17 患者カウンセリング情報

患者に、FDA が承認した患者向け添付文書（患者向け情報）を読むよう助言する。

LEUKINE は、医療従事者の指導監督のもとで使用すること。ただし、病院、診療所以外で本剤を使用してもよいと医師が判断した場合は、本剤の適正投与量、並びに本剤の溶解・投与方法について、本剤を投与する者に指導すること〔*用法・用量（2.7）を参照*〕。家庭での使用が処方される場合、患者に適切に廃棄することの重要性を指導し、注射針、注射器、製剤及び希釈液の再使用について警告すること。患者が使用済みの注射針を廃棄する際には、穿刺抵抗性容器を使用すること。

LEUKINE による以下のリスク及び潜在的リスクについて患者に助言すること。

- 重篤なアレルギー反応〔*警告及び使用上の注意（5.1）を参照*〕
- インフュージョン関連反応〔*警告及び使用上の注意（5.2）を参照*〕
- 化学療法又は放射線療法の前後 24 時間以内に LEUKINE を投与した場合の重度骨髄抑制リスク〔*警告及び使用上の注意（5.3）を参照*〕
- 体液貯留及び毛細血管漏出症候群〔*警告及び使用上の注意（5.4）を参照*〕
- 上室性不整脈〔*警告及び使用上の注意（5.5）を参照*〕
- 白血球増加症（好酸球増加症を含む）〔*警告及び使用上の注意（5.6）を参照*〕
- 悪性細胞に対する潜在的影響〔*警告及び使用上の注意（5.7）を参照*〕
- 疼痛（胸痛、腹痛、背部痛、関節痛を含む）〔*副作用（6.1）を参照*〕
- 血栓塞栓性イベント〔*副作用（6.3）を参照*〕
- 胚・胎児毒性：妊娠可能な女性には、LEUKINE が胎児に害を及ぼす可能性があることを説明し、妊娠していること又は妊娠の可能性があることを処方者に知らせるよう助言する〔*特別な患者集団への投与（8.1）を参照*〕
- 授乳：授乳婦には、投与中及び最終投与後少なくとも 2 週間は授乳しないよう助言する〔*特別な患者集団への投与（8.2）を参照*〕
- 骨髄抑制を起こす放射線量の急性曝露を受けた患者（H-ARS）には、本適応症に対する LEUKINE の有効性試験は、倫理的及び実行可能性の理由によりヒトで実施することができなかったため、本適応症の承認は、動物の有効性試験に基づいたものであることを説明する〔*臨床試験（14.6）を参照*〕

LEUKINE を自己投与する患者への指導

- 注射針、注射器、及びバイアルの未使用部分は再使用しない。
- 使用済み注射器、注射針、及び未使用バイアルの適切な廃棄については、各施設の要件に従う

LEUKINE®はPartner Therapeutics社にライセンスされた登録商標である。Partner Therapeutics はPartner Therapeutics社の登録商標である。

製造者：

Manufactured by: Partner Therapeutics, Inc., Lexington, MA 02421

US License No. 2087

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Phone: 1-888-4RX-LEUKINE

米国「Leukine®」の添付文書（原文）

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

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

Dosage and Administration (2.7) 05/2022

----------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 daily. (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)

----------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 Partner Therapeutics, Inc., 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: 5/2022

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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 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 reconstituted solution under refrigeration at 2°C to 8°C (36°F to 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 Preparation

Reconstitute the lyophilized powder 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) for intravenous or subcutaneous administration. Discard any unused portions.

- When reconstituted with *Sterile Water for Injection, USP (without preservative),* may store the reconstituted solution refrigerated at 2°C to 8°C and must use within 24 hours following reconstitution.
- When reconstituted with *Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol)*, may store the reconstituted solution refrigerated at 2°C to 8°C and must use within 20 days following reconstitution.

LEUKINE for Intravenous Administration

Dilute reconstituted LEUKINE in 0.9% Sodium Chloride Injection, USP. If the final concentration of LEUKINE is less than 10 mcg/mL, add Albumin (Human) to a final concentration of 0.1% [1 mL 5% Albumin (Human) per 1 mL 0.9% Sodium Chloride Injection,

USP] to prevent adsorption of LEUKINE to the drug delivery system. LEUKINE for intravenous administration must be used immediately after dilution with 0.9 % Sodium Chloride Injection, USP.

3 DOSAGE FORMS AND STRENGTHS

- For injection: 250 mcg of sargramostim as a white lyophilized powder in a single-dose vial for reconstitution

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 for injection reconstituted with Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol). The "gasping syndrome" is characterized by central nervous system depression, metabolic acidosis, and gasping respirations.

Avoid administration of solutions containing benzyl alcohol (including LEUKINE for injection 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 for injection 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 for injection reconstituted with Bacteriostatic Water contains 9 mg of benzyl alcohol per mL). 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					
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
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

Adverse Reactions by Body System	LEUKINE (n=53) %	Placebo (n=56) %	Adverse Reactions by Body System	LEUKINE (n=53) %	Placebo (n=56) %
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
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

Adverse Reactions by Body System	LEUKINE (n=52) %	Placebo (n=47) %	Adverse Reactions by Body System	LEUKINE (n=52) %	Placebo (n=47) %
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

LEUKINE for injection reconstituted with Bacteriostatic Water for Injection, USP contain 0.9% 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, reconstitute LEUKINE for injection only 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 post implantation 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 were 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 [LEUKINE for injection 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 for injection 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 for injection reconstituted with Bacteriostatic Water for Injection, USP [0.9% benzyl alcohol] contains 9 mg of benzyl alcohol per mL). 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 a sufficient number 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

Sargramostim is a glycosylated recombinant human granulocyte-macrophage colonystimulating factor (rhu GM-CSF) produced by recombinant DNA technology in a yeast (*S. cerevisiae*) expression system. Sargramostim 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 sargramostim 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. Sargramostim differs from human GM-CSF by one amino acid at position 23, where leucine is substituted for arginine.

LEUKINE (sargramostim) for injection is supplied as a sterile, preservative-free, white lyophilized powder in a single-dose vial for subcutaneous or intravenous use. 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.

Subcutaneous Administration (SC)

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	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)

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

LEUKINE administered SC to healthy adult volunteers, GM-CSF 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 ≤100 cells/mm^3 by day 28 post transplantation);
2. patients displaying a delay in neutrophil recovery (ANC ≤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 ≥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 ≤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 $[LD]_{50-60/60}$). 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 71837-5843-5).

Storage and Handling

Store LEUKINE vials refrigerated at 2°C to 8°C (36°F to 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).

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:

- 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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Phone: 1-888-4RX-LEUKINE

1.7 同種同効品一覧表

自己免疫性肺胞蛋白症又は類似の効能・効果を有する同種同効品はない。

審査段階の添付文書（案）であるため、最新の添付文書を参照すること。

添付文書案

20XX 年 X 月（第 1 版）

日本標準商品分類番号
87229

生物由来製品
処方箋医薬品[注)]

遺伝子組換えヒト GM-CSF 製剤
サルグラモスチム（遺伝子組換え）吸入剤

サルグマリン®吸入用 250μg

Sargmalin® for inhalation 250μg

承認番号	
販売開始	

貯法：2～8℃保存
有効期間：18 箇月

注）注意―医師等の処方箋により使用すること

2. 禁忌（次の患者には投与しないこと）
本剤の成分に対する過敏症の既往歴のある患者[15.1.1 参照]

3. 組成・性状

3.1 組成

サルグマリン吸入用 250μg

有効成分（1 バイアル中）	サルグラモスチム（遺伝子組換え）	264μg
添加剤（1 バイアル中）	D-マンニトール	42mg
	精製白糖	10.5mg
	トロメタモール	1.27mg
	塩酸	適量

本剤は 1 回の投与で 125μg を吸入できるように過量充填されている。
本剤は酵母を用いて製造される。製造工程で、ウシ組織（脊柱骨を含む骨、結合組織、胆汁、皮膚）由来バクトペプトン、ウシ乳由来カゼイン加水分解物を使用している。また、マスターセルバンク構築時にウシ乳由来カザミノ酸を使用している。

3.2 製剤の性状

サルグマリン吸入用 250μg

剤形	凍結乾燥製剤（吸入剤）（バイアル）
色・性状	本剤は白色の粉末又は塊であり、生理食塩液 4mL を加えて溶かすと無色澄明の液となる。
pH	7.1～7.7 注 1)

注 1）注射用水 1mL で溶解した液

4. 効能又は効果

自己免疫性肺胞蛋白症

6. 用法及び用量

通常、成人にはサルグラモスチム（遺伝子組換え）として 125μg を 1 日 2 回、ネブライザーを用いて 7 日間連日吸入投与し、7 日間休薬する。これを 1 クールとし、投与を繰り返す。

7. 用法及び用量に関連する注意

12 クールを目安に有効性及び安全性を評価し、投与継続について判断する。投与継続する場合は、定期的に有効性及び安全性を評価し、投与継続の可否を判断すること。

8. 重要な基本的注意

8.1 過敏症等の反応を予測するために、使用に際しては薬物過敏症の既往歴、アレルギー既往歴等について十分な問診を行うこと。[9.1.1、9.1.2、15.1.1 参照]

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 薬物過敏症の既往歴のある患者
[8.1、15.1.1 参照]

9.1.2 アレルギー素因のある患者
[8.1、15.1.1 参照]

9.1.3 肺の線維化を有する患者
肺の線維化所見は本疾患の予後不良因子とされている。本剤投与中は定期的に肺線維化進展の有無を確認し、投与により肺線維化の進展が疑われる場合は投与継続の可否を検討すること。

9.5 妊婦

妊婦又は妊娠している可能性のある女性には治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。動物試験（ウサギ）では、本剤の皮下投与で自然流産の増加等が報告されている[1)]。

9.6 授乳婦

治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。

9.7 小児等

小児等を対象とした臨床試験は実施していない。

9.8 高齢者

患者の状態を観察しながら慎重に投与すること。一般に生理機能が低下している。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.2 その他の副作用

