**Report on the Deliberation Results**

March 4, 2024
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

| | |
|---|---|
| **Brand Name** | Sargmalin for Inhalation 250 μg |
| **Non-proprietary Name** | Sargramostim (Genetical Recombination) (JAN*) |
| **Applicant** | Nobelpharma Co., Ltd. |
| **Date of Application** | June 30, 2023 |

**Results of Deliberation**

In its meeting held on March 4, 2024, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product. The re-examination period is 10 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

**Approval Conditions**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product, until data from a certain number of patients are accrued and to promptly obtain safety and efficacy data on the product. On the basis of the obtained data, the applicant should take necessary actions for the proper use of the product.

**Japanese Accepted Name (modified INN)*

**Review Report**

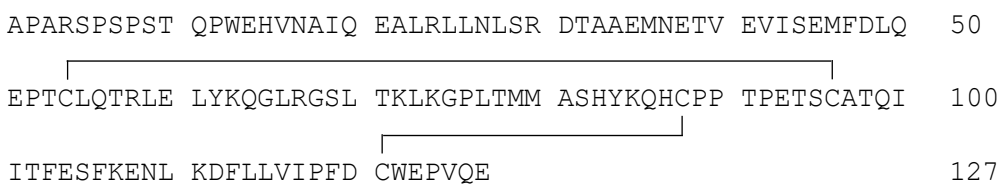
February 21, 2024
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

| | |
|---|---|
| **Brand Name** | Sargmalin for Inhalation 250 μg |
| **Non-proprietary Name** | Sargramostim (Genetical Recombination) |
| **Applicant** | Nobelpharma Co., Ltd. |
| **Date of Application** | June 30, 2023 |
| **Dosage Form/Strength** | Lyophilized powder to be reconstituted before inhalation[1)]: Each vial contains 264 μg of sargramostim (genetical recombination) |
| **Application Classification** | Prescription drug, (1) Drug with a new active ingredient |
| **Definition** | Sargramostim is a recombinant human granulocyte-macrophage colony-stimulating factor analog (R23L). Sargramostim is a glycoprotein (molecular weight: ca. 17,000) consisting of 127 amino acid residues. |

**Structure**

Amino acid sequence and disulfide bonds:




Partial processing: A1 to P2

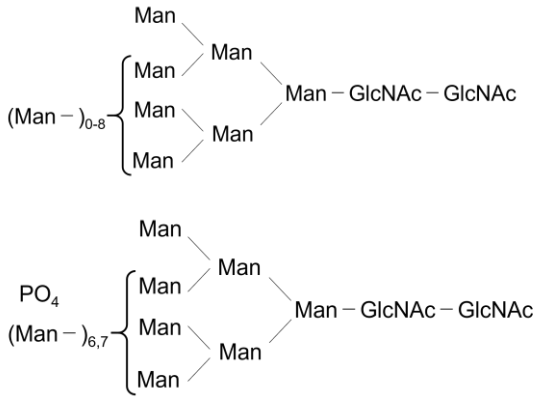
Glycosylation: S9, N27

Main proposed carbohydrate structure:

S9


[1)] To allow for loss in drawing and inhaling, the volume contained in each vial exceeds the labeled amount so that, following reconstitution with an isotonic sodium chloride solution to prepare an inhalation solution, 2 doses of sargramostim (genetical recombination) 125 μg can be obtained.

N27




GlcNAc, *N*-acetylglucosamine; Man, mannose; $PO_4$, phosphoric acid

Molecular formula: $C_{639}H_{1002}N_{168}O_{196}S_8$ (protein moiety)
Molecular weight: ca. 17,000

**Items Warranting Special Mention**

Orphan drug (Orphan Drug Designation No. 484 of 2020 [*R2 yaku*]; PSEHB/PED Notification No. 0918-6, dated September 18, 2020, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

**Reviewing Office** Office of New Drug IV

**Results of Review**

On the basis of the data submitted, PMDA has concluded that the product is expected to have efficacy in the treatment of autoimmune pulmonary alveolar proteinosis, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. The safety and other aspects of the product in clinical use should be further evaluated in the post-marketing surveillance and other investigations.

**Indication**

Autoimmune pulmonary alveolar proteinosis

**Dosage and Administration**

The usual adult dosage is 125 μg/dose of inhaled sargramostim (genetical recombination) administered twice daily for 7 consecutive days using a nebulizer, followed by a 7-day rest period. The treatment cycle is repeated.

**Approval Conditions**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product, until data from a certain number of patients are accrued and to promptly obtain safety and efficacy data on the product. On the basis of the obtained data, the applicant should take necessary actions for the proper use of the product.

**Attachment**

**Review Report (1)**

February 1, 2024

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | Sargmalin for Inhalation 250 μg |
| **Non-proprietary Name** | Sargramostim (Genetical Recombination) |
| **Applicant** | Nobelpharma Co., Ltd. |
| **Date of Application** | June 30, 2023 |
| **Dosage Form/Strength** | Lyophilized powder to be reconstituted before inhalation[1)]: Each vial contains 264 μg of sargramostim (genetical recombination) |
| **Proposed Indication** | Autoimmune pulmonary alveolar proteinosis |

**Proposed Dosage and Administration**

The usual adult dosage is 125 μg/dose of inhaled sargramostim (genetical recombination) administered twice daily for 7 consecutive days using a nebulizer, followed by a 7-day rest period. The treatment cycle is repeated.

[1)] To allow for loss in drawing and inhaling, the volume contained in each vial exceeds the labeled amount so that, following reconstitution with an isotonic sodium chloride solution to prepare an inhalation solution, 2 doses of sargramostim (genetical recombination) 125 μg can be obtained.

**Table of Contents**



**List of Abbreviations**

See Appendix.

## 1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Sargramostim (genetical recombination) (hereinafter referred to as sargramostim), which is the active ingredient of Sargmalin for Inhalation 250 μg (hereinafter referred to as Sargmalin), is a recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) developed by Immunex Corporation, a biopharmaceutical company in the US. At present, inhaled formulations containing sargramostim as an active ingredient have not been approved in Japan or other countries. In the US, Leukine® (brand name) for injection (active ingredient, sargramostim) has been approved for several indications including neutrophil recovery in patients with acute myeloid leukemia after undergoing remission induction chemotherapy.

Pulmonary alveolar proteinosis (PAP) is a disease characterized by abnormal surfactant accumulation in pulmonary alveoli due to dysfunction such as impaired surfactant degradation, resulting in respiratory failure. Pulmonary alveolar proteinosis can be etiologically classified into autoimmune, secondary, congenital/hereditary, and unclassified types (The JRS Clinical Practice Guideline for Pulmonary Alveolar Proteinosis 2022, edited by the Japanese Respiratory Society PAP Clinical Practice Guideline Committee; hereinafter referred to as "PAP Clinical Practice Guidelines"). It has been suggested that due to excess production of autoantibodies against granulocyte-macrophage colony-stimulating factor (GM-CSF), the function of alveolar macrophages is disrupted, decreasing their capacity to degrade pulmonary surfactant and causing autoimmune pulmonary alveolar proteinosis (aPAP) (*Journal of the Japanese Society of Internal Medicine.*[in Japanese] 2015;104:314-22, PAP Clinical Practice Guidelines). In Japan, PAP is classified as a designated intractable disease (No. 229, "pulmonary alveolar proteinosis (autoimmune or congenital)," Ministerial Announcement No. 393 of the Ministry of Health, Labour and Welfare, dated October 21, 2014). In Japan, it is reported that aPAP accounts for approximately 90% of PAP, which has a prevalence of 6.2 per million persons and an incidence rate of 0.49 per million persons per year (*Am J Respir Crit Care Med.* 2008;177:752-62). Based on the report, it is estimated that there are 776 patients with aPAP.

The PAP Clinical Practice Guidelines propose a treatment algorithm for PAP depending on the symptoms and partial pressure of oxygen in arterial blood ($PaO_2$). In patients with $PaO_2 \geq 70$ mmHg, the guidelines recommend close monitoring of the clinical course and administration of expectorant and antitussive drugs as symptomatic therapies. Conversely, for patients with $PaO_2 < 70$ mmHg whose gas exchange is more severely disrupted, in addition to the above symptomatic therapies, whole lung lavage, segmental lavage, and long-term oxygen therapy are recommended. However, lavage therapies are highly invasive and put significant strain on patients; moreover, lavage removes the pulmonary surfactant physically, and it has been pointed out that there are many cases of relapsed PAP after lung lavage. As an experimental therapy for the treatment algorithm, the PAP Clinical Practice Guidelines list rhGM-CSF inhalation therapy, which aims to promote degradation of pulmonary surfactant by neutralizing overproduced anti-GM-CSF autoantibodies and promoting differentiation of macrophages. Clinical research has demonstrated the efficacy of inhaled rhGM-CSF therapy (*Am J*

*Respir Crit Care Med.* 2005;171:1142-9, *Am J Respir Crit Care Med*. 2010;181:1345-54, *Eur Respir J*. 2006;27:585-93). At present, no inhaled rhGM-CSF formulations have been approved in any countries or regions.

Based on the above, an investigator-initiated clinical trial of Sargmalin was conducted in patients with aPAP with the aim of developing a drug that can be used as minimally invasive treatment for an extended duration in patients with aPAP for whom lung lavage is indicated. The study, which started from June 2016, was supported by the Practical Research Project for Rare/Intractable Diseases (FY2015) of the Japan Agency for Medical Research and Development. Recently, the applicant filed an application for marketing approval of Sargmalin based on data including results from this study. Sargramostim was designated as an orphan drug for the intended indication of "autoimmune pulmonary alveolar proteinosis" on September 18, 2020 (Designation No. 484 of 2020 [*R2 yaku*]).

