.0%) -
Bacteria (extravascular in tissue; of any morphology)	SE	0 (0%) -	0 (0.0%) -	0 (0.0%) -
	ME	5 (26.3%) 2.2	4 (23.5%) 2.0	4 (33.3%) 2.3
	FD	1 (16.7%) 3.0	0 (0.0%) -	1 (50.0%) 2.0

[a]Number of animals examined. Minor variation in total tissues examined may be present for some specific tissues (see pathology appendices for specific information).
[b]Number of animals within Group and Removal Reason (RR) with finding.
[c]Incidence of finding (%) where denominator is total number of animals in Group with the specified RR.
[d]Average severity score among animals within Group and RR with the finding.

LIVER				
Hemorrhage[b]	SE	0 (0.0%) -	0 (0.0%) -	0 (0.0%) -
	ME	2 (10.5%) 1.0	2 (11.8%) 1.5	0 (0.0%) -
	FD	0 (0.0%) -	0 (0.0%) -	0 (0.0%) -
Necrosis, Focal/ Multifocal[b]	SE	1 (10.0%) 2.0[d]	0 (0.0%) -	0 (0.0%) -
	ME	6 (31.6%) 2.0	5 (29.4%) 2.2	3 (25.0%) 2.0
	FD	2 (33.3%) 2.0	0 (0.0%) -	1 (50.0%) 1.0
Necrosis, Focal /Multifocal (Centrilobular)	SE	0 (0.0%) -	0 (0.0%) -	0 (0.0%) -
	ME	2 (10.5%) 2.0	2 (11.8%) 2.5	0 (0.0%) -
	FD	1 (16.7%) 2.0	0 (0.0%) -	0 (0.0%) -
Bacteria, Cocci (Intravascular)	SE	0 (0.0%) -	0 (0.0%) -	0 (0.0%) -
	ME	6 (31.6%) 3.2	4 (23.5%) 2.8	3 (25.0%) 2.3
	FD	5 (83.3%) 2.4	0 (0.0%) -	0 (0.0%) -
Bacteria (extravascular in tissue; of any morphology)	SE	0 (0.0%) -	0 (0.0%) -	0 (0.0%) -
	ME	6 (31.6%) 1.7	5 (29.4%) 2.2	2 (16.7%) 2.5
	FD	1 (16.7%) 2.0	0 (0.0%) -	1 (50.0%) 1.0

[a]Number of animals examined. Minor variation in total tissues examined may be present for some specific tissues (see pathology appendices for specific information).
[b]Number of animals within Group and Removal Reason (RR) with finding.
[c]Incidence of finding (%) where denominator is total number of animals in Group with the specified RR.
[d]Average severity score among animals within Group and RR with the finding.

KIDNEY				
Hemorrhage	SE	0 (0.0%) -	0 (0.0%) -	0 (0.0%) -
	ME	3 (15.8%) 1.3	2 (11.8%) 2.0	3 (25.0%) 2.0
	FD	0 (0.0%) -	0 (0.0%) -	0 (0.0%) -
Necrosis, Focal /Multifocal	SE	0 (0.0%) -	0 (0.0%) -	0 (0.0%) -
	ME	6 (31.6%) 2.0	2 (11.8%) 2.0	2 (16.7%) 2.5
	FD	3 (50.0%) 2.3	0 (0.0%) -	1 (50.0%) 2.0
Bacteria, Cocci (Intravascular)	SE	0 (0.0%) -	0 (0.0%) -	0 (0.0%) -
	ME	2 (10.5%) 1.0	2 (11.8%) 2.0	1 (8.3%) 2.0
	FD	1 (16.7%) 3.0	0 (0.0%) -	0 (0.0%) -
Bacteria (extravascular in tissue; of any morphology)	SE	0 (0.0%) -	0 (0.0%) -	0 (0.0%) -
	ME	6 (31.6%) 2.0	1 (5.9%) 2.0	2 (16.7%) 2.0
	FD	3 (50.0%) 2.3	0 (0.0%) -	1 (50%) 1.0

[a]Number of animals examined. Minor variation in total tissues examined may be present for some specific tissues (see pathology appendices for specific information).
[b]Number of animals within Group and Removal Reason (RR) with finding.
[c]Incidence of finding (%) where denominator is total number of animals in Group with the specified RR.
[d]Average severity score among animals within Group and RR with the finding.

HEART				
	SE	0 (0.0%) -	0 (0.0%) -	0 (0.0%) -
Hemorrhage	ME	10 (52.6%) 1.3	7 (41.2%) 1.6	9 (75.0%) 1.9
	FD	5 (83.3%) 2.2	0 (0.0%) -	2 (100.0%) -
	SE	0 (0.0%) -	0 (0.0%) -	0 (0.0%) -
Necrosis, Focal /Multifocal	ME	0 (0.0%) -	0 (0.0%) -	2 (16.7%) 1.5
	FD	0 (0.0%) -	0 (0.0%) -	0 (0.0%) -
	SE	0 (0.0%) -	0 (0.0%) -	0 (0.0%) -
Bacteria, Cocci (Intravascular)	ME	3 (15.8%) 1.7	1 (5.9%) 3.0	0 (0.0%) -
	FD	1 (16.7%) 2.0	0 (0.0%) -	0 (0.0%) -
	SE	0 (0.0%) -	0 (0.0%) -	0 (0.0%) -
Bacteria (extravascular in tissue; of any morphology)	ME	1 (5.3%) 2.0	0 (0.0%) -	1 (8.3%) 2.0
	FD	0 (0.0%) -	0 (0.0%) -	0 (0.0%) -

[a]Number of animals examined. Minor variation in total tissues examined may be present for some specific tissues (see pathology appendices for specific information).
[b]Number of animals within Group and Removal Reason (RR) with finding.
[c]Incidence of finding (%) where denominator is total number of animals in Group with the specified RR.
[d]Average severity score among animals within Group and RR with the finding.

Gastrointestinal Tract (Stomach, Duodenum, Jejunum, Ileum, Cecum, Rectum)[e]				
	SE	0[b] (0.0%)[c] -[d]	0 (0.0%) -	0 (0.0%) -
Hemorrhage	ME	14 (73.7%) P[f]	11 (64.7%) P	10 (83.3%) P
	FD	6 (100.0%) P	1 (100%) P	2 (100%) P
	SE	0 (0.0%) -	0 (0.0%) -	0 (0.0%) -
Necrosis, Focal/ Multifocal	ME	5 (26.3%) P	3 (17.6%) P	3 (25.0%) P
	FD	1 (16.7%) P	1 (100%) -	0 (0.0%) -
	SE	0 (0.0%) -	0 (0.0%) -	0 (0.0%) -
Bacteria, Cocci (Intravascular)	ME	2 (10.5%) P	0 (0.0%) -	1 (8.3%) P
	FD	1 (16.7%) P	0 (0.0%) -	0 (0.0%) -
	SE	0 (0.0%) -	0 (0.0%) -	0 (0.0%) -
Bacteria (extravascular in tissue; of any morphology)	ME	5 (26.3%) P	1 (5.9%) P	3 (25%) P
	FD	0 (0.0%) -	1 (100%) P	0 (0.0%) -

[a]Number of animals examined. Minor variation in total tissues examined may be present for some specific tissues (see pathology appendices for specific information).
[b]Number of animals within Group and Removal Reason (RR) with finding.
[c]Incidence of finding (%) where denominator is total number of animals in Group with the specified RR.
[d]Average severity score among animals within Group and RR with the finding.
[e]All findings for gastrointestinal tract (GIT) are composite, *i.e.* hemorrhage in any 1 or more of the GIT sites is counted for that animal.
[f]P = Present. Severity scores not calculated due to composite nature of this tissue summary.

Overall, the data suggest that Leukine provides a survival benefit when treatment is started up to 2 days after acute lethal radiation exposure and Leukine is administered once daily for 18 days or until the most recent neutrophil count increased to above 1000 cells/µL.

Confirmatory Efficacy Study TSK0144

Study title: rhGM-CSF [(sargramostim)]: Blinded Efficacy Study of Leukine in Irradiated Rhesus Primates

Study no.:	1014-2323
Conducting laboratory and location:	(b)(4)
Date of study initiation:	October 29, 2015
GLP compliance:	Yes
QA statement:	Yes
Drug, Lot #	Leukine, Batch # E5013

METHODS

Study Design

The overall study design is outlined in Table 4. Animals were randomly assigned to irradiation groups based on sex and body weight. Five animals were replaced prior to irradiation due to health or abnormal hematology findings. No animals were replaced after irradiation was initiated.

Table 4 Study Design for Study TSk0144

Treatment Group	Dose Level (µg/kg/day)	Dose Level (µg/m^2/day)*	Dose Conc. (µg/mL)	Dose Volume (mL/kg)	Targeted Radiation Level (cGy)	Targeted Radiation Dose Rate (cGy/min)	Number of Animals	
							Male	Female
1. reference item/vehicle	0	0	0	0.2	655 ($LD_{50-60/60}$)	50	18	18
2. Leukine	7	84	35				18	18
3. reference item/vehicle	0	0	0		713 ($LD_{70-80/60}$)		9	9
4. Leukine	7	84	35				9	9

*k_m (factor for converting µg/kg dose to µg/m^2 dose) of 12 was used as per FDA guidelines:

[Source: page 1962 of the Applicant's study report]

Radiation Source:	Co^{60} (b)(4)
Radiation Procedure:	Animals were acclimated to being placed into a radiotherapy restraining apparatus. Fasted animals were transported to a facility for irradiation, placed into the restraining apparatus, and placed in a vertical position for total body irradiation (TBI) exposure. Animals were exposed to 655 or 713 cGy TBI at a rate of 60 cGy/min (TBI delivered as 50% to the anterior position and 50%

	to the posterior position). Following TBI, animals were transported back to the housing facility.
Frequency of Drug Dosing:	Leukine or vehicle was administered beginning 48 hours after irradiation and continued daily until the absolute neutrophil count was ≥ 1000/µL for 3 consecutive days.
Route of Administration:	Subcutaneous
Formulation/Vehicle:	Solution/Water for injection
Species/Strain:	Monkey/Rhesus (all animals received from a single source)
Age:	3 years and 1 month to 5 years and 4 months
Weight:	2.9-6.2 Kg at initiation of dosing
Sex:	Male and Females
Protocol Deviations:	There was one major protocol deviation. A vehicle control animal was inadvertently administered Leukine on Day 19. There were several minor protocol deviations that had no impact on study outcome or interpretation.

Blinding

Personnel conducting the study were blinded to experimental groups except for staff involved with test item preparation/analysis, the study team leader and the unblinded support scientist. Personnel that performed clinical observations were blinded.

Supportive Care

The medications provided as prophylactic supportive care are listed in Table 5.

Table 5 Products Provided as Prophylactic Supportive Care

Drug Class	Allowed Medication or Supportive Care Agents	Indication
Anti-ulcer	Sucralfate 1g/day, ((b)(4) daily from days 5-30	For treatment of possible ulcers of the stomach or proximal small intestine.
Antibiotics	Enrofloxacin (b)(4) subcutaneous, SID from Day 5 to Day 27	Prophylactic treatment of antibiotics during predicted period of neutropenia.
Anti-emetics	Ondansetron (b)(4) IM 30-90 minutes prior to irradiation and 30-45 minutes following irradiation to suppress emesis.	Administered pre and post radiation to suppress emesis.

The following table lists the medications administered as supportive care based on the clinical judgement of the veterinarian. See Table 6.

Table 6 Products Available as Supportive Care Based on Veterinarian

Drug Class	Allowed Medication or Supportive Care Agents	Indication and/or Criterion for Administration
Analgesics	Buprenorphine approximately (b)(4) (b)(4) (b)(4) bupivacaine), topical	**Pain Management:** • (b)(4) bupivacaine) was used topically in the oral cavity for mouth ulcers. • Buprenorphine was used for pain management and a special attention was made between Day 3 to Day 30 as prescribed by the Clinical Veterinarian(s). In cases of frank hematemesis (vomiting blood), hematochezia (blood in feces) or mucositis/stomatitis, the dose of buprenorphine was increased to (b)(4) mg/kg/dose until symptoms resolve. Doses was increased based on the judgment of the Veterinarian up to (b)(4)
Parenteral fluids	Equal volume of Ringer's lactate and Ringer's lactate with 5% dextrose. (b)(4) reverse osmosis water or PO (b)(4) of body weight.	**Dehydration:** • Mild dehydration or presence of loose or watery stools: Ringer's lactate and Ringer's lactate with 5% dextrose ((b)(4) via slow IV push and hydration fluids (reverse osmosis water or oral electrolyte solution), (b)(4) orally.

		• Mild dehydration: Bolus of Lactated Ringer's Solution ((b)(4) by slow IV push. The bolus was administered subcutaneously if PLT>50x10^9/L. Additionally, hydration fluids (reverse osmosis water or oral electrolyte solution) (b)(4) was provided. • Moderate dehydration: Ringer's lactate and Ringer's lactate with 5% dextrose (b)(4) (b)(4) via slow IV push (15-20 minutes) and hydration fluids (reverse osmosis water or oral electrolyte solution) (b)(4) orally. • Severe dehydration. Ringer's lactate, (b)(4) (b)(4) by slow IV push (15-20 min). Following bolus, Ringer's lactate via slow IV infusion (b)(4) over 2-4 hours and hydration fluids (reverse osmosis water or oral electrolyte solution), (b)(4) orally. • I (b)(4) or similar commercial solutions containing sodium, potassium, and glucose were used if IV access was difficult or precluded. **Fever (temperature ≥ 105F/40.6° C):** • Animals with temperatures ≥ 105F and decreased activity level were administered equal volume of Ringer's lactate and Ringer's lactate with 5% dextrose each (b)(4) (b)(4) body weight via slow IV push.
Anti-emetics	Ondansetron ((b)(4)	• When there were signs of emesis or nausea seen in animals during the observation period.
Nutritional Support	crushed cookies with banana, fruit and/or vegetable buffets, juice and/or Ensure®	**Weight Loss (Anorexia):** Nutritional support was administered via oral when body weight was <90% of baseline and continued as long as the body weight remains <90% of baseline, and the animal was not eating or when an animal presented mouth lesion which hinder its food intake.

The supportive care was administered without knowledge of the treatment assignment and was documented. The supportive care did not include transfusions to simulate limited resources in a mass casualty scenario.

Euthanasia Criteria

Animals were euthanized if one of the following criteria was observed:

- Respiratory distress
  - Open mouth breathing, cyanosis, exaggerated component to respiration.
  - Inability to maintain adequate SpO_2 (> 85%) when breathing room air.
- Anorexia/Decreased appetite
  - Complete anorexia for 3 days with deteriorating conditions based on the clinical examination. Animal not taking nutritive supplement offered orally.
- Weight Loss
  - Loss of weight >20% of baseline body weight for greater than 3 days
- Decreased Level of Activity
  - Recumbent in the cage with decreased or absent responsiveness to touch
- Acute, gross blood loss
  - Hemorrhage in excess of 20% estimated blood volume
  - Source of acute blood loss not expected to respond to local measures, for example, gastrointestinal (emesis, per rectum)
- Generalized seizure activity from which the animal did not recover (i.e., after examination by a Clinical Veterinarian)
- Clinical Condition: severe dehydration with hypothermia (non-responsive to IV fluid therapy and/or unable to maintain a rectal temperature above 35.0°C following 2-4 hr IV fluid therapy and severely decreased activity level or decreased rectal body temperature reaching <34.6°C and severely decreased activity level) or hyperthermia (temperature >40.1°C and severely decreased activity level).
- Severe pain associated with a condition considered inhumane which could not be significantly alleviated with administration of buprenorphine three times daily.

The euthanasia criteria were prespecified in the protocol. The numbers of animals found dead were similar among the study arms. There were 3 deaths >30 days in the Leukine treatment arms related to wounds. The number of unscheduled euthanasia events was similar across treatment arms.

Dosimetry

Chest and waist dimensions were measured for animals and used to calculate radiation exposure time. Prior to Day 0, radiation dose was calibrated using an acrylic phantom. During radiation exposure, two nanodot dosimeters were placed on animals. A Farmer ionization chamber was also included in each radiation treatment field to provide primary quantification of radiation dose. The nanodots were used as backup in the event that the Farmer chamber failed. Dosimetry results are summarized in the study report Table 7 below. Based on the more accurate Farmer chamber, radiation exposure was similar between control and treatment groups.

Table 7 Dosimetry Results for TSK-0144

Treatment Group	Irradiation dose (cGy)	Nanodots (% From Targeted Irradiation Dose)	Farmer electrode chamber (% From Targeted Irradiation Dose)
1. Reference item/vehicle	655	-10.2 to +3.8%	+0.2 to +1.2%
2. Leukine		-3.5 to +5.1%	+0.3 to +1.2%
3. Reference item/vehicle	713	-5.9 to +5.6%	-1.4 to +1.3%
4. Leukine		-4.7 to +5.3%	+0.3 to +1.3%

The radiation exposure in TSK0144 is consistent with technique used in a radiation oncology clinic. The doses for $LD_{50\text{-}60/60}$: 655 cGy and $LD_{70\text{-}80/60}$: 713 cGy, were delivered using a 60Co source with AP:PA fields @ 50cGy/min. The radiation was delivered over 6 days (1 group/day). The animals were acclimated to the process and thus did not require the use of anesthesia. Males and females were irradiated on different dates. Animals from the various arms of the study were distributed throughout each day to minimize the potential impact of circadian effects on the primary outcome of the study. Dosimetry and quality control were conducted by a health physicist and a dosimetry report provided. The radiation was found to be within acceptable range as determined by the use of Nanodots and a Farmer chamber for dose confirmation.

Dosing Solution Analysis

The stability of the dosing formulations under the condition of use were validated. Two samples were collected from the drug formulations used on the 1st and the 14th Day of dosing. Samples were analyzed using a validated HPLC-UV method. Dosing solutions were determined to be within (b)(4) of the nominal dose.

Mortality

See Section 8.1.2.

Clinical Signs

Clinical signs (particularly signs of infection, hemorrhage, and mucositis) were monitored twice daily. Detailed exams were performed pre-dose and twice weekly throughout the study. Additional clinical observations were performed when deemed necessary and additional night time monitoring was performed from Day 8 to Day 24 (i.e., the high mortality period). Expected ARS clinical signs were observed. These included decreased appetite, decreased activity, weakness, hunched back posture, dehydration (e.g., skin turgor low), diarrhea, skin wound, dyspnea (e.g., labored breathing), tremors, petechia and buccal ulceration. The major clinical sign observed during the first 14 days after irradiation was a decrease in appetite. Decreased

activity and hunched back were also frequently observed with the highest incidence occurring towards the end of this 14-day period. The incidence of these 3 clinical signs was similar in surviving animals across groups.

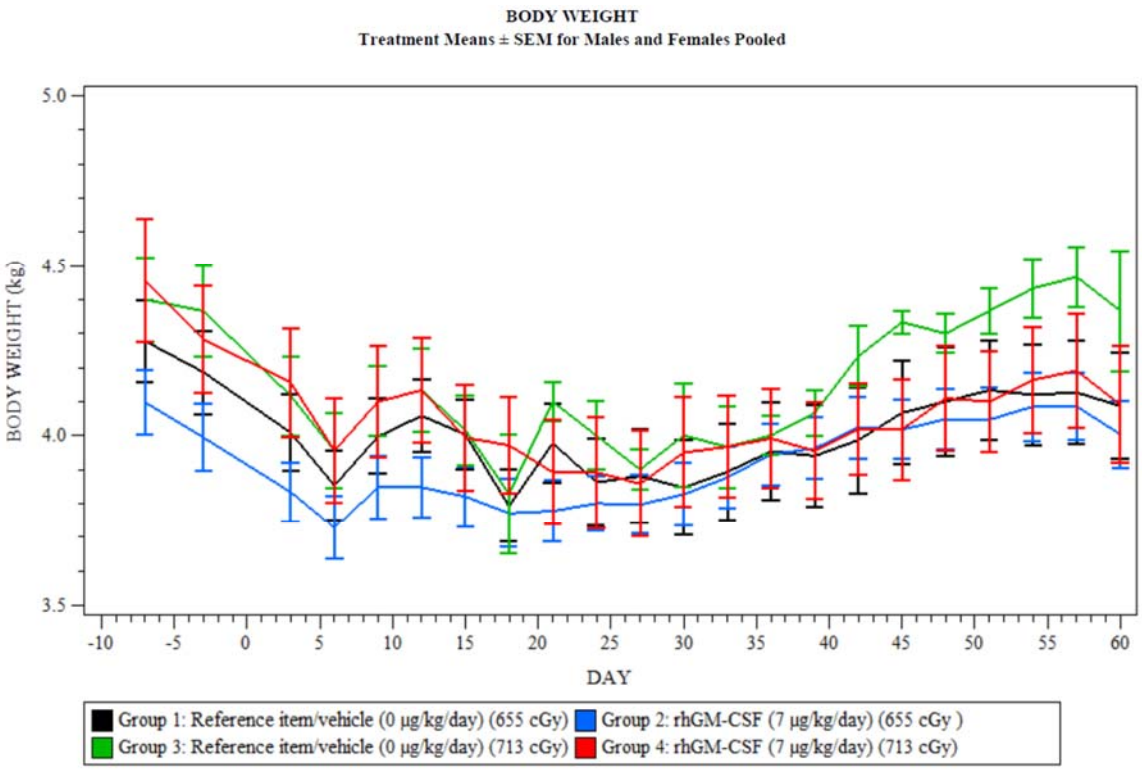
Between Days 15 and 20, a numerically lower percentage of animals with weakness, tremors, hunched back posture, decreased activity, and petechia was observed in Leukine-treated animals compared to vehicle-treated animals receiving 655 cGy. At the higher radiation dose (713 cGy), a numerically lower percentage of Leukine-treated than vehicle-treated animals had decreased activity, weakness, decreased appetite, hunched back posture and presence of petechia. The occurrence of adverse clinical signs deceased in all groups after Day 25. Sporadic skin wounds and decreased appetite were the primary clinical signs observed after Day 30.

Body Weights

Body weights were recorded for all animals at least as follows: prior to animal assignment, **the day before irradiation and every 3 days thereafter. If the period between animal assignment and irradiation was more than 3 weeks, body weight measurements were performed weekly between those 2 dates. Mean body weight results are summarized in the study report**

Figure 3 below. Mean body weights decreased in all groups up to Day 6. Mean body weights for all groups showed a general trend to increase from Day 30 on. There were no treatment-related effects on mean body weights and irradiation was more than 3 weeks, body weight measurements were performed weekly between those 2 dates. Mean body weight results are summarized in the study report.

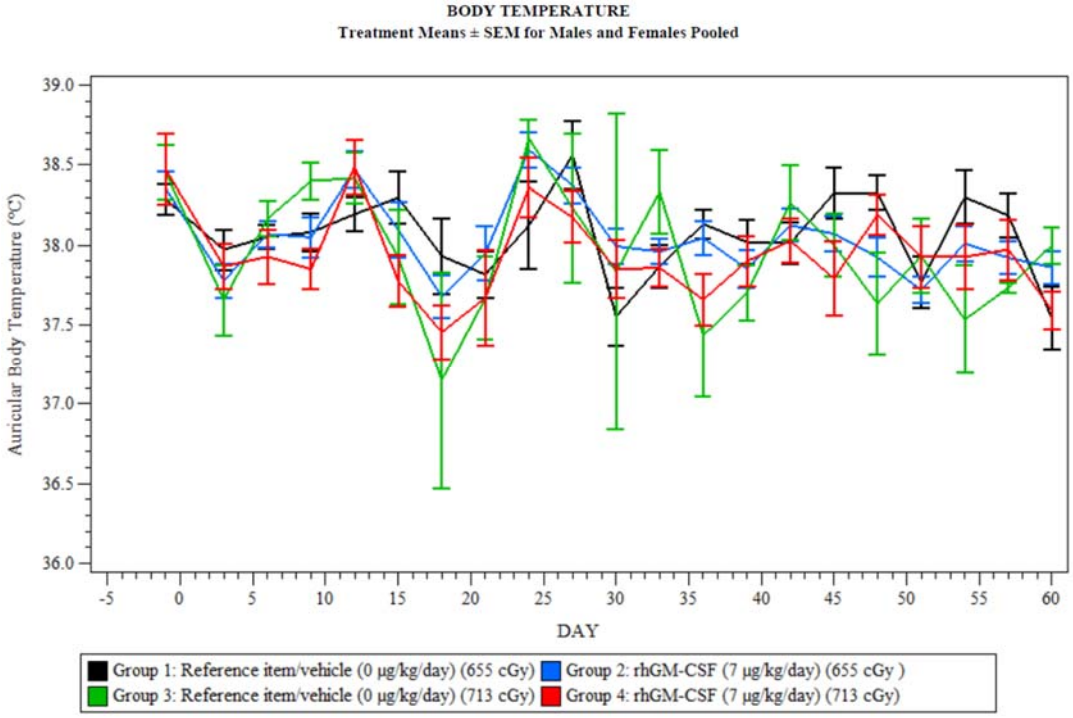
Figure 3 Body Weight for Study TSK0144



Body Temperature

Body temperature was taken on all surviving animals the day prior to irradiation, every 3 days after irradiation, and whenever clinically justified. Mean body temperature results are summarized in the study report Figure 4 . No differences between groups in mean body temperature were observed in this study.

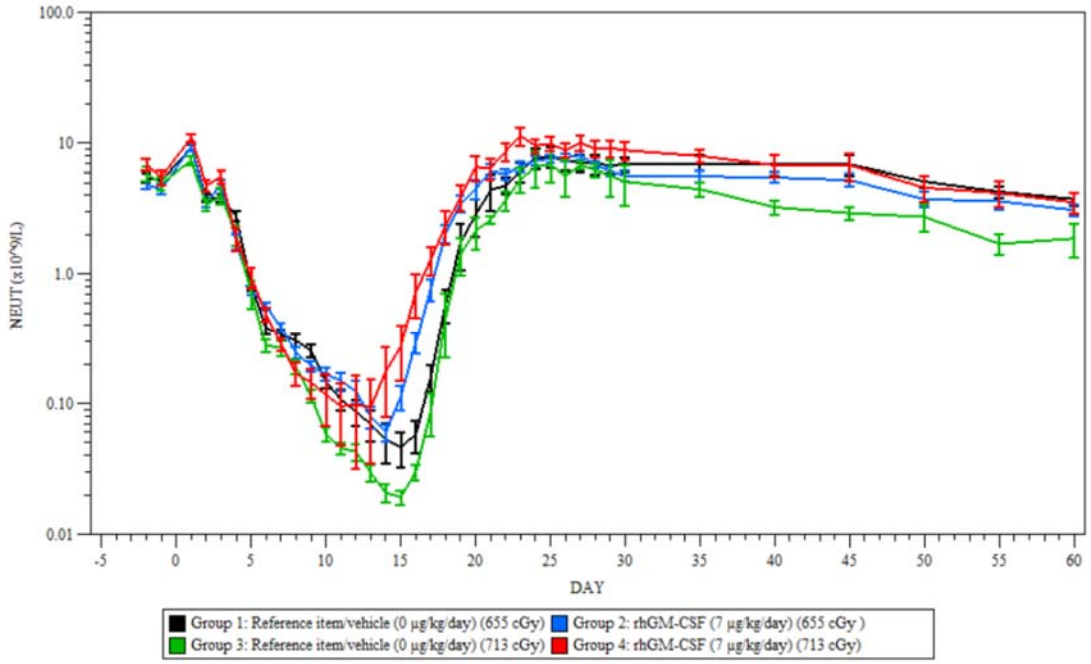
Figure 4 Body Temperature for Study TSK0144



Hematology

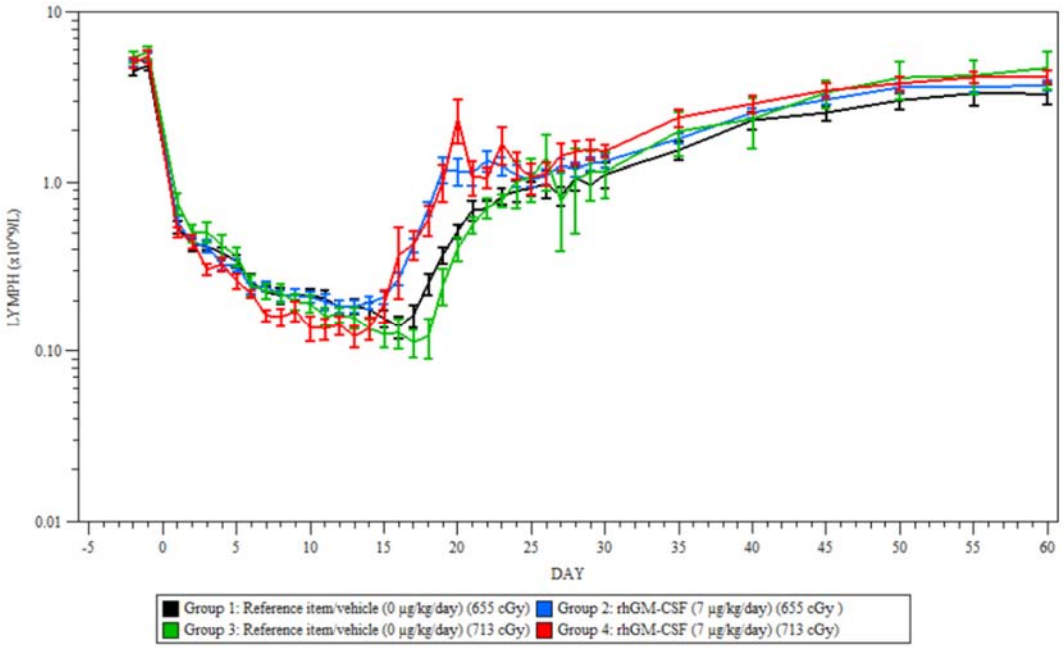
Blood samples for hematology evaluation were collected twice prior to irradiation and on Days 1-30, 35, 40, 45, 50, 55, and 60 as well as prior to unscheduled euthanasia whenever possible. Mean ANC results are summarized in the study report Figure 5. Mean ANC increased on Day 1. Mean ANC decreased rapidly afterwards. The mean ANC count at nadir was numerically higher and the duration of neutropenia (ANC $<0.5x10^9$/L) and severe neutropenia (ANC $<0.1x10^9$/L) were numerically shorter in treated groups compared to controls. The median time to recovery to ANC ≥ 500/µL and ANC ≥ 1000/µL was numerically lower in treated groups compared to controls.

Figure 5 Mean ANC for Study TSK0144



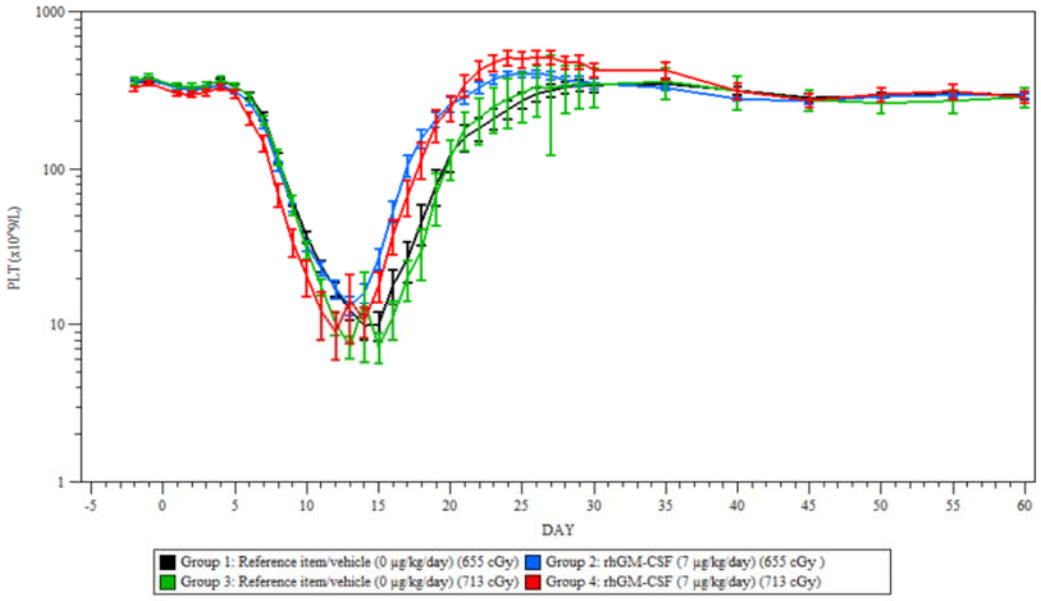
Mean absolute lymphocyte count results are summarized in the study report figure 6 below. Lymphocyte counts decreased drastically immediately following irradiation. The mean lymphocyte count at nadir and the time to lymphocyte recovery appeared to be numerically more favorable in treated groups compared to controls.

Figure 6 Mean Absolute Lymphocyte Count for Study TSK0144



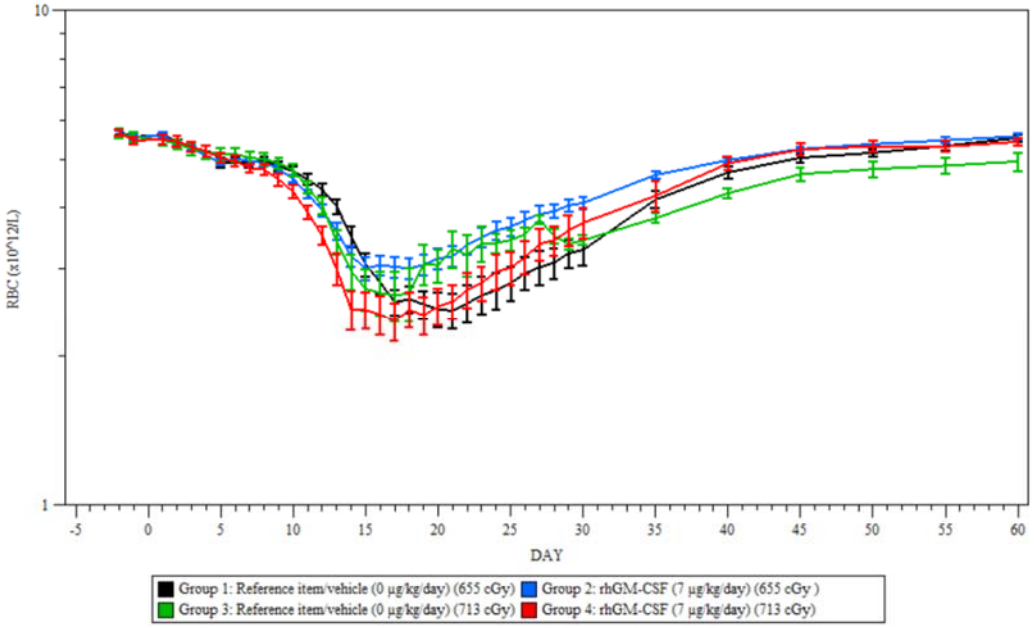
Mean platelet counts are summarized in the study report figure 7 and figure 8 below. Mean platelet counts began rapidly decreasing on Day 6. The mean platelet count at nadir was numerically higher in treated groups compared to vehicle controls. The median time to platelet recovery appeared to be lower in treated groups compared to controls.