	2%未満
血液	赤血球増加症、白血球数増加
呼吸器	咳嗽、発声障害
消化器	口の感覚鈍麻
その他	頭痛、尿中血陽性

14. 適用上の注意

14.1 薬剤交付時の注意

14.1.1 本剤はネブライザーを用いて吸入するタンパク製剤であり、加熱により活性が失われるおそれがあることから、超音波式（メッシュ式を除く）以外のネブライザーを使用するよう指導すること。また、ネブライザーは機種により使用方法及び性能が異なるため、患者に対してその使用方法及び性能をよく説明すること。

14.1.2 本剤を交付する際には、患者用説明文書を渡し、本剤の調製方法及び吸入方法を指導すること。

14.1.3 バイアルは遮光して冷蔵保存（2～8℃）するように指導すること。[20. 参照]

14.2 薬剤調製時の注意

14.2.1 本剤は日局生理食塩液 4mL を用いて溶解し、1 回に 2mL の薬液を使用すること。残りの薬液 2mL は冷蔵保存（2～8℃）して 18 時間以内に使用すること。

14.2.2 冷蔵保存（2～8℃）した残りの薬液を使用する場合は、常温に戻してから使用すること。

15. その他の注意

15.1 臨床使用に基づく情報

15.1.1 GM-CSF製剤の皮下又は静脈内投与時にアナフィラキシーがあらわれたとの外国での報告がある[1]。[2.、8.1、9.1.1、9.1.2参照]

15.1.2 本剤の投与による抗顆粒球マクロファージコロニー刺激因子（GM-CSF）抗体濃度の増加が報告されている[2]。

16. 薬物動態

16.1 血中濃度

16.1.1 単回投与（健康成人）

健康成人9例に本剤125、250又は500μg（各3例）を単回吸入投与したとき、125及び250μg投与例では、いずれの時点でも血清中サルグラモスチム濃度が定量下限付近又はそれ以下であり、500μg投与例における血清中サルグラモスチム濃度は、投与後1又は2時間で最大となり、C_{max}の個別値は11.0、12.3及び2.32pg/mLであった。なお、承認用量は1回125μgを1日2回である。

16.1.2 単回投与（自己免疫性肺胞蛋白症患者）

自己免疫性肺胞蛋白症患者5例に本剤125μgを単回吸入投与したとき、血清中サルグラモスチム濃度を定量可能であったのは1例の投与4時間後のみ（1.12 pg/mL）であり、その他の被験者及び測定時点ではいずれも定量下限未満であった[3]。

16.3 分布

自己免疫性肺胞蛋白症患者では、血液中に抗GM-CSF自己抗体が存在しており、循環血中に移行したサルグラモスチムは速やかに中和抗体と複合体を形成すると考えられている[4]。

16.4 代謝

サルグラモスチムは、ペプチド及びアミノ酸に代謝分解されると考えられている。

17. 臨床成績

17.1 有効性及び安全性に関する試験

17.1.1 国内第Ⅲ相試験（二重盲検比較試験）

自己免疫性肺胞蛋白症患者64例を対象にプラセボ対照無作為化二重盲検並行群間比較試験を実施した。二重盲検期（24週間）の用法・用量は、1回あたり本剤125μg又はプラセボを1日2回ネブライザーで吸入投与することとし、投与期間は7日間の連日投与と、続く7日間の休薬期間を1クールとし、12クール施行した。主要評価項目である投与開始後24週における肺胞気動脈血酸素分圧較差（A-aDO_2）のベースラインからの変化量（平均±標準偏差）は、プラセボ群（31例）で0.17±10.50mmHg、実薬群（33例）で-4.5±9.03mmHgであり、群間差の推定値［95%信頼区間］は-4.68［-9.6, 0.24］mmHgであった（U検定：P=0.016）。

二重盲検期の副作用は、プラセボ群で12.9%（4/31例）、実薬群で9.1%（3/33例）に認められた。二重盲検期と同様の投与方法で実施した後治療／後観察期を含めた全期間（42週間）で本剤が投与された患者において副作用は8.3%（5/60例）に7件認められ、認められた副作用は口の感覚鈍麻、赤血球増加症、咳嗽、発声障害、頭痛、尿中血陽性、白血球数増加（各1例）であった[2),5)]。

18. 薬効薬理

18.1 作用機序

サルグラモスチムは肺胞マクロファージの成熟を促し、それに続く成熟マクロファージによる肺サーファクタントの分解により肺機能を改善すると考えられている[6]。

18.2 薬理作用

18.2.1 肺胞マクロファージの増殖／生存増強作用

サルグラモスチムはサル肺胞マクロファージの増殖／生存を高めた[7]（*in vitro*）。

19. 有効成分に関する理化学的知見

一般名：サルグラモスチム（遺伝子組換え）
（Sargramostim(Genetical Recombination)）

本　質：サルグラモスチムは、遺伝子組換えヒト顆粒球マクロファージコロニー刺激因子の類縁体（R23L）である。サルグラモスチムは、127個のアミノ酸残基からなる糖タンパク質（分子量：約17,000）である。

20. 取扱い上の注意

外箱開封後は遮光して冷蔵保存（2～8℃）すること。[14.1.3参照]

22. 包装

1日分[凍結乾燥品1バイアル、4mL計量カップ1個、薬液採取用スポイト1本、バイアル保護シール1枚]

23. 主要文献

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24. 文献請求先及び問い合わせ先

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フリーダイヤル：0120-003-140

26. 製造販売業者等

26.1 製造販売元

ノーベルファーマ株式会社
東京都中央区新川1-17-24

NPC20230428（作成分）

1.8.2 効能又は効果、用法及び用量（案）の設定根拠

1.8.2.1 効能又は効果

1.8.2.1.1 効能又は効果の設定根拠

効能又は効果（案）：
自己免疫性肺胞蛋白症

検証試験として実施したプラセボ対照二重盲検比較試験である医師主導第Ⅲ相試験（以下、「PAGE 試験」）では、自己免疫性肺胞蛋白症患者を対象に、本剤の有効性及び安全性を評価した。主要評価項目である投与開始後 24 週における肺胞気動脈血酸素分圧格差（$A\text{-}aDO_2$）のベースラインからの変化量は、プラセボ群で 0.17±10.50 mmHg、実薬群で-4.50±9.03 mmHg であり、プラセボ群と実薬群の間に有意な差を認め、有効性が確認された。また、副次評価項目である息切れ、肺機能及び画像所見でも実薬群で改善がみられた。

自己免疫性肺胞蛋白症の重症度は、症状と動脈血酸素分圧（PaO_2）の値により、最も軽症の重症度 1 から最も重症の重症度 5 までの 5 段階に分類される[1]。重症度 2～4 の患者を対象とした PAGE 試験では、重症度により主要評価項目である $A\text{-}aDO_2$ の変化量に大きな違いはみられなかった。また、PAGE 試験に先行して実施された臨床研究では、重症度 5 の患者に対しても本剤が有効であったと報告されており[2]、本剤は重症度に関わらず有効性が期待できると考えられる。

これまでの臨床報告、臨床研究及び PAGE 試験で自己免疫性肺胞蛋白症の重症度が本剤の安全性に影響を与えるという報告はない。

以上より、本剤の効能又は効果を「自己免疫性肺胞蛋白症」と設定した。

1.8.2.2 用法及び用量

1.8.2.2.1 用法及び用量の設定根拠

用法及び用量（案）：
通常、成人にはサルグラモスチム（遺伝子組換え）として 125μg を 1 日 2 回、ネブライザーを用いて 7 日間連日吸入投与し、7 日間休薬する。これを 1 クールとし、投与を繰り返す。

自己免疫性肺胞蛋白症は血清中に抗 GM-CSF 抗体が検出されるが、肺以外には病理学的な所見がみられないことから、rhGM-CSF 製剤の吸入が試みられてきた。rhGM-CSF 製剤の皮下投与についての臨床報告も散見されるが[3-6]、注射部位の副反応がみられる他、皮下投与よりも吸入投与の方が高い有効性を示すとする報告もある[7]。

rhGM-CSF 製剤の吸入投与については、1999 年に転移性肺腫瘍患者を対象として試験が実施され、本剤 60～240μg を 1 日 2 回、7 日間連日吸入投与し、安全性に問題がないことが確認された[8]。その後、同グループが肺胞蛋白症患者に対して rhGM-CSF 製剤の吸入治療を行い、肺機能が改善したことを 2000 年に報告した[9]。

国内では、上記の報告を基に、自己免疫性肺胞蛋白症患者 3 例に対し、大腸菌由来の rhGM-CSF（モルグラモスチム）を 1 回あたり 125μg、1 日 2 回、隔週で吸入投与するパイロット試験が実施され[10]、$A\text{-}aDO_2$ の改善が認められた。その後、本剤 125μg を連日吸入投与する試験が自

己免疫性肺胞蛋白症患者 13 例を対象に実施され[2]、A-aDO_2の改善が認められた。これらの試験の結果を受け、臨床研究[2]では、本剤を 1 回あたり 125μg、1 日 2 回 8 日間吸入後、6 日間休薬を 1 コースとして 6 コース繰り返し、計 12 週間継続した。続いて本剤を 1 回あたり 125μg、1 日 1 回 4 日間吸入後、10 日間休薬を 1 コースとして 6 コース繰り返し、計 12 週間継続した。その結果、投与開始後 24 週における A-aDO_2のベースラインからの変化量は-12.3±1.9 mmHg であり、奏効率は 62%（24/39 例）であった。

上記の臨床研究の結果及びこれまでの rhGM-CSF 製剤の吸入投与試験成績を踏まえ、検証試験として実施したプラセボ対照二重盲検比較試験である PAGE 試験では、本剤を 1 回あたり 125μg、1 日 2 回 7 日間吸入後、7 日間休薬を 1 クールとして 12 クール繰り返し、計 24 週間継続した。その結果、主要評価項目である投与開始後 24 週における A-aDO_2のベースラインからの変化量で、実薬群のプラセボ群に対する有意な改善が認められた。また、副次評価項目として設定した肺機能及び自己免疫性肺胞蛋白症の主症状である息切れにも改善を認め、さらに臨床で病勢の判断に重要とされる画像所見に改善がみられた。

以上より、用法及び用量を「通常、成人にはサルグラモスチム（遺伝子組換え）として 125μg を 1 日 2 回、ネブライザーを用いて 7 日間連日吸入投与し、7 日間休薬する。これを 1 クールとし、投与を繰り返す。」と設定した。