## 2. Quality and Outline of the Review Conducted by PMDA

### 2.1 Drug substance

#### 2.1.1 Generation and control of cell substrate

A gene fragment encoding GM-CSF was isolated from human [redacted] and a gene fragment was produced to improve yield by introducing changes including substitution of leucine for arginine at position 23. A gene expression construct of sargramostim was produced by inserting the gene fragment into the expression vector. The expression construct was introduced to the budding yeast *Saccharomyces cerevisiae*. From a single colony, the master cell bank (MCB) and working cell bank (WCB) were prepared.

Characterization and purity tests were performed on the MCB, WCB, and end of production cell (EOPC). The results confirmed genetic stability during the manufacturing period, and no microbiological contamination was detected except for yeasts within the range studied.

The MCB is stored at ≤−60°C and the WCB is stored at −70[redacted]°C. While there is no plan to generate a new MCB, a new WCB is generated on an as-needed basis.

#### 2.1.2 Manufacturing process

The manufacturing process of the drug substance consists of [redacted] culture, [redacted] culture, production culture, [redacted] filtration, [redacted] filtration, [redacted] chromatography, [redacted] chromatography, [redacted] chromatography, cation exchange chromatography, and bulk drug substance filtration/filling/testing/storage steps.

Critical steps are production culture, [redacted] chromatography, and [redacted] chromatography steps.

Process validation is performed on a commercial scale for the manufacturing process of the drug substance.

### 2.1.3 Safety evaluation of adventitious agents

Raw materials of biological origin used are as follows: in MCB production, casein hydrolysate from bovine milk; in the manufacturing process of the drug substance, Bacto peptone derived from bovine bone or other tissues from US cattle and porcine pancreas, as well as casein hydrolysate from bovine milk.

The casein hydrolysate from bovine milk used in MCB production meets the requirements provided in the "Handling of Drugs etc. Produced from Master Cell Banks or Master Seeds That Do Not Meet the Standards for Biological Raw Materials" (Administrative Notice dated March 27, 2009), and therefore its use is acceptable. Bovine bone or other tissues from US cattle, the raw materials of Bacto peptone, which is used in the manufacturing process of the drug substance, contains backbone, the use of which is prohibited in Section 1. Standards for Ruminant-Derived Raw Materials, IV. General Rules for Animal-Derived Raw Materials, the Standards for Biological Raw Materials [see Section 2.R.1]. It has been confirmed that the other raw materials conform to the Standards for Biological Raw Materials.

### 2.1.4 Manufacturing process development

The major changes to the manufacturing process during the development of the drug substance are as follows (the manufacturing processes are referred to as Process A, the proposed commercial process 1, and proposed commercial process 2). The formulation produced from the drug substance manufactured by Process A and the proposed commercial process 1 were used in the clinical study.

- From Process A to the proposed commercial process 1: changes in the manufacturing site, the culture step, and purification step
- From the proposed commercial process 1 to proposed commercial process 2: change in the culture step

When these changes were made to the manufacturing process, comparability was evaluated with respect to the quality attributes. The results demonstrated the comparability of the drug substance before and after the changes.

### 2.1.5 Characterization

#### 2.1.5.1 Structure and characterization

Table 1 summarizes the characterization performed.

Table 1. Evaluation items for characterization

| | |
|---|---|
| Primary/higher-order structure | Amino acid sequence, amino acid composition, N- and C-terminal amino acid sequence, disulfide bonds, [redacted], [redacted], [redacted], phosphorylation, secondary structure, tertiary structure |
| Physicochemical properties | Molecular weight, absorption coefficient, size variants, charge variants |
| Glycan structure | N-linked glycosylation site, O-linked glycosylation site, N-linked glycan profiles, O-linked glycan profiles |
| Biological properties | Cell proliferation activity |

The evaluation of biological properties showed the sargramostim's activity to promote GM-CSF dependent cell proliferation of human erythroleukemic cell line [redacted].

### 2.1.5.2 Product-related substances/Product-related impurities

Based on data including the results of characterization in Section 2.1.5.1, [redacted] molecular species ([redacted]), [redacted], and [redacted] were defined as product-related substances. [redacted] molecular species ([redacted] and [redacted]), Impurity A, and Impurity B were defined as product-related impurities. All the product-related impurities are controlled by the specifications for the drug substance and drug product.

### 2.1.5.3 Process-related impurities

[redacted], host cell proteins, host cell DNA, residual solvents, and elemental impurities were defined as process-related impurities. It has been confirmed that all the process-related impurities are adequately removed during the manufacturing process.

### 2.1.6 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (peptide mapping, isoelectric focusing, non-reducing and reducing sodium dodecyl sulfate-polyacrylamide gel electrophoresis [SDS-PAGE; silver staining]), pH, monosaccharide composition, purity testing (glycan variants [reverse phase high-performance liquid chromatography (RP-HPLC)], non-reducing and reducing SDS-PAGE [silver staining], protein purity [reducing SDS-PAGE; coomassie brilliant blue (CBB) staining], Impurity A [size exclusion liquid chromatography (SEC)]), bacterial endotoxins, microbial limit, biological activity (cell proliferation activity), and assay (ultraviolet-visible spectrophotometry).

### 2.1.7 Stability of drug substance

Table 2 shows the main stability studies for the drug substance.

Table 2. Summary of main stability studies for drug substance

| | Drug substance manufacturing process | Number of batches | Storage condition | Test period | Storage form |
|---|---|---|---|---|---|
| Long-term | Proposed commercial process 1 | 3 | −70°C ± [redacted]°C | 108 months[a)] | [redacted] container and [redacted] screw cap |
| | Proposed commercial process 2 | 3 | | 24 months[b)] | |
| Accelerated | Proposed commercial process 1 | 1 | 5°C ± 3°C | 12 months | |
| | Proposed commercial process 2 | 1 | | 6 months | |
| | Proposed commercial process 1 | 2 | 15°C ± [redacted]°C | 12 months | |
| Stress (light) | Proposed commercial process 1 | 1 | Overall illumination of ≥1.2 million lux·h and integrated near ultraviolet energy of ≥200 W·h/m$^2$ | | |

a) The stability testing of 1 batch has been performed for up to 120 months.
b) The stability testing is ongoing for up to 60 months.

The long-term tests showed no marked change in quality attributes throughout the test period.

The accelerated tests (5°C ± 3°C) showed a trend towards increases in peaks containing Impurity B, [redacted], and [redacted] by [redacted]high performance liquid chromatography (HPLC).

The accelerated test (15°C ± [redacted]°C) showed increased peaks containing Impurity B, [redacted], and [redacted] by [redacted]HPLC, and changes in the electrophoretic pattern of non-reducing and reducing SDS-PAGE ([redacted]).

The results of stress testing (light) showed that the drug substance is photolabile.

Based on the above results, a shelf life of 60 months has been proposed for the drug substance when stored at −70°C ± [redacted]°C in a [redacted] container with [redacted] screw cap.

## 2.2 Drug product

### 2.2.1 Description and composition of drug product and formulation development

The drug product is a lyophilized powder for inhalation supplied in a glass vial (8 mL) containing 264 μg of sargramostim. Excipients contained in the drug product are D-mannitol, sucrose, trometamol, and hydrochloric acid. To allow for loss in drawing and inhaling, the volume contained in each vial exceeds the labeled amount so that, following reconstitution with 4 mL of an isotonic sodium chloride solution (protein concentration after reconstitution, 65 μg/mL), 2 doses of sargramostim 125 μg can be obtained.

### 2.2.2 Manufacturing process

The manufacturing process for the drug product consists of thawing of the frozen bulk drug substance, excipient solution preparation, drug product solution preparation, [redacted] filtration, sterile filtration, filling, lyophilization, capping, inspection, and labeling/packaging/storage/testing steps.

The sterile filtration, filling, and lyophilization have been defined as critical steps.

Process validation is performed on a commercial scale for the manufacturing process of the drug product.

### 2.2.3 Manufacturing process development

The major changes to the manufacturing process during the development of the drug product include the manufacturing site, the amounts of excipients, and primary packaging. (The manufacturing processes before and after the change are referred to as the pre-change process and the proposed commercial process, respectively.) The formulation produced by the pre-change process was used in the clinical study. When these changes were made to the manufacturing process, comparability was evaluated with respect to the quality attributes. The results demonstrated the comparability of the formulation before and after the changes [see Section 2.R.2].

### 2.2.4 Control of drug product

The proposed specifications for the drug product include strength, description, identification (peptide mapping, non-reducing and reducing SDS-PAGE [silver staining]), uniformity of dosage units, purity testing (glycan variants [RP-HPLC], non-reducing and reducing SDS-PAGE [silver staining], Impurity A [SEC]), biological activity (cell proliferation activity), and assay (HPLC).

### 2.2.5 Stability of drug product

Table 3 shows the main stability studies for the drug product.