Figure 7 Mean Platelet Count for Study TSK0144



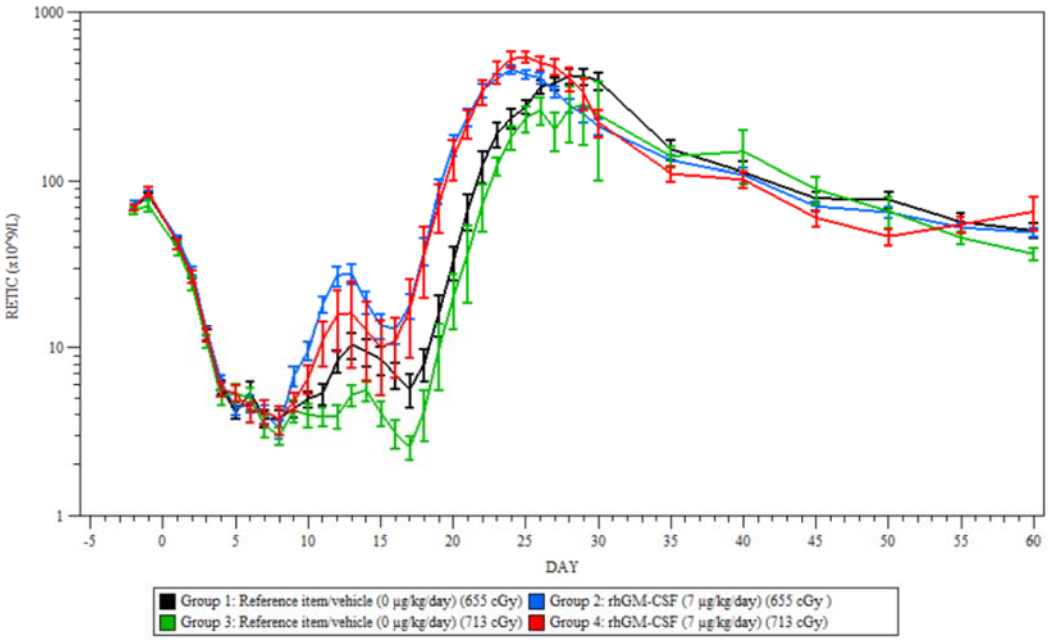
Mean RBC results are summarized in the study report figure below. Mean RBC began dramatically decreasing around Day 10.

Figure 8 Mean RBC for Study TSK0144



Mean reticulocyte count results are summarized in the study report figure 9 below. Mean reticulocyte counts began decreasing the day after irradiation with a similar nadir observed on Day 8 in all groups. Mean counts began increasing thereafter with the magnitude of increase numerically higher in treated groups compared to controls.

Figure 9 Mean Reticulocyte Counts for Study TSK0144



Bacteriology

The following tissues were collected at necropsy from all animals for microbiological analysis:

- Liver (medial lobe or lobe with most severe lesions)
- Lungs (right caudal lobe and left cranial lobe separately)
- Spleen (part of remaining tissues)
- Kidney (right or one with most severe lesions)
- Heart (apex)
- Brain (left hemisphere)

When macroscopic lesions were present at necropsy in organs to be sent for bacteriological analysis, a representative area was kept for histological examination and the largest sample possible was selected for bacteriological analysis. Section of organ samples submitted for bacteriological analysis may be different than listed above based on the judgment of the technical staff to ensure adequate tissue sampling for bacteriology and histology. An animal was considered positive for infection when two positive results for the same bacterial strain were observed. As shown in the study report Table 8 below, in the Leukine groups, the number of deaths attributed to infection was numerically lower than in control groups. *S. aureus* followed by *E. coli* were the most frequent bacterial strains isolated. Only two animals that survived until scheduled death were positive for infection. A total of 17 blood cultures were collected from animals with febrile neutropenia with only 1 positive blood culture result.

Table 8 Percentage of animals with at least 2 positive results for the same bacterial strain at organ culture.

Treatment Group	Irradiation dose (cGy)	% of animals presented at least 2 positive results for the same bacterial strain at organ culture
1. Reference item/vehicle	655	19/21 (90%)
2. Leukine		5/8 (63%)
3. Reference item/vehicle	713	15/15 (100%)
4. Leukine		4/7 (57%)

Immunogenicity

Blood samples for anti-drug antibody formation were collected pre-treatment and on Days 16, 21, 30 and at unscheduled euthanasia if prior to Day 30. The presence of anti-drug antibodies was evaluated using a validated ELISA assay. Low level anti-Leukine antibodies were detected in 4 animals at all timepoints including pretreatment.

Macroscopic Findings

A full necropsy was performed on all animals including unscheduled deaths. A standard set of organs/tissues including bone marrow smears and tissues from macroscopic findings were collected and prepared for microscopic evaluation. Macroscopic findings observed in unscheduled death animals were those typically observed following acute lethal radiation exposure. Common macroscopic findings included dark foci/areas and ulcers in the GI tract and dark areas of various other tissues. Dark areas were associated with hemorrhage microscopically. Lymphoid tissue was often small or gelatinous and this observation was associated with lymphoid atrophy microscopically. Pale areas were occasionally observed and were often associated with necrosis or bacteremia microscopically. The same macroscopic findings observed in unscheduled death animals were also observed in scheduled death animals, but at lower incidence. There were no apparent differences in the incidence of macroscopic findings in treated versus control animals.

Microscopic Findings

Blinded histopathological evaluation was performed on lymph nodes, bone marrow, heart, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, kidneys, liver, lungs, spleen, thymus, injection site, and abnormal findings. Microscopic findings were peer reviewed. Microscopic findings observed in unscheduled death animals were those typically observed following acute lethal radiation exposure. Common microscopic findings included hemorrhage in various tissues especially the GI tract, and lymphoid atrophy. There were no apparent differences in the incidence of microscopic findings in treated versus vehicle control groups. A total of 10/28 (36%) of 655 cGy Leukine treated scheduled death animals exhibited normal bone marrow compared to 1/15 (7%) vehicle controls. An apparent increased in the incidence and extent of extramedullary hematopoiesis was noted in the mandibular, cervical, and mesenteric lymph nodes in 655 and 713 cGy Leukine treated scheduled death animals compared to vehicle controls. However, it was unclear whether this increased incidence was associated with Leukine treatment or was simply due to more Leukine treated animals surviving until scheduled necropsy.

CONCLUSIONS

Treatment of NHPs with Leukine starting at 2 days after exposure to 655 or 713 cGy TBI resulted in a significant increase in survival at 60 days compared to vehicle controls. In general, the clinical signs and the hematologic and microbiologic laboratory data appeared to be more favorable in the Leukine-treated groups compared to vehicle controls; overall these secondary assessments are judged to be supportive of the treatment effect of Leukine.

5.4.ADME/PK

Type of Study	Major Findings
Absorption	
Leukine (b)(4) Pharmacokinetics in Male Rhesus Monkeys (Study # DDK0110). Monkeys were administered via sc injection 7.0 or 20.8 µg/kg/day sargramostim for 14 consecutive days.	Systemic exposure (AUC) increased in a greater than dose proportional manner on Day 1, but in a dose-proportional manner on Day 14. Systemic exposure was similar on Day 14 compared to Day 1 in the low dose group. Systemic exposure was approximately half the value on Day 14 for the high dose group compared to Day 1 values. All plasma samples collected on Day 15 contained anti-Leukine antibodies. The mean half-life ranged from 1.2 hrs (Day 1 low dose group) to 2.2 hrs (Day 14 high dose group).
TK data from general toxicology studies Systemic Toxicity Study with Sargramostim in Cynomolgus Monkeys (M+F) after Daily S.C. Application Over 6 Weeks and a recovery period of about 12 Weeks (Study Number TXST20050052)	Monkey *T1/2: Not calculated* *Accumulation: No* *Dose proportionality: AUC increased in a dose-related fashion*
TK data from reproductive toxicology studies See individual reproductive toxicology study below. Immunogenicity a major issue with study design.	

5.5.Toxicology

5.5.1. General Toxicology

Study title/ number: Systemic Toxicity Study with Sargramostim in Cynomolgus Monkeys (M+F) after Daily S.C. Application Over 6 Weeks and a recovery period of about 12 Weeks (Study Number TXST20050052)

Sargramostim has no activity in rodents, therefore toxicity studies were limited to Cynomolgus monkeys and rabbits. A pivotal repeat-dose toxicity study in monkeys was conducted to support a risk assessment of chronic subcutaneous treatment of patients with sargramostim. Given a strong immunological reaction and formation of neutralizing antibodies demonstrated in a pilot study, the maximum exposure period was limited to approximately 6 weeks due to a neutralization of the pharmacological effect. Sargramostim dosages evaluated in 7 male and 7 female monkeys were: 20, 63 and 200 ug/kg/day, defined as low (LD), mid (MD) and high (HD) doses, respectively.

Key Study Findings

- Three monkeys (1 male and 2 females) were sacrificed moribund between days 14 and 18 following repeated dosing with 200 µg/kg/day (HD) sargramostim. All other animals survived to scheduled sacrifice at the end treatment or recovery periods at 6 and 12 weeks, respectively. Based on mortality occurring at the HD, the no-observed-adverse-effect-level (NOAEL was determined to be 63 µg/kg/day (or 3 times the recommended dose of 250 µg/m^2/day).
- Other notable findings include drug-related organ or bone marrow effects. Marked to massive bone marrow hyperplasia in animals sacrificed following the 6-week treatment period and affected predominantly granulocytic cells in the femur in all females and in the sternum of 1 male and 1 female that were sacrificed moribund. The bone marrow effect was reversible following the recovery period. Reversible injection-site inflammatory reactions (reddening, scab formation, skin induration, hemorrhages and necrosis) occurred to varying degrees in animals across all test article dose groups. Body weight loss was transient and coincided with emaciation and apathy. A slight but reversible prolongation of activated partial thromboplastin time (APTT) at 200 µg/kg/day did not appear dose-related. Based on findings in recovery group animals, results observed at the end of the treatment period were reversible or showed a tendency towards reversibility.
- A pronounced increase in white blood cell (WBC) count was observed, mainly due to increases in neutrophils, monocytes and eosinophils with peak counts between days 15 and 22 without clear dose dependence. Increased platelet count (peak between days 7 and 14) was also observed. The hematology findings are a consequence of the pharmacological activity of the test compound, which stimulates (acting as a multi lineage factor) mainly granulopoietic and monopoietic progenitor cell lines in the bone marrow.
- Time and dose dependent neutralizing anti-drug antibodies were detected in all treated animals at ≥ low dose from 3 weeks onwards except for 1 female in dose group 3 showing antibody titer at week 2. In most animals of both sexes across the dose groups antidrug antibodies increased in a dose-dependent manner, reaching peak levels between weeks 4 and 6. The increase in anti-drug antibodies coincided with a fall in WBC and platelet numbers. Toxicokinetic (TK)

data showed a reduction in C_{max} on day 42. The differences in WBC and platelet numbers and TK data were attributed to the generation of neutralizing antibodies that blocked the test article-related pharmacological activity.

Conducting laboratory and location: [redacted](b)(4), [redacted](b)(4)

GLP compliance: Yes

Methods [see Table 9]

Dose and frequency of dosing:	Single daily doses of 0 (vehicle), 20 (low dose, LD), 63 (mid dose; MD), or 200 µg (HD)/kg/day (high dose) for 6 weeks
Route of administration:	Sc
Formulation/Vehicle:	Solution/Vehicle (40 mg Mannitol, 10 mg Sucrose, 1.2 mg Tromethamine, 11.5 mg Benzyl Alcohol, 5.5 mM EDTA, ad 1 mL Aqua p.i)
Species/Strain:	Monkey/Cynomolgus
Number/Sex/Group:	4/sex/group main study; 3/sex/group recovery
Age:	Male 47-68 months; Female 41-75 months
Satellite groups/ unique design:	No
Deviation from study protocol affecting interpretation of results:	No

Table 9 Study Design for TXST20050052

Groups	**Dose Levels** (µg/kg/day)		**No. of Monkeys/group**		**Duration of Treatment (Weeks)**	
	Main	Recovery	Main	Recovery	Main	Recovery
1 (Control)	0 (Veh)	0 (Veh)	4M+4F	3M+3F	6	12
2 (LD)	20	20	4M+4F	3M+3F	6	12
3 (MD)	63	63	4M+4F	3M+3F	6	12
4 (HD)	200	200	4M+4F	3M+3F	6	12

Reviewer's Table; Main (main study groups); Recovery (Recovery groups to test reversibility of effects of the test article; animals were observed for additional 12 weeks after treatment termination); LD, MD & HD (Low, Mid & High dose, respectively); M+F (Males and Females)

Table 10 Observations and Results for Study TXST20050052

Parameters	Major findings
Mortality	1/7 (males) and 2/7 (females) at the high dose were euthanized between days 14-18 due to test article-related moribundity; no other deaths were reported.
Clinical Signs	Test article-related clinical signs in males and females included apathy, emaciation, swelling, reddening of skin, abscess, hematoma, skin pustules and diarrhea; signs occurred predominantly at ≥MD and were not completely reversed in the recovery period.
Body Weights	A slight decrease in body weight was observed at ≥LD; no remarkable changes in body weight were observed in recovery period.
Ophthalmoscopy	No compound-related effects were observed.
ECG	Test article-related increases in ECG parameters: HR at MD, QRS interval at LD MD & HD, R-wave height at LD & MD, and QTc at ≥MD. However, the increases lacked a dose-dependence or were restricted to a single sex.
Hematology	WBCs: At ≥MD (males and females), there was a test article-related increase in white blood cell count, neutrophils, monocytes, eosinophils, basophils and large unstained cells on post-treatment days 7-29 reaching maximum at days 15-22 before gradually returning to baseline. RBCs: Decreases in RBC parameters (RBC counts, Hemoglobin, PCV, MCV, MCH or MCHC) occurred in males at ≥MD between days 8-29 and in females at HD on day 15. Platelets: There was a treatment-related increase in platelet count in M+F at ≥LD and peaked between days 8 and 15.
Clinical Chemistry	No biologically significant serum related chemistry changes were observed.
Urinalysis	No test article-related effects observed.
Gross Pathology	Test article-related emaciation observed in 1 female at LD and 1 female and 2 males at HD.at HD. Other compound-related macroscopic findings included gray-white discolorations of liver, lungs, and heart; injection site swelling, scab formation and abscess-like lesions in skin/subcutis were observed in test article groups and 1 female control animal. Enlarged adrenal glands, spleen

Parameters	Major findings
	and lymph nodes (iliac, mandibular, and mesenteric) were dose-related; thickened and enlarged joints were observed only at the HD. In general, most findings were reversible and no longer present after recovery group sacrifice. Cellular infiltrations were not completely reversed after recovery period. No adverse effects were evident on genital organs of either gender.
Organ Weights	6-week sacrifice: At ≥LD, post-treatment organ weight changes occurred in spleen, iliac lymph nodes and thyroid gland. Increased splenic and iliac lymph node weight, appeared to be compound-related given increased lymphoid hyperplasia and dose-dependency. Decreased thyroid organ weight correlated with a decreased colloid content in thyroid follicles. 13-week sacrifice: Changes in splenic weight persisted at the LD & HD levels. Thyroid gland and iliac lymph node weight changes were reversible.
Histopathology **Adequate battery:** Yes	Marked to massive hyperplasia of red pulp in 3 (male and 2 female) animals sacrificed moribund; diffuse atrophy, hyperplasia and focal fibrosis were observed in the bone marrow (sternum and femur); minimal to massive focal inflammatory cell aggregates characterized by presence of granulocytes, lymphocytes and macrophages were observed in liver, heart, lung, epididymides, skin, cerebrum and trachea; pyogranulomatous and purulent inflammation, ulceration and necrosis of skin correlated with gross findings; slight to moderate lymphoid cell infiltration occurred in kidney, pancreas and thyroid gland; a decrease in colloid content was observed in adrenal cortex/medulla; cellular infiltrations were not completely reversed in recovery period.
[Other evaluations] **Morphometrical investigation of testes Spermatology** **Anti-drug antibody formation** **Complement hemolytic activity**	Morphometrical investigation of testes: No compound-related effects observed. Spermatology: No compound-related effects observed Anti-drug antibody formation: Anti-GM-CSF neutralizing antibodies were detected by ELISA in all test article-treated M+F animals at 3-6 weeks following administration of sargramostim. Peak antibody titer occurred at week 6 and declined through week 19. Control samples were negative for anti-GM-CSF antibodies. Complement hemolytic (CH50) activity: None detected.

Parameters	Major findings
Toxicokinetics	Mean Cmax (ng/mL) concentrations (13.7-64.2, day 1) and (10.0-46.6, day 42) of sargramostim were observed between 0.25 – 2 h after the sc administration. Mean systemic exposure (AUC (0-t_{last})) increased with increasing dose on day 1. The increase was linear but lower than the dose increase. Over the entire study period, the AUC (0-t_{last}) values were not in the same order of magnitude across all dose groups. In addition, a considerably high inter-individual variability of PK parameters was observed. In about half of the animals of all dose groups, a decrease of systemic exposure was observed over the treatment period of 42 days (R = 0.0141–0.869), whereas in the others an increase of AUC (0-t_{last}) was observed (R = 1.042 – 3.41). The high inter-individual variability of pharmacokinetic parameters after repeated administration was considered a consequence of anti-drug antibody formation.

M, F = Male(s), Female(s); LD, MD or HD = low (20), mid (63) and high (200 ug/kg/day) doses of sargramostim; HR (heart rate), QRS interval, r-wave height and corrected QT-time (QTc) are electrocardiogram (ECG)-derived parameters; WBC, RBC, PCV, MCV, MCH, MCHC are hematology parameters; ELISA = Enzyme-Linked Immunosorbent Assay

A summary of the PK parameters is shown below. Source: Applicant's Table TT20, page 77 of 2027, Systemic tolerance study with Sargramostim in Cynomolgus monkeys (Study Number: TXST20050052)

Table 11 Pharmacokinetic parameters in female Cynomolgus monkeys after daily subcutaneous treatment with 20, 63 or 200 µg/kg sargramostim over a period of 42 days (mean ± standard deviation; n=7)

Parameter	Unit	Time [day]	Group 2 [20 µg/kg]	Group 3 [63 µg/kg]	Group 4 [200 µg/kg]
C_{max}	[ng/mL]	1	13.7±2.85	21.2±7.37	64.2±16.2
		42	10.0±3.00	18.3±20.8	46.6±23.0#
t_{max}*	[h]	1	2 (0.25-2)	2 (0.25-5)	0.25 (0.25-2)
		42	2 (0.25-2)	2 (0.25-2)	0.25 (0.25-2)#
AUC(0-5h)	[ng/mL * h]	1	42.0±8.01	82.8±20.7	237±53.9
		42	32.0±10.5	71.8±90.7	182±99.7#
AUC(0-t_{last})	[ng/mL * h]	1	49.0±11.2	124±26.9	388±80.7
		42	46.5±23.0	159±222	265±154#
t_{last}*	[h]	1	24 (5-24)	24 (24)	24 (24)
		42	24 (5-24)	24 (5-24)	24 (24)#
C_{av}		1	3.82±2.83	5.17±1.12	16.2±3.36
		42	2.37±1.06	6.75±9.15	11.0±6.43#
R		42	0.999±0.656	1.12±1.53	0.653±0.420#
Dose normalized AUC(0-t_{last})	[ng/mL * h] / [µg/kg]	1	2.45±0.561	1.97±0.426	1.94±0.403
		42	2.32±1.15	2.52±3.53	1.33±0.771#

C_{max}	Maximum observed concentration of drug in serum after drug administration
t_{max}	Time to reach C_{max}
AUC(0-5h)	Area under the concentration versus time curve from dosing time to 5 h post-dose
AUC(0- t_{last})	Area under the concentration versus time curve from dosing time to the t_{last}
t_{last}	Last sampling time with a valid concentration value >LLOQ
Dose normalized AUC(0-t_{last})	AUC(0-t_{last}) divided by the dose
R	Accumulation ratio (AUC(0- t_{last}), day 42 /AUC(0- t_{last}), day 1)
C_{av}	Average concentration AUC(0-t_{last})/t_{last}
*	Values represent median (minimum-maximum).
#	n=5

General toxicology; additional studies:
No additional studies were provided and none are needed.

5.5.2. Genetic Toxicology

Genetic toxicology studies were not performed. Sargramostim (rhuGM-CSF) is a recombinant protein that exerts is pharmacological activity through a membrane bound receptor. It is not expected to reach the nucleus nor directly interact with DNA or other chromosomal material.

5.5.3. Carcinogenicity

Carcinogenicity studies were not performed because sargramostim will not be administered chronically.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study title/ number: A study of fertility and early embryonic development to implantation in female rabbits (Study Number: TXEX20050038)

The purpose of the study was to determine the potential adverse effects in the reproductive process in female rabbits following treatment with sargramostim from pre-insemination to conception and from conception to implantation. In this pivotal study 25, 70 or 200 µg/kg/day (or LD, MD or HD, respectively) of sargramostim or vehicle was administered once daily by sc injection to 3 groups of 20 female (b)(4) rabbits beginning 6 days prior to artificial insemination and continuing through gestation day GD 7, and requiring a total of 14 injections. For toxicokinetic evaluations, an additional 4 rabbits/group were administered vehicle or sargramostim at 25, 70 or 200 µg/kg once a day throughout the same time period.

Key Study Findings

- Fertility (i.e., the ability of females to conceive) was not affected by sargramostim at any of the doses tested. However, at the 200 µg/kg/day (HD), a lower embryonic survival (38% per litter), primarily due to preimplantation loss, was observed compared to the control group (16% per litter). Based on this finding, 70 µg/kg/day was considered to be the NOAEL for female reproductive and early embryonic toxicity of sargramostim in rabbits. Based on reduced body weight and food consumption at 70 µg/kg/day (MD) or higher, and mortality at 200 µg/kg/day (HD), the no-observed-adverse-effect-level (NOAEL) for systemic maternal toxicity was established as the LD (25 µg/kg/day). Other notable pharmacological effects of sargramostim included increased WBC, neutrophil, monocyte and lymphocyte counts at all dose levels. Higher spleen weights were described in the high dose group.

- GM-CSF antibodies were present in 3 of 4 of TK females evaluated at each of the administered doses (25, 70 and 200 µg/kg/day). Neutralizing antibody titer range for LD, MD and HD were respectively 3.88-6.02, 4.02-4.86, and 2.23-4.01. The return of WBC and lymphocyte counts on GD7 to control group levels observed in some instances of

treated animals was attributed to the generation of neutralizing antibodies that blocked test article-related pharmacological activity.

- Systemic exposure was linear and dose-proportional. Exposure decreased by a factor of 10 from study day 0 (6 days pre-insemination) to gestation day 7. This effect was also presumed due to the formation of anti-GM-CSF antibodies against sargramostim.

Conducting laboratory and location	(b)(4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	daily doses of 0 (vehicle), 20 (LD), 70 (MD), or 200 (HD) µg/kg/day starting 6 days before artificial insemination and continuing through gestation day (GD) 7
Route of administration:	sc
Formulation/Vehicle:	Solution/Vehicle (40 mg mannitol, 10 mg sucrose, 1.2 mg trometamol, 11.5 mg benzyl alcohol, 1.9 mg edentate sodium and 1 mL sterile water for injection, USP)
Species/Strain:	Rabbit (b)(4)
Number/Sex/Group:	20/F/group
Satellite groups:	4/F/group (TK)
Deviation from study protocol affecting interpretation of results:	None

Table 12 Study Design (Fertility and Early Embryonic Development)

Groups	Dose Levels (µg/kg/day)	Dose volumes (mL/kg)	No. of Animals/group/study	
			Main study	Toxicokinetic (TK) study
1 (Control)	0 (Veh)	0.40	20	4
2 (LD)	25	0.05	20	4
3 (MD)	70	0.14	20	4
4 (HD)	200	0.40	20	4

Reviewer's Table; Main, TK (Main or concurrent Toxicokinetic study groups); LD, MD & HD (Low, Mid & High dose groups, respectively). All test animals were female (b)(4) (b)(4) rabbits; test animals were dosed beginning 6 days from pre-insemination to conception and from conception to implantation. The study included identification of deficits in tubal transport, implantation and development of the preimplantation stages of the embryo.

For toxicokinetic evaluations, an additional 4 rabbits/group were administered the vehicle or the test article on the same regimen as the fertility and early embryonic development phase females; TK animals were administered the vehicle or the test article on the same regimen as the fertility and early embryonic development phase females. On gestation day 21, a laparohysterectomy was performed on each surviving fertility and early embryonic development phase female. The abdominal and thoracic contents examined. The number of corpora lutea on each ovary and the number of viable and nonviable embryos, early resorptions and the total number of implantations was recorded. For each surviving female, the placenta and spleen were weighed and retained. For all females, additional samples of selected tissues were retained for possible future histopathological examination.

Table 13 Observations and Results for TXEX20050038

Parameters	**Major findings** (please see Table footnotes for explanation of abbreviations)
Mortality	1 test article-related death in HD group on GD2 prior to implantation; no other deaths were reported
Clinical Signs	↓food consumption and ↓defecation prior death; Significant ↓food consumption at ≥MD in pre-insemination period; ↓defecation in 1animal that died and in 18/20 HD animals from study day 3 – GD7
Body Weights	Severe body weight (BW) loss in 1F (HD) 1 week prior to death occurring pre-insemination: ↓BW at ≥MD During gestation: BW not affected at LD & MD but ↓ at HD on GD 0-4
Necropsy findings *[Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc]*	Fertility Index: There was a slight non-significant ↓compared to controls: Control: 19/20 (95%), LD: 17/20 (85%), MD: 19/20 (95%), HD: 17/19 (89.5%) Mean No. of CL Control (10.5), LD: ↓8.9, MD: ↓8.7, HD: similar to control Mean No. implantation sites (historical mean = 6.9 [5.1-8.5]) Control (8.6), LD: ↓6.5, MD: ↓ 6.4, HD: ↓6.0 Mean No. viable embryos (historical mean = 6.5 [4.3-8.1]) Control (8.4), LD: ↓6.3, MD: ↓5.9, HD:↓ 5.5 Pre-implantation loss (% per litter) (historical mean = 31.0 [13.8-52.0]) There was an increase in pre-implantation loss Control (15.8), LD: 26.1, MD: 19.2, HD: ↑38.1

Parameters	**Major findings** (please see Table footnotes for explanation of abbreviations)
	<u>Post-implantation loss (% per litter)</u> There was a dose-related increase in post-implantation loss: Control (2.8), LD: ↑9.7, MD: ↑10.2, HD: ↑14.5 <u>Viable embryos (% per litter) (historical mean = 91.0 [76.6-99.4])</u> Control (97.2), LD: 90.3, MD: 89.8, HD: 85.5

LD: low dose (20 µg/kg/day); MD: mid dose (70 µg/kg/day); HD: high dose (200 µg/kg/day); BW: body weight; ↓: decrease; ↑: increase; CL: corpora lutea per litter; GD = gestation day

The following table summarizes the effects of sargramostim on hematology counts. The data are consistent with the pharmacologic activity of sargramostim as a hematopoietic growth factor that stimulates proliferation and differentiation of hematopoietic progenitor cells.

Table 14 Test article-related effects of SC sargramostim on Hematology

Dosage (µg/kg/day):	0[a]	25	70	200	GD
Mean white blood cell count (thousand/µL)	7.79	**10.34****	**10.07****	**11.37****	0
Mean neutrophil count (thousand/µL)	1.43	1.54	**2.10**	**3.37****	0
	1.67	1.45	1.62	**2.30****	7
Mean neutrophil (%)	18.3	14.7	20.6	**28.1****	0
	19.4	16.5	20.7	**25.9****	7
Mean monocyte count (thousand/µL)	0.10	**0.19**	**0.23***	**0.45****	0
	0.11	0.11	0.09	**0.23****	7
Mean monocyte (%)	1.3	**1.9**	**2.2**	**3.8****	0
	1.2	1.2	1.2	**2.4****	7
Mean lymphocyte count (thousand/µL)	5.75	**7.82****	**6.87**	**6.80**	0
Mean lymphocyte (%)	73.8	75.8	**68.5**	**61.2****	0
	72.3	76.9	73.1	**67.2***	7
Mean eosinophil count (thousand/µL)	0.12	**0.26****	**0.31****	**0.19**	0
	0.17	0.13	**0.10****	**0.09****	7
Mean eosinophil (%)	1.6	**2.4***	**3.0****	**1.8**	0
	2.0	**1.4***	**1.2****	**1.0****	7
Mean basophil count (thousand/µL)	0.30	**0.43**	**0.46***	**0.48***	0
	0.34	**0.22****	**0.19****	**0.20****	7
Mean basophil (%)	4.0	4.1	**4.6**	**4.5**	0
	4.0	**2.5****	**2.4****	**2.3****	7
Mean platelet count (thousand/µL)	487	582	**628****	**733****	7
Mean absolute reticulocyte count (thousand/µL)	182.2	201.7	171.3	**125.7****	0
	210.5	**252.6**	**238.7**	**331.3****	7
Mean reticulocyte (%)	3.1	3.6	3.0	**2.2****	0
	3.6	**4.6***	**4.4**	**6.3****	7
Mean red blood cell count (million/µL)	5.84	**5.55***	**5.48***	**5.31****	7
Mean hemoglobin (g/dL)	12.5	12.0	**11.7****	**11.3****	7
Mean hematocrit (%)	37.2	**35.6***	**35.0****	**33.8****	7
MCV (fL)	63.1	62.7	62.3	**60.9****	0
MCHC (g/dL)	33.7	33.9	33.8	**34.4****	0

[a] = Vehicle µL = microliter GD = Gestation day dL = deciliter fL = femtoliter
* = $p<0.05$ ** = $p<0.01$

Source: Applicant's Table TT9, page 37 of 546, Fertility and Early Embryonic Development (Study Number: TXEX20050038)

The table below summarizes the PK parameters. Note the marked decrease in sargramostim exposure after the administration of the first dose due to the development of anti-drug antibodies.

Table 15 PK parameters after once-daily SC sargramostim administration to rabbits from pre-insemination to implantation

Parameter	Unit	Time [day]	Dosage Level (µg/kg/day) 25 Mean ± SD	70 Mean ± SD	200 Mean ± SD
C_{max}	[pg/mL]	SD 0	21000 ± 4232	51100 ± 14566*	114575 ± 20148
		GD 7	2281 ± 1266	6775 ± 7672*	11415 ± 4861
t_{max}	[h]	SD 0	0.69 ± 0.88	1.1 ± 1.2*	1.1 ± 1.0
		GD 7	0.25 ± 0.0	0.25 ± 0.0*	1.1 ± 1.0
AUC(0-t_{last})	[pg/mL x h]	SD 0	54209 ± 8690	147453 ± 9231*	540094 ± 98159
		GD 7	3735 ± 2596	20171 ± 26121*	41252 ± 21944
AUC	[pg/mL x h]	SD 0	54257 ± 8715	148522 ± 10734*	572190 ± 106236
AUC(0-24h)		GD 7	3749 ± 2582	20683 ± 26833*	42171 ± 22547
Dose normalized AUC	[pg/mL x h] / [µg/kg]	SD 0	2168 ± 348	2106 ± 132*	2700 ± 491
		GD 7	149 ± 104	288 ± 373*	206 ± 110
R			0.067 ± 0.042	0.13 ± 0.17*	0.085 ± 0.058
$t_{1/2}$	[h]	SD 0	1.0 ± 0.58	1.5 ± 0.39*	1.9 ± 0.28
		GD 7	0.71 ± 0.22*	1.1 ± 0.75*	1.3 ± 0.28
Dose proportionality		SD 0	a = 1505, b = 0.817 (0.666 – 0.968)**, r^2 = 0.951		
(Dosage vs. C_{max})		GD 7	a = 129, b = 0.828 (0.205 – 1.45)**, r^2 = 0.540		
Dose proportionality		SD 0	a = 1496, b = 1.10 (0.978 – 1.23)**, r^2 = 0.981		
[Dosage vs. AUC(0-t_{last})]		GD 7	a = 61.9, b = 1.20 (0.433 – 1.96)**, r^2 = 0.620		

N = 4, except *N = 2.

C_{max}	Maximum observed concentration of the analyte in serum after drug administration
t_{max}	Sampling time of C_{max}
AUC(0-t_{last})	Area under the concentration versus time curve from dose administration until last sampling time with a valid concentration value > LLOQ (t_{last})
AUC	On first day of dosing (SD 0), the estimate of the area under the concentration versus time curve from dose administration till infinity
AUC(0-24h)	On GD 7, the estimate of the area under the concentration versus time curve from dose administration till 24 hours post-dosing
Dose normalized AUC	AUC(0-t_{last}) divided by the dose
day	SD 0, first day of dosing = 6 days prior to insemination GD 7 = gestation day 7 (last day of dosing)
R	Accumulation ratio = AUC(0-t_{last}), GD 7/ AUC(0-t_{last}), SD 0
$t_{1/2}$	Apparent half-life for ZK 250224 in serum
Dose proportionality	C_{max} or AUC(0-t_{last}) = a × $(dose)^b$
**	95% Confidence interval for the exponent, b (low-high)
r^2	Coefficient of determination for the power regression

Source: Applicant's Table TT7, page 346 of 546, Fertility and Early Embryonic Development (Study Number: TXEX20050038)

Embryo-Fetal Development
Study title/ number: Study for effects on embryo/fetal development in rabbits (Study Number TXEX20050039)

Objective: The purpose of this study was to determine the potential adverse effects of maternal exposure from implantation to weaning to the test article, sargramostim, on pregnancy, parturition and lactation of the maternal animals and on the growth, viability and development of the F1 neonates. Reproductive performance of the F1 generation was also assessed. In this GLP-compliant pivotal study, sargramostim at dosages of 0, 25, 70 and 200 µg/kg/day was administered once daily by sc injection to 20-25 female (b)(4) rabbits/group during Collectives A and B representing animals dosed during gestation days (GD) 6-19 or GD19-28, respectively.

Key Study Findings

- Based on a lower embryofetal survival at 70 µg/kg/day (MD) for Collective B and/or 200 µg/kg/day (HD) from combined data for Collectives A and B, 25 µg/kg/day (LD) was determined as the NOAEL (no-observed-adverse-effect-level) for embryofetal toxicity. In both Collective A and B, increases in monocytes and granulocytes were attributed to the pharmacologic activity of the test article. The higher absolute and/or relative (to final body weight) spleen weights in HD Collective A females and all Collective B female groups were consistent with these hematological changes.
- A marked decrease in systemic exposure to sargramostim was observed on the last day of dose administration for females in Collective A (toxicokinetic phase) compared to the first day. $AUC_{(0\text{-}tlast)}$ and C_{max} decreased by approximately 85% from GD6 to GD19 at the LD and MD and about 30 times at the HD. With the exception of one animal in the LD group, antibodies to sargramostim were detected in all toxicokinetic phase animals administered sargramostim. The decrease in exposure to the test article on GD19 compared to GD6 can be explained by the development of antibodies to sargramostim during the course of dosing.
- Based on lower embryofetal survival at the MD (Collective B) and/or HD (Collectives A and B), the LD was considered as the NOAEL for embryo/fetal developmental toxicity of sargramostim when administered by subcutaneous injection to New Zealand White rabbits. No test article-related fetal malformations were noted up to HD. Based on the LD, body weight losses and/or reduced body weight gains in the LD group, the NOAEL for systemic toxicity was <LD.