1.8.2.2.2 用法及び用量に関連する注意の設定根拠

用法及び用量に関連する注意（案）： 12 クールを目安に有効性及び安全性を評価し、投与継続について判断する。投与継続する場合は、定期的に有効性及び安全性を評価し、投与継続の可否を判断すること。

PAGE 試験では、主要評価項目を投与開始後 24 週（12 クール）における A-aDO_2のベースラインからの変化量と設定し、投与開始後 24 週（12 クール）時点における本剤の有効性が確認されたことから、投与開始から 12 クールを目安に本剤の有効性及び安全性を評価することが適切であると考える。

PAGE 試験では、投与開始後 24 週で A-aDO_2が 10 mmHg 以上改善した被験者に対し、後観察として 24 週以降 42 週まで無治療の経過観察を実施し、10 mmHg 以上の改善が認められなかった被験者に対しては、後治療として本剤を 1 回あたり 125μg、1 日 2 回 7 日間吸入後、7 日間休薬の 2 週間を 1 クールとして投与開始後 42 週まで継続投与した。実薬群のうち無治療の後観察に移行した被験者（NPC-26→後観察：7 例）では、投与開始後 24 週から 42 週の A-aDO_2は悪化傾向にあった。一方、実薬群のうち後治療に移行し、本剤による治療を継続した被験者（NPC-26→NPC-26：25 例）では、投与開始後 24 週から 42 週の A-aDO_2は維持されていた。

また、PAGE 試験終了後に実施したフォローアップ調査では、NPC-26→後観察の 7 例中 1 例、NPC-26→NPC-26 の 26 例中 9 例で追加治療が行われた[11]。PAGE 試験に先行して実施した臨床研究のフォローアップ調査でも、本剤の 24 週間の投与終了後、35 例中 12 例で追加治療が必要となった[12]。

これらの情報から、本剤投与により有効性が得られた場合においても、投与を中止することで症状が悪化する患者が一定数存在すると想定されるため、24 週以降も必要に応じて投与を継続することが必要と考えた。

また、NPC-26→NPC-26 の中には、投与開始後 24 週から 42 週までの間に A-aDO_2 が大きく改善する被験者もみられた。PAGE 試験とは用法及び用量が異なるものの、本剤を長期投与した臨床報告[13,14]でも、効果発現までの期間に個人差があることが報告されており、24 週以降の投与継続により、十分な治療効果が期待できる患者も想定される。

以上より、用法及び用量に関連する注意を「12 クールを目安に有効性及び安全性を評価し、投与継続について判断する。投与継続する場合は、定期的に有効性及び安全性を評価し、投与継続の可否を判断すること。」と設定した。

1.8.2.3 参考文献

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1.8.3 使用上の注意（案）に関する設定根拠

1.8.3.1 警告

該当する事項がないことから、設定しなかった。

1.8.3.2 禁忌

2. 禁忌（次の患者には投与しないこと） 本剤の成分に対する過敏症の既往歴のある患者

本剤の成分に対して過敏症の既往歴のある患者に対する一般的な注意として設定した。

1.8.3.3 使用上の注意

1.8.3.3.1 重要な基本的注意

8. 重要な基本的注意 8.1 過敏症等の反応を予測するために、使用に際しては薬物過敏症の既往歴、アレルギー既往歴等について十分な問診を行うこと。

8.1 本剤の成分に対する過敏症等の反応を予測するための一般的な注意として設定した。

1.8.3.3.2 特定の背景を有する患者に関する注意

1.8.3.3.2.1 合併症・既往歴等のある患者

9.1 合併症・既往歴等のある患者 9.1.1 薬物過敏症の既往歴のある患者 9.1.2 アレルギー素因のある患者 9.1.3 肺の線維化を有する患者 肺の線維化所見は本疾患の予後不良因子とされている。本剤投与中は定期的に肺線維化進展の有無を確認し、投与により肺線維化の進展が疑われる場合は投与継続の可否を検討すること。

9.1.1 及び 9.1.2 本剤の成分に対して過敏症の既往歴のある患者及びアレルギー素因のある患者に対する一般的な注意として設定した。

9.1.3 肺胞蛋白症診療ガイドラインにおいて肺の線維化所見は本疾患の予後不良因子であるとされており、進行性の線維化により呼吸不全へと至る一部の治療抵抗例においては、肺移植による治療を考慮することが記載されている[1)]。本剤の投与が肺線維化の進行に与える影響は不明であるが、本剤投与による肺線維化の進行が疑われる場合は投与を中止し、他の適切な処置を検討する必要があるため設定した。

1.8.3.3.2.2 腎機能障害患者

腎機能障害患者に対する本剤の投与について、特段の懸念はないことから設定しなかった。

1.8.3.3.2.3 肝機能障害患者

肝機能障害患者に対する本剤の投与について、特段の懸念はないことから設定しなかった。

1.8.3.3.2.4 生殖能を有する者

動物実験（ウサギ）で、本剤の投与による受胎能への影響は認められなかったことから設定しなかった＜4.2.3.5.1-1＞。

1.8.3.3.2.5 妊婦

9.5 妊婦 妊婦又は妊娠している可能性のある女性には治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。動物試験（ウサギ）では、本剤の皮下投与で自然流産の増加等が報告されている。

米国添付文書[2)]では、生殖発生毒性試験で妊娠中のウサギの器官形成期に本剤を皮下投与したところ、ヒト推奨用量（米国での注射剤としての推奨用量）で予想される全身曝露量の1.3倍以上の曝露量で自然流産が増加するなどの有害な発生転帰を引き起こしたことが記載されていることから設定した。妊婦を対象とした臨床試験は実施していない。

1.8.3.3.2.6 授乳婦

9.6 授乳婦 治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。

ヒト乳汁中には内因性のGM-CSFが存在することから、本剤も乳汁に移行する可能性が想定されるため設定した。本剤の乳汁中への移行に関する非臨床及び臨床データはない。授乳婦を対象とした臨床試験は実施していない。

1.8.3.3.2.7 小児等

9.7 小児等 小児等を対象とした臨床試験は実施していない。

実施した国内臨床試験の内容に基づいて記載した。

1.8.3.3.2.8 高齢者

9.8 高齢者 患者の状態を観察しながら慎重に投与すること。一般に生理機能が低下している。

高齢者への一般的な注意として設定した。

1.8.3.3.3 相互作用

該当する事象がないため、設定しなかった。

1.8.3.3.4 副作用

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.2 その他の副作用

	2%未満
血液	赤血球増加症、白血球数増加
呼吸器	咳嗽、発声障害
消化器	口の感覚鈍麻
その他	頭痛、尿中血陽性

国内臨床試験で認められた副作用を記載した。

1.8.3.3.5 臨床検査結果に及ぼす影響

該当する事象がないため、設定しなかった。

1.8.3.3.6 過量投与

該当する事象がないため、設定しなかった。

1.8.3.3.7 適用上の注意

14. 適用上の注意

14.1 薬剤交付時の注意

14.1.1 本剤はネブライザーを用いて吸入するタンパク製剤であり、加熱により活性が失われるおそれがあることから、超音波式（メッシュ式を除く）以外のネブライザーを使用するよう指導すること。また、ネブライザーは機種により使用方法及び性能が異なるため、患者に対してその使用方法及び性能をよく説明すること。

14.1.2 本剤を交付する際には、患者用説明文書を渡し、本剤の調製方法及び吸入方法を指導すること。

14.1.3 バイアルは遮光して冷蔵保存（2～8℃）するように指導すること。

14.2 薬剤調製時の注意

14.2.1 本剤は日局生理食塩液 4mL を用いて溶解し、1回に 2mL の薬液を使用すること。残りの薬液 2mL は冷蔵保存（2～8℃）して 18 時間以内に使用すること。

14.2.2 冷蔵保存（2～8℃）した残りの薬液を使用する場合は、常温に戻してから使用すること。

14.1 本剤を適正に使用するための注意として設定した。

14.2 本剤は1バイアルを2回に分けて使用することから設定した。

1.8.3.3.8 その他の注意

15. その他の注意
15.1 臨床使用に基づく情報
15.1.1 GM-CSF 製剤の皮下又は静脈内投与時にアナフィラキシーがあらわれたとの外国での報告がある。
15.1.2 本剤の投与による抗顆粒球マクロファージコロニー刺激因子（GM-CSF）抗体濃度の増加が報告されている。

15.1.1 本剤は米国で注射剤（Leukine®）として販売されている。Leukine®の臨床使用時に報告された事象を記載した。

15.1.2 PAGE 試験では、本剤の投与により抗 GM-CSF 抗体濃度の増加が認められた。PAGE 試験では試験期間中に明らかな効果の減弱は認められなかったが、抗体濃度の増加により本剤の効果が減弱する可能性は否定できないため、設定した。

1.8.3.4 参考文献

1) 日本呼吸器学会. 肺胞蛋白症診療ガイドライン 2022.
2) Leukine®添付文書（2022 年）

1.9 一般的名称に係る文書

1.9.1 JAN

平成 18 年 7 月 12 日付薬食審査発第 0712001 号により通知された。

JAN（日本名）：サルグラモスチム（遺伝子組換え）

JAN（英　名）：Sargramostim (Genetical Recombination)

薬食審査発第 0712001 号
平 成 18 年 7 月 12 日

各都道府県衛生主管部（局）長　殿

厚生労働省医薬食品局審査管理課長

医薬品の一般的名称について（通知）

今般、医薬品の一般的名称命名の申請又は届出のありました物質につきまして、新たに一般的名称を別表１及び別表２のとおり定めましたので、御了知の上、関係方面に周知方よろしく御配慮願いたい。

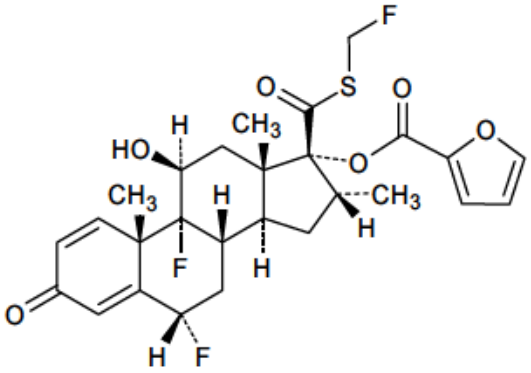
別表１：医薬品名称専門協議において結論を得た JAN
（ただし、今後、INN との整合が図られる可能性のある物質）