Table 3. Summary of main stability studies for drug product

| | Manufacturing process[a)] of the drug product | Number of batches | Storage condition | Test period | Storage form |
|---|---|---|---|---|---|
| Long-term | Pre-change process | 3 | 5°C ± 3°C | 48 months | Manufacturing process before changes: glass vial and halobutyl isoprene blend rubber stopper<br>Proposed commercial process: glass vial and chlorobutyl rubber stopper |
| | Proposed commercial process | 3 | | 18 months[b)] | |
| | Proposed commercial process | 2 | | 6 months[c)] | |
| Accelerated | Pre-change process | 3 | 25°C ± 2°C | 12 months | |
| | Proposed commercial process | 3 | | 12 months | |
| | Proposed commercial process | 2 | | 6 months[d)] | |
| Stress (temperature) | Proposed commercial process | 3 | 40°C ± 2°C | 9 months | |
| | Proposed commercial process | 1 | | 6 months | |
| Stress (light) | Pre-change process | 1 | Overall illumination of ≥1.2 million lux·h and integrated near ultraviolet energy of ≥200 W·h/m$^2$ | | |

a) The drug substance produced by the proposed commercial process 1 was used in all the formulations.
b) One batch has been tested for up to 24 months, and the stability testing is ongoing for other batches for up to 60 months.
c) The stability testing is ongoing for 1 batch for up to 60 months.
d) The stability testing is ongoing for 1 batch for up to 12 months.

In the long-term testing using the formulation manufactured by the process before the change (pre-change formulation), the results showed trends towards increases in peaks containing Impurity B, [redacted], and [redacted] as measured by [redacted]HPLC, biological activity in the cell proliferation activity test, and Impurity A as measured by [redacted].

In the long-term testing using the formulation produced by the proposed commercial process, the results showed an increase in Impurity A in [redacted] in 1 batch [see Section 2.R.3]. In the remaining 4 batches produced by the proposed commercial process, no marked change in quality attributes were detected in the completed test period (3 batches as of 18 months and 1 batch as of 6 months).

The accelerated tests showed a trend towards increases in peaks containing Impurity B, [redacted], and [redacted] as measured by [redacted]HPLC and an increase in Impurity A as measured by [redacted].

The stress test (temperature) results showed the following: in the analysis of [redacted]HPLC, increases in peaks containing Impurity B, [redacted], and [redacted], an increase in peaks containing non-glycosylated forms, and a trend towards decreasing peaks containing N-linked glycosylated and O-linked glycosylated forms. A decrease in the biological activity in the cell proliferation activity test; a change in [redacted] molecular species in peptide mapping; an increase in Impurity A by [redacted]; and changes in the electrophoretic pattern of reducing SDS-PAGE ([redacted]).

The results of stress testing (light) showed that the drug product is photolabile.

Based on the above results and discussion in Section 2.R.3, a shelf life of 18 months has been proposed for the drug product when stored at 2°C to 8°C in a glass vial with a chlorobutyl rubber stopper as primary packaging, in a paper box protected from light.

### 2.3 Quality control strategy

Based on the following investigation and other data, the method for control of quality attributes of the drug product, which comprises a combination of process parameter control, in-process control, and specifications of the drug product, has been established.

- Identification of critical quality attributes (CQAs):
  The following CQAs were identified.
  CQAs: protein concentration, potency, peptide mapping ([redacted] molecular species), glycan variants, Impurity A, reconstitution time, pH of reconstituted solution, water content, insoluble particulate matter, bacterial endotoxins, and sterility
- Process characterization of the drug product
  In the process risk assessment, risks for each process parameter were rated to identify input variables that have a critical impact on CQAs (critical process parameters) and the control range for each process parameter was evaluated.

## 2.R Outline of the review conducted by PMDA

On the basis of the submitted data and discussions in the following sections, PMDA concluded that the quality of the drug substance and drug product is adequately controlled.

### 2.R.1 Bacto peptone, used in the manufacturing process of the drug substance

Bovine bone or other tissues from US cattle, the raw materials of Bacto peptone, which is used in the manufacturing process of the drug substance, contains backbone, the use of which is prohibited in Section 1. Standards for Ruminant-Derived Raw Materials, IV. General Rules for Animal-Derived Raw Materials, the Standards for Biological Raw Materials. The applicant explained that it is difficult to switch Bacto peptone to another material because when an attempt was made in the development process to manufacture the drug substance with a peptone that did not use biological materials, this resulted in variations in the glycan pattern and equivalent quality could not be obtained.

PMDA concluded that the clinical use of Sargmalin is acceptable because the risk for transmission of transmissible spongiform encephalopathy (TSE) associated with the use of Bacto peptone is considered to be minimal given the following factors.

- Bovine bone or other tissues used in the production of Bacto peptone are derived from cattle aged <30 months, and it is considered that the risk of transmission of TSE originating from the backbone of cattle aged <30 months is low.
  - ✓ In the US, the use of backbone from cattle aged ≥30 months was prohibited in the past; however, the regulation was withdrawn in 2018 (83 FR 49023).
  - ✓ In Europe, the use of raw materials derived from backbone of cattle aged <30 months in pharmaceutical products is allowed ("Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products–Revision 3 [EMA/410/01 rev.3]"; hereinafter referred to as the European medicines agency [EMA] Guidelines).
  - ✓ Based on the results of discussion in the Food Safety Commission of Japan, backbone from cattle aged <30 months is excluded from the specified risk material specified in the Slaughterhouse Act ("Regarding the Ministerial Order for partial revisions of the Enforcement Regulation of the Slaughterhouse Act and the Enforcement Regulation for the Act on Special Measures Against Bovine Spongiform Encephalopathy Under the Jurisdiction of the Ministry of Health, Labour and Welfare, and partial revision of standards for foods and excipients" [PFSB/FSD Notification No. 0201-5, dated February 1, 2013]).
- The acid and/or base treatments in the manufacturing process of Bacto peptone are implemented in accordance with the EMA Guidelines. It is considered that the risk of TSE transmission has been adequately reduced.
- It is considered that Sargmalin meets the requirements to assure safety as set out in the "Handling of Risk Assessment in Application for Approval of Partial Change in Pharmaceutical Product and

Medical Device Using Bovine-derived Raw Materials" (PFSB/ELD Notification No. 0801001, and PFSB/SD Notification No. 0801001, dated August 1, 2003).

- The applicant explains that Leukine®, an intravenous formulation that has an active ingredient identical to that of Sargmalin, was approved in the US in 1991 and has been used in approximately ≥500,000 patients for more than 30 years. No TSE-related adverse reactions associated with Leukine® have been reported. Currently no drugs indicated for the treatment of aPAP have been approved in Japan. It is considered that the medical benefits outweigh the risks given the efficacy [see Section 7.R.2] and safety [see Section 7.R.3] demonstrated in the clinical study of Sargmalin.

The Expert Discussion[2)] discussed the use of Bacto peptone in the manufacturing process of the drug substance. Bacto peptone contains backbone, the use of which is prohibited in Section 1. Standards for Ruminant-Derived Raw Materials, IV. General Rules for Animal-Derived Raw Materials, the Standards for Biological Raw Materials. In addition to comments supporting the PMDA's conclusion described above, the following comment was also made: in the event of abnormal prion protein contamination, proliferation of an abnormal prion protein is not considered to occur in yeast culture; additionally, the capability to remove this source of contamination in the manufacturing process of the drug substance is expected to be high. Therefore, the risk of TSE transmission associated with the use of the Bacto peptone is low.

### 2.R.2 Comparability between the pre-change formulation and the proposed commercial process formulation

The applicant's explanation about the comparability between the pre-change formulation and the proposed commercial process formulation, in terms of changes including the manufacturing site, the amount of excipients, and primary packaging:

The comparability between the pre-change formulation and the proposed commercial process formulation was demonstrated in terms of the quality attributes of the drug product. The results for the 3 batches of the proposed commercial process formulation used in the stability study (formulation batches except for 1 batch that showed an increase in Impurity A by [redacted] [see Section 2.R.3]) were similar to the results for the 12-month storage samples of the pre-change formulation for all test items. It is unlikely that the difference in the manufacturing process before and after the changes would affect the stability of the formulation. Therefore, the pre-change formulation and the proposed commercial process formulation were shown to be comparable.

PMDA accepted the applicant's explanation.

[2)] The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

### 2.R.3 Control of Impurity A in the drug product and shelf life setting

The applicant's explanation about the cause for the higher-than-expected increase in Impurity A by [redacted] in 1 batch of the formulation manufactured by the proposed commercial process at 3 months in the long-term storage study, as well as the corrective and preventive measures:

When the batch in question was manufactured, a different manufacturer's silicone tubes were used for the tubing connecting the [redacted] retention tank to the filling supply pipe. These tubes were expected to function in a manner equivalent to that of the previously used tubes. There was only 1 batch of formulation manufactured using the tubes in question, in which an increase in high molecular weight was observed. After the event, formulation batches were manufactured using the previously used tubes, and no similar events for Impurity A were detected at 3 months in the long-term storage study. Therefore, the applicant considers it is likely that the difference in the tube is responsible for the increase in Impurity A. As corrective and preventive measures, in the production hereafter, the applicant decided to use only the same tube product as those used previously and considers that these measures can minimize the increase in Impurity A, assuring stable production.

PMDA's view:

While the applicant's explanation about the investigation of the cause and corrective/preventive measures is acceptable to some extent, the cause has not been identified, and the applicant is required to verify in a continuous manner that an increase in Impurity A will not occur in formulation batches manufactured hereafter. A shelf life of [redacted] months for the drug product had been proposed by the applicant initially based on the results of the stability study that used the pre-change formulation. PMDA instructed the applicant to set the shelf life based on the results of the stability study of the proposed commercial process, and the applicant agreed to take action accordingly. PMDA accepted the applicant's response.

### 2.R.4 Novel excipients

The drug product contains D-mannitol and sucrose, which are novel excipients with no previous use in inhaled formulations, and trometamol, a novel excipient in amounts exceeding that of the previous uses in an inhaled formulation.