Conducting laboratory and location:	(b)(4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	single daily doses of 0 (vehicle), 25 (LD), 70 (MD) or 200 (HD) during gestation days (GD) 6-19 (Collective A) or GD 19-28 (Collective B).
Route of administration:	Sc
Formulation/Vehicle:	Solution/Vehicle (40 mg mannitol, 10 mg sucrose, 1.2 mg trometamol, 11.5 mg benzyl alcohol, 1.9 mg edetate sodium and 1 mL sterile water for injection, USP)
Species/Strain:	Rabbit (b)(4)
Number/Sex/Group:	Collectives A and B (20 females/group), except for the 200 µg/kg/day in Collective A with 25 animals because of higher postimplantation loss at this high dose
Satellite groups:	4/F/group (TK)
Deviation from study protocol affecting interpretation of results:	None

Table 16 Study Design (Embryo-Fetal Development) for Study TXEX20050039

Groups	Dose Levels (µg/kg/day)	Dose volumes (mL/kg)	No. of Animals/group/study		
			Main study		Toxicokinetic (TK) study (Coll. A only)
			Coll. A (GD6-19)	Coll. B (GD19-28)	
1 (Control)	0 (Veh)	0.40	20	20	4
2 (LD)	25	0.05	20	20	4
3 (MD)	70	0.14	20	20	4
4 (HD)	200	0.40	25	20	4

Reviewer's Table; Main, TK (Main or concurrent Toxicokinetic study groups); LD, MD & HD (Low, Mid & High Dose groups, respectively). All test animals were female time-mated (b)(4) (b)(4) rabbits. For toxicokinetic evaluations, additional 4 rabbits/dose group were administered the vehicle or the test article on the same regimen as the main study group animals. Rabbits were dosed during gestation days (GD) 6-19 (Collective [Coll.] A) or during GD 19-28 (Coll. B); concurrent control groups received the vehicle control article on a comparable regimen for each collective at dosage volumes of 0.40 mL/kg. Twenty (20) females/group/collective were selected for the embryo/fetal development phase, except for **25 animals** in the 200 µg/kg/day (HD) group in Collective A. A total of 25 females was selected for this group because higher postimplantation loss following this treatment regimen was expected

at this dosage level. For toxicokinetic evaluations, an additional 4 satellite rabbits/group in Collective A, including the control group, were dosed using the same regimen as the main phase animals. On GD 29, a laparohysterectomy was performed on each surviving female. The uteri, placentae and ovaries were examined, and the numbers of fetuses, early and late resorptions, total implantations and corpora lutea were recorded. Gravid uterine weights were recorded and net body weights and net body weight changes were calculated. The fetuses and placentae were weighed, and the fetuses were examined for external, visceral and skeletal malformations and developmental variations. Hematology parameters were evaluated for each embryo/fetal development phase female in Collective A on the 1st, 7th and 14th days of dose administration (gestation days 6, 12 and 19, respectively) and in Collective B on the 1st, 7th and 10th days of dose administration (gestation days 19, 25 and 28, respectively). Blood samples were also collected for toxicokinetic evaluation from the 4 toxicokinetic phase females per group in Collective A on gestation days 6 and 19 at 15 minutes, and 2, 4, 8 and 24 hours following dose administration. Blood samples for binding and neutralizing antibodies were collected from the Collective A toxicokinetic phase females on gestation day 19.

Table 17 Observations and Results for Study TXEX20050039

Parameters	**Major findings** (please see Table footnotes for explanation of abbreviations)
Mortality	Coll A: *Mortality*: 1/20 MD with excessive BW loss/low FC was euthanized *in extremis* on GD13 *Abortions:* 1/25 HD with ↓FC /↓BW loss had test article-related abortion on GD28. *Survival:* All other animals survived to the GD29 necropsy. Coll B: *Mortality:* 2/20 HD with excessive BW loss/low FC died on GD25 & 26, respectively; Deaths were test article-related. *Abortions:* 1/20 LD on GD26 was not test article-related; 5/20 HD on GD23-28 following ↓FC /↓BW loss for most of the gestation period; Additional 3/20 HD delivered on GD29.
Clinical Signs	Injection site: In Coll A, there were no signs of irritation/erythema/edema at ≤MD. These signs were minimal in 1/25 HD; higher incidences of edema/erythema were observed at the HD when compared to controls. (Coll B). Injection site changes were not dose/test article-related. Food consumption: Dose-dependent ↓FC was observed at ≥MD (Coll A) and at ≥LD (Coll B). Defecation: Test article-related ↓defecation (Coll A HD) as from GD9. This finding was dose-related in Coll B at ≥MD beginning on GD20 and GD21-26 at the MD and HD, respectively; there were higher incidences at HD.

Parameters	**Major findings** (please see Table footnotes for explanation of abbreviations)
Body Weights	Mean body/gravid uterine weight not affected by treatment at ≤MD. At the HD (Coll A), there were test article-related changes and the mean body/gravid uterine weights were 10 and 17% lower than controls. <u>Spleen weights:</u> - Coll A: Unaffected by test article at ≤MD; increase of 19% occurred at the HD. - Coll B: Test article-related increase at HD and consistent with effects on hematological parameters.
Necropsy findings Cesarean Section Data	<u>Coll A</u>: Mean CL and implantation sites and mean litter proportions of pre- and post-implantation loss were similar across dose groups and were within the historical range. Differences were not dose-related. *Postimplantation loss (%/litter)*: Control: 0.9 (historical control mean = 4.8 [1.1-13.2]); LD: 5.3; MD: 2.5; HD: 9.4 *Viable fetuses (%/litter):* Control: 99.1; LD: 94.7; MD: 97.5; HD: 90.6 (historical control mean = 95.2 [86.8-98.9]) <u>Coll B:</u> No test article-related effects on placental weights at ≤MD but slightly reduced at HD; no effects on intrauterine growth/survival at LD. The mean number of CL/implantation sites and mean litter proportions of preimplantation loss were similar across dose groups. Male, female and combined fetal weight were reduced at ≥MD. *Postimplantation loss (%/litter):* Control: 4.2 (historical control mean = 4.8 [1.1-13.2]); LD: 4.2; MD: 7.0; HD: 12.2 *Late resorptions (%/litter):* Control: 0.6; LD: 0.4; MD: 4.2; HD: 8.6. (historical control mean = 2.0 [0.0-3.8]) *Viable fetuses (%/litter)* Control: 95.8; LD: 95.8; MD: 93.0; HD: 87.8. (historical mean = 95.2 [86.8-98.9]).

Parameters	**Major findings** (please see Table footnotes for explanation of abbreviations)
	Male fetal wt (g): Control: 45.6; LD: 42.4; MD: 41.0 (p <0.001); HD: 31.1 (historical control mean = 43.8 [41.5 – 45.8]) Female fetal wt (g): Control: 44.2; LD: 40.5; MD: 38.8; HD: 28.7 (historical control mean = 42.3 [40.4 – 44.8]) Combined fetal wt (g): Control: 45.0; LD: 41.8; MD: 40.1; HD: 30.3 (historical control mean = 42.3 [40.9 – 45.4])
Necropsy findings Offspring	Coll A: Malformations (external, visceral and skeletal) in test article groups occurred in single fetuses and the occurrences appeared to be test article-related albeit within the range of historical control data. - *Total malformations (%/litter):* Control: 0.5; LD: 1.3; MD: 1.7; HD: 5.8 Soft tissue visceral malformation and variations e.g. hydrocephaly and meningoencephalocele, occurred in only a few animals - *Total soft tissue malformations (%/litter)* Control: 0.0; LD: 0.7; MD: 0.6; HD: 1.2 - *Total Skeletal malformations (%/litter)* Control: 0.0; LD: 0.5; MD: 1.2; HD: 5.8 Coll B: Findings of malformations and variations are described below: - *Total malformations (%/litter)* Control: 0.0; LD: 0.0; MD: 0.6; HD: 0.0 Soft tissue visceral malformation and variations e.g. hydrocephaly and meningoencephalocele, occurred in a few animals and was not dose-related. - *Total soft tissue malformations (%/litter)* Control: 0.0; LD: 2.2; MD: 0.0; HD: 0.0 - *Total Skeletal malformations (%/litter)* Control: 0.0; LD: 0.0; MD: 0.5; HD: 0.0
Hematology Findings	Collectives A and B: Test article related changes in hematological parameters based on magnitude and/or dose relationship are shown in bold in the Table below.

Parameters	Major findings (please see Table footnotes for explanation of abbreviations)
	Collective B; Hematological findings for Collective B are shown in Table below. Test article related changes in hematological parameters based on magnitude and/or dose relationship are shown in bold font.

LD (low dose), MD (mid dose), HD (high dose); Coll: Collective; Coll A or B (treatment during GD 6-19 or GD 19-28, respectively); FC (Food consumption); ↑, ↓: increase, decrease; GD = gestation day.

Tables 18 and 19 show the hematologic changes attributable to the pharmacologic activity of sargramostim as a hematopoietic growth factor.

Table 18 Test article-related effects on hematology (Collective A)

Dosage (µg/kg/day):	0[a]	25	70	200	GD
Mean neutrophil count (thousand/µL)	1.53	1.41	1.60	**2.61****	19
Mean neutrophil (%)	19.0	18.7	21.9	**27.1****	19
Mean monocyte count (thousand/µL)	0.14 0.16	0.19 0.12	0.17 0.12	**0.42**** **0.28**	12 19
Mean monocyte (%)	1.5 2.1	1.8 1.6	1.8 1.7	**3.7**** **2.8**	12 19
Mean eosinophil count (thousand/µL)	0.15	**0.36****	**0.47****	**0.26**	12
Mean eosinophil (%)	1.6	**3.4**	**5.4****	**2.4**	12
Mean basophil count (thousand/µL)	0.25	**0.47****	**0.42***	**0.53****	12
Mean basophil (%)	2.9	**4.2***	**4.5****	**4.9****	12
Mean platelet count (thousand/µL)	506	527	**619**	**637***	19
Mean absolute reticulocyte count (thousand/µL)	213.6 292.4	**181.1*** 303.1	**167.4**** 313.0	**135.0**** **370.5****	12 19
Mean reticulocyte (%)	3.7 5.4	3.2 5.5	**2.9**** 6.0	**2.3**** **7.2****	12 19
Mean hemoglobin (g/dL)	11.8	12.2	11.6	**11.1***	19

[a] = Vehicle
µL = microliter
GD = Gestation day
dL = deciliter
* = p<0.05
** = p<0.01

Source: Applicant's Table TT6, page 37 of 1059; Embryo-Fetal Development in rabbits (Study Number TXEX20050039)

Table 19 Test article-related effects on hematology (Collective B)

Dosage (µg/kg/day):	0[a]	25	70	200	GD
Mean white blood cell count (thousand/µL)	6.05	6.28	6.32	**9.18****	25
	5.86	5.11	6.23	**8.67****	28
Mean neutrophil count (thousand/µL)	1.26	1.17	1.47	**2.63****	25
	1.35	0.97	1.10	**2.41****	28
Mean neutrophil (%)	20.7	18.3	22.6	**29.3****	25
	23.4	19.5	17.9*	**27.4**	28
Mean monocyte count (thousand/µL)	0.13	0.16	0.17	**0.26****	25
	0.12	0.13	**0.24**	**0.41****	28
Mean monocyte (%)	2.1	2.4	**3.7**	**4.3***	28
Mean lymphocyte count (thousand/µL)	4.29	4.36	4.06	**4.85**	25
	4.02	3.54	4.41	**5.16***	28
Mean lymphocyte (%)	70.9	69.5	65.0	**53.1****	25
	68.2	68.9	70.3	**59.8***	28
Mean eosinophil count (thousand/µL)	0.09	**0.27****	**0.30****	**0.20**	25
	0.08	**0.20***	**0.19***	0.12	28
Mean eosinophil (%)	1.5	**4.6****	**4.8****	**2.3**	25
	1.3	**3.8****	**3.2***	1.4	28
Mean basophil count (thousand/µL)	0.17	0.16	0.20	**0.29***	28
Mean red blood cell count (thousand/µL)	5.62	5.34	**5.18****	**4.85****	28
Mean hemoglobin (g/dL)	12.6	12.1	**11.7***	**11.0****	25
	12.5	**11.5****	**11.0****	**10.5****	28
Mean hematocrit (%)	36.2	35.2	**33.8***	**31.9****	25
	36.3	**33.8***	**32.2****	**30.4****	28
Mean platelet count (thousand/µL)	393	**512***	**605****	**648****	28
Mean absolute reticulocyte count (thousand/µL)	212.3	197.7	**164.0****	**89.8****	25
	116.1	116.2	125.1	**190.4****	28
Mean reticulocyte (%)	3.8	3.6	**3.0***	**1.8****	25
	2.1	2.2	2.4	**3.9****	28
Mean large unstained cell count (thousand/µL)	0.14	0.12	0.13	**1.05****	25
	0.12	0.11	0.11	**0.29****	28
Mean large unstained cell (%)	2.3	1.9	1.9	**10.4****	25
Mean corpuscular volume (fL)	65.1	64.1	**62.4****	**62.5****	25
	64.8	63.4	**62.4***	**62.8**	28
Mean corpuscular hemoglobin (pg)	22.6	22.0	**21.5****	**21.6****	25
	22.2	21.6	**21.3****	**21.6**	28

[a] = Vehicle
GD = Gestation day
* = p<0.05
** = p<0.01
µL = microliter
dL = deciliter
fL = femtoliter
pg = picogram

Source: Applicant's Table TT13, page 48 of 1059; Embryo-fetal development in rabbits (Study Number TXEX20050039)

Table 20 summarizes the PK parameters. Note the marked decrease in sargramostim exposure after the administration of the first dose due to the development of anti-drug antibodies.

Table 20 Mean (±SD) pharmacokinetic parameters for sargramostim after once-daily sc administration of 25, 70, or 200 µg/kg/day [redacted](b)(4) to rabbits from gestation day 6 through gestation day 19

Parameter	Unit	Time [day]	Dosage Level (µg/kg/day) 25 Mean ± SD	70 Mean ± SD	200 Mean ± SD
C_{max}	[pg/mL]	GD 6	22075 ± 6182	50825 ± 15545	106867 ± 17049*
		GD 19	3615 ± 3047	6242 ± 6583	8467 ± 4821*
t_{max}	[h]	GD 6	0.69 ± 0.88	2.0 ± 0.0	2.0 ± 0.0*
		GD 19	0.25 ± 0.0	1.1 ±1.0	0.25 ±0.0*
AUC(0-t_{last})	[pg/mL x h]	GD 6	73350 ± 7792	216372 ± 43656	519436 ± 57905*
		GD 19	12491 ± 18000	18810 ± 22533	19435 ± 11844*
AUC AUC(0-24h)	[pg/mL x h]	GD 6	74375 ± 8631	228993 ±36494	629892 ± 150982*
		GD 19	16614 ± 19598	24980 ± 23207*	26204 ± 4048*
Dose normalized AUC	[pg/mL x h] / [µg/kg]	GD 6	2934 ± 312	3091 ± 624	2597 ± 290*
		GD 19	500 ± 720	269 ± 322	97.2 ± 59.2*
R			0.17 ± 0.24	0.14 ± 0.18	0.039 ± 0.026*
$t_{1/2}$	[h]	GD 6	1.4 ± 0.45	1.8 ± 0.57	2.9 ± 2.2*
		GD 19	1.2 ± 1.1*	0.70 ± 0.081*	1.2 ± 0.75**
Dose proportionality (Dosage vs. C_{max})		GD 6	a = 1826, b = 0.770 (0.572 – 0.967)***, r^2 = 0.896		
		GD 19	a = 176, b = 0.683 (-0.605 – 1.97)***, r^2 = 0.138		
Dose proportionality [Dosage vs. AUC(0-t_{last})]		GD 6	a = 3589, b = 0.946 (0.826 – 1.07)***, r^2 = 0.972		
		GD 19	a = 253, b = 0.777 (-0.784 – 2.34)***, r^2 = 0.123		

N = 4, except *N = 3 or **N=2.

C_{max}	Maximum observed concentration of the analyte in serum after drug administration
t_{max}	Sampling time of C_{max}
AUC(0-t_{last})	Area under the concentration versus time curve from dose administration until last sampling time with a valid concentration value > LLOQ (t_{last})
AUC	On first day of dosing (GD 6), the estimate of the area under the concentration versus time curve from dose administration till infinity
AUC(0-24h)	On GD 19, the estimate of the area under the concentration versus time curve from dose administration till 24 hours post-dosing
Dose normalized AUC	AUC(0-t_{last}) divided by the dose
day	GD 6, first day of dosing = gestation day 6 GD 19 = gestation day 19 (last day of dosing)
R	Accumulation ratio = AUC(0-t_{last}), GD 19/ AUC(0-t_{last}), GD 6
$t_{1/2}$	Apparent half-life for ZK 250224 in serum
Dose proportionality	C_{max} or AUC(0-t_{last}) = a × $(dose)^b$
***	95% Confidence interval for the exponent, b (low-high)
r^2	Coefficient of determination for the power regression

Source: Applicant's Table TT1, page 760 of 1059; Embryo-fetal Development in rabbits (Study Number TXEX20050039)

Prenatal and Postnatal Development

Study title/ number: A Study of the effects of sargramostim (b)(4)) on pre- and postnatal development, including maternal function in rabbits (Study Number TXEX20050040)

Objectives: The purpose of the this pivotal GLP study was to determine the potential adverse effects of maternal exposure to sargramostim on pregnancy, parturition, and lactation of maternal animals when administered from implantation to weaning. The effect on growth, viability and development and reproductive performance of F1 neonates was also evaluated. Sargramostim was administered by daily sc injection to 3 collectives, each collective consisting of 3 sargramostim-treated groups and 1 control group. of time-mated female (b)(4) rabbits comprising 10-15 animals per group. The dose administration period was gestation day (GD) 6 through 19 for Collective A, GD 19 through the day of parturition for Collective B and lactation days (LDs) 1 through 14 for Collective C. The sargramostim dosages evaluated were 25, 70 and 200 µg/kg/day. As used in this review, F0 = maternal/parental generation; F1 or filial generation = offspring(s) of F0 generation; F2 or second filial generation = cross between two F1 animals.

Key Study Findings

- Abortion, complete litter resorption and total litter loss were limited to the HD group in Collectives A or B. In Collective C, a total litter loss with a corresponding decreased F1 postnatal survival occurred at ≥LD a finding that occurred in in conjunction with F0 maternal toxicity. F0 maternal toxicity was evidenced by mortality, body weight losses and/or reduced body weight gains, reduced food consumption and associated clinical signs (decreased defecation) at ≥LD for Collectives B and C) groups; and at HD for Collective A groups. Lower mean number of kits born and live litter size were observed on PND 0 in the Collective A HD group. Lower F1 mean kit body weights were observed in the Collective B and C HD groups. Based on these results, the NOAEL for F0 maternal systemic toxicity and F1 neonatal toxicity was determined as <25 µg/kg/day.
- There were no effects on F1 reproductive performance or the clinical status of F1 animals following weaning at any dosage in any Collective group; therefore, the NOAEL for F1 reproductive and systemic toxicity was 200 µg/kg/day. Intrauterine growth and survival of the F2 fetuses was unaffected by treatment, and there were no external malformations in the F2 fetuses that were attributed to F0 maternal exposure to the test article. Therefore, the NOAEL for F2 embryo/fetal development was 200 µg/kg/day.
- Administration of sargramostim to female rabbits during gestation or lactation was not associated with hematological changes in kits sampled at approximately 6 months of age.

Conducting laboratory and location:	(b)(4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	single daily doses of 0 (vehicle), 25 (low dose), 70 (mid dose) or 200 (high dose) from gestation day (GD) 6 through 19 for Collective A, GD 19 through day of parturition for Collective B and lactation days 1 through 14 for Collective C.
Route of administration:	Sc
Formulation/Vehicle:	(40 mg mannitol, 10 mg sucrose, 1.2 mg trometamol, 11.5 mg benzyl alcohol, 1.9 mg edentate sodium and 1 mL sterile water for injection, USP)
Species/Strain:	Rabbit (b)(4)
Number/Sex/Group:	Rabbits were divided into 3 Collectives (A, B and C) as follows: 10 females/group in Collectives A (GD 6-19) and B (GD 19-Parturition or GD 19-36 for females that did not deliver) and on lactation days 1-14 for Collective C. A total of 15 females were assigned to the high dose level in Collectives A and B to account for an expected increase in postimplantation loss and/or abortion and to allow evaluation of an adequate number of kits.
Satellite groups:	No
Deviation from study protocol affecting interpretation of results:	None

The design of Study TXEX20050040 is summarized in the following table.

Table 21 Study Design (Prenatal and Postnatal Development)

Groups	**Dose Levels** µg/kg/day	**Dose volumes** mL/kg	**Main study No. of Animals/group**		
			Coll. A GD 6-19	**Coll. B** GD 19-Day of Parturition	**Coll. C** Lactation day 1-14
1 (Control)	0 (Veh)	0.40	10	10	10
2 (LD)	25	0.05	10	10	10
3 (MD)	70	0.14	10	10	10
4 (HD)	200	0.40	15	15	10

Reviewer's Table; The study involved a main group comprising 4 dose groups; LD, MD & HD (Low, Mid and High dose, respectively). All test animals were female time-mated (b)(4) (b)(4) rabbits. Rabbits were dosed during gestation days (GD) 6-19 (Collective A), GD 19-Day of Parturition (Collective B) and from Lactation Days 1-14 (Collective C). Concurrent control groups received the vehicle control article on a comparable regimen for each collective at dosage volumes of 0.40 mL/kg. With the exception of the high-dose group in Collectives A and B with 15 females to account for expected higher postimplantation loss, each group consisted of 10 females/group.

All animals were observed twice daily for mortality and moribundity. Individual detailed clinical observations, body weights and food consumption were recorded at appropriate intervals. All F0 females were allowed to deliver and rear their offspring to lactation day 42. Clinical observations, body weights and sexes were recorded for F1 kits at appropriate intervals.

Indicators of physical and functional development were evaluated for F1 kits as follows. Two males and 2 females per litter were randomly selected for attainment of vaginal perforation or balanopreputial separation on PND 21 and 60, respectively, and continued to be evaluated until vaginal perforation or balanopreputial separation was present. From these 2 kits/sex/litter, 1 male and 1 female in each litter were randomly assigned to 1 of 2 subsets. Subset A was selected for measurements of functional observational battery (FOB) and hematology parameters; conditioned eye blink response was also assessed for these animals on PND 162 ± 9. The remaining 1 male and 1 female selected from each litter were assigned to Subset B that was subjected to the conditioned eye blink test on PND 105 ± 9. The F1 kits selected for Subset A were assigned to an F1 maturational phase, including reproductive functional assessment. The F1 females were artificially inseminated using semen collected from the males of the same treatment group (avoiding sibling mating). On gestation day 29, F1 females were necropsied,

and fetuses were examined externally for malformations and developmental variations. The F1 males were necropsied following the last laparohysterectomy.

Table 22 Observations and Results for Study TXEX20050040

Generation	Major Findings
F0 Dams	*Mortality* Coll A (dosed GD 6-19): no deaths occurred in the dosing period; 1/10 MD died on lactation Day 14 Coll B (dosed GD19-Parturition): 2/15 HD (on GD23 and 30 Coll C (Lactation days 1-14): 2/15HD (1 on lactation day 40; 1 rabbit was euthanized in extremis on lactation Day 6); between lactation days 3 and 14, 6 others were euthanized (1 at LD, 2 at MD and 3 at HD); only females that delivered were assigned to Coll C.
	Abortions, resorptions and litter loss: *Abortions* Coll A: Con (0/10), LD (0/10), MD (0/10), HD (2/15) Coll B: Con (2/10), LD (5/10), MD (3/10), HD (3/15) Coll C: Con (1/10), LD (1/10), MD (2/10), HD (3/10)
	Complete resorptions Coll A: Con (1/10), LD (0/10), MD (0/10), HD (1/15) Coll B: Con (1/10), LD (0/10), MD (1/10), HD (0/15) Coll C: Con (0/10), LD (0/10), MD (0/10), HD (0/10)
	Total litter loss: Coll A: Con (0/10), LD (0/10), MD (0/10), HD (2/15) Coll B: Con (2/10), LD (5/10), MD (3/10), HD (3/15) Coll C: Con 0/10), LD (1/10), MD (2/10), HD (3/10)
	Injection sites There were limited signs of local irritation at injection sites
	Food consumption: There were no remarkable changes in food consumption in Coll A-C.
	Body weight: There were slight decreases in body weight at each Collective.

F1 Generation	Clinical findings: There were no test article related clinical findings in Collectives A or B
	Body weights (Preweaning period): There were no remarkable changes in body weight in Collectives A and B
	F1 Developmental landmarks (a) Balanopreputial separation: Mean ages for attainment of balanopreputial separation were comparable between treatment and control groups in Coll A and B (b) Vaginal perforation: Mean ages for attainment of vaginal perforation were comparable between treatment and control groups in Coll A and B.
	Reproductive performance: No test article-related effects were observed at any dose in Coll A and B or fertility indices
	Hematology: There were no test article-related hematology effects in F1 kits born to F0 maternal females in Collectives A and B
	F1 Necropsy: Coll A and B: There were no test article-related macroscopic findings at any dose level.
	F1 Summary: Intrauterine growth and survival of the F2 fetuses were unaffected, and there were no external malformations in the F2 fetuses that were attributed to F0 maternal exposure to sargramostim. Therefore, the NOAEL for F2 embryo/fetal development was the HD.
F2 Generation:	**F2 Summary:** Intrauterine growth and survival of F2 fetuses was unaffected, and there were no external malformations in the F2 fetuses that were attributable to F0 maternal exposure to sargramostim. Therefore, the NOAEL for F2 embryo/fetal development was the HD.

5.5.5. Other Toxicology Studies

No other toxicology studies were needed and none were provided.

6 Clinical Pharmacology

6.1. Executive Summary

Human dose selection for Leukine in H-ARS was based on the totality of evidence from efficacy studies in irradiated rhesus monkeys, PK studies in healthy and irradiated rhesus monkeys, and PK studies in healthy adult humans. The clinical pharmacology review focused on evaluating the acceptability of the following: monkey and adult human PK studies, adult population PK (popPK) model development, and the overall approach to human dose selection.

6.1.1. The applicant's approach to selection of the human dose

Per the dose selection considerations from the FDA Animal Rule guidance, the proposed adult human dose was selected so as to provide exposures in humans that exceed those observed in animal efficacy studies with the fully effective dose of 7 mcg/kg/day SC. The proposed pediatric weight-tiered dosing for H-ARS was based on scaling the adult population PK model to pediatrics using allometry and selecting pediatric doses that match adult exposures corresponding to the adult dose of 7 mcg/kg/day.

Human sargramostim PK data included four single-dose PK studies in healthy adults and one PK study in pediatric subjects with Crohn's disease. The applicant only modeled PK data from (b)(4) (b)(4) in adult PK studies 15367 and 309404. The popPK of sargramostim was characterized by a one compartment model with linear clearance and covariate effect of body weight on clearance and volume. The adult popPK model was scaled to pediatric subjects down to birth using allometric scaling. Simulations were conducted based on the developed popPK model to predict human exposure in adults and pediatrics following the proposed dosing regimen.

6.1.2. Review team assessment of human dose selection

Overall, we find the applicant's approach to selection of the human dose to be acceptable.

We found the monkey PK studies to be acceptable. The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the monkey PK studies and recommended accepting the data (please refer to OSIS letter dated March 7, 2018, for more details).

A significant impact of neutropenia or immunogenicity on the PK of sargramostim in monkeys is not likely based on the observation of overlapping exposures in healthy vs. irradiated monkeys, and a trend towards lower day 14 vs. day 1 exposures in both healthy and irradiated monkeys.

We reviewed the human PK studies 15367 and 309404 that were included in the popPK model. Study 309404 was overall acceptable, while we found that study 15367 utilized an unacceptable bioanalytical assay. Upon request, utilizing the same structural model, the applicant re-

estimated model parameters and evaluated goodness-of-fit based on data from study 309404 only. Both the final model (defined as model parameters estimated from a dataset consisting of studies 15367 and 309404) and the revised model (defined as model parameters estimated from a dataset consisting of study 309404 alone) had adequate model performance. Simulations conducted using parameters from both models showed that at the proposed human dose, human exposures are predicted to exceed exposures associated with efficacy in monkeys. Due to potential bioanalytical issues with study 15367, our review focused on the results obtained from the revised model.

Due to uncertainty in the exponent describing the clearance-body weight relationship, especially in neonates and infants, we asked the applicant to perform sensitivity analyses using clearance-body weight exponent values between 0.5 and 1.0 to evaluate the impact on predicted pediatric exposures. In all scenarios, predicted exposures in the majority of pediatric subjects exceed those associated with efficacy in monkeys. Thus, the choice of exponent is not expected to impact human pediatric dose selection in terms of efficacy. Regarding safety, use of an exponent of 1.0 results in higher predicted exposure in pediatric subjects weighing < 15 kg than those in adults with 7 mcg/kg/day dosing. However, the applicant cites pediatric safety data at much higher doses (1500 mcg/m^2/day IV and 2000 mcg/m^2/day SC) than proposed for H-ARS (10-12 mcg/kg/day SC for pediatrics < 40 kg, which approximates 200-400 mcg/m^2/day) to support safety of proposed pediatric dose.

6.1.3. Recommendations

The applicant's PK data in monkeys, human PK from study 309404, revised population PK model (contains study 309404 only), use of allometry to support pediatric dosing of pediatric patients and the general approach to human dose selection, are acceptable.

6.2. Summary of clinical pharmacology findings

6.2.1. Pharmacokinetic studies in healthy and irradiated monkeys

Effectiveness of sargramostim for H-ARS was established at a dosage of 7 mcg/kg/day SC in nonclinical efficacy (rhesus monkey) studies FY14-045 and TSK0144 (8.1.1, 8.1.2). PK was not assessed in the nonclinical efficacy studies. Exposures corresponding to the efficacious dose of 7 mcg/kg/day in monkeys were evaluated in monkey PK studies DDK0110 (healthy rhesus) and DDK0111 (irradiated rhesus). Sargramostim dosing in these PK studies was 7 mcg/kg/day SC for 14 days. In study DDK0111, the radiation dose evaluated was 646 cGy, which is sufficiently similar to the radiation doses evaluated in nonclinical efficacy studies. We requested a GLP inspection of studies DDK0110 and DDK0111; the Office of Study Integrity and Surveillance conducted an inspection of the monkey PK studies and recommended accepting the data (BLA 103362 letter dated March 7,2018).

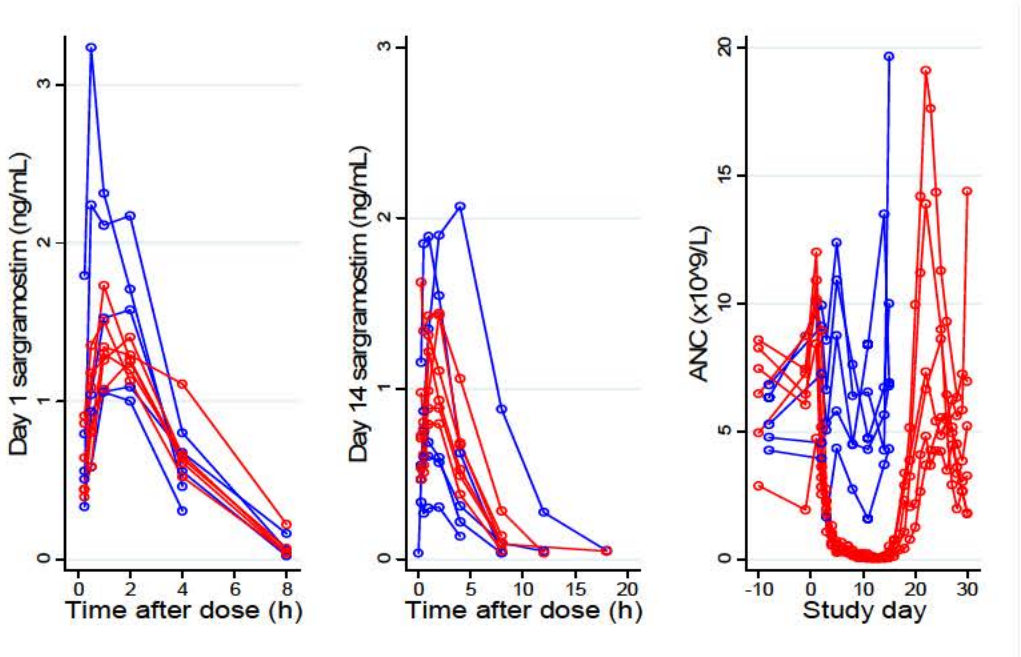
Effect of neutropenia on sargramostim PK

One review issue concerned the effect of neutropenia on PK in monkeys. This is of interest because sargramostim human PK data are only available for healthy adults, therefore any understanding of the impact of neutropenia on PK would be obtained from monkeys and potentially extrapolated to humans. In addition, the PK of filgrastim, approved for H-ARS under the Animal Rule pathway and with a similar mechanism of action as sargramostim, is nonlinear with clearance dependent on filgrastim concentrations and neutrophil count (NEUPOGEN label). Finally, for the purpose of human dose selection under the Animal Rule, it is important that the selected human dose provides human exposures that exceed efficacious exposures in diseased animals; thus PK collection in both healthy and neutropenic monkeys are needed.

In monkey PK studies, dosing was 7 mcg/kg/day SC or 20.8 mcg/kg/day on days 1-14, with intensive PK measured on days 1 and 14. White blood cell concentrations were measured before and during dosing in healthy and irradiated monkeys, and after treatment ended in irradiated monkeys. Antidrug antibody responses were also assessed.

We found studies DDK0110 and DDK0111 to be acceptable. Sargramostim exposures after dosing of 7 mcg/kg/day (Figure 10, Table 23) and 20.8 mcg/kg/day (data not shown) were found to overlap between healthy and irradiated monkeys on day 1 and day 14. As expected, irradiated monkeys showed plummeting ANC counts after irradiation, followed by a rebound concurrent with sargramostim treatment (Table 23).

Figure 10 Day 1 and day 14 sargramostim concentration-time profiles and absolute neutrophil count vs study day in healthy (blue) and irradiated (red) rhesus monkeys administered 7 mcg/kg/day SC on days 1-14.



Source: Plotted by reviewer from DDK0110 Bioanalytical dataset, \\cdsesub1\evsprod\bla103362\0030\m4\datasets\ddk0110\tabulations\legacy\bioanal.xpt, DDK0110 Hematology dataset, \\cdsesub1\evsprod\bla103362\0030\m4\datasets\ddk0110\tabulations\legacy\hemato.xpt, DDK0111 Bioanalytical dataset, \\cdsesub1\evsprod\bla103362\0030\m4\datasets\ddk0111\tabulations\legacy\bioanal.xpt, DDK0111 Hematology dataset, \\cdsesub1\evsprod\bla103362\0030\m4\datasets\ddk0111\tabulations\legacy\hemato.xpt. Blue = healthy monkeys; red = irradiated monkeys; thin lines = individual subjects.

Table 23 Mean (CV%) Cmax and AUC of sargramostim in healthy and irradiated monkeys administered 7 mcg/kg/day on days 1-14. Study DDK0110.

Study	Population	Gender	n	Dosing	Day	Cmax [ng/mL]	AUC0-24h [ng*h/mL]
DDK0110	Healthy rhesus monkeys	Male	5	7 mcg/kg/day SC on days 1-14	1	1.8 (50%)	6.2 (31%)
					14	1.1 (70%)	5.9 (99%)
DDK0111	Irradiated rhesus monkeys	Male	3		1	1.4 (6%)	6.1 (21%)
		Female	3			1.4 (18%)	5.5 (9%)
		Male	3		14	1.4 (14%)	6.4 (24%)
		Female	3			1.0 (28%)	4.5 (26%)

Source: Page 11, DDK0110 study report, \\cdsesub1\evsprod\bla103362\0030\m4\42-stud-rep\422-pk\4222-absorp\ddk0110\study-ddk0110.pdf. Page 17, DDK0111 study report, \\cdsesub1\evsprod\bla103362\0030\m4\42-stud-rep\422-pk\4222-absorp\ddk0111\study-ddk0111.pdf.

In our view, the observation of overlapping exposures in healthy and irradiated monkeys indicates that neutropenia does not significantly impact the PK of sargramostim in monkeys.