別表２：本体若しくは遊離体について r－INN 又は ISO 規格として採択されたものであって、医薬品名称専門協議において JAN に収載するべきとされたもの

（別表１）

登録番号：　　17-4-A1
ＪＡＮ（日本名）：　　B 型ボツリヌス毒素
ＪＡＮ（英　名）：　　Botulinum Toxin Type B

登録番号：　　17-4-A2
ＪＡＮ（日本名）：　　フルチカゾンフランカルボン酸エステル
ＪＡＮ（英　名）：　　Fluticasone Furoate

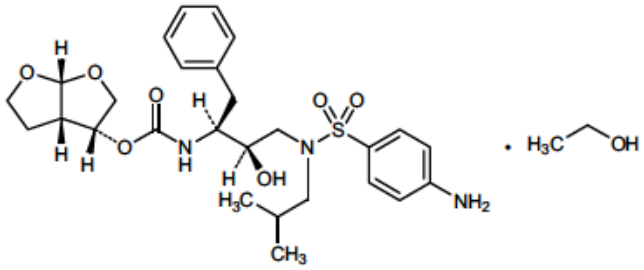


（別表２）

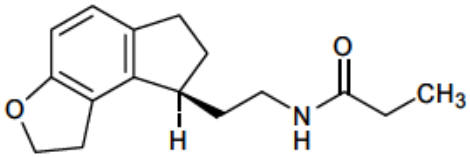
登録番号：　16-3-B9
ＪＡＮ（日本名）：　サルグラモスチム（遺伝子組換え）
ＪＡＮ（英　名）：　Sargramostim (Genetical Recombination)

登録番号：　16-3-B10
ＪＡＮ（日本名）：　イブリツモマブ　チウキセタン（遺伝子組換え）
ＪＡＮ（英　名）：　Ibritumomab Tiuxetan (Genetical Recombination)

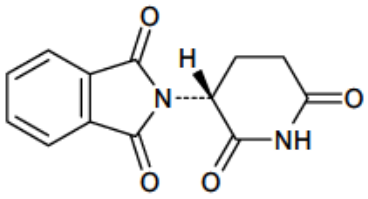
登録番号：　17-4-B1
ＪＡＮ（日本名）：　ダルナビル　エタノール付加物
ＪＡＮ（英　名）：　Darunavir Ethanolate



登録番号：　17-4-B2
ＪＡＮ（日本名）：　ラメルテオン
ＪＡＮ（英　名）：　Ramelteon



登録番号：　　17-4-B3
ＪＡＮ（日本名）：　サリドマイド
ＪＡＮ（英　名）：　Thalidomide



及び鏡像異性体

登録番号：　　17-4-B4
ＪＡＮ（日本名）：　インスリン　グルリジン（遺伝子組換え）
ＪＡＮ（英　名）：　Insulin Glulisine (Genetical Recombination)

登録番号：　　17-4-B5
ＪＡＮ（日本名）：　ラスブリカーゼ（遺伝子組換え）
ＪＡＮ（英　名）：　Rasburicase (Genetical Recombination)

登録番号：　　17-3-A3
ＪＡＮ（日本名）：　インドキサカルブ
ＪＡＮ（英　名）：　Indoxacarb

1.10 毒薬・劇薬等の指定審査資料のまとめ

<table>
<tr><td>化学名・別名</td><td>酵母由来の遺伝子組換えヒト顆粒球・マクロファージコロニー刺激因子である、127 個のアミノ酸からなる糖タンパク質（分子量：19,500、16,800、15,500）（別名 サルグラモスチム（遺伝子組換え））及びその製剤</td></tr>
<tr><td>構造式</td><td>Ala-Pro-Ala-Arg-Ser-Pro-Ser-Pro-Ser-Thr-Gln-Pro-Trp-Glu-His-Val-Asn-Ala-Ile-Gln-Glu-Ala-Leu-Arg-Leu-Leu-Asn-Leu-Ser-Arg-Asp-Thr-Ala-Ala-Glu-Met-Asn-Glu-Thr-Val-Glu-Val-Ile-Ser-Glu-Met-Phe-Asp-Leu-Gln-Glu-Pro-Thr-Cys-Leu-Gln-Thr-Arg-Leu-Glu-Leu-Tyr-Lys-Gln-Gly-Leu-Arg-Gly-Ser-Leu-Thr-Lys-Leu-Lys-Gly-Pro-Leu-Thr-Met-Met-Ala-Ser-His-Tyr-Lys-Gln-His-Cys-Pro-Pro-Thr-Pro-Glu-Thr-Ser-Cys-Ala-Thr-Gln-Ile-Ile-Thr-Phe-Glu-Ser-Phe-Lys-Glu-Asn-Leu-Lys-Asp-Phe-Leu-Leu-Val-Ile-Pro-Phe-Asp-Cys-Trp-Glu-Pro-Val-Gln-Glu</td></tr>
<tr><td>効能・効果</td><td>自己免疫性肺胞蛋白症</td></tr>
<tr><td>用法・用量</td><td>通常、成人にはサルグラモスチム（遺伝子組換え）として 125μg を 1 日 2 回、ネブライザーを用いて 7 日間連日吸入投与し、7 日間休薬する。これを 1 クールとし、投与を繰り返す。</td></tr>
<tr><td>劇薬等の指定</td><td></td></tr>
<tr><td>市販名及び有効成分・分量</td><td>原体：サルグラモスチム（遺伝子組換え）
製剤：サルグマリン吸入用 250μg（1 バイアル中サルグラモスチム（遺伝子組換え）250μg 含有）</td></tr>
<tr><td>毒性</td><td>単回投与毒性
<table>
<tr><th>動物種</th><th>投与経路</th><th>性</th><th>最大非致死量（μg/kg）</th></tr>
<tr><td>サル</td><td>静注</td><td>♂♀</td><td>>300</td></tr>
</table>
反復投与毒性
<table>
<tr><th>動物種</th><th>投与期間</th><th>性</th><th>投与経路・投与量（μg/kg/日）</th><th>無毒性量（μg/kg/日）</th><th>主な毒性所見</th></tr>
<tr><td>カニクイザル</td><td>2 週間</td><td>♂♀</td><td>静注
0, 1, 10, 100</td><td>10</td><td>100：白血球系パラメータ（白血球数・好中球数・リンパ球数・単球数・好酸球数・好塩基球数）の高値、骨髄増生、精巣上体の細胞浸潤
≥10：脾臓の腫大、脾臓重量の高値、脾臓の組織球の増殖</td></tr>
<tr><td>カニクイザル</td><td>1 ヵ月間</td><td>♂♀</td><td>皮下投与
0, 20, 200</td><td>20</td><td>200：白血球系パラメータの高値傾向、赤血球系パラメータ（赤血球数・ヘマトクリット値・ヘモグロビン濃度）の低値傾向、アルブミン及び A/G 比の低値傾向、グロブリンの高値傾向、投与部位の硬化、脾臓の実重量・相対重量の高値傾向、骨髄の増生、胸腺の萎縮
≥20：投与部位の浮腫</td></tr>
<tr><td>カニクイザル</td><td>6 週間</td><td>♂♀</td><td>皮下投与
0, 20, 63, 200</td><td>20 未満</td><td>200：♂1 匹、♀2 匹が死亡、心膜嚢及び関節の漿液貯留、脾臓・各種リンパ節の肥大、各種臓器における炎症性細胞浸潤及びリンパ様細胞浸潤
≥63：リンパ節の腫大、投与部位の潮紅・浮腫・痂疲形成、脾臓の実重量・相対重量の高値
≥20：白血球系パラメータ及び血小板の高値傾向、グロブリンの高値、アルブミン及び A/G 比の低値傾向、肝</td></tr>
</table></td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td></td><td></td><td></td><td></td><td></td><td>臓・心臓・肺・膀胱・精巣・精巣上体・皮膚・脈絡叢（大脳）・気管・下顎腺における炎症性細胞浸潤、腎臓・食道・下顎腺・甲状腺・副甲状腺・下垂体・副腎・膵臓・精巣上体・大脳におけるリンパ様細胞浸潤、腸間膜リンパ節・下顎リンパ節などにおけるリンパ組織の過形成</td></tr>
<tr><td>カニクイザル</td><td>26 週間間歇</td><td>♂♀</td><td>吸入投与
0, 5, 100, 500</td><td>500</td><td>500：好塩基球比の高値
≥100：白血球数パラメータの高値
≥5：肺門及び気管リンパ節の大型化、気管支関連リンパ節の増加、肺門及び気管リンパ節の過形成</td></tr>
</table>
</td></tr>
<tr><td>副作用</td><td>
国内で実施された自己免疫性肺胞蛋白症患者を対象とした医師主導第Ⅲ相試験（PAGE 試験）で、本剤を投与した被験者に発現した副作用の発現率（臨床検査値異常を含む）は、以下のとおりである。

副作用発現率：8.3%（5/60 例）

<table>
<tr><th>副作用の種類</th><th>発現率</th></tr>
<tr><td>口の感覚鈍麻</td><td>1.7%（1/60 例）</td></tr>
<tr><td>赤血球増加症</td><td>1.7%（1/60 例）</td></tr>
<tr><td>咳嗽</td><td>1.7%（1/60 例）</td></tr>
<tr><td>発声障害</td><td>1.7%（1/60 例）</td></tr>
<tr><td>頭痛</td><td>1.7%（1/60 例）</td></tr>
</table>

<table>
<tr><th>臨床検査値異常の種類</th><th>発現率</th></tr>
<tr><td>尿中血陽性</td><td>1.7%（1/60 例）</td></tr>
<tr><td>白血球数増加</td><td>1.7%（1/60 例）</td></tr>
</table>
</td></tr>
<tr><td>会社</td><td>ノーベルファーマ株式会社　製剤：輸入</td></tr>
</table>