#### 2.R.4.1 Specifications and stability

D-mannitol and sucrose conform to the requirements specified in the Japanese Pharmacopoeia, while trometamol conforms to the requirements specified in the Japanese Pharmaceutical Codex. PMDA concluded that there are no particular problems with these excipients in terms of specifications and stability.

#### 2.R.4.2 Safety

As a result of reviewing the submitted data, PMDA concluded that D-mannitol, sucrose, and trometamol are unlikely to raise safety concern within the range of the dosage regimen for Sargmalin.

## 3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The applicant submitted the results of an *in vitro* study that evaluated the effects on monkey alveolar macrophages and the results of evaluation of the effects on leukocytic cells in peripheral blood in the repeated dose toxicity study in monkeys. Although no safety pharmacology studies were conducted, the effects on the central nervous system, respiratory system, and cardiovascular system were evaluated in the repeated dose toxicity study in monkeys [see Section 5.2].

### 3.1 Primary pharmacodynamics

#### 3.1.1 Effects on monkey alveolar macrophages (CTD 4.2.1.1-3, reference data[3])

The effects of sargramostim on the survival and proliferation of alveolar macrophages obtained from an experiment on bronchoalveolar lavage in cynomolgus monkeys were investigated. Within the concentration range studied (5, 10, and 20 pmol/L), an increase in the survival rate[4] and proliferation were observed in a sargramostim concentration-dependent manner. When sargramostim and an excess amount of anti-GM-CSF antibodies (1 μg/mL) were added simultaneously, there was no sargramostim concentration-dependent increase in either the survival rate or proliferation.

Using alveolar macrophages obtained from an experiment of bronchoalveolar lavage in cynomolgus monkeys, the effect of sargramostim on the capacity of alveolar macrophages to degrade[5] bovine pulmonary surfactant was investigated. When sargramostim (10 pmol/L) and an excess amount of anti-GM-CSF antibodies (1 μg/mL) were added simultaneously, undegraded surfactant-like materials were present in macrophage cells, and foamy macrophages were also present. Conversely, when only sargramostim (10 pmol/L) was added, these materials and foamy macrophages were not observed to be present.

#### 3.1.2 Effects on leukocytic cells in peripheral blood in monkeys (CTD 4.2.3.2-5)

The effects of sargramostim on leukocytic cells in peripheral blood were investigated in a 26-week intermittent inhalation toxicity study in cynomolgus monkeys [see Section 5.2]. Sargramostim 5, 100, or 500 μg/kg was administered to male and female cynomolgus monkeys (N = 3/sex) by inhalation once daily consecutively for 1 week, followed by a 1-week recovery period. After repeating intermittent administration in cycles for 26 weeks, the white blood cell count, neutrophil count, monocyte count, eosinophil count, basophil count, and large unstained cell count tended to increase on Day 8 at sargramostim 100 and 500 μg/kg regardless of sex. All of these changes were almost undetectable on Days 92 and 176.

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[3] Hashimoto Atsushi, et al. Health and Labor Sciences Research Grants, "Non-clinical studies on novel GM-CSF formulations for inhalation in the treatment of pulmonary alveolar proteinosis" Fiscal Year 2014 General/Partial Research Report, 2015:p11-3.

[4] Measured by a colorimetric assay that uses WST-8, a water-soluble tetrazolium salt which produces color when reduced by dehydrogenase in a viable cell.

[5] Evaluated by observation using Wright-Giemsa staining, Oil-Red O staining, and phase-contrast microscopy.

### 3.2 Safety pharmacology (CTD 4.2.3.2-5)

Evaluation items for safety pharmacology were investigated in the 26-week intermittent inhalation toxicity study in cynomolgus monkeys [see Section 5.2]. Sargramostim 5, 100, or 500 μg/kg was administered to male and female cynomolgus monkeys by inhalation once daily consecutively for 1 week, followed by a 1-week recovery period. After repeating intermittent administration in cycles for 26 weeks, there were no treatment-related effects of sargramostim on the central nervous system, respiratory system (clinical observations), or cardiovascular system (blood pressure and electrocardiogram).

### 3.R Outline of the review conducted by PMDA

#### 3.R.1 The mechanism of action of sargramostim against aPAP

As a result of reviewing the submitted data, PMDA concluded that the pharmacological effect of sargramostim has been demonstrated and sargramostim is expected to be effective in the treatment of aPAP.

## 4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The applicant submitted the results data from the 26-week intermittent inhalation toxicity study of sargramostim in cynomolgus monkeys as absorption data. Plasma sargramostim concentrations (lower limit of quantitation, 7.86 pg/mL) and anti-GM-CSF antibodies in serum (lower limit of quantitation, 2.34 μg/mL) were determined by enzyme-linked immunosorbent assay (ELISA). Sargramostim is a glycoprotein consisting of natural amino acids only. Since sargramostim is considered to be broken down into peptides and amino acids, which will be reused or excreted, the distribution, metabolism, or excretion of sargramostim were not evaluated.

### 4.1 Absorption

#### 4.1.1 Repeated-dose study (toxicokinetics) (CTD 4.2.3.2-5)

Sargramostim 5.0, 100, or 500 μg/kg was administered to male and female cynomolgus monkeys by inhalation once daily consecutively for 1 week, followed by a 1-week recovery period. Table 4 shows pharmacokinetic parameters after repeating intermittent administration in cycles for 26 weeks. There was no clear difference in sargramostim exposure between the sexes at the time of first dose administration at 100 and 500 μg/kg/day. Only the concentrations at 5.0 μg/kg/day were below the lower limit of quantitation after administration of the first dose of sargramostim; however, all data, except for data from 1 animal each in the 100 and 500 μg/kg/day groups, decreased to below the lower limit of quantitation on Days 91 and 175 (both are the seventh day of a 1-week consecutive administration period). Anti-GM-CSF antibodies in serum were detected in all animals; therefore, decreased exposure could be due to the effect of anti-GM-CSF antibodies in serum. Two animals whose plasma

sargramostim concentrations were quantifiable had serum anti-GM-CSF antibody concentrations lower than those in other animals in the same dose group.[6)]

Table 4. Pharmacokinetic parameters following intermittent administration of inhaled sargramostim to cynomolgus monkeys for 26 weeks

| Time point | Dose (μg/kg/day) | $C_{max}$ (pg/mL) | | $AUC_{0\text{-}24h}$ (pg·h/mL) | | $t_{max}$ (h) | |
|---|---|---|---|---|---|---|---|
| | | Male | Female | Male | Female | Male | Female |
| Day 1 | 5.0 | BLQ | BLQ | NC | NC | NC | NC |
| | 100 | 384 ± 478<br>933/151/66.5 | 200 ± 101<br>83.7/267/248 | 1,060 ± 1,270<br>2,520/207/438 | 639 ± 199<br>480/574/862 | 0.25 [0.25, 1.0] | 0.25 [0.25, 0.25] |
| | 500 | 2,960 ± 2,960<br>1,540/979/6,370 | 3,300 ± 3,020<br>6,720/996/2,190 | 9,750 ± 5,360<br>3,640/11,900/13,700 | 14,100 ± 8,300<br>23,700/8,590/10,100 | 0.25 [0.25, 1.0] | 1.0 [0.25, 1.0] |
| Day 91[a)] | 5.0 | BLQ | BLQ | NC | NC | NC | NC |
| | 100 | BLQ | 144[c)] | NC | 1,010[c)] | NC | 1[c)] |
| | 500 | BLQ | BLQ | NC | NC | NC | NC |
| Day 175[b)] | 5.0 | BLQ | BLQ | NC | NC | NC | NC |
| | 100 | BLQ | 78.6[c)] | NC | 774[c)] | NC | 2[c)] |
| | 500 | 18.3[c)] | BLQ | 177[c)] | NC | 1[c)] | NC |

N = 3/sex; $C_{max}$ and $AUC_{0\text{-}24h}$ in upper row; mean ± standard deviation; individual values in lower row; $t_{max}$, median [Min, Max]
BLQ = below the lower limit of quantitation for all animals; NC = not calculated
a) The seventh day of the seventh 1-week consecutive administration period; b) the seventh day of the 13th (final) 1-week consecutive administration period; c) a quantifiable value from 1 animal

## 4.R Outline of the review conducted by PMDA

As a result of reviewing the submitted non-clinical pharmacokinetic data, PMDA concluded that it is possible to some extent to keep track of the *in vivo* behavior of sargramostim after inhalation.

## 5. Toxicity and Outline of the Review Conducted by PMDA

The applicant conducted the following toxicity studies of sargramostim: a single-dose toxicity study, repeated-dose toxicity studies, and reproductive and developmental toxicity studies. Since sargramostim is pharmacologically active in cynomolgus monkeys [see section 3.1] and rabbits,[7)] the single-dose and repeated-dose toxicity studies were conducted in cynomolgus monkeys and the reproductive and developmental toxicity studies were conducted in rabbits.

### 5.1 Single-dose toxicity

In the single intravenous-dose toxicity study in cynomolgus monkeys, there were no deaths or acute symptoms in the sargramostim 300 μg/kg group. The approximate lethal dose was determined to be >300 μg/kg (Table 5).