Time-dependence of sargramostim PK in monkeys

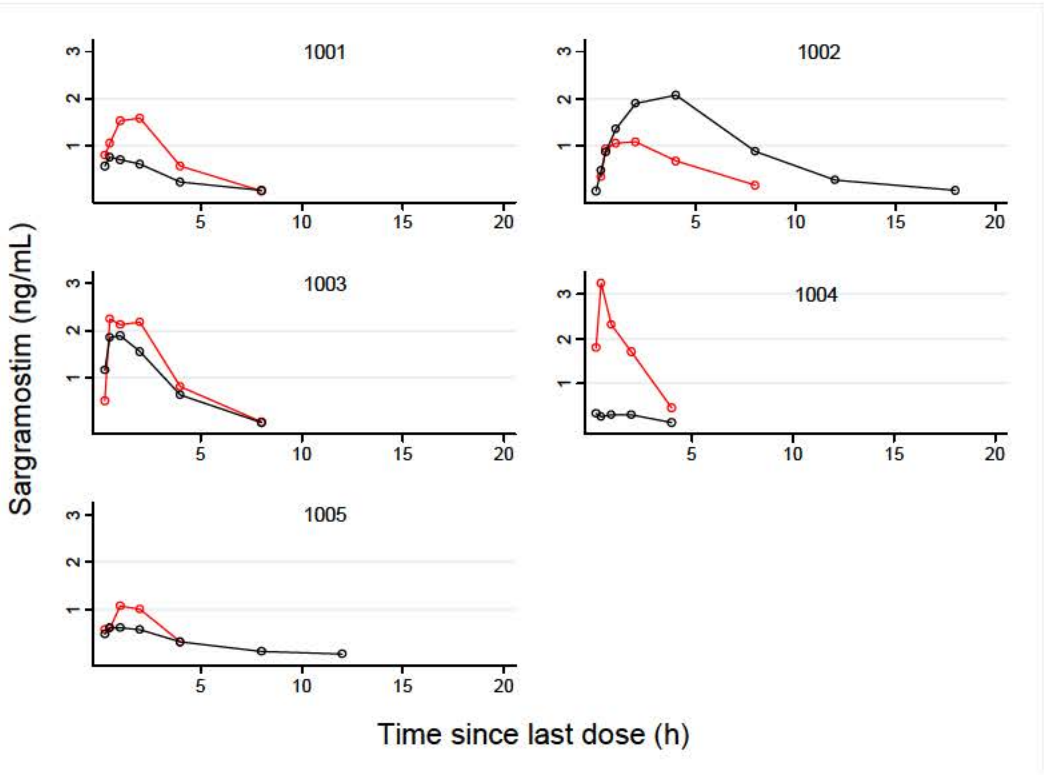
In both healthy and irradiated monkeys administered 7 mcg/kg/day, there was a tendency toward lower exposures on Day 14 relative to Day 1 (Figure 11, Table 23 Table 24). This was the case in four of five healthy monkeys and four of six irradiated monkeys (Figure 12)The applicant provided no explanation for this observation.

Table 24 Day 14 vs day 1 Cmax and AUC ratios in healthy and irradiated monkeys administered 7 mcg/kg/day SC. Study DDK0110.

Study	Population	Animal ID	Day 14 / day 1 AUC ratio	Day 14/ day 1 Cmax ratio	Day 15 antidrug antibody titer
DDK0110	Healthy	1001	0.46	0.48	1000
		1002	2.83	1.90	800
		1003	0.80	0.84	300
		1004	0.17	0.10	100
		1005	0.90	0.57	200
DDK0111	Irradiated	1001	1.02	1.06	Undetectable
		1002	1.23	1.15	
		1003	0.90	0.81	
		1501	0.96	0.76	
		1502	0.66	0.61	
		1503	0.84	0.71	

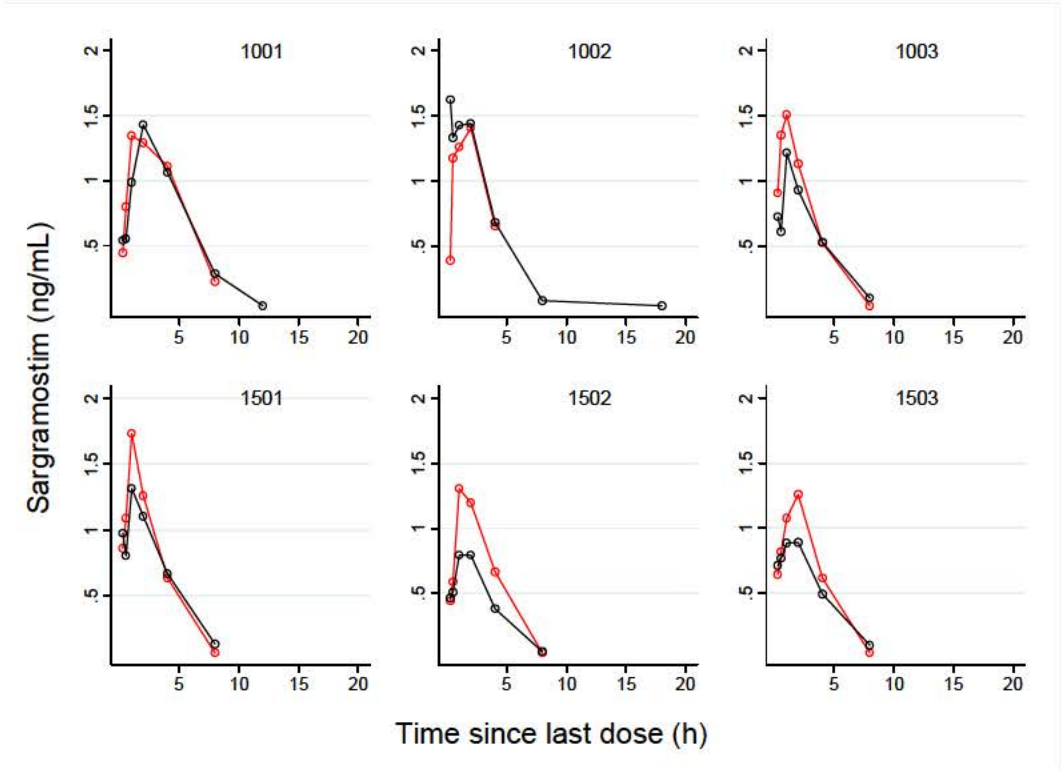
Source: Ratios calculated by reviewer from the DDK0110 Toxicokinetics dataset, \\cdsesub1\evsprod\bla103362\0030\m4\datasets\ddk0110\tabulations\legacy\toxicok.xpt, and DDK0111 Toxicokinetics dataset, \\cdsesub1\evsprod\bla103362\0030\m4\datasets\ddk0111\tabulations\legacy\toxicok.xpt.

Figure 11 Day 1 vs day 14 sargramostim concentration-time profiles in individual healthy monkeys administered 7 mcg/kg/day SC. Study DDK0110.



Source: Plotted by reviewer from DDK0110 Bioanalytical dataset, \\cdsesub1\evsprod\bla103362\0030\m4\datasets\ddk0110\tabulations\legacy\bioanal.xpt. Red = day 1; black = day 14.

Figure 12 Day 1 vs day 14 sargramostim concentration-time profiles in individual irradiated monkeys administered 7 mcg/kg/day SC. Study DDK0110.



Source: Plotted by reviewer from DDK0111 Bioanalytical dataset, \\cdsesub1\evsprod\bla103362\0030\m4\datasets\ddk0111\tabulations\legacy\bioanal.xpt. Red = day 1; black = day 14.

Effect of immunogenicity on sargramostim PK

Antidrug antibody responses to sargramostim were seen in 100% of healthy monkeys and 0% of irradiated monkeys. Thus, it is not possible to separate the impact of neutropenia vs. ADA response on sargramostim PK. Nevertheless, the observation of overlapping exposures in healthy and irradiated monkeys suggests that ADA is unlikely to significantly impact the PK of sargramostim in monkeys.

Available sargramostim human PK studies were single dose studies in healthy humans and thus did not evaluate the relevant dosing regimen (once daily dosing) or patient population (neutropenia) relevant to H-ARS. Antidrug antibody responses cannot be extrapolated from monkeys to humans because sargramostim is a humanized antibody and is likely more antigenic in monkeys than in humans. Sargramostim labeling contains language describing the risk of immunogenicity in humans after prolonged sargramostim treatment. This language focuses on the oncology and transplant indications and describes the potential but unconfirmed impact of

immunogenicity on sargramostim safety and efficacy. Sargramostim labeling does not discuss the potential impact of immunogenicity on PK.

After consultation with the Office of Biotechnology Products, we decided not to review the binding ADA assay for monkey serum that was utilized to measure ADA titers in monkey PK studies DDK0110 and DDK0111. This is because ADA rates observed in monkeys cannot be extrapolated to humans, and because the assay appeared to be sufficiently sensitive in that ADA was detected in 100% of healthy monkeys in study DDK0110.

6.2.2. Human pharmacokinetic studies and population PK modeling

No new human PK studies were conducted to support the H-ARS indication. Instead, the applicant submitted four single-dose PK studies in healthy adults (Studies 15367, 308626, 309404, and 309901) and one PK study in pediatric subjects with Crohn's disease (Study 308001). These studies were conducted by different license holders between 2004-2011. The applicant identified these studies for submission based on the availability of sufficient bioanalytical information to allow for FDA review. No human PK data were submitted in the settings of multiple dosing or neutropenia.

The applicant used popPK to characterize sargramostim PK in an integrated manner across studies. The four healthy adult studies included a total of 6714 samples from 225 subjects. Dosing was SC except for six subjects with IV dosing. Dosages were fixed (500 mcg) or based on body weight (2-8 mcg/kg) or body surface area (125-250 mcg/m^2). Note that the proposed adult H-ARS dose of 7 mcg/kg is predicted to result in similar exposures compared to the approved dosage of 250 mcg/m^2 (Table 25).

Table 25 Sargramostim PK parameters after SC administration.

Data type	Dose	Mean Cmax (CV%) [ng/mL]	Mean AUC (CV%) [ng*h/mL]
Observed	250 mcg/m^2	3.8 (46%)	21.9 (28%)
Observed	6.5 mcg/kg	3.15 (35%)	20.4 (29%)

Source: Draft Leukine labeling dated 2/22/2018.

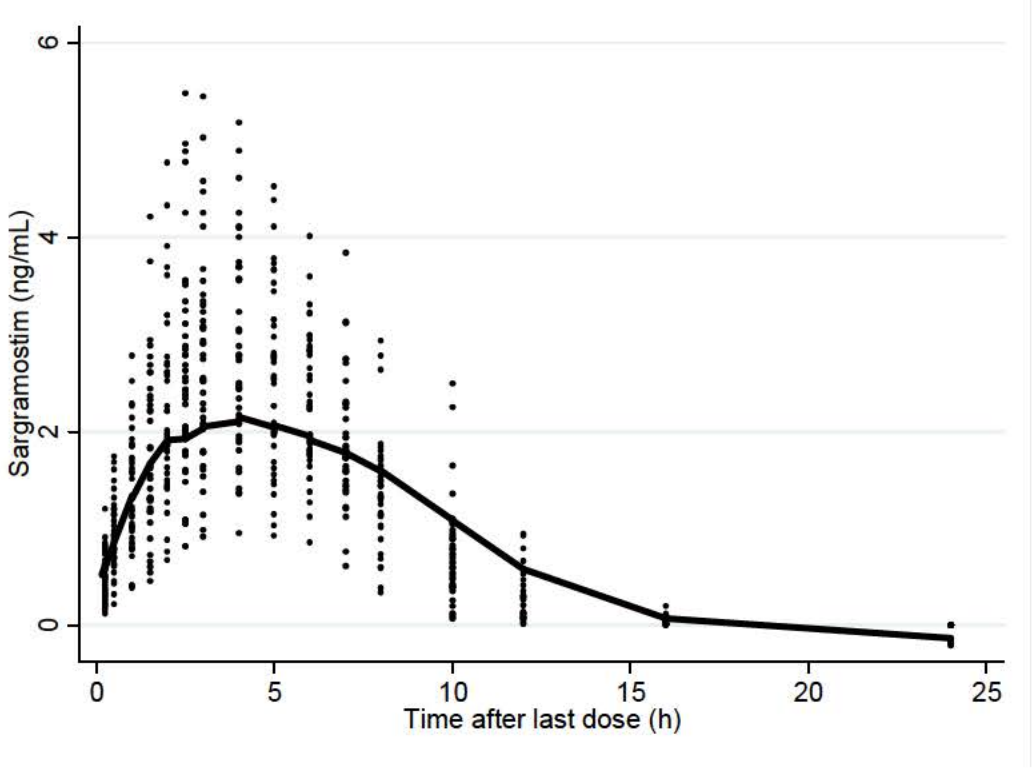
The applicant found that PK profiles differed significantly based on formulation (b)(4) (b)(4) and route of administration. Therefore, they only included PK data from SC dosing (b)(4) into the popPK model dataset; these data are from healthy adult PK studies 15367 and 309404 (Table 26). Based on this dataset, the applicant developed a one compartment model with linear clearance and covariate effect of body weight on clearance and volume. Overall the model had acceptable performance, although observed concentrations from 12-24 hours post dose were overpredicted (17.2.1).

In our review of the adult PK studies included in the popPK model (studies 309404 and 15367), we found that study 309404 was overall acceptable but that the (b)(4)

(b)(4) assay used to measure sargramostim in study 15367 was not acceptable. During method validation of the (b)(4) assay, there were many failed validation runs. Per the applicant, acceptable validation data were obtained upon repeat of these runs. The applicant cited high background in blank matrix, high variability in stock solutions from using dilutions of high concentration material, and plate drift as reasons for failed validation runs (page 12-13, \\cdsesub1\evsprod\bla103362\0043\m1\us\111-info-amend\response-info-req-20180213.pdf). We did not find this to be a convincing explanation.

Due to the bioanalytical issues in study 15367, we asked the applicant to re-fit the model after exclusion of study 15367. Utilizing the same structural model, the applicant re-estimated model parameters and evaluated goodness-of-fit. Both the final model (defined as model parameters estimated from a dataset consisting of studies 15367 and 309404) and the revised model (defined as model parameters estimated from a dataset consisting of study 309404 alone) had adequate model performance. The main difference in model parameters between the two models was the clearance-body weight exponent (Table 40). Due to potential bioanalytical issues with study 15367, our emphasis was on results obtained from the revised model.

Figure 13 Sargramostim concentration-time data from study 309404.



Source: Plotted by reviewer from the final popPK dataset, \\cdsesub1\evsprod\bla103362\0030\m5\datasets\poh0547\analysis\legacy\datasets\poppk.xpt\\cdsesub1\evsprod\bla103362\0030\m5\datasets\poh0547\analysis\legacy\datasets\initial.xpt. Circles = observed concentrations; line = lowess.

Table 26 Number of subjects and PK samples in studies 15367 and 309404.

Study years	Study	Population	Body weight (kg)	(b)(4)	Liquid or lyophilized formulation?[1]	Route	Dosing (all single dose)	Number of subjects	Number of samples
2005	309404	Healthy males	77 (62, 115)		Lyophilized	SC	6 mcg/kg	39	599
2011	15367	Healthy males and females	74 (53, 108) 80 (51, 98)		Lyophilized Liquid	SC	125 mcg/m^2 250 mcg/m^2	60	1747
Total			77 (51, 115)					99	2346

Source: Tabulated by reviewer from final popPK dataset, \\cdsesub1\evsprod\bla103362\0030\m5\datasets\poh0547\analysis\legacy\datasets\poppk.xpt.
Body weights are median (min, max).
[1]Approved LEUKINE formulations are liquid (b)(4) and lyophilized powder (b)(4)

6.2.3. Human dose selection

Per the dose selection considerations from the FDA Animal Rule guidance, the proposed adult human dose was selected to provide exposures in humans that exceed those observed in animal efficacy studies with the fully effective dose of 7 mcg/kg/day SC. To identify the pediatric dosing, the adult popPK model was scaled to pediatrics through allometry and then used for subsequent simulation. Given there is lack of elimination pathway-specific information, the body weight scaling factor for clearance and volume was fixed to be 0.75 and 1.

Simulations were conducted based on a virtual subject dataset of adult and pediatric subjects to predict exposures for each virtual subject following a single dose of proposed sargramostim SC dosing regimen (Table 27).

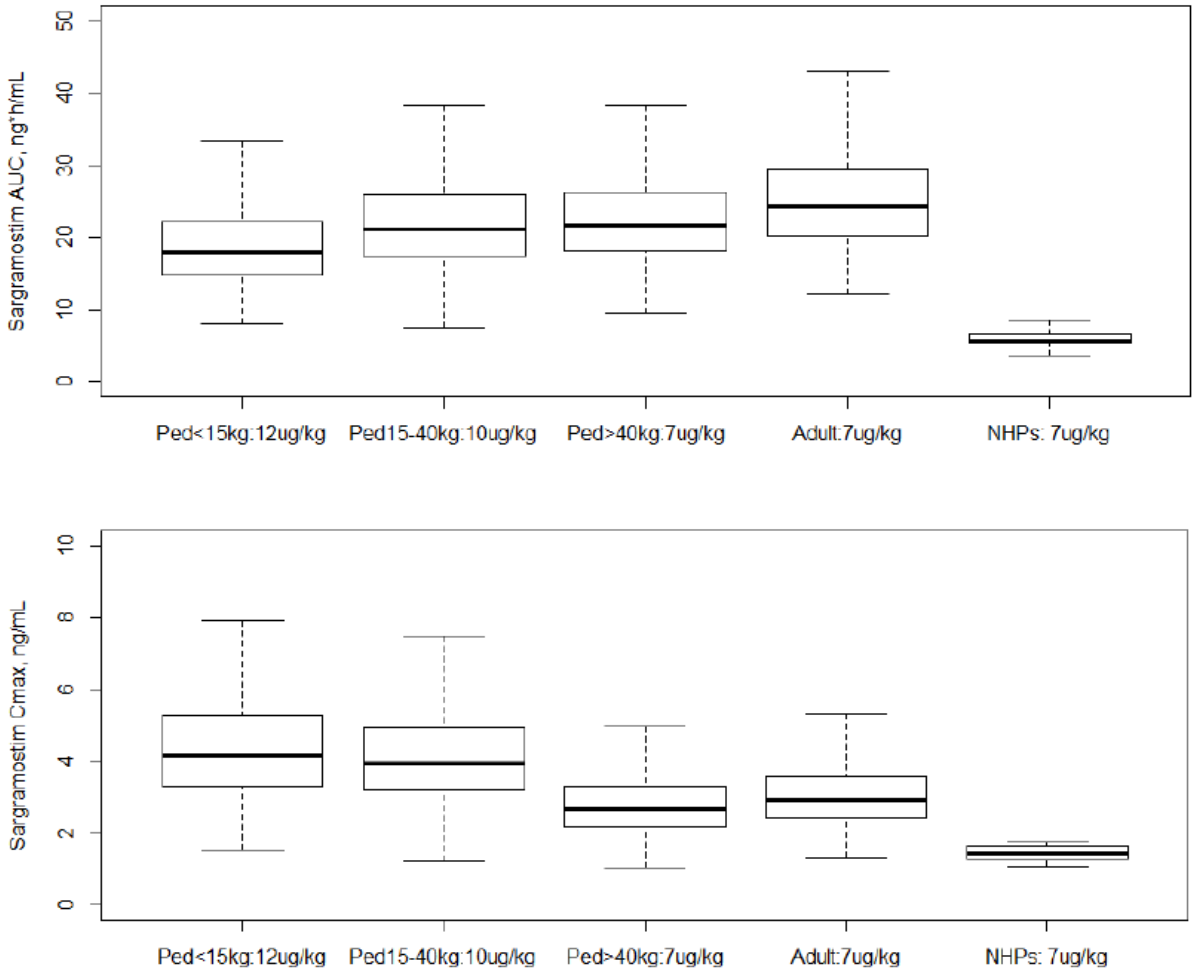
Table 27 Adult and pediatric body weights in the virtual subject dataset used for simulations.

Age category	Weight category (kg)	Median (5^{th}, 95^{th}) percentile weight (kg)	Number of simulated subjects
Adult	NA	78.4 (57.4, 98.4)	500
Pediatric	>40	60.6 (41.9, 92.6)	1000
	15 - 40	25.1 (15.7, 37.9)	1000
	0 - <15	10.8 (5.4, 14.6)	1000

Source: Tabulated by reviewer from page 36, \\cdsesub1\evsprod\bla103362\0030\m2\27-clin-sum\summary-clin-pharm.pdf.

Using the revised model, the predicted exposures in adults exceed the range of exposures associated with efficacy in monkeys (Figure 18). Since the safety profile of the proposed 7 mcg/kg/day SC dosing regimen has been well characterized in adults, the proposed human adult dose is acceptable. The predicted exposures in pediatrics across body weight categories are also comparable to those in adults, which supports the proposed weight-tiered based dosing regimen for pediatrics.

Figure 14 Revised model[1] - observed sargramostim exposures in monkeys corresponding to the efficacious dose in monkeys and predicted sargramostim exposures in humans corresponding to the proposed human dosage regimen.



Source: page 6, \\cdsesub1\evsprod\bla103362\0047\m1\us\111-info-amend\eff-info-amend-20180227.pdf.
[1]The revised model refers to model parameters estimated using a dataset consisting of study 309404 only.

For pediatrics, due to uncertainty in the allometric exponent describing the clearance-body weight relationship, especially in neonates and infants, we asked the applicant to perform sensitivity analyses using exponent values between 0.5 and 1.0 to evaluate the impact on predicted pediatric exposures. The applicant conducted this analysis using both the final and revised model, stated that results were similar for both, and submitted results for the final model only. Because the main difference in model parameters between the final and revised models is the clearance-body weight exponent, and this is the parameter being evaluated in the sensitivity analysis, we consider the sensitivity analysis results using the final model to be acceptable.

As expected, the predicted exposure is most sensitive to the change with the allometric exponent in the pediatric group weighing <15 Kg. With the exponent of 0.5, the predicted AUC

and Cmax appear to be 10-30% lower than adults. However, these predicted exposure levels still exceed those associated with efficacy in monkeys.

Regarding safety, the use of an exponent value of 1.0 for prediction of pediatric PK results in 95th percentile values of Cmax and AUC in pediatrics that exceed 95th percentile values of observed Cmax and AUC values in healthy adult PK study 309404. However, the applicant cites pediatric safety data at much higher doses (1500 mcg/m2/day IV and 2000 mcg/m2/day SC) to support safety of predicted pediatric exposures corresponding to dosing for H-ARS (page 3, \\cdsesub1\evsprod\bla103362\0051\m1\us\efficacy-response-08mar2018.pdf) (

, Table 29, **Figure 15**). We consider the proposed weight-tiered based pediatric dosing regimen to be generally supported by the simulation and sensitivity analyses.

Table 28 Summary of predicted AUC0-24 in pediatrics using different clearance-body weight exponents and observed AUC0-24 in NHP and adult humans.

Simulated exposures in pediatric population [a]

Species	Population	Dose	AUC_{0-24} (ng·h/mL): Mean (CV%) [5th – 95th Percentile]		
			$EXPO_{CLWT}$=0.5	$EXPO_{CLWT}$=0.75	$EXPO_{CLWT}$=1.0
Human	>40 kg (N=1000)	7 µg/kg	18.7 (34.5) [9.95 – 31.0]	19.2 (32.5) [10.8 – 30.3]	20.3 (31.9) [10.8 – 32.7]
	15 to 40 kg (N=1000)	10 µg/kg	16.8 (37.0) [8.71 – 29.0]	22.3 (35.5) [11.8 – 37.7]	28.4 (32.2) [15.9 – 45.4]
	<15 kg (N=1000)	12 µg/kg	13.3 (37.2) [7.15 – 22.0]	21.7 (35.1) [11.5 – 35.5]	34.5 (32.5) [19.3 – 56.7]

Observed exposure in NHP and adult humans

Species	Population	Dose	AUC_{0-24} (ng·h/mL): Mean (CV%) [Min – Max]
NHP	Adult (N=11) ([Study DDK0110] and [DDK0111])	7 µg/kg	5.49 (26.6) [b]
Human	Adult (N=39) ([Study 309404])	6 µg/kg	20.4 (28.7) [8.8 – 32.1] [c]

AUC_{0-24}: area under the curve from time zero to 24 hours; CV: coefficient of variation; $EXPO_{CLWT}$: clearance-body weight exponent; Min: minimal value; Max: maximal value; NHP: non-human primate; N: number of animals or human subjects.

a Simulations were conducted using clearance-body weight exponents of 0.5, 0.75 and 1.0, and volume of distribution-body weight exponent of 1.0.

b AUC_{last} for NHPs. In NHPs, due to the short terminal half-life, AUC_{last} is similar to AUC_{0-24}.

c AUC_{last} for adult human subjects in Study 309404. Due to the short terminal half-life, AUC_{last} in humans is similar to AUC_{0-24}.

Source: page 3, \\cdsesub1\evsprod\bla103362\0051\m1\us\efficacy-response-08mar2018.pdf.

Table 29 Summary of predicted pediatric Cmax using different clearance-body weight exponents and observed Cmax in NHP and adult humans.

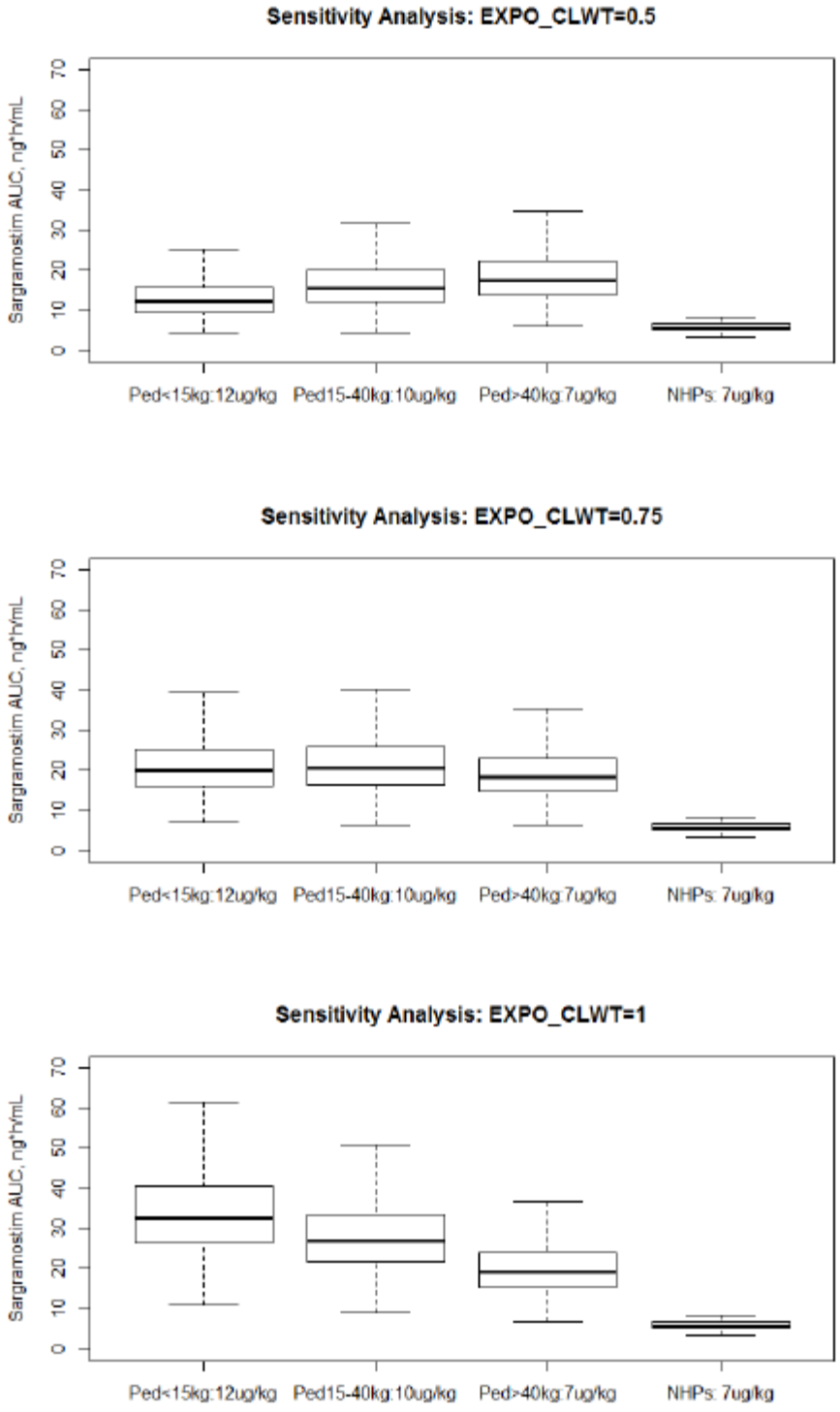
Simulated exposures in pediatric population [a]					
Species	**Population**	**Dose**	**C_{max} (ng/mL):** Mean (CV%) [5th – 95th Percentile]		
			$EXPO_{CLWT}$=0.5	**$EXPO_{CLWT}$=0.75**	**$EXPO_{CLWT}$=1.0**
Human	>40 kg (N=1000)	7 µg/kg	2.62 (35.1) [1.44 - 4.35]	2.65 (32.4) [1.49 – 42.6]	2.74 (34.2) [1.52 – 4.55]
	15 to 40 kg (N=1000)	10 µg/kg	2.93 (34.8) [1.57 - 4.97]	3.47 (34.0) [1.91 – 5.71]	3.90 (32.6) [2.19 – 6.29]
	<15 kg (N=1000)	12 µg/kg	2.69 (37.5) [1.46 - 4.44]	3.69 (34.0) [1.94 – 5.96]	4.64 (33.4) [2.73 - 7.46]
Observed exposures in NHP and adult humans					
Species	**Population**	**Dose**	**C_{max} (ng/mL):** Mean (CV%) [Min – Max]		
NHP	Adult (N=11) ([Study DDK0110] and [DDK0111])	7 µg/kg	1.61 (39.2)		
Human	Adult (N=39) (Study [309404])	6 µg/kg	3.15 (35.3) [1.4 – 5.5]		

C_{max}: Maximum serum concentration; CV: coefficient of variation; $EXPO_{CLWT}$: clearance-body weight exponent; Min: minimal value: Max: maximal value; NHP: non-human primate; N: number of animals or human subjects.

a Simulations were conducted using clearance-body weight exponents of 0.5, 0.75 and 1.0, and volume of distribution-weight exponents of 1.0.

Source: page 4, \\cdsesub1\evsprod\bla103362\0051\m1\us\efficacy-response-08mar2018.pdf.

Figure 15 Comparison of predicted sargramostim AUC in pediatrics using different clearance-body weight exponents with observed AUC in NHP.



Source: page 5, \\cdsesub1\evsprod\bla103362\0051\m1\us\efficacy-response-08mar2018.pdf.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Section 7 is not applicable to this review. No new clinical safety or efficacy studied were necessary and none were submitted.

7.2. Review Strategy

Not applicable.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Supportive Efficacy Study FY14-045

8.1.1.1 Study Design and Methods

Study FY14-045 was a randomized, vehicle-controlled, nonclinical study to evaluate the treatment effects of Leukine for H-ARS in male Rhesus macaques. The study was conducted at [redacted](b)(4) The targeted single uniform total body radiation (TBI) level of 680 cGy, considered as $LD_{50/60}$ in this study, and the drug dose of 7.0 µg/kg/day were used.

A total of 105 male Rhesus macaques were planned to be used. The treatment assignment is presented in Table 1. Rhesus macaques were given daily subcutaneous injections until Day 18 or until the ANC returned to ≥ 1000/µL. There were two groups with Leukine injections in this study: one with Leukine injected one day after radiation (referred to as Leukine group 1); the other with Leukine injected two days after radiation (referred to as Leukine group 2). In the study, minimal supportive care was planned for the animals.

The statistical reviewer found that the primary endpoint and analysis method were not clearly stated in the protocol. A statistical survival report was submitted by the Applicant.

8.1.1.2 Study Results

Data Location and Quality

The electronic submissions of the study are located at
\\CDSESUB1\evsprod\BLA103362\0030\m4\42-stud-rep\421-pharmacol\4211-prim-pd\fy14-045\
\\CDSESUB1\evsprod\BLA103362\0030\m4\datasets\fy14-045\

The data quality and analysis quality are adequate. The statistical reviewer performed an independent review using Applicant's submitted datasets and confirmed the Applicant's analysis results.

Efficacy Results

The analysis population for the survival rate excluded one animal in the control group that had to be euthanized due to clinical observations unrelated to irradiation.

The analysis results on survival rate are presented in Table 30. The survival rate of the Leukine group 1 and Leukine group 2 were both higher than that of the control. Nominal significances were reached for comparing Leukine group 2 and the control group.

Table 30 Survival analysis Study FY14-045

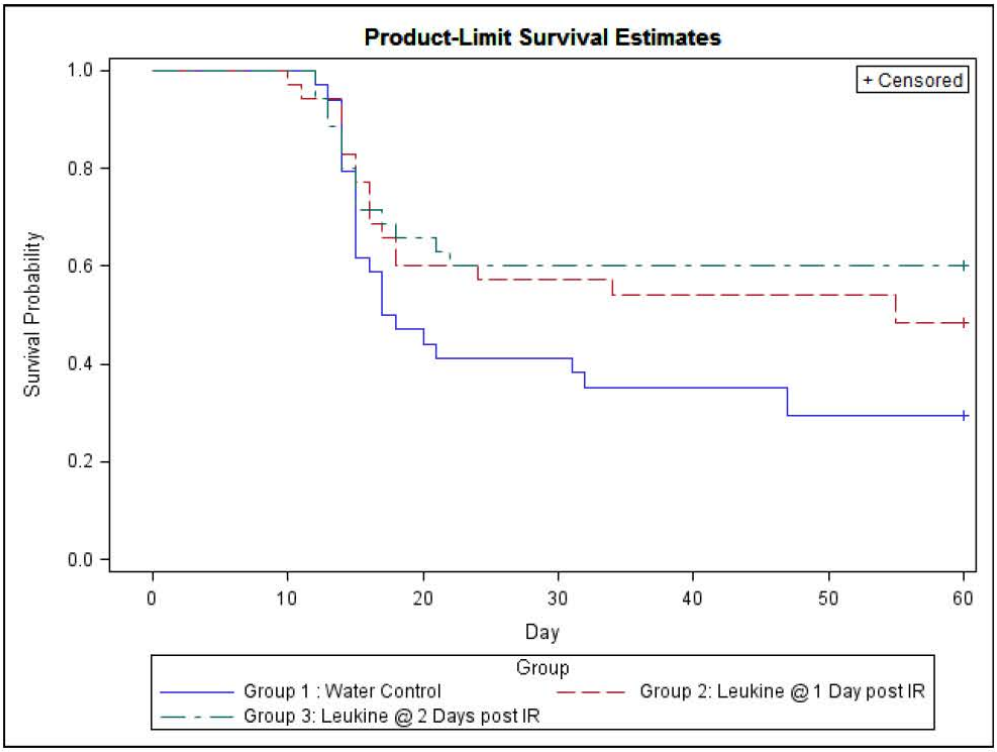
	Control	Leukine Group 1	Leukine Group 2
Mortality Rate	10/34 (29.4%)	17/35 (45.6%)	11/35 (60.0%)
Two-sided p-value under the fisher exact test for comparison with Control	--	0.14	0.02
Two-sided p-value under the log-rank test for comparison with Control	--	0.11	0.03

[Source: selected from results on pages 180 and 182 of the Applicant's study report]

Mortality rate (70.6%) for the control group in this study was higher than the targeted rate (50%). The cause of the shift from LD_{50} to LD_{70} could not be determined.

The Kaplan-Meier curves in Table 16 demonstrated numerical survival advantage over time of the two Leukine groups over control.

Figure 16 Study FY14-045 Kaplan-Meier curves



8.1.2. Confirmatory Efficacy Study TSK0144

8.1.2.1 Study Design and Methods

Study TSK0144 was a randomized, vehicle-controlled, nonclinical study to evaluate the treatment effects of Leukine for hematopoietic acute radiation syndrome in male and female Rhesus macaques. The study was conducted at [redacted] (b)(4) In this study, the targeted single uniform TBI levels of 655 cGy and 713 cGy, considered as $LD_{50\text{-}60/60}$ and $LD_{70\text{-}80/60}$ respectively, were chosen based on historical data; the drug dose of 7.0 µg/kg/day was chosen based on results from a previous exploratory study TSK0143.