別紙様式１

生物由来製品又は特定生物由来製品の指定資料のまとめ

一般名：	サルグラモスチム（遺伝子組換え）
販売名：	サルグマリン 250μg セット、吸入剤
申請者：	ノーベルファーマ株式会社
効能・効果：	自己免疫性肺胞蛋白症
用法・用量：	1 回 125μg を 1 日に 2 回吸入する
生物由来原料等の使用の有無	☑使用→ 使用している場合は以下の欄を記入 ☐不使用
使用した生物由来原料等	☐ヒト由来細胞・組織、 ☐ヒト由来成分(血液、尿、その他)、 ☐動物由来細胞・組織、 ☑動物由来成分(血液、その他) 原材料名；Bacto ペプトン、Hy-Case SF（カゼイン加水分解物）、カザミノ酸
生物由来原料等の使用目的	☐宿主細胞、☑培地添加物、☐その他の製造原材料、☐製剤添加物、☐その他( )
原料等の由来となるヒト・動物のスクリーニング・管理の内容：	合致する基準の告示・通知等があれば引用 (動物由来原料基準、反芻動物由来原料基準)
生物由来原料等に対する不活化処理等の内容：	個々の原料に対して不活化処理が行われている（別紙様式２参照）。
ウイルスクリアランス試験結果の概要：	原薬は酵母 *saccharomyces cerevisiae* で拡大培養され、ヒト動物由来ウイルスは増殖する可能性は低い。よってウイルスクリアランス試験は不要と判断されている。

製造工程の概要(フローチャート)： (不活化処理には下線を付し、処理条件を具体的に記載)	セルバンク解凍→[redacted]培養→[redacted]培養→生産培地成分 SIP→生産培養→[redacted]ろ過→[redacted]ろ過→[redacted]→[redacted]→[redacted]→陽イオン交換→原薬バルクろ過→原薬バルク凍結→解凍→製剤化→無菌ろ過→分注→凍結乾燥 以下に詳細を記す • 生産培地成分 SIP：Bacto ペプトンを含む生産培地成分は、122℃、30 分間の条件で不活化する。 • [redacted]～陽イオン交換：連続するクロマトグラフィー工程でタンパク質を精製する。この間有機溶媒との長時間の接触がある（[redacted]）。[redacted]及び[redacted]工程では低 pH（< 3 pH）に曝露される。 • 無菌ろ過：孔径 0.22 μm フィルターによるろ過（[redacted]ろ過含め 2 回実施）

別紙様式２

使用した生物由来原料等の名称[注1),注2)]	Bacto ペプトン（ウシの組織（骨及び胆汁等）及び米国産 24 月齢未満のブタ膵臓）
使用した生物由来原料等の分類	□ヒト血液由来成分、□ヒト細胞組織、□ヒト尿由来成分、□ヒト由来成分(血液、細胞組織又は尿を除くもの)、☑反芻動物由来成分、□動物細胞組織、☑動物由来成分、□その他（ ）
生物由来原料等の使用目的	□有効成分、□宿主細胞、☑培地添加物（生産培養）、□その他の製造原料等（ ）、□製剤添加物、 □その他（ ）
生物由来原料等の由来となるヒト・動物のスクリーニング・管理の内容 [注3)]	骨成分等は 2019 年以降採取された健康な米国産 30月齢未満のウシを、膵臓は健康な米国産 24 月齢未満のブタを使用している。骨成分には脊柱骨が含まれるが、頭蓋骨、脊髄は排除されている。30 月齢未満の脊柱骨に由来する TSE 伝播のリスクは極めて低い。 • 米国では、30 月齢以上のウシの脊柱骨が過去に使用禁止とされていたが、2018 年に当該法令が撤廃されている（83 FR 49023）。 • 欧州では、医薬品への 30 月齢未満のウシの脊柱骨由来の原料の使用は許容されている（EMA/410/01）。 • 本邦では、30 月齢未満のウシの脊柱骨は、と畜場法における特定危険部位から除かれている（「と畜場法施行規則及び厚生労働省関係牛海綿状脳症対策特別措置法施行規則の一部を改正する省令並びに食品、添加物等の規格基準の一部を改正する件について」〔平成 25 年 2 月 1 日付 食安発 0201 第 5 号〕）。 「ウシ等由来原材料を使用した医薬品、医療用具等の一部変更承認申請等におけるリスク評価等の取扱いについて」（平成 15 年 8 月 1 日付け薬食審査発第 0801001 号・薬食安発第 0801001 号）に示される安全性確保の目安を満たしている。 当該原料は ISO9000 に準拠し、米国農務省及び FDA の認定施設で製造されている。 国内外に自己免疫性肺胞蛋白症を効能・効果とする医薬品はなく、サルグラモスチムは自己免疫性肺胞蛋白症に対する新しい治療薬として自己免疫性肺胞蛋白症の治療方法を改善し、医療に貢献する有用な薬剤である。米国で 1991 年の製造販売開始から 30 年間以上、約 50 万人以上の患者がサルグラモスチムで治療されているが、伝達性海綿状脳症（TSE）の副作用は報告されていない。本剤を吸入することにより患者が TSE に感染するリスクは極めて低く、本剤の臨床試験から認められた有効性及び安全性を踏まえると医療上のベネフィットがリスクを大きく上回ると考える。

生物由来原料等のウイルス等の不活化及び除去処理等の内容　注４）	骨成分は、強酸及び／又は強塩基処理がされている。 Bacto ペプトンとして最低 85℃で 10 時間加温する。 さらにサルグラモスチム（遺伝子組換え）製造時に、SIP（122℃、30 分間）を実施している。
製造工程の概要(フローチャート) 注5)注6) (不活化及び除去処理には下線を付し、条件を具体的に記載)	供給元より、申請者宛に欧州医薬品品質部門（EDQM）の証明書（CEP）が発行されている。それによると、Bacto ペプトンは TSE リスクを低減させるため欧州薬局方に規定された酸及び／又は塩基処理がなされ、TSE 伝播のリスクは十分に低減されている。 サルグラモスチム（遺伝子組換え）の製造方法は別添様式 1 参照。
ウイルスクリアランス試験結果の概要 注7)	本原料の SIP 処理は、生物由来原料基準の運用通知別添 1 に規定された以上の苛酷な条件に該当し、ウイルス不活化の検証がなされた条件に相当する。製品原薬は酵母 *saccharomyces cerevisiae* で拡大培養され、ヒト動物由来ウイルスの増殖する可能性は低い。

注１）複数の生物由来原料等を使用している場合、別紙様式２は当該原料等ごとに作成する。

注２）動物種及び使用部位も記載する。

注３）合致する告示・通知等がある場合は引用する。

注４）生物由来原料等の製造工程におけるすべての不活化処理等の内容を記載する。
なお、別紙として記載してもよい。

注５）滅菌工程については、方法・条件も含めて記載する。なお、別紙として記載してもよい。また、複数の生物由来原料等を使用している場合には本欄は共通となるので、「○○(共通となる原材料名)と同じ」と記載してもよい。

注６）生物由来原料等の製造工程については、記載する必要はない。

注７）ウイルスクリアランス試験を行っている場合には全て記載する。生物由来原料等の製造工程での結果と製品の製造工程での結果に分けられるものは分けて記載する。なお、別紙として記載してもよい。

別紙様式２

使用した生物由来原料等の名称[注1),注2)]	Hy-Case SF（ウシ乳由来カゼイン加水分解物）
使用した生物由来原料等の分類	□ヒト血液由来成分、□ヒト細胞組織、□ヒト尿由来成分、□ヒト由来成分(血液、細胞組織又は尿を除くもの)、☑反芻動物由来成分、□動物細胞組織、☑動物由来成分、□その他（ ）
生物由来原料等の使用目的	□有効成分、□宿主細胞、☑培地添加物（WCB の培養から■培養まで）、□その他の製造原料等( )、□製剤添加物、 □その他( )
生物由来原料等の由来となるヒト・動物のスクリーニング・管理の内容 注3)	オーストラリア及びニュージーランドを原産国とする健康なウシ由来の食用に適した牛乳を使用する。 cGMP に適合の FDA の認定施設で原料を製造している。
生物由来原料等のウイルス等の不活化及び除去処理等の内容 注４）	Hy-Case SF 製造工程では 135℃で 8 時間の不活化処理が実施されている。
製造工程の概要(フローチャート) 注5)注6) (不活化及び除去処理には下線を付し、条件を具体的に記載)	Hy-Case SF の詳細な製造工程は不明である。サルグラモスチム（遺伝子組換え）の製造方法は別添様式 1 参照。
ウイルスクリアランス試験結果の概要 注7)	本原料の不活化処理は、生物由来原料基準の運用通知別添 1 に規定された以上の苛酷な条件に該当し、ウイルス不活化の検証がなされた条件に相当する。製品原薬は酵母 *saccharomyces cerevisiae* で拡大培養され、ヒト動物由来ウイルスの増殖する可能性は低い。

注１）複数の生物由来原料等を使用している場合、別紙様式２は当該原料等ごとに作成する。

注２）動物種及び使用部位も記載する。

注３）合致する告示・通知等がある場合は引用する。

注４）生物由来原料等の製造工程におけるすべての不活化処理等の内容を記載する。
なお、別紙として記載してもよい。

注５）滅菌工程については、方法・条件も含めて記載する。なお、別紙として記載してもよい。また、複数の生物由来原料等を使用している場合には本欄は共通となるので、「○○(共通となる原材料名)と同じ」と記載してもよい。

注６）生物由来原料等の製造工程については、記載する必要はない。

注７）ウイルスクリアランス試験を行っている場合には全て記載する。生物由来原料等の製造工程での結果と製品の製造工程での結果に分けられるものは分けて記載する。なお、別紙として記載してもよい。

別紙様式２

使用した生物由来原料等の名称[注1),注2)]	カザミノ酸（ウシ乳）
使用した生物由来原料等の分類	□ヒト血液由来成分、□ヒト細胞組織、□ヒト尿由来成分、□ヒト由来成分(血液、細胞組織又は尿を除くもの)、☑反芻動物由来成分、□動物細胞組織、☑動物由来成分、□その他（ ）
生物由来原料等の使用目的	□有効成分、□宿主細胞、□培地添加物(WCB の培養から種細胞の培養まで)、□その他の製造原料等（ ）、□製剤添加物、☑その他(MCB 培養の培地添加剤)
生物由来原料等の由来となるヒト・動物のスクリーニング・管理の内容 注3)	カザミノ酸について、以下に示す安全性確保措置が講じられており「生物由来原料基準の規定を満たさないマスターセルバンク又はマスターシードを使用した医薬品等の取扱いについて」（平成 21 年 3 月 27 日付 事務連絡）の条件を満たしている。
生物由来原料等のウイルス等の不活化及び除去処理等の内容 注４）	1989 年に MCB の培養前に、カザミノ酸を含む培地成分がオートクレーブ（121℃、30 分以上）されている。
製造工程の概要(フローチャート) 注5)注6) (不活化及び除去処理には下線を付し、条件を具体的に記載)	1989 年に MCB が構築された際に使用された。 サルグラモスチム（遺伝子組換え）の製造方法は別添様式１参照。
ウイルスクリアランス試験結果の概要 注7)	本原料のオートクレーブは生物由来原料基準運用通知別添１ウイルス不活化の検証がなされた条件に相当する。製品原薬は酵母 *saccharomyces cerevisiae* で拡大培養され、ヒト動物由来ウイルスの増殖する可能性は低い。