Table 5. Summary of the single dose toxicity study results

| Test system | Route of administration | Dose (μg/kg) | Major findings | Approximate lethal dose (μg/kg) | CTD |
|---|---|---|---|---|---|
| Male/female cynomolgus monkeys | IV | 0,[a)] 300 | None | >300 | 4.2.3.1-1 |

a) 0.9% sodium chloride aqueous solution

[6)] On Day 182, the anti-GM-CSF antibody concentration in serum was 4.13 μg/mL in 1 female cynomolgus monkey in the 100 μg/kg group whose plasma sargramostim concentration was quantifiable, while the concentrations were 70.1 and 35.6 μg/mL in the other 2 animals of the same dose group. The anti-GM-CSF antibody concentration in serum was 9.22 μg/mL in 1 male cynomolgus monkey in the 500 μg/kg group whose plasma sargramostim concentration was quantifiable, while the concentrations were 101 and 32.0 μg/mL in the other 2 animals of the same dose group.
[7)] *Pediatr Res*. 1999;46:613-20

## 5.2 Repeated-dose toxicity

Repeated-dose toxicity studies were conducted in cynomolgus monkeys by subcutaneous administration and by inhalation, which is the route of administration for clinical use (Table 6). In the 6-week repeated subcutaneous administration study, the following changes related to the leukocytic cell activation effect by GM-CSF were observed: increased white blood count, bone marrow hyperplasia, inflammatory cell infiltration in systemic organs/tissues and lymphoid tissue hyperplasia, abnormal blood/blood biochemistry parameters related to inflammatory response, and histopathological changes. In the 26-week intermittent inhalation study, the following changes were observed: changes related to the immune cell activation effect by GM-CSF, namely, high levels of leukocytic parameters and high C-reactive protein levels in blood; changes related to the production of antibodies against sargramostim, namely, increase in bronchus-associated lymphoid tissue, increase in the size of pulmonary hilar lymph nodes and tracheal lymph nodes, and lymphocytic cell hyperplasia. However, there were no findings suggestive of tissue damage; therefore, these changes were not determined to be toxicities. The no observed adverse effect level (NOAEL) was determined to be 500 μg/kg/week.

Table 6. Summary of repeated-dose toxicity study results

| Test system | Route of administration | Treatment duration | Dose (μg/kg/day) | Major findings | NOAEL (μg/kg/week) | CTD |
|---|---|---|---|---|---|---|
| Male/ female cynomolgus monkeys | SC | 6 weeks + Recovery 12 weeks | 0,[a] 20, 63, 200 | **Died/early necropsied animals**<br>At 200, 1 animal (M), 2 animals (F)<br>Decreased food consumption, unable to eat/drink, decrease in spontaneous activity, lethargic, injection site skin swelling/induration, systemic skin disseminated crust formation/multiple abscesses, multiple skin necrosis in the right thigh, forelimb redness, head/inguinal disseminated redness, ilium/axilla/inguinal lymph nodes swelling/lymphocyte hyperplasia, spleen swelling, adrenal gland swelling, pericarditis, hindlimb joint fluid turbidity, joint capsule thickening, splenic red pulp hyperplasia, splenic white pulp depletion, femoral/sternal bone marrow hyperplasia, bone marrow atrophy/localized fibrosis in the sternal bone marrow cavity, liver/heart/lung/epididymis/choroid plexus/trachea inflammatory cell infiltration, myocardial degeneration, pericarditis, extramedullary hematopoiesis, pyogenic granuloma inflammation/thrombosis/fibrosis in systemic/injection site skin, kidney/spleen/thyroid gland/adrenal cortex/adrenal medulla lymphocytic cell infiltration<br><br>**Animals reached planned necropsy**<br>At ≥20, (Males/females) skin swelling/induration/crust formation, increase in food consumption,[b), c)] high white blood cell count, high neutrophil count, high lymphocyte count, high monocyte count, high eosinophil count, high basophil count, high large unstained cell count, high platelet count, low blood albumin, low A/G ratio, high fibrinogen, fibrous capsule of liver, grayish white focal discoloration of the liver/heart, high spleen weight, spleen swelling, femoral/sternal[b), d)] bone marrow hyperplasia, liver/heart/lung[e)] inflammatory cell infiltration, kidney/adrenal gland[b), c)] lymphocytic cell infiltration, spleen lymphoid hyperplasia, injection site pyogenic granuloma inflammation;<br>(Males) low calcium in blood, low thyroid gland weight, thymic atrophy, epididymis[b)] inflammatory cell infiltration, epididymis lymphocytic cell infiltration, tongue lymphocyte hyperplasia[f)];<br>(Females) decreased body weight, high iliac lymph node weight, bladder[e)]/skin[e)]/cerebral choroid plexus[d), e)] inflammatory cell infiltration, thyroid gland/esophagus[f)]/mandibular gland[e)] lymphocytic cell infiltration, sternal localized fibrosis[f)]<br>At ≥63, (Males/females) skin erythema/swelling, splenic white pulp deficiency,[b), e)] esophageal lymphocyte hyperplasia[b)];<br>(Males) decreased food consumption, low body weight gain,[b)] low red blood cell count, low MCV, low MCH, low MCHC, low potassium in blood, high iliac lymph node weight, mandibular gland/testicular inflammatory cell infiltration,[b)] pituitary gland/thyroid gland lymphocytic cell infiltration,[b)] iliac lymph node lymphocyte hyperplasia/increased granulocytes,[b)] perisplenic inflammation,[b)] femoral bone marrow cavity localized fibrosis[b)];<br>(Females) skin pustule, low calcium in blood, sternal bone marrow atrophy,[e)] tracheal inflammatory cell infiltration,[e)] pancreas lymphocytic cell infiltration,[e)] tracheal lymphocyte hyperplasia[e)];<br>At 200, (Males/females) decrease in spontaneous activity, weakening, APTT prolongation, mesenteric lymph node/mandibular lymph node lymphocyte hyperplasia;<br>(Males) decreased body weight, cerebral choroid plexus inflammatory cell infiltration, mandibular gland/parathyroid gland/pancreas/cerebral lymphocytic cell infiltration;<br>(Females) low red blood cell count, low MCV, low MCH, low MCHC, splenic fibrin-like film<br><br>Reversibility: reversible | <20 | 4.2.3.2-4 |
| Male/ female cynomolgus monkeys | Inhalation | 26 weeks (1-week consecutive treatment, followed by 1-week recovery period; the treatment is repeated in cycles) | 0,[g)] 50, 100, 500 | At ≥5 (Males/females) increased bronchus-associated lymphoid tissue, pulmonary hilar lymph nodes lymphocyte hyperplasia[e)];<br>(Males) increase in the size of pulmonary hilar/bronchial lymph nodes;<br>At ≥100 (Males/females) high or trend towards higher count of white blood cell/neutrophil/monocyte/eosinophil/basophil/large unstained cell,[h)] low lymphocyte ratio, tracheal lymph node lymphocyte hyperplasia;<br>(Females) increase in the size of pulmonary hilar/bronchial lymph nodes;<br>At 500, (Males/females) high or trend towards higher levels of C-reactive protein[h)];<br>(Males) high basophil ratio in bone marrow<br><br>Reversibility: reversible | 500 | 4.2.3.2-5 |

a) an aqueous solution containing (per 1 mL) mannitol 40 mg, sucrose 10 mg, tromethamine 1.2 mg, benzyl alcohol 11.5 mg, and EDTA 5.5 mmol
b) excluding males in the 200 μg/kg group; c) excluding males in the 63 μg/kg group; d) excluding females in the 63 μg/kg group; e) excluding females in the 200 μg/kg group; f) 20 μg/kg group only
g) an aqueous solution containing (per 1 L) Tris 1.2 g, mannitol 40 g, and sucrose 10 g (pH 7.4)
h) on Day 8

### 5.3 Genotoxicity

Sargramostim, a glycoprotein consisting exclusively of natural amino acids, is not considered to interact directly with DNA or other nuclear chromosomal materials. The risk of genotoxicity is considered to be low, and no genotoxicity studies were conducted.

### 5.4 Carcinogenicity

No carcinogenicity studies in rodents were conducted because sargramostim shows low amino acid sequence homology to rat GM-CSF (63.2%) and mouse GM-CSF (59.4%). In the 26-week intermittent inhalation toxicity study in cynomolgus monkeys [see Section 5.2], no proliferation of precancerous lesions suggestive of sargramostim's carcinogenicity was noted in the respiratory system organs or the local administration sites; and no evidence suggesting a relationship between GM-CSF and carcinogenicity has been obtained. Therefore, the risk of developing cancer associated with the clinical use of sargramostim was considered to be low.

### 5.5 Reproductive and developmental toxicity

A fertility and early embryo development (FEED) study, an embryo fetal development (EFD) study, and pre- and postnatal development (PPND) study were conducted in female rabbits in which sargramostim was administered subcutaneously (Table 7). The effects on male reproductivity, sperm maturation, testicular volume, and sperm count were evaluated using biopsy specimens obtained from male animals at Week 2, Week 4, and 16 weeks from the start of treatment (during the recovery period) in the 6-week repeated subcutaneous dose toxicity study in cynomolgus monkeys. The evaluation results showed no effect of sargramostim on male reproductivity. The effects on embryonic development noted at the middle and higher dose levels in the FEED and EFD studies, and abortion in dams that occurred at the high dose level in the EFD and PPND studies were determined to be secondary effects associated with decreased food consumption and decreased body weight gain. In the PPND study, when sargramostim was administered to lactating dams, decreased survival rates (at the low dose level and higher) and decreased body weight (at the high dose level) were noted in the $F_1$ offspring. Based on the above, the NOAELs were determined to be 70 μg/kg/day for fertility and early embryonic development, 25 μg/kg/day for embryo and fetal development, <25 μg/kg/day for general toxicity in $F_1$ offspring, 200 μg/kg/day for the fertility of $F_1$ offspring and development of $F_2$ offspring.