A total of 108 Rhesus macaques were planned to be used, with equal numbers of females and males. The treatment assignment is presented in Table 2. Rhesus macaques were given daily subcutaneous injections until the ANC returned to ≥ 1000/µL for three consecutive days or ANC returned to ≥ 10000/µL. In case the neutrophil count returned below 1000/µL after being ≥ 1000/µL for 3 consecutive days, dosing could be re-initiated after approval by the Applicant and the Study Director. The first injection was planned to be performed at 48 ± 1 hours after irradiation. In the study, minimal supportive care was planned for the animals.

All analyses were planned to be performed on the intent-to-treat population, defined as all Rhesus macaques randomized with TBI. The analyses were planned for two cohorts: (1) Rhesus macaques randomized to receive 655 cGy radiation and (2) Rhesus macaques randomized to receive 713 cGy radiation.

The primary endpoint was the mortality rate, i.e. the proportion of Rhesus macaques died before 60 days after TBI. A one-sided Fisher exact test at the significance level of 0.025 was used for testing the mortality rate difference between Leukine and the control.

The secondary endpoints included

- Overall survival, defined as time (in days) from TBI to death
- Neutrophil-related parameters
  - ANC nadir
  - Duration of neutropenia (ANC < 500/µL and < 100/µL)
  - Time to ANC recovery (ANC ≥ 500/µL and ≥ 1000/µL)
  - Recovery from febrile neutropenia (ANC < 500/µL, core body temperature > 103°F concurrently)
- Platelet-related parameters
  - Nadir
  - Duration of platelet count (< 20,000/µL)
  - Recovery to platelet count (≥ 20,000/µL)

Although the Applicant had pre-specified that the analyses would be performed separately for each cohort, the statistical analysis plan did not contain any multiplicity testing rule for the two cohorts. The study plan, however, did pre-specify that the primary objective of the study is to assess mortality for cohort (1). Without control of overall type I error, all analyses on the secondary endpoints are considered exploratory.

8.1.2.2 Study Results

Data Location and Quality

The electronic submission of the study is located at
\\CDSESUB1\evsprod\BLA103362\0030\m4\42-stud-rep\421-pharmacol\4211-prim-pd\tsk0144\
\\CDSESUB1\evsprod\BLA103362\0030\m4\datasets\tsk0144\
\\CDSESUB1\evsprod\BLA103362\0036\

The data quality and analysis quality are adequate. The reviewer performed independent review using Applicant's submitted datasets and confirmed the Applicant's analysis results.

Analysis Population

The numbers of Rhesus macaques in each treatment group in the analysis population were the same as the planned numbers of randomized Rhesus macaques, as presented in Table 4.

Efficacy Results for the Primary Endpoint

The primary analysis results are presented inTable 31. The mortality rate of the Leukine group was lower than that of the control: under $LD_{50\text{-}60/60}$, the mortality rate was 36% significantly lower (one-sided p-value = 0.0018); under $LD_{70\text{-}80/60}$, the mortality rate was 44% lower (one-sided nominal p-value = 0.0076). These results are equivalent to increased survival rate in the Leukine group, compared to the control group under each cohort.

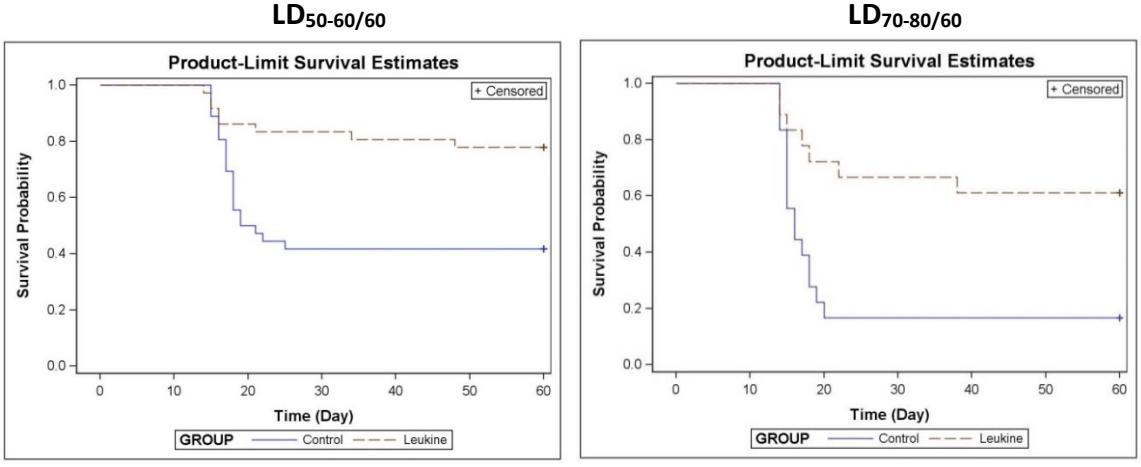
Table 31 Primary analysis on mortality rate Study TSK0144

	$LD_{50\text{-}60/60}$		$LD_{70\text{-}80/60}$	
Mortality Rate	Control	Leukine	Control	Leukine
	58% (21/36)	22% (8/36)	83% (15/18)	39% (7/18)
Fisher exact test one–sided p-value	0.0018		0.0076	

[Source: selected from results on pages 1897 and 1906 of the Applicant's study report]

The Kaplan-Meier curves in Figure 17 demonstrate survival advantage over time of Leukine over control under each cohort. These observed time-related effects support the survival benefits of Leukine demonstrated in the primary analysis.

Figure 17 Kaplan-Meier curves Study TSK0144



[Source: Figures 1 and 5 on pages 1898 and 1907, respectively, of the Applicant's study report]

Additional survival analyses (not shown) using log rank test and cox model (without adjusting for any covariates) had conclusions consistent with that from the primary endpoint: under both $LD_{50\text{-}60/60}$ and $LD_{70\text{-}80/60}$, Leukine showed survival advantages over control.

Efficacy Results for Secondary Endpoints

Descriptive statistics for nadir, onset and duration of neutropenia are presented in Table 32 and Table 33. The durations of onsets in these tables were based on Rhesus macaques that developed neutropenia in the study.

Table 32 Analyses on neutrophil related parameters, $LD_{50\text{-}60/60}$ cohort, Study TSK0144

Treatment	Nadir @ (cell/uL) (± SE)	Day of Onset # ANC<500/uL (± SE, range)	Duration (days)* ANC<500/uL (± SE, range)	Day of Onset # ANC<100/uL (± SE, range)	Duration (days)* ANC<100/uL (± SE, range)
Control	20.3±2.8	6.3±0.31[a] (4-16)	11.5±1.0[e] (2-17)	11.2±0.31[a] (8-17)	5.9±0.61[c] (2-11)
Leukine	34.4±6.0	6.3±0.26[a] (4-10)	9.9±0.76[f] (2-16)	11.2±0.41[b] (7-16)	4.7±0.42[d] (2-12)

@ Includes both survivors and nonsurvivors.
# Includes data from animals that developed neutropenia.
*Note that durations do not include data from decedent animals unless recovery occurred prior to death, nor from animals that did not develop neutropenia.
a n=36, b n=34, c n=20, d n=32, e n=18, f n=33

[Source: Table 3 on page 1898 of the Applicant's study report]

Table 33 Analyses on neutrophil related parameters, $LD_{70\text{-}80/60}$ cohort, Study TSK0144

Treatment	Nadir @ (cell/uL) (± SE)	Day of Onset # ANC<500/uL (± SE, range)	Duration (days)* ANC<500/uL (± SE, range)	Day of Onset # ANC<100/uL (± SE, range)	Duration (days)* ANC<100/uL (± SE, range)
Control	15.0±1.67	5.4±0.15[a] (4-6)	7.4±3.12[b] (2-16)	9.6±0.20[a] (8-11)	8.8±0.37[b] (8-10)
Leukine	23.3±6.57	6.6±0.68[a] (4-17)	11.6±0.55[c] (7-15)	9.2±0.36[d] (7-12)	5.9±0.79[e] (2-10)

@ Includes both survivors and nonsurvivors.
# Includes data from animals that developed neutropenia.
*Note that durations do not include data from decedent animals unless recovery occurred prior to death, nor from animals that did not develop neutropenia.
a n=18, b n=5, c n=14, d n=17, e n=13

[Source: Table 14 on page 1907 of the Applicant's study report]

Descriptive statistics for nadir and duration of thrombocytopenia are presented in Table 34 and

Table 35.

Table 34 Analyses on platelet related parameters, $LD_{50\text{-}60/60}$ cohort, Study TSK0144

Treatment	Nadir # (Platelet/uL) (± SE)	Duration (days)* <20,000/uL (± SE, range)
Control	6944.4±1326.7	6.0±0.62[a] (2-12)
Leukine	11,805.6±1821.7	4.8±0.46[b] (2-11)

Includes both survivors and nonsurvivors.
*Note that durations do not include data from decedent animals unless recovery occurred prior to death, nor from animals that did not develop thrombocytopenia.
a n=17, b n=28

[Source: Table 5 on page 1901 of the Applicant's study report]

Table 35 Analyses on platelet related parameters, $LD_{70\text{-}80/60}$ cohort, Study TSK0144

Treatment	Nadir # (Platelet/uL) (± SE)	Duration (days)* <20,000/uL (± SE, range)
Control	5000.0±1057.2	6.8±1.11[a] (5-10)
Leukine	4722.2±955.9	6.6±0.59[b] (2-10)

Includes both survivors and nonsurvivors.
*Note that durations do not include data from decedent animals unless recovery occurred prior to death, nor from animals that did not develop thrombocytopenia.
a n=4, b n=15

[Source: Table 16 on page 1910 of the Applicant's study report]

Subgroup Analysis by Sex

The mortality rates by sex were presented in Table 36. The observed cohort-wise mortality rates of the control groups for males appeared more consistent with the target lethal doses of 50-60% and 70-80%, respectively. Compared to males, females appeared to have higher mortality rates in both the control and Leukine groups and larger control-Leukine differences. For the $LD_{50\text{-}60/60}$ cohort, the sex difference of the control-Leukine differences was not substantial; for the $LD_{70\text{-}80/60}$ cohort, it should be noted that the female or male control-Leukine differences was observed and calculated based on small sample sizes of 9 in the control group and 9 in the Leukine group.

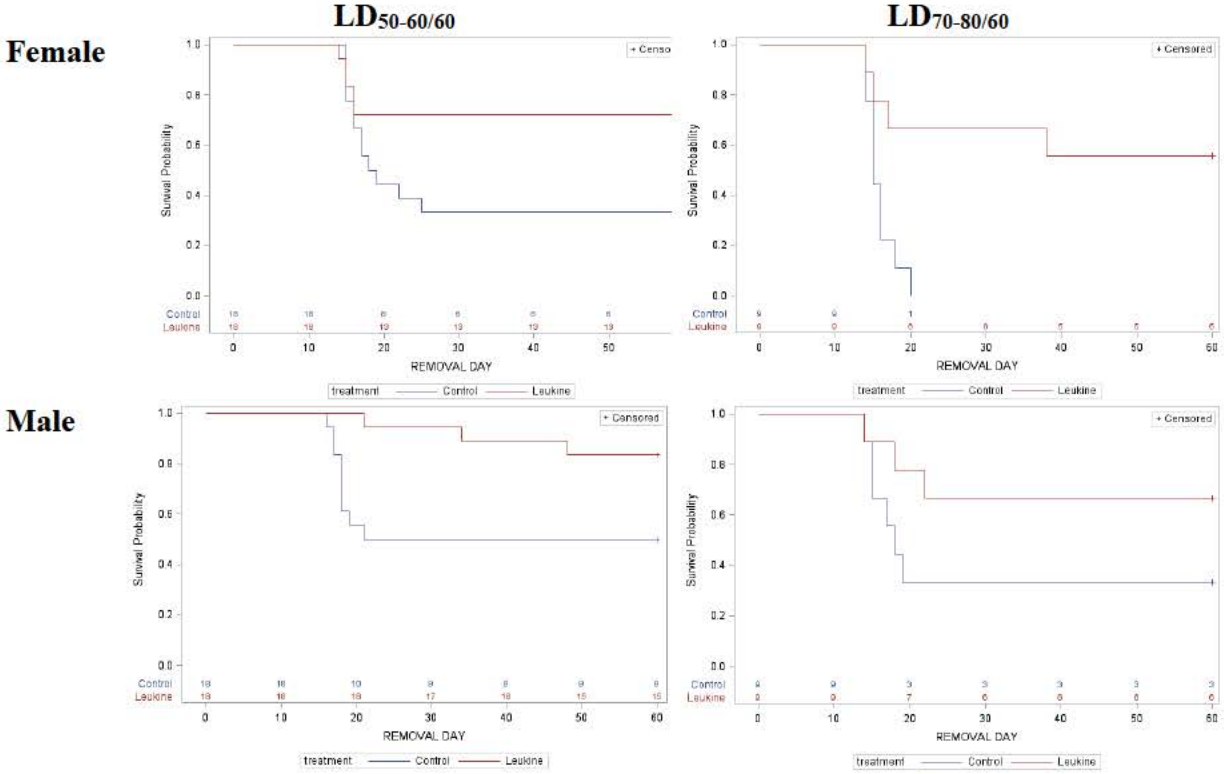
Table 36 Mortality rates by sex, Study TSK0144

Mortality Rate	$LD_{50\text{-}60/60}$			$LD_{70\text{-}80/60}$		
Treatment Group	**Control**	**Leukine**	**Control-Leukine Difference**	**Control**	**Leukine**	**Control-Leukine Difference**
Female	67% (12/18)	28% (5/18)	39%	100% (9/9)	44% (4/9)	56%
Male	50% (9/18)	17% (3/18)	33%	67% (6/9)	33% (3/9)	34%

[Source: selected from results on pages 1- 2 of the Applicant's December 12, 2017 responses to information request]

The Kaplan-Meier curves in Figure 18 demonstrated survival advantage over time of over control under each cohort and sex combination.

Figure 18 Study TSK0144 Kaplan-Meier curves by sex



[Source: statistical reviewer]

The Applicant's analyses by sex on neutrophil and platelet related parameters (not shown here) were based on small sample sizes or sometimes very small subsets of the study population, for example, duration of neutropenia for female in the control group was only based on two animals that developed neutropenia, which greatly limits the ability to generalize the analysis results. All analyses by sex were post-hoc and exploratory in nature. There is no compelling evidence that a specific sex benefits differently from Leukine.

[redacted] Assessment of Efficacy Across Trials

Study TSK0144 demonstrated the survival benefits of Leukine injected 48 hours after TBI over control. The findings from Study TSK0144 supported the Applicant's proposed indication of [redacted]. (b)(4) In the exploratory study FY14-045, the mortality rate (71%) for the control group deviated from the targeted rate of 50%, which raised the question of study quality; the study results are deemed less reliable.

8.1.4. Additional Efficacy Considerations

There is no biologic or clinical explanation for a non-significant comparison between the group that received Leukine starting one day after radiation and the group that received control in Study FY14-045. Study TSK0144 did not include a treatment group that received Leukine starting one day after radiation, therefore it remains unclear whether Leukine applied from one day after TBI could have statistically significant survival benefit too.

8.2. Review of Safety

No new clinical studies were conducted in support of this application. Clinical safety information to support use of Leukine in the ARS setting was drawn from existing clinical safety data from studies conducted to support approval of Leukine for other indications. The application also relies on the clinical experience since the initial approval of Leukine in approximately (b)(4) patients.

The safety of the product in the pediatric population for the ARS indication is provided by the summarized limited pediatric exposure in legacy clinical trials for various diseases, as well as a recent literature review conducted by the Applicant.

The current safety profile of Leukine is summarized in the product labeling. The most common adverse reactions to Leukine are fever, nausea, diarrhea, vomiting, injection site reactions, pain affecting (chest, abdomen, back and joints), thromboembolic events and dyspnea.
The most serious adverse reactions include hypersensitivity and other infusion elated reactions, effusions and capillary leak syndrome, supraventricular arrhythmias, leukocytosis, potential stimulatory effect on malignant cells, development of anti-drug antibodies, serious adverse reactions in infants who receive the formulation containing benzyl alcohol preservative. Due to the sensitivity to radiation of rapidly dividing hematopoietic precursor cells, Leukine should not be administered prior to radiation exposure.

8.2.1. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Leukine is not approved outside of the US. The estimated number of patients exposed to the product since initial approval is approximately (b)(4) The overall safety profile of Leukine is summarized in the product labeling.

The most serious adverse reactions have been identified in the postmarketing setting. These include hypersensitivity and other infusion related reactions, effusions and capillary leak syndrome, supraventricular arrhythmias, leukocytosis, potential stimulatory effect on malignant cells, development of anti-drug antibodies, serious adverse reactions in infants due to benzyl alcohol preservative.

Expectations on Safety in the Postmarket Setting

In a mass casualty event, the ability to reliably estimate a patient's radiation absorbed dose and obtain baseline CBC will be limited. Given the known safety profile of Leukine, and the need to initiate therapy as soon as possible after TBI, the dosing and administration section of the labeling will recommend that the start of Leukine treatment not be delayed until exposure to myelosuppressive doses of radiation (> 2 Gy) is confirmed. Follow up clinical and laboratory evaluation would determine if the administration of Leukine should be continued.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

Based on statistical evidence in Study TSK0144, Leukine significantly (one-sided p-value = 0.0018) decreased mortality rate of non-human primates at 60 days after total body irradiation of 655 cGy. There are no statistical issues with the confirmatory efficacy Study TSK0144; there is marginal information regarding the efficacy of Leukine when administered in the first 24 hours after total body irradiation.

8.4. Conclusions and Recommendations

The approval of Leukine for (b)(4) is based on the results of two efficacy studies in non-human primates

(NHP) in conjunction with the clinical safety and efficacy of Leukine in myelosuppression induced by chemotherapy or total body irradiation (TBI). Pharmacokinetic (PK) studies in healthy and irradiated NHP, and PK studies in healthy adult humans were used for the selection of a Leukine dose to provide exposures in humans that exceed those observed in the animal efficacy studies. Pediatric use for the H-ARS indication was determined based upon a population PK study, pediatric experience, and extrapolation from adult data.

The efficacy study providing primary support was a randomized, blinded, vehicle-controlled study in 72 NHP exposed to a dose of TBI (~655 centigrays [cGy]) expected to be lethal in 50% of exposed animals in 60 days (LD50/60 dose). The animals received minimal supportive care (fluids, antimicrobials) and were treated with Leukine or vehicle control beginning 48 hours after exposure to irradiation. A statistically significant improvement in survival was shown in the Leukine group compared to the vehicle group. Exploration of higher TBI doses (713 cGy) in NHP showed higher survival in the Leukine group compared to vehicle control group.

The unanimous recommendation from this multidisciplinary review team is for approval of the sBLA under the animal efficacy rule. The efficacy studies of Leukine are particularly notable for showing a treatment effect with delay in starting treatment for up to 48 hrs, up to an LD_{70-80} dose of TBI and in the presence of minimal supportive care.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was needed for this sNDA.

10 Pediatrics

This product received orphan designation. The Applicant submitted a request for waiver of pediatric studies. The Applicant is not required to conduct pediatric studies.

The safety of Leukine for use in the pediatric patients with ARS is expected to be similar to the experience cited in the labeling. The adverse reactions reported in pediatric patients are generally consistent with reactions reported in adults.

The use of Leukine to increase survival in pediatric patients acutely exposed to myelosuppressive doses of radiation is based on extrapolation from: efficacy studies conducted in animals; clinical safety and efficacy data on the use of Leukine in pediatric patients for autologous or allogeneic bone marrow transplantation following myelosuppressive chemotherapy with or without total body irradiation; and data on use of Leukine in treatment of delayed neutrophil recovery or graft failure.

Modeling and simulation were used to derive Leukine dosing regimens that are predicted to provide pediatric patients with exposure comparable to the observed exposure in adults receiving 7 mcg/kg. The recommended doses for pediatric patients based on body weight are: 7 mcg/kg in pediatric patients weighing greater than 40 kg; 10 mcg/kg in pediatric patients weighing 15 kg to 40 kg; and 12 mcg/kg in pediatric patients weighing less than 15 kg.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The prescribing information was revised to be consistent in format to the Physician Labeling Rule and the Pregnancy and Lactation Labeling Rule. The agreed upon labeling is reflected in the final Prescribing Information.

12 Risk Evaluation and Mitigation Strategies (REMS)

None are needed.

13 Postmarketing Requirements and Commitment

Postmarketing studies
For products approved under the Animal Rule, the applicant must conduct postmarketing studies to verify and describe the drug's clinical benefit and safety when such studies are feasible and ethical if an exigency arises. 21 CFR 601.91(b)(1)

To meet this regulatory requirement, the applicant submitted a synopsis for a protocol that

would obtain real world demonstration of the safety and efficacy of the product in the event of a radiation / nuclear event. The protocol is entitled, [redacted](b)(4)

14 Division Director (DMIP)

The Division Director concurs with the unanimous recommendation by the discipline reviewers that the supplemental BLA be approved.

15 Division Director (OCP)

Not Applicable for this efficacy supplement.

16 Division Director (OB)

Not Applicable for this efficacy supplement.

17 Appendices

17.1. Financial Disclosure

Not applicable as no new clinical data was submitted.

17.2. Clinical Pharmacology Appendix (Technical documents supporting OCP recommendations)

17.2.1. Population PK

Model assessment

The applicant's popPK model included single dose human intensive PK data from 99 healthy adults given SC dosing [redacted](b)(4) formulation in studies 15367 and 309404

(Table 26). The model had one compartment, an absorption delay into the depot with first order absorption from the depot to the central compartment, linear elimination, and a covariate effect of body weight on clearance and volume. Body weight in the dataset ranged from 51-115 kg (Table 27).

When the model was fit to the dataset consisting of studies 15367 and 309404 (final model), model parameters had acceptable precision (RSE% and bootstrap), acceptable residual variability, and acceptable shrinkage values (Table 37). The model described the observed data well through 12 hours postdose, with overprediction of concentrations >12 hours after the last dose (Figure 19). Concentration-time profiles in individual subjects were predicted well (data not shown, see pages 211-215, \\cdsesub1\evsprod\bla103362\0030\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\poh0547\study-poh0547.pdf).

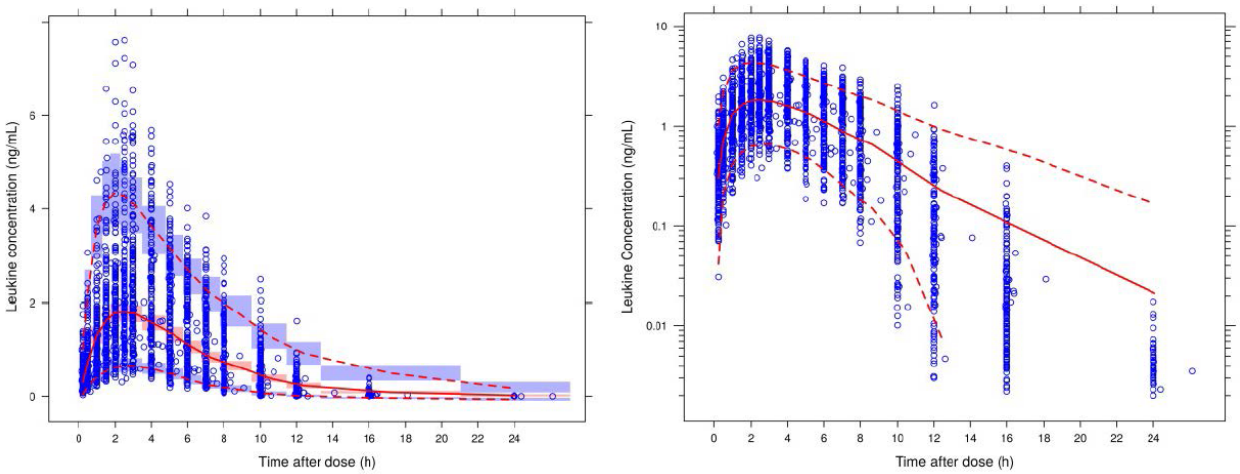
Table 37 Final population PK model parameters.

Parameter	Estimate (RSE%)	median [95% CI] (bootstrap)	Shrinkage (%)
CL/F (L/h)	26.6 (3.84%)	26.6 [25.2, 28.8]	1.68
V/F (L)	66.0 (3.87%)	65.9 [61.8, 72.1]	24.0
KA (/h)	0.395 (3.02%)	0.395 [0.372, 0.423]	34.0
ALAG1 (h)	0.083 (10.5%)	0.084 [0.067, 0.102]	23.8
$(WT/76.8)^{COV}$, CL/F	1.11 (15.4%)	1.14 [0.755, 1.50]	NA
$(WT/76.8)^{COV}$, V/F	1.90 (11.2%)	1.91 [1.44, 2.43]	NA
Interindividual variability (CV%)			
IIV (CL/F)	32.6% (14.4%)	32.2% [27.7%, 36.5%]	2.28
IIV (V/F)	41.4% (16.3%)	40.9% [34.1%, 47.8%]	23.4
IIV (KA)	34.3% (14.8%)	34.0% [28.8%, 39.5%]	34.2
IIV (ALAG1)	52.1% (30.4%)	50.9% [35.9%, 67.8%]	29.2
Residual variability			
σ1 (proportional)	27.2% (12.1%)	26.9% [24.1%, 30.6%]	5.07
σ2 (additive)	0.046 (46.5%)	0.046 [0.026, 0.074]	5.07

CL/F, apparent clearance; V/F, apparent volume of distribution, KA, absorption rate constant; ALAG1, lag time; WT, weight; COV, covariate; IIV, inter-individual variability; RSE, relative standard error; CI, confidence interval; CV, coefficient of variation; NA, not applicable

Source: Page 5, popPK report, \\cdsesub1\evsprod\bla103362\0030\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\poh0547\study-poh0547.pdf. The final model refers to model parameters obtained from fitting the model to a dataset consisting of studies 15367 and 309404.

Figure 19 Final[1] population PK model visual predictive check.



Source: Page 26, popPK report, \\cdsesub1\evsprod\bla103362\0030\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\poh0547\study-poh0547.pdf. [1]The final model refers to model parameters estimated using a dataset consisting of studies 15367 and 309404.

While model performance was acceptable, the model was overall not acceptable due to concerns over the sargramostim analytical assay in study 15367. In a sensitivity analysis, removal of study 15367 from the popPK dataset resulted in no significant change to population clearance or volume, a significant change to the estimate for the clearance-body weight exponent (from 1.11 to 0.597,Table 38, Table 39), and no significant change to goodness-of-fit (Figure 20, Figure 21).

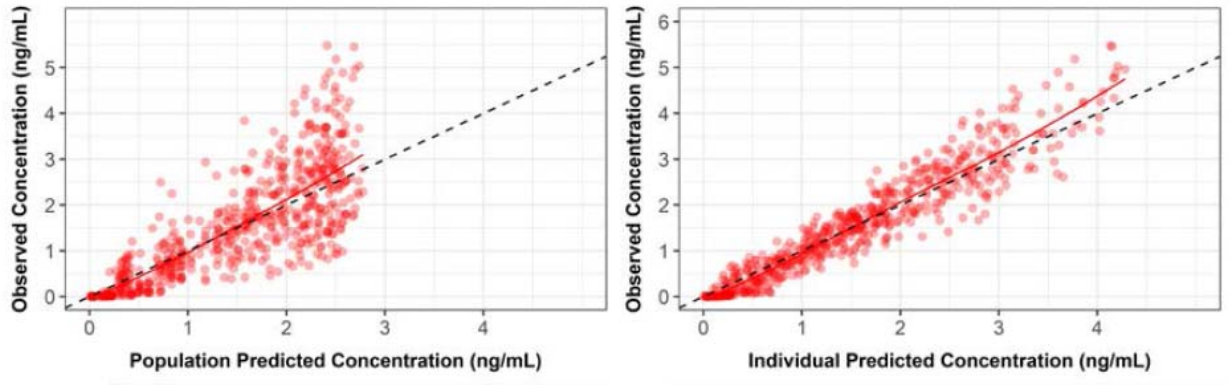
Table 39 Final model popPK parameters estimated with[1] and without[2] study 15367 in the popPK dataset.

	Final model in submission	Final model using a dataset after excluding < 3xLLOQ or > High QC samples in study 15367	Final model using a dataset after excluding study 15367
Subject number (N)	99	99	39
[redacted]			
		Population PK Parameter Estimate	
CL/F (L/h)	26.6	26.5	22.0
V/F (L)	66.0	67.3	64.3
KA (/h)	0.395	0.385	0.322
ALAG1 (h)	0.083	0.075	0.088
(WT/76.8)COV, CL/F	1.11	1.04	0.597
(WT/76.8)COV, V/F	1.90	1.83	1.77
		Interindividual variability CV%	
IIV (CL/F)	32.6%	32.1%	26.7%
IIV (V/F)	41.4%	39.1%	40.4%
IIV (KA)	34.3%	33.3%	30.6%
IIV (ALAG1)	52.1%	57.4%	27.8%
		Residual variability CV%	
σ1 (proportional)	27.2%	25.2%	18.8%
σ2 (additive)	0.046	0.066	0.201

CL/F, apparent clearance; V/F, apparent volume of distribution; KA, absorption rate constant; ALAG1, lag time; WT, weight; COV, covariate; IIV, inter-individual variability; LLOQ, lower limit of quantification; QC, quantification concentration; CV, coefficient of variation.
a: LLOQ and high QC in study 15367 are [redacted], respectively. The total numbers of concentration samples of study 15367 and the other study in the dataset are [redacted] respectively. The numbers of concentration samples used in the Final model in submission for study 15367 and the other study are [redacted]. The number of concentration samples ≥ LLOQ & < 3 × LLOQ, and > high QC for study 15367 and the other study in the dataset are [redacted], respectively.

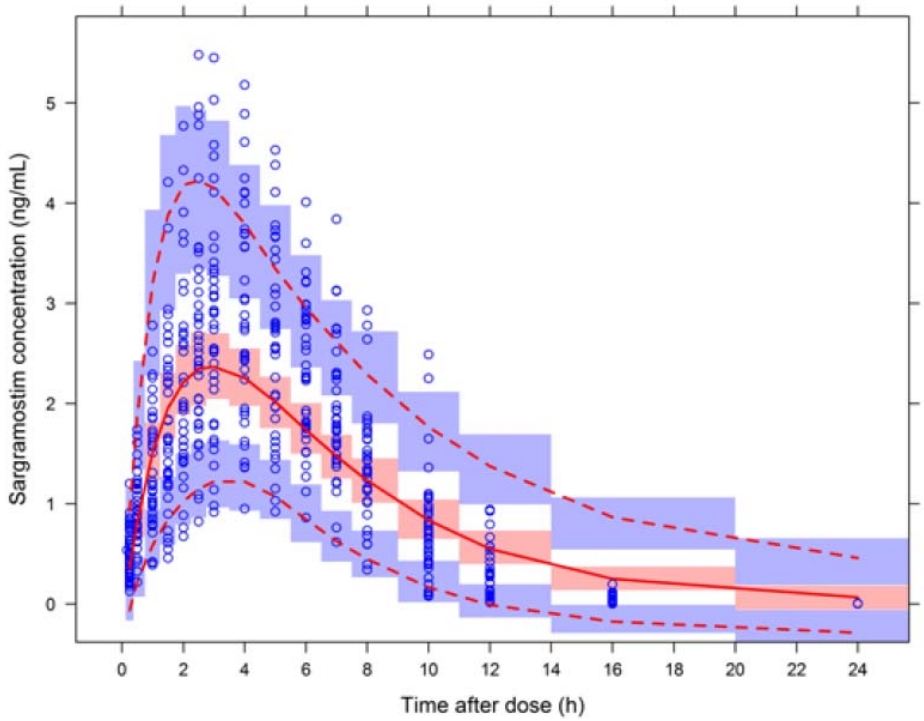
Source: Page 14, \\cdsesub1\evsprod\bla103362\0043\m1\us\111-info-amend\response-info-req-20180213.pdf.
[1]The final model refers to model parameters estimated using a dataset consisting of studies 15367 and 309404.
[2]The "Final model using a dataset after excluding study 15367" in our terminology refers to the revised model.

Figure 20 Revised model[1] - goodness-of-fit plots.



Source: page 3, \\cdsesub1\evsprod\bla103362\0047\m1\us\111-info-amend\eff-info-amend-20180227.pdf.
[1]The revised model refers to model parameters estimated using a dataset consisting of study 309404 only.

Figure 21 Revised model - visual predictive check.

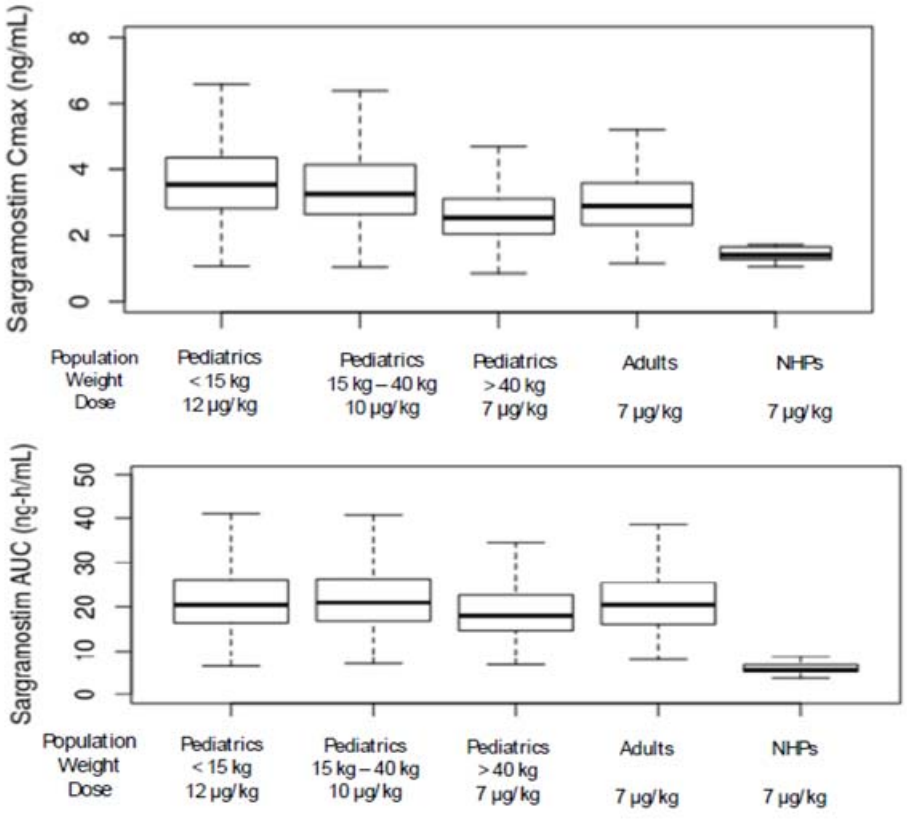


Source: page 4, \\cdsesub1\evsprod\bla103362\0047\m1\us\111-info-amend\eff-info-amend-20180227.pdf.
[1]The revised model refers to model parameters estimated using a dataset consisting of study 309404 only.

Simulations

Based on the final model, exposures associated with efficacy in monkeys are predicted to be exceeded in almost all humans (98% of humans based on Cmax, 100% of humans based on AUC, (Figure 22, Figure 23). The median fold difference in human versus monkey Cmax is 1.9-fold and 3.6-fold for AUC (Table 40).