注１）複数の生物由来原料等を使用している場合、別紙様式２は当該原料等ごとに作成する。

注２）動物種及び使用部位も記載する。

注３）合致する告示・通知等がある場合は引用する。

注４）生物由来原料等の製造工程におけるすべての不活化処理等の内容を記載する。なお、別紙として記載してもよい。

注５）滅菌工程については、方法・条件も含めて記載する。なお、別紙として記載してもよい。また、複数の生物由来原料等を使用している場合には本欄は共通となるので、「○○(共通となる原材料名)と同じ」と記載してもよい。

注６）生物由来原料等の製造工程については、記載する必要はない。

注７）ウイルスクリアランス試験を行っている場合には全て記載する。生物由来原料等の製造工程での結果と製品の製造工程での結果に分けられるものは分けて記載する。なお、別紙として記載してもよい。

第3部（モジュール3）　品質に関する文書　添付資料一覧

3.1 第3部目次

3.2 データ又は報告書

3.2.S 原薬（サルグラモスチム（遺伝子組換え）、Partner Therapeutics

資料番号	表　題	著者	評価/参考
3.2.S 原薬（サルグラモスチム、Partner Therapeutics）			
3.2.S.1 一般情報（サルグラモスチム、Partner Therapeutics）			
3.2.S.1.1 名称（サルグラモスチム、Partner Therapeutics）			
3.2.S.1-1	General information	Partner Therapeutics	評価
3.2.S.1.2 構造（サルグラモスチム、Partner Therapeutics）			
3.2.S.1-1	General information	Partner Therapeutics	評価
3.2.S.1.3 一般特性（サルグラモスチム、Partner Therapeutics）			
3.2.S.1-2	Drug Substance General Properties	[redacted]	評価
3.2.S.2 製造（サルグラモスチム、Partner Therapeutics）			
3.2.S.2.1 製造業者（サルグラモスチム、Partner Therapeutics）			
3.2.S.2.1-1	Manufacture	Partner Therapeutics	評価
3.2.S.2.2 製造方法及びプロセス・コントロール（サルグラモスチム、Partner Therapeutics）			
3.2.S.2.1-1	Manufacture	Partner Therapeutics	評価
3.2.S.2.3 原材料の管理（サルグラモスチム、Partner Therapeutics）			
3.2.S.2.1-1	Manufacture	Partner Therapeutics	評価
3.2.S.2.4 重要工程及び重要中間体の管理（サルグラモスチム、Partner Therapeutics）			
3.2.S.2.1-1	Manufacture	Partner Therapeutics	評価
3.2.S.2.5 プロセス・バリデーション／プロセス評価（サルグラモスチム、Partner Therapeutics）			
3.2.S.2.5-1	Process Validation and_or evaluation Summary	Partner Therapeutics	評価
3.2.S.2.5-2	Process Validation and_or evaluation Fermentation	Partner Therapeutics	評価
3.2.S.2.5-3	Process Validation and_or evaluation Harvest	Partner Therapeutics	評価
3.2.S.2.5-4	Process Validation and_or evaluation Purification	Partner Therapeutics	評価
3.2.S.2.5-5	Process Validation_Continuous Process Validation [redacted]	Partner Therapeutics	評価
3.2.S.2.5-6	3.2.S.2.5-6　Process Validation_Continuous Process Validation B26358_B26428	Partner Therapeutics	評価
3.2.S.2.6 製造工程の開発の経緯（サルグラモスチム、Partner Therapeutics）			
3.2.S.2.6-1	Manufacturing Process Development_Fermentation and Harvest	Partner Therapeutics	評価
3.2.S.2.6-2	Manufacturing Process Development_Purification	Partner Therapeutics	評価
3.2.S.2.6-3	Manufacturing Process Development_Comparability	Partner Therapeutics	評価
3.2.S.2.6-4	Manufacturing Process Developement_[redacted] process	Partner Therapeutics	評価
3.2.S.2.6-5	3.2.S.3.1 Elucidation of Structure and Other Characteristics [redacted] process	Partner Therapeutics	評価
3.2.S.3 特性（サルグラモスチム、Partner Therapeutics）			
3.2.S.3.1 構造その他の特性の解明（サルグラモスチム、Partner Therapeutics）			
3.2.S.3-1	Characterization of Sargramostim	[redacted]	評価
3.2.S.3.2 不純物（サルグラモスチム、Partner Therapeutics）			
3.2.S.3-2	Characterization_Impurities	Partner Therapeutics	評価
3.2.S.3-3	Impurities_[redacted] and elemental impurities	Partner Therapeutics	評価
3.2.S.3-4	RSK-0141 Nitrosamine Impurities Risk Assessment NP BDS Sargramostim	Partner Therapeutics	評価
3.2.S.4 原薬の管理（サルグラモスチム、Partner Therapeutics）			
3.2.S.4.1 規格及び試験方法（サルグラモスチム、Partner Therapeutics）			
3.2.S.4.1-1	3.2.S.4.1 Specification	Partner Therapeutics	評価
3.2.S.4.2 試験方法（分析方法）（サルグラモスチム、Partner Therapeutics）			
3.2.S.4.2-1	T-0023 Appearance Color Clarity Test Procedure	Partner Therapeutics	評価
3.2.S.4.2-2	T-0323-26 Glu-C Peptide Mapping Procedure for rhu GM-CSF	Partner Therapeutics	評価
3.2.S.4.2-3	T-0114-16 Isoelectric Focusing (IEF) Test Procedure for rhu GM-CSF	Partner Therapeutics	評価
3.2.S.4.2-4	T-0002-36 SDS-PAGE [redacted] Procedure	Partner Therapeutics	評価
3.2.S.4.2-5	T-0019-28 pH Determinations	Partner Therapeutics	評価
3.2.S.4.2-6	T-0108-18 Monosaccharide Compositional Analysis for rhu GM-CSF	Partner Therapeutics	評価

3.2.S.4.2-7	T-0075-42 Glycosylated Variants and Concentration by HPLC	Partner Therapeutics	評価
3.2.S.4.2-8	T-0013-25 Scanning Densitometry for rhu GM-CSF	Partner Therapeutics	評価
3.2.S.4.2-9	T-0154-36 Size Exclusion Chromatography of GM-CSF	Partner Therapeutics	評価
3.2.S.4.2-10	T-3007-19 Endotoxin Assay- [redacted] Method	Partner Therapeutics	評価
3.2.S.4.2-11	T-3011-15 Microbial Content Assay	Partner Therapeutics	評価
3.2.S.4.2-12	T-0091-44 [redacted] Bioassay for rhu GM-CSF	Partner Therapeutics	評価
3.2.S.4.2-13	SOP-0305-16 Secondary Reference Standard Policies for T-0091	Partner Therapeutics	評価
3.2.S.4.2-14	SOP-0319-19 Cell Passaging and Counting Procedure for the [redacted] Cell Line	Partner Therapeutics	評価
3.2.S.4.2-15	T-0315-18 Leukine (sargramostim) UV Spectrophotometer Scan	Partner Therapeutics	評価
3.2.S.4.3 試験方法（分析方法）のバリデーション（サルグラモスチム、Partner Therapeutics）			
3.2.S.4.3-1	QCMV-T3007-102913R_Compendial Verification of Endotoxin Assay	[redacted]	評価
3.2.S.4.3-2	QCMV-0174_Validation of the Glu-C Peptide Map Method for GM-CSF	Partner Therapeutics	評価
3.2.S.4.3-3	QCMV-0013.01 Validation of IEF for GM-CSF	Partner Therapeutics	評価
3.2.S.4.3-4	QCMV-T0002-041718R_Method Validation of Test Method SOP-0002 SDS-PAGE Silver Stain Procedure using WedgeWell gels	Partner Therapeutics	評価
3.2.S.4.3-5	QCMV-T0108-061715R Validation of Test Method SOP-T0108 Monosacchride Composition Analysis of rhu GM-CSF	[redacted]	評価
3.2.S.4.3-6	MVR-0004 Validation of Test Method T-0075 “Quantitative Analysis of rhu GM-CSF Glycosylated Variants by HPLC	Partner Therapeutics	評価
3.2.S.4.3-7	QCMV-0185_1026 scanning densitometory	Partner Therapeutics	評価
3.2.S.4.3-8	QCMV-T0154-101812R Validation Report Test Method SOP-T0154 SE-HPLC of GM-CSF using the [redacted] analytical column	[redacted]	評価
3.2.S.4.3-9	QCMV-0132 Immunex Quality Control Test Method Validation [redacted] Bioassay for GM-CSF	Partner Therapeutics	評価
3.2.S.4.3-10	QCMV-0132.01_T-0091 Method Validation Package of the [redacted] Bioassay for Leukine	Partner Therapeutics	評価
3.2.S.4.3-11	QCMV-T0315-051414R INDEX	[redacted]	評価
3.2.S.4.4 ロット分析（サルグラモスチム、Partner Therapeutics）			
3.2.S.4.4-1	CoAs	[redacted], [redacted], Partner Therapeutics	評価
3.2.S.4.5 規格及び試験方法の妥当性（サルグラモスチム、Partner Therapeutics）			
3.2.S.4.5-1	Justification of Specifications	Partner Therapeutics	評価
3.2.S.5 標準品又は標準物質（サルグラモスチム、Partner Therapeutics）			
3.2.S.5-1	Reference standards or materials	Partner Therapeutics	評価
3.2.S.6 容器及び施栓系（サルグラモスチム、Partner Therapeutics）			
3.2.S.6-1	Description of Container closure systems	Partner Therapeutics	評価
3.2.S.7 安定性（サルグラモスチム、Partner Therapeutics）			
3.2.S.7.1 安定性のまとめ及び結論（サルグラモスチム、Partner Therapeutics）			
3.2.S.7.1-1	2021-2022 Annual Product Review_[redacted]	Partner Therapeutics	評価
3.2.S.7.1-2	Stability Summary and Conclusions [redacted]	Partner Therapeutics	評価
3.2.S.7.2 承認後の安定性試験計画の作成及び実施（サルグラモスチム、Partner Therapeutics）			
3.2.S.7.2-1	Drug Substance Post Approval Stability Protocol and Stability Commitment	Partner Therapeutics	評価
3.2.S.7-2-2	Post-approval Stability Protocol and Stability Commitment [redacted]	Partner Therapeutics	評価
3.2.S.7.3 安定性データ（サルグラモスチム、Partner Therapeutics）			
3.2.S.7.3-1	Stability Data	Partner Therapeutics	評価
3.2.S.7.3-2	Stability Data	Partner Therapeutics	評価
3.2.S.7.3-3	Stability Data ([redacted] batches)	Partner Therapeutics	評価