Table 7. Summary of reproductive and developmental toxicity study results

| Study type | Test system | Route of administration | Treatment period | Dose (μg/kg/day) | Major findings | NOAEL (μg/kg/day) | CTD |
|---|---|---|---|---|---|---|---|
| FEED | Female rabbits | SC | 6 days prior to mating to gestational day 7 (once daily) | 0,[a] 25, 70, 200 | Parent animals<br>**Death**<br>At 200, decreased food consumption, low body weight, decreased bowel movement<br><br>**Animals reached planned necropsy**<br>At ≥25, low basophil count, low red blood cell count, low hematocrit level, high reticulocyte count, high red blood cell count<br>At ≥70, low food consumption, low body weight gain, low eosinophil count, high platelet count, low hemoglobin level<br>At 200, low body weight, decreased bowel movements, high neutrophil count, high monocyte count, low lymphocyte ratio, high relative spleen weight<br><br>Fertility/early embryonic development (females)<br>At 200, low mean number of implantations, high percentage of preimplantation embryo losses, low number of viable embryos<br>At 25 and 70, decreased number of corpus lutea[b] | Parent animal (general toxicity): 25<br><br>Fertility/early embryonic development: 70 | 4.2.3.5.1-1 |
| EFD | Female rabbits | SC | Group A, gestational days 6-19<br><br>Group B, gestational days 19-28 (once daily) | 0,[a] 25, 70, 200 | Group A<br>Dams<br>At ≥25, decreased number of bowel movements, high eosinophil count, high basophil count, low reticulocyte count<br>At ≥70, low food consumption, low body weight gain, high platelet count<br>At 200, low body weight, abortion, low mean uterus weight, high neutrophil count, high monocyte count, low blood hemoglobin level, high relative spleen weight<br><br>Embryo/fetal development<br>At 200, high post-implantation embryo losses, low number of viable fetuses<br><br>Group B<br>Dams<br>**Death**<br>At 200, low food consumption, low body weight, abortion, decreased bowel movement, decreased stool size, mucous-like stools, lacrimation<br><br>**Animals reached planned necropsy**<br>At ≥25, high eosinophil count, high platelet count, low hemoglobin level, low hematocrit level, high spleen weight<br>At ≥70, decreased bowel movement, low food consumption, low body weight gain, high monocyte count, high red blood cell count, high reticulocyte count, low MCV, low MCH<br>At 200, low body weight, decreased stool size, mucous-like stools, abortion, low white blood cell count, high neutrophil count, high lymphocyte count, high basophil count, high large unstained cell count, low placenta weight<br><br>Embryo/fetal development<br>At ≥70, low number of viable fetuses, low fetal body weight<br>At 200, high post-implantation embryo losses | Dams: <25<br>Embryo/fetal development: 25 | 4.2.3.5.2-5 |

| Study type | Test system | Route of administration | Treatment period | Dose (μg/kg/day) | Major findings | NOAEL (μg/kg/day) | CTD |
|---|---|---|---|---|---|---|---|
| PPND | Female rabbits | SC | Dams:<br>Group A, gestational days 6-19<br><br>Group B, gestational days 19 to parturition day 0<br><br>Group C, lactation days 1-14 (once daily) | 0,[a] 25, 70, 200 | Group A<br><u>Dams</u><br>At 200, low food consumption, low body weight, low body weight gain, abortion, resorption of all embryos, death of all fetuses, decreased bowel movement<br><br><u>Live $F_1$ offspring</u><br>At 200, low number of live births, low number of live neonates<br>Group B<br><u>Dams</u><br>At ≥25, low food consumption, low body weight gain<br>At ≥70, decreased bowel movements, low body weight<br>At 200, abortion, death<br><br><u>Live $F_1$ offspring</u><br>At 200, low fetal body weight<br>Group C<br><u>Dams</u><br>At ≥25, low body weight gain<br>At ≥70, low food consumption, low body weight<br>At 200, decreased bowel movements<br><br><u>Live $F_1$ offspring</u><br>At ≥25, low postnatal survival rate<br>At 200, low body weight, low body weight gain | Dams:<br><25<br><br>Live $F_1$ offspring:<br><25 (general toxicity)<br>200 (fertility)<br><br>$F_2$ embryo/fetal development:<br>200 | 4.2.3.5.3-1 |

a) A solution containing (in 1 mL of sterilized water for injection) mannitol 40 mg, sucrose 10 mg, trometamol 1.2 mg, benzyl alcohol 11.5 mg, EDTA sodium salt 1.9 mg

b) Because the incidence of the event was not correlated with dose levels, the event was determined to be of low toxicological significance.

### 5.6 Local tolerance

The local tolerance of inhaled sargramostim was evaluated based on the results of the 26-week intermittent inhalation toxicity study in cynomolgus monkeys [see Section 5.2]. No local tolerance-related histopathological findings were identified, and it was determined that the risk of local tolerance was low.

## 5.R Outline of the review conducted by PMDA

### 5.R.1 Systemic toxicity evaluation

PMDA's view:

Systemic exposure of sargramostim was confirmed when subcutaneous doses[8)] were administered to cynomolgus monkeys for 6 weeks, and the study reported abnormal findings related to the leukocytic cell activation effects, which are caused by the pharmacological action of sargramostim [see Section 5.2]. In contrast, when sargramostim was administered by inhalation intermittently for 26 weeks to cynomolgus monkeys, no abnormal findings related to the leukocytic cell activation effects were noted [see Section 5.2]. However, in all animals, production of anti-GM-CSF antibodies was detected, and plasma sargramostim concentrations were mostly below the lower limit of quantitation on Day 175, which was the seventh day of the final 1-week consecutive administration period [see Section 4.1.1]. Therefore, as a result of reviewing the above results, it is difficult to adequately evaluate the systemic

[8)] When subcutaneous doses of sargramostim 200 μg/kg/day were administered to cynomolgus monkeys, the $C_{max}$ and $AUC_{last}$ on Day 42 were 46.6 ± 23.0 ng/mL and 265 ± 154 ng·h/mL, respectively.

toxicity of sargramostim that was distributed in blood when sargramostim was administered long-term by inhalation, which is the route of administration of the clinical application.

In the PAGE study, a phase III study of Sargmalin, serum sargramostim concentrations were below the lower limit of quantitation in all subjects at all timepoints, a result similar to that of the 26-week intermittent inhalation toxicity study in cynomolgus monkeys [see Section 6.2.2]. The safety related to the leukocytic cell activation effects resulting from sargramostim exposure will be discussed in Section 7.R.3.1 based on data including the incidence of adverse events in the clinical studies.

### 5.R.2 Effects on reproductive development

#### 5.R.2.1 Effects during pregnancy

PMDA's view:

In the reproductive and developmental toxicity studies in rabbits, after administration of sargramostim, embryonic losses, low number of viable fetuses, low fetal body weight, and abortion were noted [see Section 5.5]. In pregnant rabbits, decreased embryonic survival rates and increased frequency of abortion due to undernutrition associated with decreased food consumption have been reported (*Toxicology*. 1981;22:255-9, *Teratology*. 1992;46:349-65, *Birth Defects Res B Dev Reprod Toxicol*. 2005;74:424-30). Another study shows that decreased food consumption and undernutrition occur due to secondary effects caused by stress when high doses of a drug are repeatedly administered to rabbits or other experiment animals (*Toxicol Pathol.* 2013;41:560-614). In pregnant rabbits that had abortions after repeated administration of high doses of sargramostim, significant decreases in food consumption and body weight were noted. The findings in pregnant rabbits mentioned above are therefore considered to be secondary changes resulting from undernutrition associated with decreased food consumption in dams. In addition, given that no adverse events such as undernutrition were reported when the clinical dose level of inhaled sargramostim was administered to humans [see Section 7.R.3] and that the physiological effect of GM-CSF did not adversely impact the ability to maintain pregnancy or embryo-fetal development, the findings in pregnant rabbits are not likely to be changes directly associated with the pharmacological effect of GM-CSF.

Based on the above, the possibility that sargramostim treatment could have an adverse impact on maintaining pregnancy and embryo-fetal development when administered to women who are or may be pregnant is low. However, given that the reproductive and developmental toxicity studies in rabbits were not able to determine the NOAEL for maternal animal general toxicity, it is concluded that sargramostim should be administered only when the benefits of treatment outweigh the risks.

#### 5.R.2.2 Effects during lactation

The applicant's explanation:

While a decrease in the survival rates for $F_1$ offspring was observed in the PPND study of sargramostim [see Section 5.5], it is suspected that this is a secondary effect attributable to insufficient lactation

associated with exacerbated clinical signs in the dams. Based on what is generally known about GM-CSF as detailed below, the risk to safety in neonates is considered to be low when sargramostim is administered to lactating dams. However, it was decided to provide cautionary statements to the effect that before prescribing sargramostim for breastfeeding women, whether to continue breastfeeding should be determined by taking into account the benefits of treatment and the nutritional benefits of breastmilk.

- Although GM-CSF is present in human breastmilk at concentrations higher than those in blood, GM-CSF is presumably inactivated or poorly absorbed in the digestive tract (*Eur J Pediatr.* 1996;155:69). While there is a possibility that sargramostim is distributed in breast milk, sargramostim is unlikely to have a direct effect on infants via breastfeeding.

PMDA accepted the applicant's explanation.