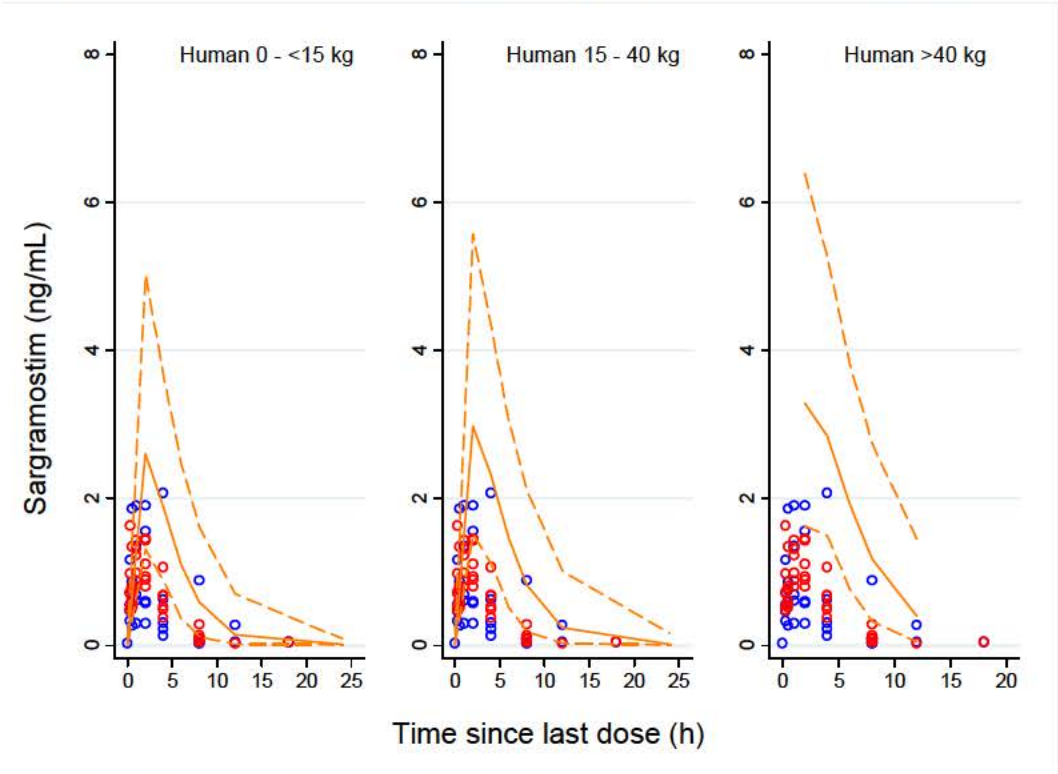
Figure 22 Final model[1] - observed sargramostim exposures in monkeys corresponding to the efficacious dose in monkeys and predicted sargramostim exposures in humans corresponding to the proposed human dosage regimen.



AUC adults and children = $AUC_{0\text{-}24}$; AUC NHP = AUC_{last};
Due to the short $t_{1/2z}$, AUC_{last} and $AUC_{0\text{-}24}$ are the same in NHPs
Black solid line: median; Box: 25th-75th percentiles; Whiskers: 5th to 95th percentiles

Source: page 37, \\cdsesub1\evsprod\bla103362\0030\m2\27-clin-sum\summary-clin-pharm.pdf.
[1]The final model refers to model parameters estimated using a dataset consisting of studies 15367 and 309404.

Figure 23 Final model[1] - observed sargramostim concentration-time profiles in monkeys corresponding to the efficacious dose in monkeys and predicted sargramostim concentration-time profiles in humans corresponding to the proposed human dosage regimen.



Source: Plotted by reviewer from DDK0110 Bioanalytical dataset, \\cdsesub1\evsprod\bla103362\0030\m4\datasets\ddk0110\tabulations\legacy\bioanal.xpt, DDK0111 Bioanalytical dataset, \\cdsesub1\evsprod\bla103362\0030\m4\datasets\ddk0111\tabulations\legacy\bioanal.xpt, PopPK adult simulation dataset, \\cdsesub1\evsprod\bla103362\0030\m5\datasets\poh0547\analysis\legacy\programs\adult-sim-predictions.txt.
Blue = healthy monkeys; red = irradiated monkeys; orange = predicted human 5th, 50th, and 95th percentiles.
[1]The final model refers to model parameters estimated using a dataset consisting of studies 15367 and 309404.

Table 40 Final model[1] - sargramostim Cmax and AUC fold differences (human / monkey) for observed exposures in monkeys after a single dose of 7 mcg/kg/day SC and predicted exposures in humans after a single SC dose under the proposed human dosage regimen for H-ARS.

									Fold difference (human / monkey)	
Species	Age	N[2]	Single SC dose (mcg/kg)	Body weight category (kg)	Observed Cmax (ng/mL)	Observed AUC24h (ng*h/mL)	Predicted Cmax (ng/mL)	Predicted AUC24h (ng/mL)	Cmax	AUC24h
Monkey	Adult	(b)(4)	7	NA	1.4 (1.1, 3.2)	5.6 (3.6, 8.5)	NA	NA	NA	NA
Human adult	Adult		7	>40	NA	NA	3.0 (1.7, 4.8)	21.3 (11.9, 34.2)	1.8 (1.1, 3.0)	3.7 (2.2, 6.2)
Human	Pediatric		7	>40	NA	NA	2.4 (1.3, 3.9)	15.8 (7.9, 27.1)	1.4 (0.8, 2.4)	2.7 (1.4, 4.9)
Human	Pediatric		10	15 - 40	NA	NA	3.4 (1.8, 5.6)	22.6 (11.1, 39.9)	2.0 (1.1, 3.5)	3.9 (2.0, 7.3)
Human	Pediatric		12	0 - <15	NA	NA	4.1 (2.2, 6.9)	27.3 (13.5, 47.5)	2.4 (1.4, 4.3)	4.6 (2.5, 8.7)
Total									**1.9 (1.0, 3.6)**	**3.6 (1.8, 7.4)**

Source: Reviewer's analysis. Monkey Cmax and AUC24h values are mean (min, max) calculated from study DDK0110 dataset \\cdsesub1\evsprod\bla103362\0030\m4\datasets\ddk0110\tabulations\legacy\toxicok.xpt and study DDK0111 dataset \\cdsesub1\evsprod\bla103362\0030\m4\datasets\ddk0111\tabulations\legacy\toxicok.xpt. Human Cmax and AUC24 values are median (5th, 95th percentile) calculated from the applicant's pediatric simulation dataset (\\cdsesub1\evsprod\bla103362\0030\m5\datasets\poh0547\analysis\legacy\programs\pediatric-sim2-indiv-exposure.txt) and adult simulation dataset (\\cdsesub1\evsprod\bla103362\0030\m5\datasets\poh0547\analysis\legacy\programs\adult-sim-individual-exposures.txt). Fold difference (human / monkey), reported as median (5th, 95th percentile), was calculated by dividing each simulated patient's Cmax or AUC by the mean Cmax or AUC in monkeys.

[1]The final model refers to model parameters estimated using a dataset consisting of studies 15367 and 309404.

[2]Note in the applicant's analysis (page 36, \\cdsesub1\evsprod\bla103362\0030\m2\27-clin-sum\summary-clin-pharm.pdf) the pediatric simulations are for a total (b)(4) subjects vs a total (b)(4) pediatrics subjects present in the pediatric simulation datset. Mean predicted pediatric PK parameters are similar in both datasets.

17.2.2. Bioanalytical methods

We reviewed sargramostim ligand binding assays used in the monkey and human PK studies. ELISA assay [redacted] was used in monkey PK studies DDK0110 and DDK0111. [redacted] was used in human PK study 15367. ELISA assay [redacted] was used in human PK study 309404. We found assays [redacted] and [redacted] to be acceptable. Due to issues with method validation, we found [redacted] to be unacceptable (6.2.2).

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/s/

LISA M SKARUPA
04/03/2018

LIBERO L MARZELLA
04/03/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ENVIRONMENTAL ASSESSMENT

103362Orig1s5240

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biotechnology Products

MEMORANDUM

DATE:	March 19th, 2018
BLA:	103362
SUPPLEMENT:	5240
FROM:	Brian Roelofs, Ph.D., Product Quality Reviewer CDER/OPQ/OBP/DBRR II
THROUGH:	Xianghong Jing, Ph.D., Product Quality Team Leader CDER/OPQ/OBP/DBRR II
PRODUCT:	Leukine (Sargramostim/rhuGM-CSF) recombinant human granulocyte macrophage colony stimulating factor (rhuGM-CSF) expressed in yeast belonging to the class of leukocyte growth factors that stimulate development of hematopoietic cells.
ROUTE OF ADMIN:	Subcutaneous
INDICATION:	This Supplement: - Hematopoietic Syndrome of Acute Radiation Syndrome (H-ARS) Previously Approved: - Following induction chemotherapy in acute myelogenous leukemia - Mobilization and following transplantation of autologous peripheral blood progenitor cells - Myeloid reconstitution after autologous bone marrow transplantation - Myeloid reconstitution after allogeneic bone marrow transplantation - Bone marrow transplantation failure or engraftment delay
DOSE REGIMEN:	- Adults and pediatric patients weighing >40 kg: 7 mcg/kg - Pediatric patients 15 kg to 40 kg: 10 mcg/kg - Pediatric patients <15 kg: 12 mcg/kg
STRENGTHS:	- For injection (lyophilized powder): 250 mcg of sargramostim, white powder in a single-patient use vial (OBP recommendation is multiple-dose) for reconstitution - Injection (solution): 500 mcg per mL clear, colorless solution of sargramostim in single-patient vials (OBP recommendation is multiple-dose)
SPONSOR:	Sanofi-Aventis U.S., LLC
CLINICAL DIVSION:	CDER/OHOP/DHP
REVIEW TEAM:	Product Quality: Brian Roelofs

RPM: Lisa Skarupa

BACKGROUND:

On September 29th, 2017, the sponsor submitted supplement 5240 to request regular approval of Leukine for the treatment [redacted] (b)(4) This request is based on the demonstrated efficacy of sargramostim in a nonhuman primate (NHP) animal model of H-ARS and the supportive data from clinical trials of sargramostim following exposure to myelosuppressive chemotherapy with or without total body irradiation in FDA-approved indications, and safety and efficacy from pediatric patients in off-label uses.

This review concerns the environmental assessment the sponsor submitted in the supplement (sequence #839, eCTD0030).

ADMINISTRATIVE INFORMATION

Environmental Assessment

Sanofi-Aventis U.S. LLC is claiming a categorical exclusion from the preparation of an environmental assessment (EA) for Leukine pursuant to 21 CFR Part 25, subpart C, Categorical Exclusions, Section 25.31 (c), Human drugs and biologics, since this application is for marketing approval of a biologic product comprised of substances that occur naturally in the environment and approval of this action would not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. Sargramostim is a glycoprotein comprised of 127 naturally-occurring amino acids which are considered to be readily metabolized in humans and degraded in the environment.

In addition, to Sanofi-Aventis's knowledge, no extraordinary circumstances exist, as referenced in 21 CFR 25.21, since no adverse effect or other significant effect on the quality of the human environment is predicted from approval of this submission.

This is considered appropriate.

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/s/

BRIAN A ROELOFS
03/19/2018

XIANGHONG JING
03/19/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

OTHER REVIEW(S)

103362Orig1s5240

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs
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 Drug Evaluation IV (ODE IV)
Office of New Drugs (OND)

Through: Mona Khurana, M.D., Pediatric Team Leader,
John Alexander, M.D., M.P.H., Deputy Director,
DPMH, ODE IV, OND

To: Division of Hematology Products (DHP)
Division of Medical Imaging Products (DMIP)

Drug: Leukine (sargramostim)

Application Number: BLA 103362/Supplement 5240 (S-5240)

Applicant: Sanofi-Aventis U.S., LLC

Approved Indications:

- Use following induction chemotherapy in older adult patients with acute myelogenous leukemia (AML) to shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death.
- The mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis, following transplantation of autologous peripheral blood progenitor cells.

- Acceleration of myeloid recovery in patients with non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL), and Hodgkin's disease undergoing autologous bone marrow transplantation (BMT).
- Acceleration of myeloid recovery in patients undergoing allogeneic BMT from human leukocyte antigen (HLA)-matched related donors.
- Use in patients who have undergone allogeneic or autologous BMT in whom engraftment is delayed or has failed.

Proposed Indication: (b)(4)

Dosage Form: 250 mcg lyophilized sargramostim in vials or
500 mcg/mL liquid sargramostim in vials

Route of Administration: Administered intravenously or by subcutaneous injection based on indication.

Approved Dosing Regimens:

- Neutrophil recovery following chemotherapy in AML:
  - 250 mcg/m^2/day administered intravenously over a 4-hour period.
- Mobilization of peripheral blood progenitor cells:
  - 250 mcg/m^2/day administered intravenously over 24 hours or subcutaneous injection once daily.
- Post peripheral blood progenitor cell transplantation:
  - 250 mcg/m^2/day administered intravenously over 24 hours or subcutaneous injection once.
- Myeloid reconstitution after autologous or allogeneic BMT:
  - 250 mcg/m^2/day administered intravenously over a 2-hour period.
- BMT failure or engraftment delay:
  - 250 mcg/m^2/day for 14 days as a 2-hour intravenous infusion.

Proposed Dosing Regimen:

- Patients acutely exposed to myelosuppressive doses of radiation, administer once daily as subcutaneous injection:
  - Adults and children weighing > 40 kg: 7 mcg/kg
  - Children 15 kg to 40 kg: 10 mcg/kg
  - Children < 15 kg: 12 mcg/kg

Consult Request:
DMIP consulted DPMH to conduct a labeling review for this efficacy supplement and to provide recommendations for pediatric use information in labeling.

Materials Reviewed:

- DPMH Consult request (dated October 18, 2017)
- Current Leukine (sargramostim) labeling (February 10, 2017 in Drugs@FDA)
- Applicant's proposed labeling (submitted September 29, 2017 in DARRTS)

I. Background

Leukine (sargramostim) is a recombinant human granulocyte-macrophage colony stimulating factor (GM-CSF) originally FDA approved on March 5, 1991. Leukine is currently approved in adults only for multiple hematologic indications related to treatment for AML, ALL, NHL, Hodgkin's disease, BMT and peripheral blood progenitor cell transplantation as noted above. There are no pending pediatric postmarketing requirements (PMRs) for these indications.

On September 29, 2017, Sanofi submitted an efficacy supplement seeking approval for a new indication to (b)(4) Of note, FDA granted Sanofi orphan designation for sargramostim for treatment of individuals acutely exposed to myelosuppressive doses of radiation (H-ARS) on November 9, 2016.

II. Neonatal Benzyl Alcohol Toxicity

Both liquid Leukine injection and the Bacteriostatic Water for Injection used to reconstitute lyophilized Leukine contain benzyl alcohol as a preservative. Benzyl alcohol 0.9% when used in flush solutions has been shown to cause severe metabolic acidosis, encephalopathy and respiratory depression with gasping leading to death in low birth-weight premature infants at doses of 99 to 234 mg/kg/day.[1] Benzyl alcohol toxicity has been particularly associated with very low birth-weight premature neonates, because of the greater dose of benzyl alcohol relative to body weight, and because the metabolic and excretory pathways for benzyl alcohol are still immature.[2] Additionally, infants in hospital

[1] Gershanik, J et al. The Gasping Syndrome and Benzyl Alcohol Poisoning. *NEJM.* 1982; 307:1384-1388.
[2] Hiller J, Benda G, Rahatzad M, et al. Benzyl alcohol Toxicity: Impact on mortality and intraventricular hemorrhage among very low birth-weight infants. *Pediatrics.* 1986; 77(4):500-6.

settings may be exposed to benzyl alcohol through routine administration of multiple medications and may be at increased risk of toxicity.[3]

In May, 1982, FDA in conjunction with the American Academy of Pediatrics (AAP) and the Centers for Disease Control and Prevention (CDC) issued a Drug Bulletin[4] containing strong recommendations to warn pediatricians and hospital personnel against using fluids preserved with benzyl alcohol as intravascular flush solutions and to not use diluents preserved with benzyl alcohol to reconstitute or dilute drugs for neonates. In addition, the AAP recommended that medications containing benzyl alcohol also be avoided in newborn infants when possible.[5] In 1997, the AAP Committee on Drugs published a review of the available published literature on neonatal benzyl alcohol toxicity and reported that most therapeutic agents, other than large-volume fluids, contain amounts of benzyl alcohol smaller than those associated with neonatal death; however, the effects of lower amounts of benzyl alcohol have not been adequately studied.[6]

III. Pediatric Assessment

A. Acute Exposure to Myelosuppressive Doses of Radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [H-ARS])

Because human clinical trials cannot be ethically conducted to study treatment of myelosuppression from radiation exposure resulting in the hematopoietic syndrome of ARS, the applicant relied on published literature and on data from a non-human primate model of radiation-induced myelosuppression to support pediatric approval for the H-ARS indication in this BLA supplement. Additionally, the applicant is relying on supportive safety and efficacy data from clinical studies in adults and pediatric patients undergoing autologous or allogeneic bone marrow transplantation following myelosuppressive chemotherapy with or without total body irradiation, including safety data from studies including 190 preterm neonates who received lyophilized sargramostim intravenously at doses ranging from 0.05 mcg/kg/day to 10 mcg/kg twice daily for up to 28 days.

The applicant submitted safety data from 15 clinical studies with 332 pediatric patients, including 1) recipients of bone marrow or peripheral stem cell transplant, 2) other

[3] Anderson C, Ng J, et al. Benzyl alcohol poisoning in a premature newborn infant. *Am J Obstet Gynecol.* 1984;148:344-346.
[4] FDA Drug Bulletin, August 1982.
[5] American Academy of Pediatrics, Committee on Fetus and Newborn, Committee on Drugs. Benzyl Alcohol: Toxic Agent in Neonatal Units. *Pediatrics.* 1983;72(3):356-8.
[6] AAP Committee on Drugs. Inactive ingredients in pharmaceutical products: update. *Pediatrics*. 1997;99 (2);268-78.

oncology indications or bone marrow insufficiency/failure, 3) Crohn's disease, or 4) prevention of nosocomial infection in premature neonates in the BLA supplement. The applicant noted, however, that pediatric patients in the first two indication groups had bone marrow suppression and low white blood cell counts before treatment with sargramostim, whereas patients with Crohn's disease and premature neonates tended to have normal white blood cell counts at study entry. The patients comprising the safety database were administered daily doses up to 1500 mcg/m^2/day as daily 2-hour intravenous infusions and 2000 mcg/m^2/day in divided doses twice daily by subcutaneous administration, which exceeds the proposed recommended dosages and resulted in a safety profile consistent with the known safety profile of the product.

The applicant established the proposed weight-based pediatric dosing for the H-ARS indication from modeling and simulation to match adult exposures comparing the observed exposure in non-human primates at the efficacious dose of 7 mcg/kg.

DPMH agrees with DMIP that the efficacy data in non-human primates and clinical data in adults and pediatric patients supports use of Leukine down to birth for the H-ARS indication.

B. Acceleration of Myeloid Reconstitution in Autologous Peripheral Blood Progenitor Cell and Bone Marrow Transplantation and Allogeneic Bone Marrow Transplantation; Treatment of Delayed Neutrophil Recovery or Graft Failure Following Allogeneic or Autologous Bone Marrow Transplantation

DHP requested that the applicant provide data on safety and efficacy of Leukine in the pediatric population to determine whether additional pediatric use information could be included in labeling for the currently approved hematologic indications. The applicant provided data from four of the pivotal studies supporting the adult indications for allogeneic and autologous bone marrow transplantation and delayed neutrophil recovery or graft failure in which pediatric patients were also enrolled. Placebo-controlled studies supporting the adult indications for autologous and allogeneic bone marrow transplantation included 12 and 23 pediatric patients, respectively, ranging from 2 to 18 years of age. Additionally, 36 pediatric patients ranging from 1 to 18 years of age were included in a retrospective study using historical controls for the treatment of delayed neutrophil recovery or graft failure following allogeneic or autologous bone marrow transplantation. Dosing in all three studies (250 mcg/m^2 administered intravenously daily) was identical in adult and pediatric patients. Furthermore, the efficacy and safety demonstrated in pediatric patients in these studies were consistent with those seen in adults.

While the BLA supplement includes dosing and safety information for patients down to birth, which is supportive of use for the H-ARS indication, the data in neonates was derived from use in non-hematologic disorders. Furthermore, the pediatric data reviewed by DHP from the four pivotal studies noted above for allogeneic and autologous bone marrow transplantation and delayed neutrophil recovery or graft failure only enrolled one patient under 2 years of age. Therefore, based on DHP's analysis of these data, they concluded that safe and effective use for these indications had been established for patients 2 years and older, but not for patients less than 2 years of age. (See the DHP Consultative Review by Aviva Krauss, MD dated March 8, 2018 in DARRTS).

DPMH agrees with DHP that efficacy can be extrapolated from adequate and well-controlled studies in adults for acceleration of myeloid reconstitution in autologous and allogeneic bone marrow transplantation and treatment of delayed neutrophil recovery or graft failure based on the similar pathophysiology and treatment effect in adult and pediatric patients. The submitted dosing and safety data further support the use of Leukine in pediatric patients at the recommended dosages. Therefore, DPMH agrees with DHP that the submitted data are adequate to support the addition of labeling for these indications down to 2 years of age. (b)(4)

IV. DPMH Review of Pediatric Use Labeling:

This DPMH labeling review will focus on edits to Section 1 (Indications and Usage) and Subsections 5.9 (Risk of Serious Adverse Reactions in Infants due to Benzyl Alcohol Preservative) and 8.4 (Pediatric Use).

See Appendix 1 for the applicant's proposed labeling for Leukine dated September 29, 2017.

The autologous and allogeneic bone marrow transplantation, and the treatment of delayed neutrophil recovery or graft failure will include patients down to 2 years of age, while the H-ARS indications will include pediatric patients down to birth. Therefore, information regarding pediatric use for these indications should be placed throughout labeling. Furthermore, labeling should clearly describe the indications and age groups for which Leukine is and is not indicated. The Pediatric Use subsection (8.4) should summarize the

data used to establish safety and effectiveness in pediatric patients for these indications discussed above with appropriate cross-references to the more detailed descriptions of the clinical studies in section 14. Additionally, labeling in section 14, Clinical Studies, should include demographic data on the pediatric patients included in the studies supporting the respective indications that are approved for pediatric patients.

Because liquid Leukine and lyophilized Leukine reconstituted with Bacteriostatic Water contain benzyl alcohol as a preservative, language regarding the associated potential for neonatal toxicity (as discussed above) should be included in the Warnings and Precautions section and the Pediatric Use subsection. Prescribers should be advised to avoid use of these formulations and instead use Leukine reconstituted with sterile water whenever possible in neonates.

V. DPMH Actions and Labeling Recommendations:

DPMH reviewed the applicant's draft labeling and participated in the internal meetings held from December 2017 to February 2018. Recommended labeling for the pediatric population based on labeling discussions between DHP, DMIP and DPMH is provided per 21 CFR 201.57(c)(9)(iv) below. 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.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Acute Myeloid Leukemia Following Induction Chemotherapy

LEUKINE is indicated to shorten time to neutrophil recovery and to reduce the incidence of severe, life-threatening, or fatal infections following induction chemotherapy in adult patients 55 years and older with acute myeloid leukemia (AML).

1.2 Autologous Peripheral Blood Progenitor Cell Mobilization and Collection

LEUKINE is indicated in adult patients with cancer undergoing autologous hematopoietic stem cell transplantation for the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis.

1.3 Autologous Peripheral Blood Progenitor Cell and Bone Marrow Transplantation

LEUKINE is indicated for the acceleration of myeloid reconstitution following autologous peripheral blood progenitor cell (PBPC) or bone marrow transplantation in

adult and pediatric patients 2 years of age and older with non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) and Hodgkin's lymphoma (HL).

1.4 Allogeneic Bone Marrow Transplantation

LEUKINE is indicated for the acceleration of myeloid reconstitution in adult and pediatric patients 2 years of age and older undergoing allogeneic bone marrow transplantation from HLA-matched related donors.

1.5 Allogeneic or Autologous Bone Marrow Transplantation: Treatment of Delayed Neutrophil Recovery or Graft Failure

LEUKINE is indicated for the treatment of adult and pediatric patients 2 years and older who have undergone allogeneic or autologous bone marrow transplantation in whom neutrophil recovery is delayed or failed.

1.6 Acute Exposure to Myelosuppressive Doses of Radiation (H-ARS)

LEUKINE is indicated to increase survival in adult and pediatric patients from birth to 17 years of age acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [H-ARS]).

5 WARNINGS AND PRECAUTIONS

5.9 Risk of Serious Adverse Reactions in Infants Due to Benzyl Alcohol Preservative

Serious and fatal adverse reactions including “gasping syndrome” can occur in neonates and low birth weight infants treated with benzyl alcohol-preserved drugs, including LEUKINE injection (solution) or LEUKINE for injection (lyophilized powder) reconstituted with Bacteriostatic Water. The “gasping syndrome" is characterized by central nervous system depression, metabolic acidosis and gasping respirations.

Avoid administration of solutions containing benzyl alcohol (including LEUKINE injection [solution] or LEUKINE for injection [lyophilized powder] reconstituted with Bacteriostatic Water for Injection, USP [0.9% benzyl alcohol]) to neonates and low birth weight infants. Instead, administer lyophilized LEUKINE reconstituted with Sterile Water for Injection, USP *[see Dosage and Administration (2.7)]*.

If LEUKINE injection (solution) or LEUKINE for injection (lyophilized powder) reconstituted with Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol) must be used in neonates and low birth weight infants, consider the combined daily metabolic load of benzyl alcohol from all sources including LEUKINE (LEUKINE injection and LEUKINE for injection reconstituted with Bacteriostatic Water contain 11 mg and 9 mg of benzyl alcohol per mL, respectively). The minimum amount of benzyl alcohol at

which serious adverse reactions may occur is not known *[see Use in Specific Populations (8.4) and Dosage and Administration (2.7)]*.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of LEUKINE have been established in pediatric patients 2 years of age and older for autologous peripheral blood progenitor cells and bone marrow transplantation, allogeneic bone marrow transplantation, and treatment of delayed neutrophil recovery or graft failure. Use of LEUKINE for these indications in this age group is based on adequate and well-controlled studies of LEUKINE in adults, in addition to clinical data in 12, 23, and 36 pediatric patients, respectively *[See Clinical Studies (14.3, 14.4 and 14.5)]*. The pediatric adverse reactions were consistent with those reported in the adult population. The safety and effectiveness of LEUKINE for pediatric patients less than 2 years of age for autologous peripheral blood progenitor cells and bone marrow transplantation, allogeneic bone marrow transplantation, and treatment of delayed neutrophil recovery or graft failure have not been established.

The use of LEUKINE to increase survival in pediatric patients acutely exposed to myelosuppressive doses of radiation (H-ARS) is based on efficacy studies conducted in animals and clinical data supporting the use of LEUKINE in patients undergoing autologous or allogeneic BMT following myelosuppressive chemotherapy with or without total body irradiation. Efficacy studies of LEUKINE could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Modeling and simulation was used to derive dosing regimens that are predicted to provide pediatric patients with exposure comparable to the observed exposure in adults receiving 7 mcg/kg *[see Clinical Pharmacology (12.3)]*. The dose for pediatric patients is based on weight *[see Dosage and Administration (2.2)]*.

Safety and effectiveness in pediatric patients have not been established in:

- Acute Myeloid Leukemia: Neutrophil Recovery Following Induction Chemotherapy
- Autologous Peripheral Blood Progenitor Cell Mobilization and Collection

Avoid administration of solutions containing benzyl alcohol [including LEUKINE injection (solution) or LEUKINE for injection (lyophilized powder) reconstituted with Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol)] to neonates and low birth weight infants. Instead, administer lyophilized LEUKINE reconstituted with Sterile Water for Injection, USP *[see Dosage and Administration (2.7)]*.

Serious adverse reactions including fatal reactions and the “gasping syndrome” occurred in premature infants in the neonatal intensive care unit who received drugs containing benzyl alcohol as a preservative. In these cases, benzyl alcohol dosages of 99 to 234

mg/kg/day produced high levels of benzyl alcohol and its metabolites in the blood and urine (blood levels of benzyl alcohol were 0.61 to 1.38 mmol/L). Additional adverse reactions included gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Preterm, low birth weight infants may be more likely to develop these reactions because they may be less able to metabolize benzyl alcohol.

If LEUKINE injection (solution) or LEUKINE for injection (lyophilized powder) reconstituted with Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol) must be used in neonates and low birth weight infants, consider the combined daily metabolic load of benzyl alcohol from all sources including LEUKINE (LEUKINE injection [solution] and LEUKINE for injection [lyophilized powder] reconstituted with Bacteriostatic Water for Injection, USP [0.9% benzyl alcohol] contain 11 mg and 9 mg of benzyl alcohol per mL, respectively). The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known *[see Dosage and Administration (2.7)]*.

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/s/

ERICA D RADDEN
03/26/2018

MONA K KHURANA
03/29/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	March 19, 2018
To:	Ann Farrell, MD Director **Division of Hematology Products (DHP)** Libero Marzella, MD Director **Division of Medical Imaging Products**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** David Foss, PharmD, BCPS Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)** Rachael Conklin, MS, RN Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	LEUKINE (sargramostim)
Dosage Form and Route:	injection, for subcutaneous or intravenous use
Application Type/Number:	BLA 103362
Supplement Number:	S-5240
Applicant:	Sanofi-Aventis U.S. LLC

1 INTRODUCTION

On September 29, 2017, Sanofi-Aventis U.S. LLC submitted for the Agency's review a Prior Approval Supplement- Efficacy to their approved Biologics License Application (BLA) 103362/S-5240 for LEUKINE (sargramostim) Injection. The purpose of this supplement is to propose (b)(4) Additionally, the labeling will undergo conversion at this time in accordance with the Physicians Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on November 14, 2017, and The Division of Medical Imaging Products (DMIP) on January 24, 2018, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for LEUKINE (sargramostim) Injection.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the PPI and IFU was completed on December 18, 2017, and February 27, 2018.

2 MATERIAL REVIEWED

- Draft LEUKINE (sargramostim) Injection PPI and IFU received on September 29, 2017 and revised on March 8, 2018 and received by DMPP on March 8, 2018 and March 13, 2018.
- Draft LEUKINE (sargramostim) Injection Prescribing Information (PI) received on September 29, 2017, revised by the Review Division throughout the review cycle, and received by DMPP on March 8, 2018 and March 13, 2018.
- Approved LEUKINE (sargramostim) Injection labeling dated February 10, 2017.
- Approved NEUPOGEN (filgrastim) injection labeling dated June 29, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using

fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI and IFU document using the Arial font, size 10 and size 11, respectively.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- rearranged information due to conversion of the PI to Physicians Labeling Rule (PLR) format
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
03/19/2018

DAVID F FOSS
03/19/2018

RACHAEL E CONKLIN
03/20/2018

LASHAWN M GRIFFITHS
03/20/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 8, 2018

To: Cindy Welsh, M.D.
Division of Medical Imaging Products (DMIP)

Lisa Skarupa, Regulatory Project Manager, (DMIP)

Michele Fedowitz, Associate Director for Labeling, (DMIP)

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for Leukine (sargramostim)

BLA: 103362/Supplement 5240

In response to DMIP consult request dated January 24, 2018, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI)/Instructions for Use (IFU) for Leukine. This supplement (S5240) proposes the new indication: (b)(4) This review was done simultaneously as the PLR conversion done by DHP, which was reviewed by Rachael Conklin of OPDP on February 6, 2018.

PI:
OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DMIP on March 2, 2018, and are provided below.

PPI/IFU:
A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI/IFU will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

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/s/

DAVID F FOSS
03/08/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Memorandum

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
10903 New Hampshire Ave
Silver Spring, MD 20903

Memorandum to File

Date: March 6, 2018

From: Aviva Krauss, MD, Clinical Reviewer

Through: Donna Przepiorka, MD, PhD, Clinical Team Leader

Ann T. Farrell, MD, Division Director

To: Cynthia Welsh, MD, DMIP

Subject: Consultative Review requested 10/6/2017

Reference: BLA 103362- supplement for the proposed indication: of (b)(4)

Regulatory Background:

The current Leukine PI includes the following Indications for its use:

- Use Following Induction Chemotherapy in Acute Myelogenous Leukemia: for use following induction chemotherapy in older adult patients with AML to shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infection and infections resulting in death. The safety and efficacy of LEUKINE has not been assessed in patients with AML under 55 years of age.
- Use in Mobilization and Following Transplantation of Autologous Peripheral Blood Progenitor Cells: for the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis.
- Use in Myeloid Reconstitution After Autologous Bone Marrow Transplantation: for acceleration of myeloid recovery in patients undergoing allogeneic BMT from HLA-matched related donors.
- Use in Bone Marrow Transplantation Failure or Engraftment Delay: in patients who have undergone allogeneic or autologous bone marrow transplantation (BMT) in whom engraftment is delayed or has failed.

With the current supplement for H-ARS, the applicant has submitted a PI that is also revised entirely to be in PLR format.

1. Consult Question from DMIP to DHP

DMIP requests DHP's assistance with PLR conversion of labeling.

2. DHP Input:

Please see the final PI for revisions and final decisions regarding labeling, as labeling negotiations are still underway. In general, the following issues have been addressed:

1. We recommended revisions of the wording of some of the indications for clarity and consistency. The indications supported include:

- Acute Myeloid Leukemia Following Induction Chemotherapy: to shorten time to neutrophil recovery and to reduce the incidence of severe, life-threatening, or fatal infections following induction chemotherapy in adult patients 55 years and older with acute myeloid leukemia (AML).
    - This is based on Study 305, a randomized, double-blind, placebo-controlled study looking at the safety and efficacy of Leukine in patients aged 55 to 70 with acute non-lymphocytic leukemia. The primary endpoint was reduction in the median duration of severe neutropenia (ANC <500/mm^3).
- Autologous Peripheral Blood Progenitor Cell Mobilization and Collection: in patients with cancer undergoing autologous hematopoietic stem cell transplantation for the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis.
    - This is based on a retrospective review (referred to as "clinical/statistical report 1.0002, or 1995-02-01-New Indication Supplement v1 of 2 under license 1132 (Immunex) page 20/215.

Reviewer comment: This review could not be located anywhere in the EDR nor in the jackets requested from the document room. However, given the inclusion of these data in the initial approval of the PI, there is no reason to remove the indication or data from the PLR version.

- Autologous Peripheral Blood Progenitor Cell and Bone Marrow Transplantation: for the acceleration of myeloid reconstitution following autologous peripheral blood progenitor cell (PBPC) or bone marrow transplantation in patients with non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) and Hodgkin's lymphoma (HL).
    - This is based on Studies 301, 302 and 303, 3 randomized, double-blind, placebo-controlled studies in the following populations:
        - 301: following autologous bone marrow transplantation (BMT) in subjects with lymphoid malignancies, with a primary endpoint of time to ANC recovery to >100, 500 and 1000/mm3.
        - 302: following autologous BMT or peripheral stem cell transplantation (PSCT) following intensive chemotherapy or chemoradiotherapy for lymphoid malignancy, with the same primary endpoint.

Reviewer comment: it is noted that the results of this study, which had a large population of patients with Hodgkin Lymphoma (HL) showed a positive trend toward early neutrophil recovery but the results was not significant. This was part of the data reviewed at an advisory committee meeting and ultimately it was decided that the results still supported the indication.

        - 303: following autologous BMT in subjects with B-cell NHL, with the same primary endpoint of days to reach an ANC of 100, 500 and 1000/mm3
- Allogeneic Bone Marrow Transplantation: for the acceleration of myeloid reconstitution in patients undergoing allogeneic bone marrow transplantation from HLA-matched related donors.
    - This is based on study 9002, a randomized, double-blind, placebo-controlled study in patients undergoing HLA-identical sibling BMT, with the primary endpoint of days to reach ANC of 100, 500 and 1000/mm^3.
- Allogeneic or Autologous Bone Marrow Transplantation: Treatment of Delayed Neutrophil Recovery or Graft Failure: for the treatment of patients who have undergone allogeneic or autologous bone marrow transplantation in whom neutrophil recovery is delayed or failed.
    - This is based on Study 501, a prospective, non-randomized, open-label, historically controlled study investigating safety and efficacy of Leukine in patients with failure or delay of engraftment after

autologous and allogeneic BMT. The primary endpoint was difference in median survival between the Leukine treated patients compared to the historical controls.