第3部（モジュール3）　品質に関する文書　添付資料一覧

3.2.P 製剤（サルグマリン吸入用250 μg、吸入剤）

資料番号	表題	著者	評価/参考
3.2.P.1 製剤及び処方（サルグマリン吸入用250 μg、吸入剤）			
3.2.P.1-1	Description and Composition of the Drug Product ([redacted])	Partner Therapeutics Inc	評価
3.2.P.2 製剤開発の経緯（サルグマリン吸入用250 μg、吸入剤）			
3.2.P.2.1-1	Components of the Drug Product ([redacted])	Partner Therapeutics Inc	評価
3.2.P.2.2-1	Drug Product ([redacted])	Partner Therapeutics Inc	評価
3.2.P.2.3-1	Manufacturing Process Development ([redacted])	Partner Therapeutics Inc	評価
3.2.P.2.4-1	Container Closure System ([redacted])	Partner Therapeutics Inc	評価
3.2.P.2.5-1	Microbiological Attributes ([redacted])	Partner Therapeutics Inc	評価
3.2.P.2.6-1	Compatibility ([redacted])	Partner Therapeutics Inc	評価
3.2.P.2.6-2	使用時安定性試験	ノーベルファーマ（株）	評価
3.2.P.2.6-3	吸入器の比較試験	ノーベルファーマ（株）	評価
3.2.P.2.6-4	空気力学的粒度ロット比較試験	ノーベルファーマ（株）	評価
3.2.P.3 製造（サルグマリン吸入用250 μg、吸入剤）			
3.2.P.3.1 製造者（サルグマリン吸入用250 μg、吸入剤）			
3.2.P.3.1-1	Manufacturers ([redacted])	Partner Therapeutics Inc	評価
3.2.P.3.2 製造処方（サルグマリン吸入用250 μg、吸入剤）			
3.2.P.3.2-1	Batch Formula ([redacted])	Partner Therapeutics Inc	評価
3.2.P.3.3 製造工程及びプロセス・コントロール（サルグマリン吸入用250 μg、吸入剤）			
3.2.P.3.3-1	Description of Manufacturing Process and Process Controls ([redacted])	Partner Therapeutics Inc	評価
3.2.P.3.4 重要工程及び重要中間体の管理（サルグマリン吸入用250 μg、吸入剤）			
3.2.P.3.4-1	Controls of Critical Steps and Intermediates ([redacted])	Partner Therapeutics Inc	評価
3.2.P.3.5 プロセス・バリデーション／プロセス評価（サルグマリン吸入用250 μg、吸入剤）			
3.2.P.3.5-1	Process Validation and-or Evaluation ([redacted])	Partner Therapeutics Inc	評価
3.2.P.3.5-2	[redacted]Additional Investigation-[redacted] (20MAR2023)	Partner Therapeutics Inc	評価
3.2.P.4 添加剤の管理（サルグマリン吸入用250 μg、吸入剤）			
3.2.P.4-1	Specifications ([redacted])	Partner Therapeutics Inc	評価
	Certificates of Excipients Used in PPQ Batches	ノーベルファーマ（株）	評価
3.2.P.4-2	公定書記載のため提出せず		
3.2.P.4-3	公定書記載のため提出せず		
3.2.P.4-4	Justification of Specifications ([redacted])	Partner Therapeutics Inc	評価
3.2.P.4-5	Excipients of Human or Animal Origin	Partner Therapeutics Inc	評価
3.2.P.4.6	2.3.A.3 記載のため提出せず		
3.2.P.5 製剤の管理（サルグマリン吸入用250 μg、吸入剤）			
3.2.P.5.1 規格及び試験方法（サルグマリン吸入用250 μg、吸入剤）			
3.2.P.5.1-1	Specifications ([redacted])	Partner Therapeutics Inc	評価
3.2.P.5.2 試験方法（分析方法）（サルグマリン吸入用250 μg、吸入剤）			
3.2.P.5.2-1	T-0397-23 GM—CSF Quantitation by Size Exclusion High Performance Liquid Chromatography	Partner Therapeutics Inc	評価
3.2.P.5.3 試験方法（分析方法）のバリデーション（サルグマリン吸入用250 μg、吸入剤）			
3.2.P.5.3-1	QCMV-T0397-040114R QC Method Validation Report, GM-CSF Quantitation by Size Exclusion High Performance Liquid Chromatography	[redacted]	評価
3.2.P.5.4 ロット分析（サルグマリン吸入用250 μg、吸入剤）			
3.2.P.5.4-1	Batch Analyses ([redacted])	Partner Therapeutics Inc	評価
3.2.P.5.4-2	Batch Analysis ([redacted]for Photo Stability Study)	[redacted]	評価
3.2.P.5.4-3	CoAs	[redacted], [redacted], Partner Therapeutics	評価
3.2.P.5.5 不純物の特性（サルグマリン吸入用250 μg、吸入剤）			
3.2.P.5.5-1	Characterization of Impurities ([redacted])	Partner Therapeutics Inc	評価
3.2.P.5.5-2	Nitrosamine Impurities Risk Assessment [redacted] DP Leukine	Partner Therapeutics Inc	評価
3.2.P.5.6 規格及び試験方法の妥当性（サルグマリン吸入用250 μg、吸入剤）			
3.2.P.5.6-1	Justification of Specifications ([redacted])	Partner Therapeutics Inc	評価
3.2.P.6 標準品又は標準物質（サルグマリン吸入用250 μg、吸入剤）			
3.2.P.6-1	Reference Standards or Materials ([redacted])	Partner Therapeutics Inc	評価
3.2.P.7 容器及び施栓系（サルグマリン吸入用250 μg、吸入剤）			
3.2.P.7-1	Container Closure System ([redacted])	Partner Therapeutics Inc	評価
3.2.P.7-2	Vial and Stopper drawing	ノーベルファーマ（株）	評価
3.2.P.8 安定性（サルグマリン吸入用250 μg、吸入剤）			
3.2.P.8-1	Stability Summary and Conclusion ([redacted])	Partner Therapeutics Inc	評価
3.2.P.8-2	Postapproval Stability Protocol and Stability Commitment ([redacted])	Partner Therapeutics Inc	評価
3.2.P.8-3	Stability Data ([redacted])	Partner Therapeutics Inc	評価
3.2.P.8-4	Stability Data ([redacted])	Partner Therapeutics Inc	評価
3.2.P.8-5	Photo Stability Data	[redacted]	評価

第3部（モジュール3）　品質に関する文書　添付資料一覧
3.2.A その他（サルグマリン吸入用250μg、吸入液剤）

資料番号	文書Title	著者（作成者）	評価/参考
3.2.A.1 製造施設及び設備（サルグマリン吸入用250μgセット、吸入液剤）			
3.2.A.1-1	Facilities and Equipment PTX Northpointe	Partner Therapeutics, Inc	評価
3.2.A.1-2	Facilities and Equipment_[redacted]	Partner Therapeutics, Inc	評価
3.2.A.1-3	Attachments	Partner Therapeutics, Inc	評価
3.2.A.2 外来性感染性物質の安全性評価（サルグマリン吸入用250μgセット、吸入液剤）			
3.2.A.2-1	Adventitious Agents Safety Evaluation	Partner Therapeutics	評価
3.2.A.2-2	生物由来原料基準適合状況付属文書	ノーベルファーマ（株）	評価
3.2.A.3 添加剤（サルグマリン吸入用250μgセット、吸入液剤）			
3.2.A.3-1	新添加剤（D-マンニトール）資料	ノーベルファーマ（株）	評価
3.2.A.3-2	新添加剤（精製白糖）資料	ノーベルファーマ（株）	評価
3.2.A.3-3	新添加剤（トロメタモール）資料	ノーベルファーマ（株）	評価

第4部　非臨床試験報告書 添付資料一覧
4.2　試験報告書
4.2.1　薬理試験
4.2.1.1　効力を裏付ける試験

資料番号	タイトル	文献	国内外別	評価/参考	実施場所
4.2.1.1-1	GM-CSF薬理試験の検討	厚生労働科学研究費補助金（医療技術実用化総合研究事業(臨床研究推進研究事業）総括研究報告書、平成24年度総括・分担研究報告書	国内	参考	国立国際医療研究センター
4.2.1.1-2	Low concentrations of recombinant granulocyte macrophage-colony stimulating factor derived from Chinese hamster ovary cells augments long-term bioactivity with delayed clearance in vitro	Cytokine、2014 Aug;68(2):118-26	国内	参考	新潟大学医歯学総合病院生命科学医療センターなど
4.2.1.1-3	サル肺胞マクロファージを用いた、in vitroでのPAP患者肺胞内の再現の試み	厚生労働科学研究費補助金（医療技術実用化総合研究事業(臨床研究・治験推進研究事業））、平成26年度総括・分担研究報告書	国内	参考	新潟大学医歯学総合病院生命科学医療センター