## 6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

### 6.1 Summary of biopharmaceutic studies and associated analytical methods

Serum sargramostim concentrations (lower limit of quantitation, 1.0 pg/mL) and serum anti-GM-CSF antibodies (lower limit of quantitation, 0.586 μg/mL) were determined by ELISA.

### 6.2 Clinical pharmacology

The results from clinical studies in healthy adults and patients with aPAP were submitted as evaluation data. Unless otherwise specified, the dose expressed is the dose level of sargramostim.

#### 6.2.1 Phase I study (CTD 5.3.3.1-1, the NTU study [June 2016 to September 2016])

A single dose of Sargmalin 125, 250, or 500 μg was administered by inhalation to healthy Japanese adults (N = 3/group). In subjects receiving 125 or 250 μg, serum sargramostim concentrations were near or below the lower limit of quantitation at all timepoints, while in subjects receiving 500 μg, serum sargramostim concentrations reached maximum at 1 or 2 hours after administration with individual $C_{max}$ values being 11.0, 12.3, and 2.32 pg/mL.

A single dose of Sargmalin 125 μg was administered by inhalation to 5 patients with aPAP. Serum sargramostim concentrations were quantifiable only in 1 subject 4 hours after administration (1.12 pg/mL). In the rest of the subjects and at other timepoints, all data were below the lower limit of quantitation.

#### 6.2.2 Phase III study (CTD 5.3.5.1-1, PAGE study [September 2016 to November 2017])

Doses of Sargmalin 125 μg were administered by inhalation to 33 patients with aPAP twice daily intermittently for 24 weeks (7 consecutive administrations followed by a 7-day rest period) and serum sargramostim concentrations were measured on Day 1, Week 13, and Week 25. The concentrations were

below the lower limit of quantitation in all subjects at all timepoints. The mean concentrations of anti-GM-CSF antibodies in serum were 66.8, 79.2, and 75.4 μg/mL on Day 1, Week 13, and Week 25, respectively.

### 6.R Outline of the review conducted by PMDA

Serum sargramostim concentrations were near or below the lower limit of quantitation in patients with aPAP. The applicant considers that since aPAP is a disease characterized by the presence of anti-GM-CSF autoantibodies, following inhalation, sargramostim is absorbed from the lungs and distributed in circulating blood, immediately forming a complex with anti-GM-CSF autoantibodies, which made it impossible to measure concentrations.

PMDA's view:

In addition to the cause explained by the applicant, another possible reason that would account for serum sargramostim concentrations being near or below the lower limit of quantitation in patients with aPAP is that the applicant used a general sandwich ELISA technique, which may have caused competition between the patient's anti-GM-CSF autoantibodies and solid-phase coated anti-GM-CSF antibodies. Considering that anti-GM-CSF autoantibodies are present in subjects receiving Sargmalin, the use of an analytical method that can measure the sargramostim-anti-GM-CSF autoantibody complex could have revealed the pharmacokinetics of sargramostim after inhalation in more detail. However, given that the pharmacological activity of GM-CSF is assumed to be neutralized in the complex, it was concluded that it is not necessary to request that a further investigation be conducted.

## 7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data in the form of results data from the study shown in Table 8.

Table 8. Clinical study on efficacy and safety

| Phase | Study ID | Location | Study population | Number of subjects enrolled | Summary of dosage regimen | Main endpoints **Primary endpoint** |
|---|---|---|---|---|---|---|
| III | PAGE study | Japan | Patients with aPAP | (1) 33<br>(2) 31 | Double-blind period<br>The dose below is administered BID by inhalation for 7 consecutive days, followed by a 7-day rest period. The treatment is repeated for 12 cycles.<br>(1) Sargmalin 125 μg<br>(2) Placebo<br><br>Post-study treatment/follow-up period<br>Subjects were to undergo treatment/observation based on the change from baseline in A-a$DO_2$ at Week 24 according to the following:<br>• Subjects improved by <10 mmHg: Sargmalin 125 μg is administered BID by inhalation for 7 consecutive days, followed by a 7-day rest period. The treatment is repeated for 9 cycles.<br>• Subjects improved by ≥10 mmHg: the patient's clinical course is observed for 18 weeks without treatment. | Efficacy/safety<br>**Change from baseline in A-a$DO_2$ at Week 24** |

## 7.1 Phase III study

### 7.1.1 Investigator-initiated study (CTD 5.3.5.1-1, PAGE study [September 2016 to November 2017])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted at 12 study sites in Japan to evaluate the efficacy and safety of Sargmalin in patients with aPAP (Table 9) (target sample size, 80 subjects [N = 40/group][9)]).

Table 9. Key inclusion/exclusion criteria

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|---|
| Key inclusion criteria |
| 1. Patients aged ≥16 years and ≤80 years |
| 2. Patients with confirmed diagnosis of PAP whose HRCT images show characteristic appearance of a shadow pattern in bilateral lungs that matches the features of PAP, who meet condition (1) or (2) below, and who tested positive for anti-GM-CSF antibodies in serum<br>(1) BALF has a white opaque appearance, and when left aside, suspended matter settles into a sediment. Under a light microscope, granular amorphous deposits stained light green with Papanicolaou stain[10)] and foamy macrophages are observed.<br>(2) Findings supporting PAP are observed in histopathological examinations (transbronchial lung biopsy and surgical lung biopsy). |
| 3. Patients with resting $PaO_2$ ≥50 mmHg and <70 mmHg under room air inhalation, or resting $PaO_2$ ≥70 mmHg and <75 mmHg accompanied by clinical symptoms including cough, sputum, and exertional dyspnea |
| Key exclusion criteria |
| 1. Patients diagnosed as having secondary PAP or hereditary PAP |
| 2. Patients who have concomitant respiratory conditions such as bronchial asthma, pulmonary infection (including pulmonary tuberculosis), pulmonary fibrosis, interstitial pneumonia, and bronchiectasis, and for whom an efficacy and safety evaluation is expected to be difficult |
| 3. Patients receiving other cytokine therapies |
| 4. Patients who have received treatment with whole lung lavage, repeated segmental lavage, or rituximab (genetical recombination) within 6 months before enrollment |
| 5. Patients receiving inhalation, oral administration or intravenous injection of corticosteroids at the time of enrollment |
| 6. Patients receiving other inhalants at the time of enrollment |

This study consisted of a double-blind period (24 weeks) and post-study treatment/follow-up period (18 weeks).

In the double-blind period, subjects were to receive Sargmalin 125 μg/dose or placebo twice daily by inhalation using a nebulizer. One cycle consists of 7 consecutive days of treatment period followed by a 7-day rest period, and the treatment was to be repeated for 12 cycles. In the post-study treatment/follow-up period, subjects whose improvement from baseline in alveolar-arterial oxygen difference ($A\text{-}aDO_2$) at Week 24 was <10 mmHg were to receive Sargmalin 125 μg/dose twice daily by inhalation using a nebulizer under open-label conditions as non-responders. One cycle consists of 7 consecutive days of treatment followed by a 7-day rest period, and treatment was to be repeated for 9 cycles. Subjects whose improvement from baseline in $A\text{-}aDO_2$ at Week 24 was ≥10 mmHg were to enter the post-study treatment/follow-up period as responders and the clinical course was to be monitored in these subjects for 18 weeks without further treatment being administered.

9) Based on the data from the preceding study (*Am J Respir Crit Care Med.* 2010;181:1345-54), the change from baseline in $A\text{-}aDO_2$ (mmHg) and the standard deviation at Week 24, the primary endpoint, were assumed to be −8.97 ± 10.21 for the Sargmalin group and 2.15 ± 6.74 for the placebo group. The effect size (between group difference/pooled standard deviation) was calculated to be 1.31. The lower bound of the 95% confidence interval for the effect size calculated based on the sample size of the preceding study was 0.76. When 0.76 was selected as the effect size, the required sample size was estimated to be 30 subjects per group (60 subjects for 2 groups) using a two-sided significance level of 5% and 80% power for testing. Assuming a dropout rate of 30%, 40 subjects/group (80 subjects for 2 groups) was selected.

10) In cases where other staining methods (e.g., Giemsa staining, PAS staining, and Diff-Quick staining) were used for reasons such as a confirmed diagnosis was made before the establishment of the "Diagnostic criteria for pulmonary alveolar proteinosis (autoimmune or congenital)" [in Japanese] (https://www.nanbyou.or.jp/entry/4775 [last accessed on January 15, 2024]), criterion (1) was deemed to have been met when the findings supporting a diagnosis of PAP, such as deposition of granular amorphous materials and foamy macrophages were observed under a light microscope.

All 64 randomized[11)] subjects (33 subjects in the Sargmalin group and 31 subjects in the placebo group) received at least 1 dose of the study drug and were included in the full analysis set (FAS) and the safety analysis set, and efficacy analyses were to be based on the FAS.

In the double-blind period, 3.2% (1 of 31) of subjects in the placebo group withdrew from the study based on "subject's request."

Table 10 shows the change from baseline in A-a$DO_2$ (mmHg) at Week 24, the primary efficacy endpoint. The difference in the change from baseline in A-a$DO_2$ between the Sargmalin and placebo groups was statistically significant, demonstrating the superiority of Sargmalin over to placebo.