2. Since it appears that the new indication extends to the pediatric population, we note that the W&P section should include the standard warning for products containing benzyl alcohol due to the risk of "gasping syndrome," and that this should be included in the highlights as well.
3. Based on the limited data available for review from the FDA review summary/advisory committee during the review of the initial BLA, (b)(4) "in adult patients 55 years and older with AML" since that is the population studied for that indication.
4. We requested that the applicant provide data on safety and efficacy of Leukine in the pediatric population to assess whether these populations can be included in the other indications or just the new indication, and consequently the wording of section 8.4. Based on Studies 301, 302, 501 and 9002, we have concluded that based on data in the pediatric population, safe and effective pediatric use has been established in the following indications, for patients 2 years of age and above:
    a. Autologous Bone Marrow Transplantation
    b. Allogeneic Bone Marrow Transplantation
    c. Allogeneic or Autologous Bone Marrow Transplantation: Treatment of Delayed Neutrophil Recovery or Graft Failure

The following is a summary of the findings supporting this decision.

a. <u>Autologous Bone Marrow Transplantation</u>

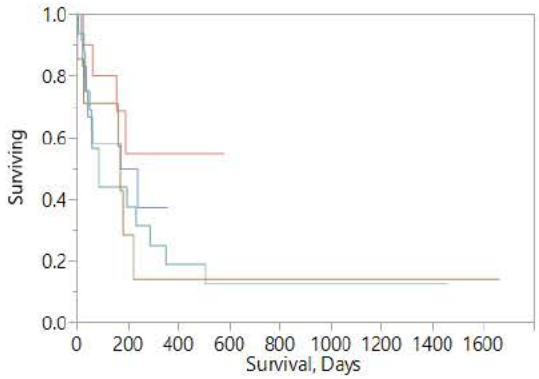
In studies 301 and 302, both adult and pediatric subjects were enrolled. Six of the 53 subjects who received Leukine were under the age of 18, including 4 children (2 to 12 years) and 2 adolescents (12 to 16 years). All were treated at a dose of 250 mcg/m2 administered IV daily. Six patients under the age of 18 received placebo. The median number of days to ANC >500/mm3 was 18.5 for those who received Leukine compared to 24.5 for the placebo group. These results were similar to those seen in the adults treated with Leukine on these studies. The toxicity profile was consistent with that reported in the adult population.

b. <u>Allogeneic Bone Marrow Transplantation</u>

Pediatric patients were eligible for inclusion on Study 9002, and 23 of the 109 subjects enrolled were under age 18; of these 11 were randomized to the Leukine arm, at a dose of 250 mg/m2 IV daily, including 6 children (2-12 years), 4 adolescents (12-16), and one 17-year-old. Twelve pediatric patients received placebo. The median number of days to ANC >500/mm3 was 13 for those who received Leukine compared to 17.5 for the placebo group. These results were similar to those seen in the adults treated with Leukine. The toxicity profile was consistent with that reported in the adult population.

c. <u>Allogeneic or Autologous BMT: Treatment of Delayed Neutrophil Recovery or Graft Failure</u>

Pediatric patients were eligible for inclusion on Study 501 as well, and 29 of the 104 patients who received LEUKINE on this study were under the age of 18 years, including 1 infant (under 2 years of age), 19 children (2-12 years), 8 adolescents (12-16), and one 17-year-old. As an analysis of pediatric outcomes was not performed, but the data was available in the CSR, FDA performed a survival analysis using Kaplan-Meier estimates for pediatric patients in the 4 groups (graft failure after allogeneic transplant, treated with Leukine, graft failure after autologous transplant, treated with Leukine, and historical control graft failures after allogeneic and autologous transplantation). Based on this analysis the efficacy of Leukine in pediatric patients treated on this study was improved compared to the pediatric historical controls as well:



Source: FDA analysis

The median survival in the 12 evaluable pediatric patients who were treated with Leukine for graft failure following autologous transplantation was 205.5 days, compared to 169 days in the 7 pediatric historical controls. The median survival in the 10 evaluable pediatric patients who were treated with Leukine for graft failure following allogeneic transplantation was not reached, compared to 86 days in 16 pediatric historical controls. The toxicity profile in the pediatric patients treated with Leukine was consistent with that reported in the adult population on this study.

Reviewer comment: In addition to the data described above from these studies to support these 3 indications, it should be noted that the BLA includes dosing and safety information for patients in patients down to age 4 months. Even if the efficacy data described above were not available, the biology of neutrophil recovery in these clinical scenarios is the same in pediatric and adult populations, and efficacy could have been extrapolated from the adult indications. Given the vast safety data available in pediatrics, all the available data support an extension to the pediatric population for the above indications. Although safety data down to the infant age group is available for other indications, it has not been reviewed by the Agency, and since Studies 301, 302, 501 and 9002 enrolled only 1 patient under the age of 2 years, these indications should be restricted to age 2 years and above.

5. We found no data from FDA review of the initial BLA that there should be a W&P regarding patients (b)(4) .
6. We found no data from FDA review of the initial BLA that Leukine (b)(4) we asked the applicant to provide this data and they were unable to do, so this has been removed.
7. (b)(4) .
8. Although many of the trials described in section 6 are placebo-controlled, and not designed with a statistical analysis plan to demonstrate superiority regarding elements other than increase in progenitor cells and/or neutrophil counts, we think that some of the descriptions included by the applicant are relevant to prescribers. Specifically, the lack of difference in relapse rates and 24-month survival between the treatment arms (6.1, autologous transplant patients) and (b)(4) are important elements of the use of Leukine in these clinical contexts. Further, the tables in section 6.1 should retain information on adverse reactions that occur in at least 5-10% of treated patients, even if there is less than a 5% difference between the treatment arms, to ensure that all adverse reactions with LEUKINE are included in the PI.
9. We recommend (b)(4) "Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biologic Products-Content and Format."

10. Per labeling guidance, we have changed the passive voice, where relevant, to active voice.

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/s/

AVIVA C KRAUSS
03/08/2018

DONNA PRZEPIORKA
03/08/2018

ALBERT B DEISSEROTH
03/08/2018

Division of Hematology Products (DHP) Labeling Review

NDA/BLA Number	BLA 103362 S-5240 (Sanofi Genzyme)
Supporting Document Number	0044
Proprietary Name **(nonproprietary name)**	LEUKINE® sargramostim
Receipt Date	9/29/17
PDUFA Goal Date	3/29/18
Review Classification	Priority
Proposed Indication (or current indication if unchanged)	Supplement 5240 proposes new indication being reviewed by DMIP [redacted](b)(4) PLR and PLLR updates are also proposed.
From	Virginia Kwitkowski, MS, ACNP-BC Associate Director for Labeling, DHP

Background of Application:

Sanofi/Genzyme submitted this supplemental BLA for Leukine (sarmgramostim), a leukocyte growth factor (initially approved in 1991), proposing a new indication [redacted](b)(4) Submission of an efficacy supplement triggers the requirement to revise labeling in accordance with the Physician's Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR). DMIP has consulted DHP to review the PLR and PLLR revisions in the proposed Prescribing Information because DHP is the primary BLA holder for this application. DHP held 4 multi-disciplinary labeling meetings to discuss and revise the Leukine PI before sending the revised PI to DMIP for their review and revision of the labeling text specific to the new indication. DMIP asked DHP to consider whether the existing Leukine indications could be revised to include pediatric indications. The DHP clinical team sent an information request to the Applicant requesting information about available pediatric data in the use of Leukine. The review of the response to this Information Request and the pediatric data is ongoing and is not captured in this review.

The following FDA staff participated in the review of the PI PLR and PLLR revisions:

- DHP: Michael Gwathmey (RPM), Donna Przepiorka (Clin TL), Aviva Krauss (Clinical Reviewer), Virginia Kwitkowski (Assoc. Director for Labeling). DHP Leadership involved Ann Farrell, Edvardas Kaminskas, and Albert Deisseroth.

- DHOT: Christopher Sheth (Pharm Tox TL), Michael Manning (Pharm Tox Reviewer),
- Clinical Pharmacology: Christy John (Clin Pharm Reviewer), Gene Williams (Clin Pharm TL)
- OPQ: Juhong Liu and Brian Roelofs (CMC).
- Labeling Development Team: Ann Marie Trentacosti

This review summarizes DHP's review of the PLR and PLLR labeling revisions. Given the ongoing negotiation process with the Applicant, all revisions are not captured by this review. We proposed labeling recommendations and edits in the Leukine prescribing information to ensure that the prescribing information is a useful communication tool for healthcare providers and uses clear, concise language; is based on regulations and guidances; and conveys the essential scientific information needed for the safe and effective use of Leukine.

Summary of Labeling Recommendations:

Labeling Section	Proposed Text (if applicable)	Proposed Revisions or Requests to Applicant
Throughout PI	Applicant proposed incorrect format for cross-references.	-Per the PLR Implementation Guidance, the preferred format for cross-references from one section of the PI to another, is the section heading followed by numerical identifier of the sections or subsections being referenced in parentheses; this information should be italicized and presented within brackets; e.g. *[see Warnings and Precautions (5.x)]*. Per the PLLR Labeling Guidance, the correct format for within section cross-references is the subsection heading within parentheses and italicized; e.g. *(see Data)*. - (b)(4).
Highlights, overall	(b)(4).	(b)(4)
Highlights, Product Title	(b)(4)	(b)(4) • LEUKINE® (sargramostim) for injection, for subcutaneous or intravenous use. • LEUKINE® (sargramostim) injection, for subcutaneous or intravenous use (b)(4)
Highlights, Recent	(b)(4)	(b)(4)

Major Changes	(b)(4)	(b)(4) . (b)(4)
Highlights and Section 1 of FPI, Indications and Usage	No change, except for new HARS indication.	Indications revised to clearly state intended use of product (b)(4) Where feasible, the ages of the indicated populations were added to each indication to improve clarity on the indicated population. We recommended to DMIP that they include the ages for the newly indicated population per OND policy.
Highlights, Dosage Forms and Strength	(b)(4)	Revised to: • For injection (lyophilized powder): 250 mcg of sargramostim in single-dose vial for reconstitution (3) • Injection (solution): 500 mcg per mL sargramostim in single-patient use vial (3) Rationale: Revised package type per current guidance and to provide a concise summary of dosage forms and strengths incorporate appropriate headings identifying the dosage forms ("for injection" and "injection") and the strength or potency of the dosage form in metric terms.
Highlights and FPI, Contraindications	(b)(4)	Removed (b)(4)
Highlights, Warnings and Precautions	Too long to provide here.	To reduce the length of HL, (b)(4) shortened the warnings that are left in HL.
Highlights, Adverse Reactions	(b)(4)	Revised to: "The most common adverse reactions (incidence >25%) were (6.1):" to reflect our current approach; removing source of data, name of drug, and

	[redacted] (b)(4)	including the cutoff rate for inclusion in the list (per PLR Guidance).
Highlights, Use in Specific Populations	[redacted] (b)(4)	Revised to reflect inclusion of the benzyl alcohol language and fetal harm; added pediatric bullet, and our current approach to lactation language. "•Pregnancy: Benzyl alcohol-free formulation recommended. May cause fetal harm. (8.1) •Pediatrics: In infants, avoid use of benzyl alcohol-containing solutions when feasible. (2.7, 5.10, 8.4) •Lactation: Advise women not to breastfeed. (8.2)"
Full Prescribing Information (FPI), Dosage and Administration	Too long to include	We revised the entire section to reflect (as much as possible) the organization of Section 1 (Indications), to avoid the use of error prone abbreviations and symbols, and to avoid the use of passive voice. [redacted] (b)(4) "benzyl alcohol" as it is our standard approach to include this in sections 5 and 8. Revised subsection 2.7 name to reflect contents of the section; "Preparation and Administration of LEUKINE".
FPI, Dosage Forms and Strengths	n/a	Revised package terms per guidance (see earlier discussion); [redacted] (b)(4) Deleted text that was duplicative from other sections [redacted] (b)(4)
FPI, Contraindications	n/a	Asked the applicant to revise per the Contraindications guidance, [redacted] (b)(4) .
FPI, Warnings and Precautions	Too long to include	Revised the Warnings and Precautions section to avoid the use of passive voice and to reflect the recommendations in the Warnings and Precautions Guidance. Added new warning "Risk of Severe Myelosuppression When Leukine Administered within 24 hours of Chemotherapy or Radiation". [redacted] (b)(4)

		[redacted] (b)(4) We recommended [redacted] (b)(4) . We revised the warning on risks associated with benzyl alcohol to be consistent with the recommendations in the Labeling Review Tool (internal document).
FPI, Adverse Reactions	Too long to include	We proposed revisions to reorganize this section to make the AR data presented in [redacted] (b)(4) We recommended the inclusion of a description of the overall clinical trial database from which the ARs are obtained (per the Adverse Reactions guidance). Revised [redacted] (b)(4)
FPI, Drug Interactions	n/a	FDA recommended the [redacted] (b)(4)
FPI, Use in Specific Populations	Too long to include	Sections 8.1 and 8.2 were heavily revised to be consistent with the current approach to products that contain benzyl alcohol (per Labeling Review Tool), our current approach to the presentation of animal and human data for pregnancy and lactation, and background risk statement for pregnancy. Section 8.4, Pediatric Use is currently under revision as the clinical team reviews the submitted pediatric data. The revisions are being made to be consistent with the Pediatric Labeling guidance.

		Section 8.5, Geriatric Use: We asked the Applicant to revise per the Geriatric Labeling Guidance.
FPI, Overdosage	OVERDOSAGE (b)(4)	Per 21CFR 201.57(c)(11), the overdosage section must be based on human overdosage data (or animal data if no human data are available. We recommended revisions to this section. (b)(4) Doses up to 100 mcg/kg/day (4,000 mcg/m2/day or 16 times the recommended dose) were administered to four patients in a Phase 1 uncontrolled clinical study by continuous IV infusion for 7 to 18 days. Increases in WBC up to 200,000 cells/mm3 were observed. Adverse events reported were dyspnea, malaise, nausea, fever, rash, sinus tachycardia, headache, and chills. All these events were reversible after discontinuation of LEUKINE. In case of overdosage, discontinue LEUKINE therapy and monitor the patient for WBC increase and respiratory symptoms.
FPI, Description	(b)(4)	We asked the Applicant to revise this section per 21CFR201.57(c)(12). This section must contain: qualitative and/or quantitative ingredient information (see 21CFR 610.61); if product is sterile, a statement of that fact; Chemical name and structural formula of drug. We deleted the last two sentences as they were not relevant to this

	(b)(4)	section. "LEUKINE (sargramostim) injection and for injection for subcutaneous or intravenous use is a recombinant human granulocyte-macrophage colony stimulating factor (rhu GM-CSF) produced by recombinant DNA technology in a yeast (S. cerevisiae) expression system. LEUKINE is a glycoprotein of 127 amino acids characterized by three primary molecular species having molecular masses of 19,500, 16,800 and 15,500 daltons."
FPI, Clinical Pharmacology	Text was not consistent with current Clinical Pharmacology labeling guidance.	We asked the Applicant to revise this section to be consistent with the Clinical Pharmacology labeling guidance (https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm109739.pdf)
FPI, Clinical Studies	Too long to include	We revised the headings to reflect the indication revisions. We asked the Applicant to add protocol identifiers, NCT#; (b)(4)
FPI, References (15)	Applicant proposed (b)(4) .	(b)(4)
FPI, How	(b)(4)	We asked the Applicant to include (per 21CFR 201.57) the

Supplied/Storage and Handling	(b)(4).	(b)(4)
FPI, Patient Counseling Section	Too long to include.	We revised this section to include the new risks identified, to use the current format recommendations, and to remove the " (b)(4) .

Given that the scientific review of the labeling is ongoing, our labeling recommendations in this review should be considered preliminary and may not represent DHP's final recommendations for the Leukine PI.

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/s/

VIRGINIA E KWITKOWSKI
03/07/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 2/6/2018

To: Michael Gwathmey, Regulatory Project Manager, DHP

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Mathilda Fienkeng, Team Leader, OPDP

Subject: OPDP Labeling Comments for LEUKINE® (sargramostim) for injection, for subcutaneous or intravenous use

BLA: 103362/S-5240

In response to DHP's consult request dated November 14, 2017, OPDP has reviewed the proposed product labeling (PI) for LEUKINE® (sargramostim) for injection, for subcutaneous or intravenous use (Leukine) S-5240. This supplement convers the label to PLR format.

PI and PPI/Medication Guide/IFU: OPDP's comments on the proposed labeling are based on the draft PI emailed to OPDP on January 23, 2018, and are provided below.

Thank you for your consult. If you have any questions, please contact Rachael Conklin at 240-402-8189 or rachael.conklin@fda.hhs.gov.

PI

Section	Statement from Draft (if applicable)	OPDP Comment
2.7 Preparation and Administration of Leukine	(b)(4)	Should the statement " (b)(4) This statement seems to be redundant given that the first sentence of this paragraph instructs providers to (b)(4) Additionally, given the addition of the instruction not to " (b)(4) the statement (b)(4)
5.3 Risk of Severe Myelosuppression When LEUKINE Administered Within 24 hours of Chemotherapy or Radiotherapy	"Due to the potential sensitivity of rapidly dividing hematopoietic progenitor cells, LEUKINE **should not be administered** simultaneously with cytotoxic chemotherapy or radiotherapy or within 24 hours preceding or following chemotherapy (b)(4))	We note that the Dosage and Administration section specifies, (b)(4) We recommend that the language in these sections be revised to be consistent—i.e., the recommendation should be "do not use" or "should not be administered" in both places. Given that there is a Warning and Precaution for this risk, OPDP recommends using the stronger "do not administer" language, but we defer to DHP. E.g., Due to the potential sensitivity of rapidly dividing hematopoietic progenitor cells, **do not administer** LEUKINE simultaneously with cytotoxic chemotherapy."
5.3 Risk of Severe Myelosuppression When LEUKINE Administered Within 24 hours of Chemotherapy or Radiotherapy	"The patients randomized to LEUKINE had significantly higher incidence of adverse reactions, including higher mortality and a higher incidence of grade 3 and 4 infections and grade 3 and 4 thrombocytopenia."	If available, OPDP recommends including incidence rate data to characterize the "significantly higher incidence of adverse reactions," "higher mortality," and "higher incidence of grade 3 and 4 infections and grade 3 and 4 thrombocytopenia" seen with Leukine. E.g., "The patients randomized to LEUKINE had significantly higher incidence of adverse reactions (X% vs X%) . . ."

14.4 Allogeneic Bone Marrow Transplantation	"Accelerated myeloid engraftment was associated with significant laboratory and clinical benefits."	OPDP recommends deleting this sentence, which is promotional in tone.
14.4 Allogeneic Bone Marrow Transplantation	"LEUKINE-treated patients also had a shorter median duration of posttransplant IV antibiotic infusions, and a shorter median number of days to last platelet and RBC transfusions compared to placebo patients, but none of these differences reached statistical significance."	OPDP recommends revising to include the rates for these endpoints. E.g., "LEUKINE-treated patients also had a shorter median duration of posttransplant IV antibiotic infusions (X time vs X time) . . ."

Fifty-three (53) have been withheld as (b)(4), draft labeling, immediately following this page.

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/s/

RACHAEL E CONKLIN
02/06/2018

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:	December 18, 2017
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 103362/ S-5240
Product Name and Strength:	Leukine (sargramostim) injection Lyophilized 250 mcg/ vial Liquid 500 mcg/ mL
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Sanofi Genzyme
Submission Date:	September 29, 2017
OSE RCM #:	2017-2326
DMEPA Safety Evaluator:	Idalia E. Rychlik, PharmD.
DMEPA Team Leader:	Hina Mehta, PharmD.

1 REASON FOR REVIEW

The Division of Hematology Products (DHP) requested that DMEPA review the proposed Prescribing Information (PI), Patient Information and Instructions for Use (IFU) for Luekine (sargramostim) BLA 103362/ S-5240 to determine if it is acceptable, from a medication error perspective. Sanofi Genzyme submitted an efficacy supplemental Biologics Application (sBLA) proposing the addition of a new indication and converting the existing prescribing information (PI) to the Physician's Labeling Rule (PLR) format. The proposed indication is (b)(4)

1.1 REGULATORY HISTORY

Leukine (sargramostim) was approved in 1991 and currently is indicated to accelerate neutrophil recovery following exposure to myelosuppressive chemotherapy with or without radiation treatment, for treatment of engraftment delay or failure after bone marrow transplantation, and for mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis. Orphan Drug Designation was granted for treatment with sargramostim to "increase survival of individuals acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)" on November 9, 2016.

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 our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

This review assessed the PI, Patient Information and IFU as they pertain to medication error. Specifically, changes that were made to the product indication and dosage and administration information. We performed a risk assessment of the labels and labeling changes to identify deficiencies that may lead to medication errors. Utilizing the FAERS database, DMEPA analyzed medication errors that occurred with the currently marketed product. Our review identified zero relevant reports for this review. (See Appendix E for additional details). We also searched the Institute for Safe Medication Practices (ISMP) newsletters—returning two articles—and previous DMEPA reviews of Leukine and Sargramostim—returning zero reviews.

We identified areas in the PI that can be improved to increase readability of important information.

4 CONCLUSION & RECOMMENDATIONS

We find the Patient Information guide and IFU acceptable from a medication error perspective and have no further recommendations at this time.

DMEPA identified areas in the PI labeling that can be improved to promote the safe use of the product. We provide further recommendations for the Division in Section 4.1.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. HIGHLIGHTS OF PRESCRIBING INFORMATION

1. **Dosage Forms and Strength**
    i. Revise the dosage forms and strengths to align with dosing administration units to read as follows:
        - For injection: 250 mcg of lypholized powder in a single-dose vial for reconstitution
        - Injection: 500 mcg/ mL in a single-dose vial

A. PRESCRIBING INFORMATION

a. To avoid a ten-fold misinterpretation of dose, as referenced in ISMP's List of Error-Prone Abbreviations, Symbols and Dose Designations, (b)(4) (b)(4)
b. We recommend eplacing all dangerous symbols and spelling out intended meaning (e.g. (b)(4) throughout the PI to prevent misinterpretation and confusion.
c. To align with the units of measure described in the Dosage and Administration section of the PI, product strength should be expressed consistently throughout the PI.
    i. Remove (b)(4)
d. Remove all information not directly related to (b)(4) (b)(4)
e. Remove all information not directly related to (b)(4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Leukine that Sanofi Genzyme submitted on September 29, 2017.

Table 2. Relevant Product Information for Leukine	
Initial Approval Date	3/5/1991
Active Ingredient	sargramostim
Indication	(b)(4)
Route of Administration	(b)(4)
Dosage Form	(b)(4)
Strength	250 mcg/ vial, 500 mcg/ mL
Dose and Frequency	Neutrophil recovery following chemotherapy in AML: 250 mcg/m2/day administered intravenously over a 4-hour period. Mobilization of peripheral blood progenitor cells: 250 mcg/m2/day administered intravenously over 24 hours or subcutaneous injection once daily. Post peripheral blood progenitor cell transplantation:

	250 mcg/m2/day administered intravenously over 24 hours or subcutaneous injection once. Myeloid reconstitution after autologous or allogeneic BMT: 250 mcg/m2/day administered intravenously over a 2-hour period. BMT failure or engraftment delay: 250 mcg/m2/day for 14 days as a 2-hour intravenous infusion.
How Supplied	(b)(4)
Storage	(b)(4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On 12/14/2017, we searched DMEPA's previous reviews using the terms, leukine and sargramostin. Our search identified 0 previous reviews.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On 12/14/2017, 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)	Acute Care
Search Strategy and Terms	Match Exact Word or Phrase: Leukine

D.2 Results

Our search identified 2 articles, of which 0 described errors relevant for this review. One article highlighted a name confusion medication error between Neumega and Neupogen, the patient in question was concurrently on Leukine. The second article referenced using Leukine to reduce the risk of neutropenia for a patient who mistakenly received a fluorouracil infusion.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

On 12/14/2017, we searched FAERS using the criteria in the table below and identified 26 cases. We individually reviewed the cases, and 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.[a] We excluded 26 cases because they described errors of accidental exposure (n=1), overdose (n= 3), under-dose due to administration error (n=1), wrong drug (n=3), dose omission (n-4), wrong strength (n=1), expired product (n=1), allergy (n=1), incorrect route of administration (n=2), clinical trial medication errors (n=2), drug preparation error (n=1), reports not specifying the occurrence of a medication error (n=2) and reports lacking complete medication error information (n=4).

Criteria Used to Search FAERS	
Initial FDA Receive Dates:	- 12/14/2017
Product Name:	Leukine
Product Active Ingredient (PAI):	Sargramostim
Event:	SMQ *Medication errors* (Narrow)
Country (Derived):	USA

E.2 Results

Our search identified 26 cases, of which 0 described errors relevant for this review.

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.

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.

[a] 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.

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,[b] along with postmarket medication error data, we reviewed the following Leukine (sargramostim) labels and labeling submitted by Sanofi Genzyme on September 29, 2017.

- Prescribing Information (Image not shown)

G.2 Labeling

Prescribing Information
\\cdsesub1\evsprod\bla103362\0030\m1\us\annotatedpi.doc

Patient Information and Instructions for Use
\\cdsesub1\evsprod\bla103362\0030\m1\us\annotatedppi.pdf

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

IDALIA E RYCHLIK
12/18/2017

MISHALE P MISTRY on behalf of HINA S MEHTA
12/18/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ADMINISTRATIVE

103362Orig1s5240

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	pre-sBLA
Meeting Date and Time:	June 1, 2017
Meeting Location:	White Oak Campus, Bldg 22, Conference Room 1315
Application Number:	(b)(4)
Product Name:	Leukine® sargramostim (recombinant human granulocyte macrophage-colony stimulating factor (rhu GMCSF))
Proposed Indication:	(b)(4)
Sponsor Name:	Sanofi Genzyme
Meeting Chair:	Libero Marzella, M.D., Ph.D., Division Director
Meeting Recorder:	Lisa Skarupa, Senior Regulatory Health Project Manager

FDA ATTENDEES

Libero Marzella, M.D., Ph.D., Division Director, DMIP
Alex Gorovets, M.D., Deputy Division Director, DMIP
Nushin Todd, M.D., Ph.D., Clinical Team Leader, DMIP
Cynthia Welsh, M.D., Clinical Reviewer, DMIP
Michele Fedowitz, M.D., Associate Director of Labeling, DMIP
Adebayo Laniyonu Ph.D., Pharmacology/Toxicology Team Leader, DMIP
Islam Younis, Ph.D., Clinical Pharmacology Team Leader, DCPIV
Brad Leissa, M.D., Deputy Director, CTECS
Rosemary Roberts, M.D., Director, CTECS
Alla Shapiro, M.D., Ph.D., Clinical Reviewer, CTECS
Kelly Ngan, Pharm.D., Senior Regulatory Project Manager, CTECS
Susan McDermott, M.D., Clinical Team Leader, CTECS
Zishan (Susan) Zhao, Ph.D., Senior Advisor, MCMi PHSAT (OCET)
Virginia Kwitkowski, MS, ACNP-BC, Associate Director of Labeling, CDER/OHOP/DHP
Mona Khurana, M.D., Pediatric Team Leader, DPMH
Denise Pica-Branco, Ph.D., Senior Regulatory Health Project Manager
Xiangmin Zhang, Ph.D., Statistical Reviewer, OTS/OB/DBI
Sue Jane Wang, Ph.D., Acting Deputy Director, OTS/OB/OBI
Lisa Skarupa, Senior Regulatory Project Manager, DMIP

Reference ID: 4246824

Sanofi Genzyme Attendees:
Joan Keutzer, PhD, Vice President and Head, Integrated Solutions, Rare Disease Franchise
Alison McVie-Wylie, PhD, Senior Director, Nonclinical Pharmacology
Emily LaCasse, BS, Scientist, Nonclinical Pharmacology
Gary Emmons, PhD, Senior Director, Pharmacokinetics, Dynamics and Metabolism, & Interdisciplinary
Pharmacometric Program, Translational Medicine & Early Development
Representative from Biostatistics and Programming Department
(b)(4)
(b)(4)
Sunil Gupta, MD, Associate Vice President, Global Regulatory Affairs
Cordula Schwarz, MS, Manager, Global Regulatory Affairs
(b)(4)

1.0 BACKGROUND

Sanofi Genzyme submitted their Meeting Request on March 9, 2017. The meeting was granted and scheduled on June 1, 2017. The meeting package was submitted on April 24, 2017. The following are the preliminary responses to their nine questions. The following minutes reflect the meeting discussions for Questions 2, 4, and 9, for the detailed responses to the other questions please see the attached Sponsor response received May 31, 2017.

2. DISCUSSION

Non-Clinical

Question 1: The confirmatory NHP study, TSK0144, sponsored by Sanofi Genzyme to support the H-ARS indication has been completed and demonstrated that sargramostim treatment significantly decreased the mortality rate at Day 60 (primary endpoint). The study results were also positive for the key secondary endpoints (including ANC parameters and overall survival). In addition, the nonclinical program included 4 other NHP studies. The first 2 studies, DDK0110 and DDK0111, were sponsored by Sanofi Genzyme and were Good Laboratory Practice (GLP)-compliant pharmacokinetic (PK) studies performed to identify a sargramostim dose that resulted in a systemic exposure in NHPs (with and without irradiation) that was less than or similar to that achieved with the 250 µg/m2 human dose. The third study, TSK0143, was sponsored by Sanofi Genzyme and was a non-GLP exploratory/ pilot study that provided preliminary evidence of efficacy in the H-ARS NHP model, as measured by decreased mortality rate at Day 45 in sargramostim-treated NHPs. The fourth study, FY14-045, was a GLP-compliant, placebo-controlled, pivotal efficacy study that was sponsored by (b)(4) (b)(4) (b)(4) This study demonstrated that sargramostim significantly reduced mortality rate at Day 60 in the NHP H-ARS model. Based on the results from the TSK0144 study and the data from the overall nonclinical development

program, Sanofi Genzyme proposes to submit an efficacy supplement of sargramostim for the H-ARS indication.

Does the Agency agree that the nonclinical data from the confirmatory NHP TSK0144 study, in addition to data from the overall nonclinical development program, provide an adequate basis for filing and review of the sargramostim sBLA for the H-ARS indication?

FDA Response to Question 1:
Yes. We agree that the nonclinical data from the confirmatory NHP TSK0144 study, in addition to data from the overall nonclinical development program, provides an adequate basis for submission of the sargramostim sBLA for the H-ARS indication.

Meeting Discussion:
Sanofi Genzyme had no further comments, no meeting discussion.

Non-Clinical and Clinical Pharmacology

Question 2:

At the Type C meeting (FDA meeting minutes from the 28-Apr-2016 Pre-IND Type C Meeting), Sanofi Genzyme asked if the Agency concurred that the 7 µg/kg/day dose of sargramostim administered SC to NHPs results in an exposure profile that is similar to or less than that observed in humans after the dose of 250 µg/m2/day. The Agency responded that it was premature to make this conclusion and requested a comparison of the PK exposure profiles with the anticipated variability in both NHPs and humans. The Agency recommended Sanofi Genzyme develop a population PK (PopPK) model by incorporating all PK data available, and conduct simulations using the model to predict the PK profiles of sargramostim in adult patients exposed to radiation.

Sanofi Genzyme is conducting a PopPK analysis on available and relevant clinical PK data. As noted by the Agency in the Type C meeting minutes (FDA meeting minutes from the 28-Apr-2016 Pre-IND Type C Meeting), there is a difference in the systemic concentration values of sargramostim between the studies. Sanofi Genzyme has determined this is likely due to differences in the bioanalytical assay methodology. Of the 3 different methods that had been used, one assay method used a similar technology platform and reagents as that used in the NHP studies. Therefore, Sanofi Genzyme proposes to combine PK data from healthy volunteer studies using similar assays as used in the NHP studies to develop a PopPK model for sargramostim with the intent to demonstrate that the recommended dose provides sufficient exposure in comparison to the NHP data.

Does the Agency agree with the strategy for the proposed PopPK analysis of relevant clinical PK data in combination with the NHP study results to support the recommended sargramostim dose(s) for treatment of H-ARS?

FDA Response to Question 2:
The proposed approach is acceptable in principle based on the provided justification. (b)(4)

(b)(4)

Meeting Discussion:

- **Sanofi Genzyme reiterated their response to preliminary responses submitted on 05/31/2017 explaining why:**

(b)(4)

- **DMIP acknowledged the response and requested Sanofi Genzyme include the detailed justification in the sBLA submission.**

- **DMIP will leave it to Sanofi Genzyme to decide whether to include** (b)(4) **in the POPPK analysis. DMIP requested that Sanofi Genzyme provide justification in the sBLA submission if they decide not to include the study.**

Non-Clinical Efficacy and Safety Analysis

Question 3:

The approved sargramostim indications, for autologous bone marrow transplant (BMT), allogeneic BMT, and acute myelogenous leukemia (AML), are for the acceleration of neutrophil recovery following exposure to myelosuppressive chemotherapy with or without total body irradiation (TBI) (see meeting package Section 12.1). These 3 approvals were based on prospective, randomized, placebo-controlled trials of sargramostim. Clinical endpoints in the studies included outcomes such as time to neutrophil recovery, infections, days of antibiotics, and hospital days. In these 3 settings, sargramostim significantly shortened the time to neutrophil recovery (defined as days to ANC >500/mm^3) compared to placebo.

In the settings of autologous and allogeneic BMT, patients receiving myelosuppressive chemotherapy experienced accelerated neutrophil recovery with sargramostim treatment compared to placebo regardless of whether TBI was included as part of the preparative regimen.

While the patients received bone marrow cells that had not been exposed to radiation, these data support that the exposure of the bone marrow stroma to irradiation does not limit sargramostim's ability to stimulate healthy bone marrow cells in the radiation-exposed bone marrow microenvironment. In addition, the activity of sargramostim in patients with AML indicates sargramostim can accelerate neutrophil recovery in the absence of an infusion of healthy bone marrow cells. Overall, these studies all contained aspects of myelosuppression that are relevant to the myelosuppression observed after exposure to radiation and indicated the ability of sargramostim to accelerate neutrophil recovery across these distinct clinical settings. Sanofi Genzyme is planning to summarize this efficacy data in the sBLA. No datasets or pooled summaries of efficacy data from these studies will be provided.

a) *Does the Agency agree that the proposed clinical data package from relevant clinical studies provides adequate supportive data for the filing and review of the sargramostim sBLA for the H-ARS indication?*

b) *Does the Agency agree with the presentation of select clinical efficacy data from the existing BLA?*

FDA Response to Question 3 a)
Yes. We agree.

FDA Response to Question 3 b):
Yes. We agree.

Meeting Discussion:
Sanofi Genzyme had no further comments, no meeting discussion.

Question 4:
During a radiological emergency, individuals throughout the age spectrum may be exposed to ionizing radiation. A report by the American Academy of Pediatrics entitled, *Pediatric Terrorism and Disaster Preparedness: A Resource for Pediatricians*, prepared for the US Department of Health and Human Services in 2006 noted that "the clinical manifestations of radiation injury in children are generally similar to those in adults".

To address the needs of the pediatric population, Sanofi Genzyme is planning to provide safety, efficacy, and PK data, as it relates to the proposed dosing in pediatric subjects. A total of 15 studies have been identified that have safety information on pediatric subjects ranging from preterm neonates through the age of 17 years and include a total of 314 subjects exposed to sargramostim. Two of the 15 studies contain useful clinical data on the efficacy of sargramostim to accelerate neutrophil recovery in a setting of myelosuppression (Study 301 and Study 9002), which would be relevant to the treatment of neutropenia in H-ARS. Data to support the pediatric dose selection is from a single study with PK data in 22 children with Crohn's disease (Study 308001).