4.2.2　薬物動態試験
4.2.2.1　分析法及びバリデーション報告書

資料番号	タイトル	試験番号	国内外別	評価/参考	実施場所
4.2.2.1-1	ELISA法によるサル血漿中Sargramostim（GM-CSF）の濃度測定法バリデーション試験	[redacted]	国内	参考	[redacted]
4.2.2.1-2	ELISA法によるカニクイザル抗GM-CSF抗体（GMAb）測定法バリデーション試験	[redacted]	国内	参考	[redacted]

4.2.2.2　吸収

資料番号	タイトル	文献/試験番号	国内外別	評価/参考	実施場所
4.2.2.2-1	Pharmacokinetics of recombinant human granulocyte macrophage colony-stimulating factor in Macaca mulatta	Acta pharmacologica Sinica 1998;19(1):50-3	-	参考	-

4.2.2.3　分布

資料番号	タイトル	文献/試験番号	国内外別	評価/参考	実施場所
4.2.2.3-1	Analysis of radiolabeled CHO cell-derived rHuGM-CSF pharmacokinetics and biodistribution in rhesus monkeys following intravenous and subcutaneous injection	Int J Immunopharmacol 1994;16(2):75-90	-	参考	-
4.2.2.3-2	Serum half-life and organ distribution of radiolabeled colony stimulating factor in mice	Exp Hematol 1977;5(6):456-64	-	参考	-
4.2.2.3-3	The passage of granulocyte-macrophage colony-stimulating factor across the human placenta perfused in vitro	J Soc Gynecol Investig 1999;6(6):307-10	-	参考	-

4.2.3　毒性試験
4.2.3.1　単回投与毒性試験

資料番号	タイトル	文献/試験番号	国内外別	評価/参考	実施場所
4.2.3.1-1	Acute intravenous toxicity study in cynomolgus monkeys	[redacted]	-	評価	[redacted], USA

4.2.3.2　反復投与毒性試験

資料番号	タイトル	試験番号	国内外別	評価/参考	実施場所
4.2.3.2-1	14-day subacute intravenous toxicity study in cynomolgus monkeys with a 14-day recovery period	[redacted]	-	評価	[redacted], USA
4.2.3.2-2	30-day repeated dose subcutaneous toxicity study in cynomolgus monkeys with a 14-day recovery period	[redacted]	-	評価	[redacted], USA
4.2.3.2-3	Orientating systemic toxicity study of sargramostim (ZK 250224) in monkeys(M/F) after daily subcutaneous administration over 42 days	[redacted]	-	評価	[redacted] ([redacted], USA)
4.2.3.2-4	Systemic toxicity study with sargramostim in Cynomolgus monkeys (M+F) after daily s. c. application over ca. 6 weeks and a recovery period of about 12 weeks	[redacted]	-	評価	[redacted]
4.2.3.2-5	Sargramostimのカニクイザルにおける26週間間歇吸入投与毒性試験	[redacted]	国内	評価	[redacted]

4.2.3.5　生殖発生毒性試験
4.2.3.5.1　受胎能及び着床までの初期胚発生に関する試験

資料番号	タイトル	試験番号	国内外別	評価/参考	実施場所
4.2.3.5.1-1	ZK 250224: A study of fertility and early embryonic development to implantation in female rabbits	[redacted]	-	評価	[redacted]

4.2.3.5.2　胚・胎児発生に関する試験

資料番号	タイトル	試験番号	国内外別	評価/参考	実施場所
4.2.3.5.2-1	ZK 250224 - Determination of the maximum tolerated dose by the subcutaneous route in the non-pregnant rabbits	[redacted]	-	参考	[redacted]
4.2.3.5.2-2	Determination of the maximum tolerated dose by the subcutaneous route over 14-days in the non-pregnant rabbit	[redacted]	-	参考	[redacted]

4.2.3.5.2-3	A dose range-finding study for effects on embryo/fetal development and early postnatal survival in rabbits	[redacted]	-	評価	[redacted]
4.2.3.5.2-4	ZK 250224 - Dose range-finding fertility and embryo-/fetotoxicity study by the subcutaneous route in the rabbit	[redacted]	-	参考	[redacted]
4.2.3.5.2-5	ZK 250224: Study for effects on embryo/fetal development in rabbits	[redacted]	-	評価	[redacted]

4.2.3.5.3　出生前及び出生後の発生並びに母体の機能に関する試験

資料番号	タイトル	試験番号	国内外別	評価/参考	実施場所
4.2.3.5.3-1	A study of the effects of ZK 250224 on pre- and postnatal development, including maternal function in rabbits	[redacted]	-	評価	[redacted]

4.3　参考文献

非臨床試験の概括評価(2.4)

資料番号	タイトル	報告書/文献	国内外別	評価/参考	実施場所
4.3-1	Granulocyte-macrophage colony-stimulating factor increases surfactant phospholipid in premature rabbits.	Pediatr Res. 1999;46(5):613-20.	-	参考	-
4.3-2	医薬品非臨床ガイドライン解説2013（2-9 バイオテクノロジー応用医薬品の非臨床における安全性評価）	薬事日報社、p119-136.	-	参考	-
4.3-3	肺胞蛋白症の病態と治療の最前線	日内会誌、2015;104:314-322.	-	参考	-

緒言(2.6.1)

資料番号	タイトル	報告書/文献	国内外別	評価/参考	実施場所
4.3-4	Inhaled GM-CSF for Pulmonary Alveolar Proteinosis.	N Engl J Med 2019;381:923-932.	-	参考	-

薬理試験(2.6.2)

資料番号	タイトル	報告書/文献	国内外別	評価/参考	実施場所
4.3-5	Involvement of granulocyte-macrophage colony-stimulating factor in pulmonary homeostasis.	Science 1994;264:713-716.	-	参考	-
4.3-6	Granulocyte/macrophage colony-stimulating factor-deficient mice show no major perturbation of hematopoiesis but develop a characteristic pulmonary pathology.	Proc. Natl. Acad. Sci. USA 1994;91: 5592-5596.	-	参考	-
4.3-7	Mice deficient for the IL-3/GM-CSF/IL-5 βc receptor exhibit lung pathology and impaired immune response, while βIL3 receptor-deficient mice are normal.	Immunity 1995;2:211-222.	-	参考	-
4.3-8	Hematopoietic and lung abnormalities in mice with a null mutation of the common β subunit of the receptors for granulocyte-macrophage colony-stimulating factor and interluekins 3 and 5.	Proc Natl Acad Sci USA 1995;92:9565-9569.	-	参考	-
4.3-9	Idiopathic pulmonary alveolar proteinosis as an autoimmune disease with neutralizing antibody against granulocyte/macrophage colony-stimulating factor.	J Exp Med 1999;190:875-880.	-	参考	-
4.3-10	Patient-derived granulocyte/macrophage colony-stimulating factor autoantibodies reproduce pulmonary alveolar proteinosis in nonhuman primates.	Am J Respir Crit Care Med 2010;182:49-61.	-	参考	-
4.3-11	Pulmonary alveolar proteinosis : progress in the first 44 years.	Am J Respir Crit Care Med 2002;166:215—235.	-	参考	-
4.3-12	Whole lung lavage therapy for pulmonary alveolar proteinosis: a global survey of current practices and procedures.	Orphanet J Rare Dis 2016;11:115.	-	参考	-
4.3-13	Pulmonary alveolar proteinosis.	N Engl J Med 2003;349:2527—2539.	-	参考	-
4.3-14	Aerosolized GM-CSF ameliorates pulmonary alveolar proteinosis in GM-CSF-deficient mice.	Am J Physiol (Lung Cell Mol Physiol) 1999:276:L556-L563.	-	参考	-
4.3-15	Granulocyte-macrophage colony-stimulating factor and lung immunity in pulmonary alveolar proteinosis.	Am J Respir Crit Care Med 2005;171:1142-9.	-	参考	-
4.3-16	Inhaled granulocyte/macrophage-colony stimulating factor as therapy for pulmonary alveolar proteinosis.	Am J Respir Crit Care Med 2010;181:1345-54.	-	参考	-

薬物動態試験(2.6.4)

資料番号	タイトル	報告書/文献	国内外別	評価/参考	実施場所
4.3-17	Quantikine® ELISA Human GM-CSF Immunoassay.	2015; R&D Systems, Inc.	-	参考	-
4.3-18	Comparative pharmacokinetics of single-dose administration of mammalian and bacterially-derived recombinant human granulocyte-macrophage colony-stimulating factor.	Eur J Haematol 1993;50(1):32-6	-	参考	-
4.3-19	遺伝子組換え型ヒト顆粒球コロニー形成刺激因子(rG-CSF)の体内動態における糖鎖の役割(1)：脱糖鎖型rG-CSFおよび大腸菌産生rG-CSFを用いた検討.	薬物動態. 1993;8(6):1181-90	-	参考	-
4.3-20	Assay system development to measure the concentration of sargramostim with high specificity in patients with autoimmune pulmonary alveolar proteinosis after single-dose inhalation.	J Immunol Methods 2018;460:1-9	-	参考	-

4.3-21	Physiological parameters in laboratory animals and humans.	Pharm Res 1993;10(7):1093-5	-	参考	-
4.3-22	Pharmacokinetic evaluation of technetium-99-metallothionein-conjugated mouse monoclonal antibody B72.3 in rhesus monkeys.	J Nucl Med 1989;30(8):1351-7	-	参考	-
4.3-23	Granulocyte-macrophage colony-stimulating factor in human milk.	Eur J Pediatr 1996;155(1):69	-	参考	-

毒性試験(2.6.6)

資料番号	タイトル	報告書/文献	国内外別	評価/参考	実施場所
4.3-24	Granulocyte macrophage-colony stimulating factor crosses the blood-testis barrier in mice.	Biol Reprod. 1997;57(4):822-6.	-	参考	-
4.3-25	Long Term Administration of Granulocyte-Macrophage Colony Stimulating Factor Decreases Development of 1-2 Dimethylhydrazine-Induced Colon Cancer in Rats.	Journal of Surgical Oncology 2007;95:12-21	-	参考	-
4.3-26	Granulocyte Macrophage Colony-Stimulating Factor Inhibits Breast Cancer Growth and Metastasis by Invoking an Anti-Angiogenic Program in Tumor-Educated Macrophages.	Cancer Res. 2009;69(5):2133-40	-	参考	-
4.3-27	Effects of combined granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2, and interleukin-12 based immunotherapy against intracranial glioma in the rat.	J.Neurooncol.2004;66 :39-49	-	参考	-