Sanofi Genzyme has outlined the planned summaries of data from pediatric clinical experience with sargramostim that will be included in the sBLA. These data will be used to support the extrapolation of data to support a pediatric indication for H-ARS.

Does the Agency agree with this approach to support the pediatric indication for H-ARS?

FDA Response to Question 4:
Yes, we agree. Include in your submission PK data from (b)(4) (b)(4) along with a comparison of the bioanalytical methods used to quantify sargramostim in these studies.

Your proposal to rely on supportive PK, safety, and efficacy data from clinical studies evaluating pediatric patients for other indications is reasonable. Include PK, safety, and efficacy data from all known off-label uses for your product in pediatric patients of all ages. We (b)(4) If your product is approved across the full pediatric age range, then we recommend strengthening the existing safety labeling language to convey the following: (1) the potentially fatal risks of benzyl alcohol toxicity in neonates and infants; ((b)(4)

We also recommend that you consider the potential for these data to support pediatric use in other approved indications.

Meeting Discussion:

- **DMIP agreed with Sanofi Genzyme's approach of (b)(4) It (b)(4) .**
- **DMIP agreed that the approach for providing supportive pediatric data for efficacy and safety in support of the pediatric H-ARS indication was reasonable. There was agreement that Sanofi Genzyme will focus on two studies that were prospective, randomized, double-blind and placebo-controlled (Studies 301 and 9002), and additional information from other studies would be summarized as well. DMIP requested justification and rationale for inclusion/exclusion of the pediatric data.**

  Regarding DMIP's position on expansion of use for the existing approved adult indications to pediatric patients, DMIP reiterated that the feasibility of expanding use to pediatric patients would depend on how robust the pediatric data are that they collect for other uses.

  DMIP also reiterated that expansion of use of the existing approved adult indications to pediatric patients could be valuable; however, discussions on this matter will take place with Division of Hematology Products (DHP) before any decisions are made.
- **DMIP will also confer with DHP regarding the available efficacy/safety information to**

support pediatric use in other indications and the conversion of the USPI to PLR format.

- **Sanofi Genzyme is planning to submit the BLA (b)(4).**

Question 5:

A large body of safety data exists with sargramostim, in both approved and investigational therapeutic settings, representing over 25 years of postmarketing experience. From the time of product launch in March 1991 through January 2017, approximately (b)(4) patients have received sargramostim treatment in the postmarketing setting. In the sBLA, Sanofi Genzyme plans to submit a summary of postmarketing data for the period from March 1991 (US licensure of sargramostim) through 04 March 2017.

Sargramostim's safety profile has been characterized in company- and investigator-sponsored clinical trials and postmarketing experience. Risks associated with the product use are described in the USPI, and the most frequent adverse events (AEs) were fever, asthenia, headache, bone pain, chills, and myalgia. These systemic events were generally mild or moderate and were usually prevented or reversed by administration of analgesic and antipyretic medications.

No new clinical studies were conducted to support the H-ARS indication. Postmarketing safety data summarized in Periodic Adverse Drug Experience Reports (PADER) from 2002 to 2016 have shown a safety profile for sargramostim that is consistent with the information presented in the USPI.

As discussed during the Type B meeting with the Agency (previously submitted [FDA meeting minutes from the 27-Aug-2013 Pre-SBLA meeting]), safety data in healthy volunteer subjects would be relevant to the use of sargramostim following a radiation incident. Therefore, Sanofi Genzyme plans to cross-reference or submit study reports for healthy volunteer studies in the sBLA. Sanofi Genzyme also plans to provide by-study summaries of safety data from the healthy volunteer studies. No datasets or pooled summaries of safety data from these studies will be provided.

As discussed during the Type B meeting with the Agency, safety data in pediatric subjects are relevant to the use of sargramostim in the H-ARS indication. Therefore, Sanofi Genzyme plans to provide by-study summaries of safety data from clinical studies that included pediatric subjects. No datasets or pooled summaries of safety data from these studies will be provided.

Does the Agency agree with the proposed safety analyses and the presentation of the safety data, specifically:

a) Does the Agency agree with the strategy of summarizing safety data from postmarketing experience with sargramostim, and does the Agency agree to the proposed date for data cut-off?

b) Does the Agency agree with the strategy of summarizing the sargramostim safety data from the healthy volunteer studies?

c) Does the Agency agree with the strategy of summarizing pediatric safety data from studies of sargramostim?

FDA Response to Question 5 a):
Yes. We agree with the cutoff date.

FDA Response to Question 5 b):
Yes we agree.

FDA Response to Question 5 c):
Yes we agree.

We agree with your proposal to provide a post-marketing review and literature review of the safety of sargramostim in the pediatric population, in addition to data from clinical studies which included pediatric patients, in support of the safety of sargramostim for the H-ARS indication in the pediatric population. The safety data should be representative of the pediatric doses anticipated to be given for the H-ARS indication. Ensure that information obtained from each of these sources is stratified by age as described in your meeting package. Justify the safety of the proposed subcutaneous route of administration and clarify the planned site of administration, particularly for the smallest pediatric patients (e.g. neonates). Consider how the Centers for Disease Control and Prevention guidelines for safe vaccine administration to pediatric patients would be applicable to your product with regards to needle size and injection site (http://www.immunize.org/catg.d/p3085.pdf).

Meeting Discussion:
Sanofi Genzyme had no further comments, no meeting discussion.

Labeling

Question 6:
Based on the nonclinical data package to be included in the sBLA, Sanofi Genzyme proposes the following indication for sargramostim in H-ARS:

(b)(4)

Does the Agency agree that the data to be provided in the sBLA will be sufficient to support the proposed indication for sargramostim?

FDA Response to Question 6:
Preliminarily, yes. However, the sufficiency of the data is a review issue.

Meeting Discussion:
Sanofi Genzyme had no further comments, no meeting discussion.

Question 7

Sanofi Genzyme is planning to convert the current USPI for sargramostim to Physician Labeling Rule (PLR) format. The strategy for the conversion to PLR format will follow the FDA guidance for industry: *Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements* (February 2013). (b)(4)

Please refer to the draft TPP for a suggested draft label for sargramostim in meeting package.

a) ***Does the Agency agree with Sanofi Genzyme's proposal to convert the existing USPI labeling language to PLR format?***

b) ***Does the Agency agree to the proposed revisions to the label as described in the draft TPP?***

FDA Response to Question 7 a):
We agree.

FDA Response to Question 7 b):
The acceptability of the proposed revisions will be determined during review of the application. For PLLR update, the submission should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Meeting Discussion:
Sanofi Genzyme had no further comments, no meeting discussion.

Organization of Submission

Question 8

A proposed table of contents to outline the structure and the information that will be submitted in the sBLA is provided in meeting package. The planned contents of the Summary of Clinical Efficacy (Module 2.7.3), Summary of Clinical Safety (Module 2.7.4), and the Postmarketing Safety Report are described in the meeting package. Nonclinical efficacy studies will be summarized in the Pharmacology Written Summary (Module 2.6.2) and cross-referenced in the Summary of Clinical Efficacy (Module 2.7.3).

Does the Agency agree with the sBLA organizational structure and format in the proposed table of contents?

FDA Response to Question 8:
We agree with your proposal.

We remind you of the requirement noted in 21 CFR 601.91 (b)(1):
"Postmarketing studies. The applicant must 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. Such postmarketing studies would not be feasible until an exigency arises. When such studies are feasible, the applicant must conduct such studies with due diligence. Applicants must include as part of their application a plan or approach to postmarketing study commitments in the event such studies become ethical and feasible."

We request that you include a report on the immunogenicity results in the NHP studies.

Meeting Discussion:
Sanofi Genzyme had no further comments, no meeting discussion.

Question 9

As agreed, nonclinical datasets and definition files will be provided for nonclinical efficacy and PK studies ([FDA meeting minutes from the 28-Apr-2016 Pre-IND Type C Meeting]).

In addition to the datasets for Studies TSK0144 and FY14-045, the Agency also requested baseline information, efficacy information, derived datasets, SAS PROCS, and other programs.

Baseline information and efficacy information (ie, mortality data at Day 60) will be included in the datasets, but derived datasets were not planned for this submission.

Please refer to meeting package Section 13.3.5.2 for details regarding the presentation of these datasets.

Does the Agency agree with the proposed format of the nonclinical datasets? Specifically, can the Agency provide clarification as to whether additional baseline information, derived datasets or other programs are also still needed?

FDA Response to Question 9:
We agree with your proposal. During the review, there may be additional comments for derived datasets.

For Study TSK0144 and Study FY14-045, please submit all datasets in which you store raw data, efficacy outcome measures, and baseline information and all datasets (raw and derived (if any)) that you use for data analyses. All submitted datasets should be in XPT format. Please also submit the definition files. You may also provide all programs you used to create derived datasets and run analyses.

Since Studies DDK0110 and DDK0111 are the PK studies that will be used to select a dose in humans, please provide datasets for both studies in XPT format.

Meeting Discussion:
Sanofi Genzyme agreed to provide the requested datasets in XPT format.

3.0
DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding

implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/Electr onicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at
http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

Responses to meeting preliminary comments received May 31, 2017.

Twelve pages (12) have been withheld as (b)(4), sponsor's draft meeting minutes, immediately following this page.

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
07/28/2017

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-sBLA
Meeting Date and Time:	Tuesday, August 27, 2013, 2:00PM to 3:30PM
Meeting Location:	White Oak Building 22, Conference Room: 1421 Silver Spring, Maryland 20903
Application Number:	(b)(4)
Product Name:	Leukine® (recombinant human granulocyte macrophage-colony stimulating factor (rhu GM-CSF)).
Indication:	(b)(4)
Sponsor Name:	Sanofi U.S. Services
Meeting Chair:	Libero Marzella
Meeting Recorder:	Frank Lutterodt

FDA ATTENDEES
Louis Marzella, M.D., Ph.D. Acting Division Director, DMIP
Ira Krefting, M.D. Deputy Director for Safety, DMIP
Alex Gorovets, M.D. Clinical Team Lead, DMIP
Albert Deisseroth, M.D., Clinical Team Leader, DOP1
William Dickerson, M.D., Clinical Reviewer, DMIP
Susan Kirshner, Ph.D., Team Leader, Immunology, DTP/ OBP
Rosemary Roberts, M.D., Director, OCTEC
Brad Leissa, M.D., Deputy Director, OCTEC
Susan McDermott M.D., Medical Team Lead, OCTEC
Joel Beren, DVM, Animal Model Qualification Team Leader, OCTEC
Alla Shapiro, M.D., Ph.D., Clinical Reviewer, OCTEC
Zishan (Susan) Zhao, PhD Senior Advisor, MCMi PHSAT (OCET)
Alan Liss, Ph.D., Director, MCMi, PHSAT, OCET.
Christy John, Ph.D., Clinical Pharmacology Reviewer, DCP5 (Phone)
Gene Williams Ph.D., Clinical Pharmacology Team Leader, DCP5
Yanli Ouyang, Ph.D. Pharm/Tox Reviewer, DMIP
Adebayo Laniyonu, Pharm/Tox Team Leader, DMIP
Valerie Jimenez, M.S., Senior Regulatory Project Manager, OCTEC
Frank Lutterodt, M.S., Regulatory Project Manager

SPONSOR ATTENDEES

Jörg Adamczewski, Ph.D., Development Head Leukine, Sanofi

Ted Ashburn, M.D., Ph.D. Project Head Leukine (sargramostim), Sanofi

Eric Charpentier, M.S., Assistant Director, Statistical Oncology, Sanofi

Peter Douglas Cheverton M.D. Senior Director Medical, Sanofi

Andrew Ferguson, Ph.D., Medical Science Liaison, Medical Affairs Oncology America, Sanofi

Sunil Gupta, M.D., Associate Vice President, Regulatory Affairs Oncology, Sanofi

William B. Jones, Ph.D., Director Regulatory Affairs Oncology, Sanofi

Gurdip Kabra, BSc Pharmacy, Director of Development Operations, Sanofi

Serena Masciari, MD, MSc Associate Director of Safety, Global Pharmacovigilance and Epidemiology Oncology, Sanofi

Alan Roberts, Ph.D., Senior Director, Drug Safety, Sanofi

1.0 BACKGROUND

Sanofi US Services Corporation submitted a meeting request dated June 21, 2013, received June 24, 2013, requesting a meeting with the Division of Medical Imaging Products (DMIP) to meeting to come to agreement on Sanofi's plan for submitting a sBLA for Leukine. The FDA provided preliminary responses to the questions in the meeting background package dated July 24, 2013 on August 23, 2013. The sponsor provided feedback to FDA on August 26, 2013. The sponsor's responses served as the basis for discussions on the August 27, 2013, 2:00PM-3:30PM face-to-face meeting.

2. DISCUSSION

Sanofi Question 1: Sanofi plans to include and/or cross reference the following information in the sBLA:

(b)(4)

In the pre-IND meeting held on 12 November 2012 [Appendix 9] and a teleconference held on 12- June-2013 with the DMIP, it was suggested that a NHP study with sargramostim may be required. At the meeting, it was suggested (b)(4)

received from the Advisory Committee meeting at the joint MIDAC/ODAC meeting on 03-May-2013. (b)(4)

Sanofi was recently informed that (b)(4)

Does the FDA agree that the following is adequate to support the filing of the sBLA: (b)(4)

(b)(4)

FDA RESPONSE TO QUESTION 1:

We do not agree that the above items are adequate to support the sBLA and have the following comments:

(b)(4)

6. Review and discussion of the available data with FDA [redacted] reasonable approach.

SANOFI RESPONSE TO FDA RESPONSE 1

We understand the Agency's concern about the potential need for a NHP survival study in ARS. We would like to discuss the Agency's expectations for the design and outcome of a NHP study.

Meeting Discussion:

- DMIP agreed with Sanofi that the approach to NHP studies should minimize the use of animals.
- A NHP survival study will be required as a confirmatory study at the time of filing the sBLA; non-survival endpoints will be supportive.
- DMIP agreed with Sanofi that the confirmatory study [redacted]
- DMIP was not able to [redacted] for confidentiality reasons and recommended that Sanofi engage [redacted].
- DMIP will review efficacy data from any adequate and well controlled study of Leukine for which Sanofi has obtained the right of reference.
- DMIP recommended working with a [redacted],
- [redacted] minimal supportive care may better reflect a real-life crisis situation.
- Sanofi agreed to submit the protocols of their efficacy studies for review by DMIP prior to finalization but the study design is Sanofi's decision.
- DMIP emphasized that the sufficiency of the available clinical safety data will depend on the sargramostim exposures in the NHP efficacy study matching or being lower than exposures observed in patients and healthy volunteers at the recommended human regimen.

Question 2: A recent NIAID study in NHP demonstrated that filgrastim treatment following radiation exposure improved neutrophil recovery and overall survival. NIAID has generously offered to share the data with Sanofi or allow Sanofi to cross reference the data filed with the Agency for a sBLA filing.

Sanofi plans to cross reference the NIAID data filed with the Agency in its sBLA filing for sargramostim. Does the Agency agree with this strategy?

FDA RESPONSE TO QUESTION 2: We agree with the above strategy.

SANOFI RESPONSE TO FDA RESPONSE 2

Sanofi agrees with the Agency's response. No further discussion is necessary.

Question 3: A large body of safety data exists with sargramostim, in both approved and investigational therapeutic settings, representing over 21 years of post-marketing experience (Section 10.1.6). Approximately (b)(4) patients have received sargramostim treatment in the postmarketing setting from the time of product launch in March 1991 through December 2012 and over (b)(4) doses have been administered during this time period. Sargramostim's safety profile has been characterized in company- and investigator-sponsored clinical trials and post- marketing experience. Risks associated with the product use are described in the U.S. Prescribing Information and the most frequent adverse events are fever, asthenia, headache, bone pain, chills and myalgia. These systemic events were generally mild or moderate and were usually prevented or reversed by the analgesic and antipyretic administration. No new clinical studies were conducted to support this new indication, thus safety data related to new studies are not available. Post-marketing safety data have been presented in the form of Periodic Adverse Drug Experience Report (PADER) from 2002 to 2013 and they have been consistent with the information stated in the U.S. prescribing information.

Sanofi is planning to submit a summary bridging report providing highlights and an overview of data from the US PADER covering the period from the 01 March 2002, which is the date covered by the first PADER, to 04 March 2013. In addition we plan to provide line listings of the available data from the safety database from March 1991 to March 2002 and cross reference clinical safety data from approved indications.

Does the Agency agree that the proposed submission of safety data and cross reference clinical safety data from approved indications is both adequate and sufficient to support the application for the proposed indication?

FDA RESPONSE TO QUESTION 3:

We agree that the safety data for Leukine appear to be adequate for the proposed indication. Please plan to provide safety data on the use of Leukine in healthy adults and pediatric populations including infants. Please note that supplemental licensure applications will require a Pediatric Study Plan or application for a pediatric waiver.

SANOFI RESPONSE TO FDA RESPONSE 3

We understand that the Agency agrees with Sanofi's plan to submit a summary bridging report

providing highlights and an overview of data from the US PADER covering the period from the 01 March 2002 in addition to line listings of the available data from the safety database up to March 2002 and cross reference clinical safety data from approved indications.

Sanofi agrees to cross reference or submit study reports for the following five healthy volunteer studies.

- (b)(4)
- *Protocol 308626 Open-Label, Randomized, Crossover Study of Sargramostim Given Subcutaneously to Healthy Male Japanese and Caucasian Subjects*
- *Protocol 309901 Phase 1 Randomized Crossover Study to Evaluate the Bioequivalence of* (b)(4)
- *Protocol 309404 Phase 1 Randomized Two-Part Crossover Study to Evaluate the Bioavailability of* (b)(4)

The safety experience of Leukine in pediatric patients comprises:

- *124 pediatric subjects who have been treated with Leukine in clinical trials included in the current package insert*
- (b)(4)
- (b)(4)
- *22 children in Study 308-001 Phase 1/2 Safety, Pharmacokinetic, and Pharmacodynamic Study of Sargramostim (Leukine) in Pediatric Patients with Active Crohn's Disease with One-year Surveillance and Retreatment Extension*

Sanofi plans to submit information available from the listed trials.

Meeting Discussion

- DMIP confirmed the safety data from approved indications will be acceptable for filing.
- DMIP indicated that safety data in healthy volunteers is relevant to the "worried well" population following a radiation incident. Sanofi agreed to provide study reports on healthy volunteers and DMIP noted that datasets would not be required but a summary of formulations, doses and adverse events is needed. Ideally, adverse events would be described with greater specificity than provided by CTC criteria, which are not designed for characterizing events occurring in healthy volunteers.
- DMIP acknowledged that it would likely not be possible to acquire additional pediatric data with Leukine.
- To arrive as a final conclusion regarding the need to accumulate pediatric data, DMIP requires Sanofi to submit a Pediatric Study Plan as described at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf and encouraged Sanofi to file it as soon as possible but no later than the submission of the sBLA.

3.0 ATTACHMENTS AND HANDOUTS

FDA's preliminary responses issued on August 23, 2013.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

(b)(4)

MEETING PRELIMINARY COMMENTS

Genzyme A Sanofi Company
Attention: William Jones, Ph.D.
Director, Global Regulatory Affairs
500 Kendall Square
Cambridge, Massachusetts 02142

Dear Dr. Jones:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Leukine® (recombinant human granulocyte macrophage-colony stimulating factor (rhu GM-CSF)).

We also refer to your June 21, 2013, correspondence, received June 24, 2013, Type B Pre-sBLA meeting to come to agreement on Sanofi's plan for submitting a sBLA. Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

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.,
Acting Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

Reference ID: 4246824

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	Pre-sBLA
Meeting Date and Time:	Tuesday, August 27, 2013, 2:00PM to 3:30PM
Meeting Location:	White Oak Building 22, Conference Room: 1421 Silver Spring, Maryland 20903
Application Number:	(b)(4)
Product Name:	Leukine® (recombinant human granulocyte macrophage-colony stimulating factor (rhu GM-CSF)).
Indication:	(b)(4)
Sponsor/Applicant Name:	Sanofi U.S. Services

FDA ATTENDEES (tentative)
Louis Marzella, M.D., Ph.D. Acting Division Director, DMIP
Ira Krefting, M.D. Deputy Director for Safety, DMIP
Alex Gorovets, M.D. Clinical Team Lead, DMIP
William Dickerson, M.D., Clinical Reviewer, DMIP
Dov Pluznik, Ph.D., Microbiologist, DTP
Rosemary Roberts, M.D., Director, OCTEC
Brad Leissa, M.D., Deputy Director, OCTEC
Susan McDermott M.D., Medical Team Lead, OCTEC
Joel Beren, DVM, Animal Model Qualification Team Leader, OCTEC
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Adebayo Laniyonu, Pharm/Tox Team Leader, DMIP
Valerie Jimenez, M.S., Senior Regulatory Project Manager, OCTEC
Frank Lutterodt, M.S., Regulatory Project Manager

SPONSOR ATTENDEES
Ted Ashburn, M.D., Ph.D., Project Head, Leukine (sargramostim), Sanofi
Eric Charpentier, M.S., Assistant Director, Statistical Oncology, Sanofi
Peter Douglas Cheverton, M.D., Senior Director Medical, Sanofi
Andrew Ferguson, Ph.D., Medical Science Liaison, Medical Affairs Oncology America, Sanofi
Sunil Gupta, M.D., Associate Vice President, Regulatory Affairs Oncology, Sanofi
William B. Jones, Ph.D., Director, Regulatory Affairs Oncology, Sanofi

Michael Kopreski, M.D, Associate Vice President, Global Pharmacovigilance and Epidemiology Oncology, Sanofi
Serena Masciari, M.D., MSc, Associate Director of Safety, Global Pharmacovigilance and Epidemiology Oncology, Sanofi
Alan Roberts, Ph.D., Senior Director, Drug Safety, Sanofi
Tal Zaks, M.D., Ph.D, Vice President, Head of Development, Oncology Division, Sanofi

(b)(4)

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for August 27, 2013, 2:00PM to 3:30PM between Sanofi U.S. Services, the Division of Medical Imaging Products, and the Office of Counter-Terrorism and Emergency Coordination. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the Regulatory Project Manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

1.0 BACKGROUND

Sanofi US Services Corporation submitted a meeting request dated June 21, 2013, received June 24, 2013, requesting a meeting with the Division of Medical Imaging Products (DMIP) to meeting to come to agreement on Sanofi's plan for submitting a sBLA for Leukine. The meeting background package dated July 24, 2013, will serve as the basis for discussions on the August 27, 2013, 2:00PM-3:30PM face-to-face meeting.

Question 1: Sanofi plans to include and/or cross reference the following information in the sBLA:

(b)(4)

In the pre-IND meeting held on 12 November 2012 [Appendix 9] and a teleconference held on 12-June-2013 with the DMIP, it was suggested that a NHP study with sargramostim may be required. At the meeting, it was suggested that (b)(4)

.

Sanofi was recently informed that (b)(4)

Does the FDA agree that the following is adequate to support the filing of the sBLA: 1) (b)(4)

FDA Response to Question 1:
We do not agree that the above items are adequate to support the sBLA and have the following comments:

(b)(4)

Question 2: A recent NIAID study in NHP demonstrated that filgrastim treatment following radiation exposure improved neutrophil recovery and overall survival.

NIAID has generously offered to share the data with Sanofi or allow Sanofi to cross reference the data filed with the Agency for a sBLA filing.

Sanofi plans to cross reference the NIAID data filed with the Agency in its sBLA filing for sargramostim. Does the Agency agree with this strategy?

FDA Response to Question 2:
We agree with the above strategy.

Question 3: A large body of safety data exists with sargramostim, in both approved and investigational therapeutic settings, representing over 21 years of post-marketing experience (Section 10.1.6). Approximately (b)(4) patients have received sargramostim treatment in the postmarketing setting from the time of product launch in March 1991 through December 2012 and (b)(4) doses have been administered during this time period. Sargramostim's safety profile has been characterized in company- and investigator-sponsored clinical trials and post-marketing experience. Risks associated with the product use are described in the U.S. Prescribing Information and the most frequent adverse events are fever, asthenia, headache, bone pain, chills and myalgia. These systemic events were generally mild or moderate and were usually prevented

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Does the Agency agree that the proposed submission of safety data and cross reference clinical safety data from approved indications is both adequate and sufficient to support the application for the proposed indication?

FDA Response to Question 3:

We agree that the safety data for Leukine appear to be adequate for the proposed indication. Please plan to provide safety data on the use of Leukine in healthy adults and pediatric populations including infants. Please note that supplemental licensure applications will require a Pediatric Study Plan or application for a pediatric waiver.

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/s/

LIBERO L MARZELLA
08/23/2013

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/s/

FRANK A LUTTERODT
09/20/2013

LIBERO L MARZELLA
09/20/2013

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-IND

Meeting Date and Time: November 14, 2012, 11:00 AM to 12:30PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1313
Silver Spring, Maryland 20903

Application Number: (b)(4)
Product Name: Leukine® (recombinant human granulocyte macrophage-colony stimulating factor (rhu GM-CSF)).

Proposed Indication: (b)(4)

Sponsor/Applicant Name: Genzyme Corporation

Meeting Chair: Dwaine Rieves
Meeting Recorder: Frank Lutterodt

FDA ATTENDEES
Dwaine Rieves, M.D., Division Director, DMIP
Alexander Gorovets, M.D., Clinical Team Leader, DMIP
Ira Krefting, M.D., Deputy Director for Safety, DMIP
Adebayo Laniyonu Ph.D., Pharmacology/Toxicology Reviewer, DMIP-Phone
Lucie Yang, M.D., Ph.D. Acting Clinical Team Leader, DMIP
William Dickerson, M.D., Medical Officer, DMIP
Alla Shapiro M.D., Ph.D., Medical Officer, OCTEC
Susan McDermott, M.D., Clinical Team Lead, OCTEC
Joel Beren, D.V.M., Veterinary Medical Officer, OCTEC
Laura Salazar-Fontana, Ph.D., CMC (Immunogenicity) Reviewer, DTP
Dov Pluznik, Ph.D., CMC Reviewer, DTP
Christy John Ph.D., Clinical Pharmacology Reviewer, DCP5
Gene Williams Ph.D., Clinical Pharmacology Team Leader, DCP5
Yanli Ouyang, Ph.D., Pharmacology/Toxicology Reviewer, DMIP

Zishan Zhao, PhD, ARS Lead for Action Team, OCET
Alan Liss, Ph.D., Director, MCMI, PHSAT OCET.
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Howard R. Philips, Division of Information Disclosure Policy,ORP/CDER/FDA- Phone
Frank Lutterodt, M.S., Regulatory Project Manager, DMIP-Phone
Valerie Jimenez, M.S., Senior Regulatory Project Manager, OCTEC-Phone

SPONSOR ATTENDEES

Ted Ashburn, M.D., Ph.D., Project Head, Leukine (sargramostim), Sanofi Oncology
Sunil Gupta. M.D., Associate Vice President, Global Regulatory Affairs, Sanofi Oncology
Al Roberts Ph.D., Senior Director Preclinical Safety, Sanofi Oncology
Isma Benattia M.D., MBE Genzyme Pharmacovigilance Head Global Pharmacovigilance and Epidemiology
Andrew Ferguson, Ph.D., Medical Science Liaison, Medical Affairs Oncology North America, Sanofi US
Tal Zaks M.D., Ph.D., VP, Head of Development, Sanofi Oncology (Phone)
Shamim Ruff, M. Sc., Vice President, Global Regulatory Affairs Sanofi Oncology
(b)(4)

1.0 BACKGROUND

Genzyme Corporation submitted a meeting request dated September 5, 2012, received September 5, 2012, requesting a meeting with the Division of Medical Imaging Products (DMIP) to discuss the development path for Leukine (rhu GM-CSF) in order to (b)(4) (b)(4) . The meeting background package dated October 16, 2012, served as the basis for discussions on the November 14, 2012, 11:00AM-12:30PM face-to-face meeting.

2. DISCUSSION

2.0 Proposed Advisory Committee Meeting Discussion

Following introductions, the meeting began with a preface in which FDA outlined the potential to leverage the existing clinical experience with leukocyte growth factors (LGFs) to help support use of the factors in the treatment of myelosuppression due to a radiological/nuclear incident. FDA briefly outlined the sources of existing data that may be useful to help assess the usefulness of LGFs in the radiological/nuclear incident setting.

FDA further pointed out that in addition to the existing clinical data that supported LGF licensure, there have been discussions on using data form a non-human primate study that was completed by the National Institute for Allergy and Infectious Disease (NIAID). The NIAID has supplied these data to the FDA with the goal of helping to assess the role of LGFs in the radiological/nuclear incident setting.

FDA added that the NIAID report showed an almost doubling of survival after treatment with filgrastim following exposure of monkeys to 7 Gy of ionizing radiation. FDA explained that the review of these data is on-going and FDA plans to take these data to an advisory committee (AC) that will also likely consider the clinical experience with LGF therapy for chemotherapy-induced neutropenia (CIN). The AC would involve presentations by NIAID and the three companies (Amgen, Genzyme, (b)(5) who volunteer to present a brief summary of the clinical data that led to the licensure of their LGF(s). FDA explained that each of the three companies is receiving a similar invitation to participate in the advisory committee meeting.

FDA explained that no new clinical data were anticipated to be vetted at the advisory committee and the FDA hoped to minimize the advisory committee presentation challenges for the companies. FDA explained how a February 13, 2013 date had been targeted but that date is tentative and subject to change based on logistics and the availability of participants.

Genzyme expressed concern about the timeline for the advisory committee, especially considering the time that may be lost due to holidays. However, Genzyme generally agreed to participate with the advisory committee planning and expressed a willingness to further discuss the matter at follow-up telephone conversations.

After the advisory committee discussion, Genzyme requested clarification of questions 1 and 2 from FDA's preliminary responses. Clarification was not requested for the other FDA responses.

2.1 Question Number 1 Discussion

Regarding the FDA response to question 1, FDA reiterated the comments pertaining to the advisory committee plans and described how the advisory committee discussion would likely impact the development of a package insert "indication" statement.

2.2 Question Number 2 Discussion

Regarding the FDA response to question number 2, the discussion focused heavily upon the choice of a primary endpoint for study(ies) of irradiated Rhesus monkeys. FDA had emphasized the importance of a survival endpoint (b)(4)

Genzyme initially outlined their proposal (b)(4)

The meeting closed with a reiteration of how an advisory committee discussion may prove especially useful for Genzyme's development plans, including plans for additional animal studies. The company agreed to work with FDA in the development of this advisory committee and welcomes further discussion.

3.0 ATTACHMENTS AND HANDOUTS

- FDA's November 9, 2012 Pre-meeting Comments
- Genzyme's presentation slides

ADDENDUM: The Advisory Committee has tentatively been rescheduled for May 1-3, 2013.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

(b)(4)

MEETING PRELIMINARY COMMENTS

Genzyme A Sanofi Company
Attention: Sunil Gupta, M.D.
Associate Vice-President,
Global Regulatory Affairs
Sanofi Oncology
500 Kendall Street
Cambridge, Massachusetts 02142

Dear Dr. Gupta:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Leukine® (recombinant human granulocyte macrophage-colony stimulating factor (rhu GM-CSF)).

We also refer to your September 5, 2012, correspondence requesting a meeting to discuss the development path for Leukine (rhu GM-CSF) in order to expand (b)(4)

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-IND

Meeting Date and Time: November 14, 2012, 11:00 AM to 12:30PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1313
Silver Spring, Maryland 20903

Application Number: (b)(4)
Product Name: Leukine® (recombinant human granulocyte macrophage-colony stimulating factor (rhu GM-CSF)).

Proposed Indication: (b)(4)

Sponsor/Applicant Name: Genzyme Corporation

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 14, 2012, 11:00 AM to 12:30PM, at the White Oak Building 22, Conference Room: 1313 between Genzyme Corporation and the Division of Medical Imaging Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

1.0 BACKGROUND

Genzyme Corporation submitted a meeting request dated September 5, 2012, received September 5, 2012, requesting a meeting with the Division of Medical Imaging Products (DMIP) to discuss the development path for Leukine (rhu GM-CSF) in order (b)(4) . The meeting background package dated October 16, 2012, will serve as the basis for discussions on the November 14, 2012, 11:00AM-12:30PM face-to-face meeting.

2. Draft Responses to The Sponsor's Comments

2.1. Proposed Indication

Question 1: *Does the Agency agree with the proposed indication?*
FDA Response: We anticipate the need to revise the proposed indication (b)(4) (b)(4) We prefer not to definitively answer this question until after we have had an Advisory Committee (AC) Meeting on "The Use of Currently Approved Leukocyte Growth Factors (LGF) in the Treatment of Radiation-induced Myelosuppression Associated with a Radiological/ Nuclear Incident". This AC meeting is tentatively scheduled for February 13, 2013. We refer to our letter of October 31, 2012 in which we inquired about your interest in presenting at this advisory committee. We welcome the opportunity to discuss the advisory committee topic at the upcoming meeting.

1a. Does the Agency agree that in (b)(4) *?*
FDA Response: We question the relevance of this endpoint in a radiologic-nuclear setting, and want to wait until we have an advisory committee meeting before we answer this question.

1b. Does the Agency agree with the proposed target population?
FDA Response: Same answer as above.

1c. Does the Agency agree with the overall indication statement?
FDA Response: Same answer as above. We anticipate a need to revise the indication statement after we have an advisory committee meeting.

2.2. Proposed Nonclinical Approach to Support Licensure

Question 2: *Does the Agency agree with the proposed nonclinical approach?*

FDA Response to Question 2:

The agency will address this question from safety, pharmacokinetics, and efficacy perspectives.

Safety:

Based on your meeting package summary, your completed nonclinical safety studies appear adequate to support your license proposal.

Pharmacokinetics

Please refer to the response below.

Efficacy:

(b)(4)

(b)(4)

2.3. Proposed Leukine Dose, Schedule and Duration of Administration

Question 3: *Does the Agency agree with the proposed Leukine dose, schedule and route of administration?*

FDA Response to Question 3:

The dose regimen proposed for humans needs to achieve exposures (AUC and C_{MAX}) similar to (greater than) those achieved in both irradiated and healthy animals following administration of the dose regimens that are efficacious in irradiated animals. The variability of exposure parameters in animals and humans should be taken into account: the proposed human dose regimen should assure that all, or nearly all, humans will have exposures associated with efficacy in animals. The future animal efficacy program should be designed to demonstrate that animal efficacy occurs with drug exposures similar to (less than) those that occur in humans receiving the clinical dose regimen.

2.4. Drug-Drug Interaction

Question 4: (b)(4)

FDA Response to Question 4:

(b)(4)

2.5. Healthy Volunteer Safety Data

Question 5a: *Does the Agency agree that safety data from* (b)(4) *normal provide sufficient safety data to preclude the need for additional data from hematopoietically normal healthy volunteers?*

FDA Response to Question 5a:

Currently we are not advising the conduct of any additional human studies. As noted above, the advisory committee discussion may determine whether additional clinical data are necessary.

(b)(4)

Question 5b: *Specifically, does the Agency agree that a healthy volunteer study to address concerns regarding the potential risks of* (b)(4)

FDA Response to Question 5b:

As noted above, we do not currently anticipate the need for study in healthy volunteers to (b)(4)

2.6. Outstanding Post Marketing Commitments (PMCs)

Question 6: (b)(4)

6a: (b)(4)

FDA Response to Question 6a:

(b)(4)

We encourage you to work with the Division of Hematology Products (DHP) to address questions pertaining to the sufficiency of your response (b)(4).

6b. (b)(4)

FDA Response to Question 6b:
Please contact the DHP Regulatory Project Manager for BLA 103362 for the answer to your question.

2.7. Regulatory

Question 7: (b)(4)

FDA Response to Question 7:

We agree, a Pre-IND is adequate at this time.

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

/s/

FRANK A LUTTERODT
11/09/2012