Table 10. Results for the primary efficacy endpoint (FAS, OC)

| | Sargmalin | Placebo |
|---|---|---|
| A-a$DO_2$ at baseline | 37.52 ± 9.99 (33) | 35.22 ± 11.38 (31) |
| A-a$DO_2$ at Week 24 | 33.02 ± 12.87 (33) | 35.45 ± 14.10 (30) |
| Change from baseline at Week 24 | −4.50 ± 9.03 (33) | 0.17 ± 10.50 (30) |
| Between-group difference [95% CI]<br>Two-sided *P*-value[a)] | −4.68 [−9.60, 0.24]<br>0.016 | |

Mean ± standard deviation (N)
a) Two-sided significance level 5%, Mann-Whitney U-test

In the double-blind period, adverse events occurred in 90.9% (30 of 33) of subjects in the Sargmalin group and 74.2% (23 of 31) of subjects in the placebo group. Table 11 shows the main adverse events.

There were no reports of death.

Serious adverse events occurred in 9.1% (3 of 33) of subjects in the Sargmalin group (alveolar proteinosis, cardiac failure congestive, lacunar infarction in 1 subject each) and 3.2% (1 of 31) of subjects in the placebo group (peripheral sensory neuropathy). A causal relationship to the study drug could not be ruled out for peripheral sensory neuropathy (1 subject) in the placebo group.

An adverse event led to treatment discontinuation in 3.2% (1 of 31) of subjects in the placebo group (cough), and its causal relationship to the study drug was denied.

Adverse reactions occurred in 9.1% (3 of 33) of subjects in the Sargmalin group and 12.9% (4 of 31) of subjects in the placebo group.

In the overall period, adverse events occurred in 71.7% (43 of 60) of Sargmalin-treated subjects, and main adverse events are shown in Table 11.

[11)] A deterministic minimization method was used for allocation of patients, with the following allocation factors: the severity of PAP (severity score 2, 3, and 4), age (16-19 years, 20-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, 70-80 years), sex, and study site.

There were no reports of death.

Serious adverse events occurred in 10.0% (6 of 60) of Sargmalin-treated subjects (alveolar proteinosis/influenza, alveolar proteinosis, cardiac failure congestive, lacunar infarction, intestinal obstruction, breast cancer in 1 subject each). A causal relationship to the study drug was denied for all events.

No adverse events led to treatment discontinuation.

Adverse reactions occurred in 8.3% (5 of 60) of Sargmalin-treated subjects.

Table 11. Adverse events occurring in ≥2 subjects in any of the groups (the Sargmalin group, placebo group, or the group of Sargmalin-treated subjects in the overall period) (safety analysis set)

| Event | Double-blind period | | Overall period[a)] |
|---|---|---|---|
| | Sargmalin (N = 33) | Placebo (N = 31) | Sargmalin-treated subjects[b)] (N = 60) |
| Nasopharyngitis | 10 (30.3) | 9 (29.0) | 15 (25.0) |
| Upper respiratory tract infection | 6 (18.2) | 1 (3.2) | 9 (15.0) |
| Pyrexia | 3 (9.1) | 1 (3.2) | 4 (6.7) |
| Headache | 2 (6.1) | 2 (6.5) | 3 (5.0) |
| Dental caries | 2 (6.1) | 2 (6.5) | 2 (3.3) |
| Sinusitis | 2 (6.1) | 0 | 2 (3.3) |
| Pharyngitis | 2 (6.1) | 0 | 2 (3.3) |
| Back pain | 1 (3.0) | 2 (6.5) | 2 (3.3) |
| Gamma-glutamyltransferase increased | 1 (3.0) | 0 | 4 (6.7) |
| Alveolar proteinosis | 1 (3.0) | 0 | 2 (3.3) |
| Influenza | 1 (3.0) | 0 | 2 (3.3) |
| Bronchitis | 1 (3.0) | 0 | 2 (3.3) |
| Glucose urine | 1 (3.0) | 0 | 2 (3.3) |
| White blood cell count increased | 0 | 2 (6.5) | 1 (1.7) |
| Hypertension | 0 | 1 (3.2) | 2 (3.3) |
| Aspartate aminotransferase increased | 0 | 1 (3.2) | 2 (3.3) |
| Insomnia | 0 | 0 | 2 (3.3) |

n (%)
a) Adverse events that occurred after the start of Sargmalin treatment were included.
b) Subjects who were assigned to Sargmalin in the double-blind period and subjects who received placebo in the double-blind period and Sargmalin in the post-study treatment/follow-up period

## 7.R Outline of the review conducted by PMDA

### 7.R.1 Development plan

The applicant's explanation about the development plan for Sargmalin:

It is known that aPAP is caused by functional disruption of alveolar macrophages resulting from overproduction of anti-GM-CSF autoantibodies, which leads to a decrease in their capacity to degrade pulmonary surfactant. Therefore, novel drugs targeting the anti-GM-CSF autoantibodies have been developed in Japan and other countries. Attempts have been made to develop drugs for aPAP by using rhGM-CSF, and the efficacy of these therapies in the treatment of aPAP has been reported, including therapies delivered by a daily subcutaneous injection (e.g., *N Engl J Med.* 1996;335:1924-5, *Am J Respir Crit Care Med.* 2001;163:524-31) and inhalation therapies, including a study in Japan (e.g., *Am J Respir Crit Care Med.* 2005;171:1142-9, *Eur Respir J.* 2006;27:585-93, *Am J Respir Crit Care Med.* 2010;181:1345-54).

The PAGE study, which is an investigator-initiated phase III study planned and implemented based on the preceding studies, can be defined as the pivotal clinical study in the evaluation of the efficacy and safety of Sargmalin in the treatment of aPAP.

- **Study population**

The inclusion and exclusion criteria were established to allow the enrollment of patients with aPAP provided they met the criteria set out in the "Diagnostic criteria for pulmonary alveolar proteinosis (autoimmune or congenital)" [in Japanese] published in Japan (https://www.nanbyou.or.jp/entry/4775 [last accessed on January 15, 2024; the standards were not modified from the standards published at the time the PAGE study was planned]). In addition, the criteria for the severity of aPAP were established as follows: patients with resting $PaO_2$ ≥50 mmHg and <70 mmHg under room air inhalation (corresponding to Severity 3-4 of the PAP Clinical Practice Guidelines, and eligible for therapies such as whole lung lavage, segmental lavage); or resting $PaO_2$ ≥70 mmHg and <75 mmHg accompanied by clinical symptoms including cough, sputum, and exertional dyspnea (corresponding to Severity 2 and eligible for symptomatic treatment). Patients with <$PaO_2$ 50 mmHg (corresponding to Severity 5) were excluded because of possible life-threatening risks if the patient is assigned to placebo.

- **Efficacy endpoints and evaluation timepoint**

A-$aDO_2$ is the difference between the partial pressure of alveolar oxygen ($P_AO_2$) and partial pressure of oxygen in arterial blood ($PaO_2$). A higher A-$aDO_2$ indicates a gas exchange disturbance. In all the preceding studies (Table 12), which evaluated the efficacy and safety of inhaled rhGM-CSF, A-$aDO_2$ was used as the endpoint, and the data demonstrated a certain level of improvement in A-$aDO_2$ at Week 24. In the PAGE study, therefore, A-$aDO_2$ was selected as the primary endpoint, and 24 weeks was selected as the evaluation timepoint.

Table 12. Outline of preceding studies on inhaled rhGM-CSF therapies in patients with aPAP

| | Source of reference | Location | N | Dosage regimen | Timepoint | Endpoints |
|---|---|---|---|---|---|---|
| A | *Am J Respir Crit Care Med*. 2005;171:1142-9 | Japan | 3 | Molgramostim 125 μg/dose BID by inhalation for 7 consecutive days, followed by a 7-day rest period. The treatment is repeated for 12 cycles. | Week 24 | A-$aDO_2$, macrophages and anti-GM-CSF antibodies in BALF, serum markers |
| B | *Am J Respir Crit Care Med*. 2010;181:1345-54 | Japan | 39 | Weeks 1-12: Sargmalin 125 μg/dose BID by inhalation for 8 consecutive days, followed by a 6-day rest period. The treatment is repeated for 6 cycles.<br>Weeks 12-24: Sargmalin 125 μg, once daily by inhalation for 4 consecutive days, followed by a 10-day rest period. The treatment is repeated for 6 cycles. | Week 24 | A-$aDO_2$, presence/absence of dyspnea, oxygen administration, 6-minute walking test, lung function, serum markers, HRCT |
| C | *Eur Respir J*. 2006;27:585-93 | Foreign | 12 | Sargmalin 250 μg/dose BID by inhalation every other week | —[a)] | A-$aDO_2$, $PaO_2$, and lung function |

a) Since this is a retrospective study, no specific evaluation timepoint has been established.

The number of subjects whose improvement from baseline in A-$aDO_2$ at Week 24 was <10 mmHg, and who received Sargmalin after Week 24 exceeded the number estimated. Accordingly, because the study was conducted as an investigator-initiated study and it was difficult to obtain the study drug, to maximize

the opportunities for eligible subjects to receive Sargmalin in the post-study treatment/follow-up period, the duration was changed from the originally planned 12 cycles (24 weeks) to 9 cycles (18 weeks).

- **Dosage regimen**

In a Japanese clinical study (reference B in Table 12), which evaluated the efficacy of inhaled rhGM-CSF, the high dosage regimen demonstrated high efficacy (1 cycle consists of Sargmalin 125 μg/dose twice daily for 8 consecutive days by inhalation, followed by a 6-day rest period). Therefore, it was decided that Sargmalin 125 μg/dose, the highest dose level that had been used in the past in Japan, was to be administered twice daily by inhalation. Biweekly inhalation was selected to reduce the chance of potential toxicities in the blood circulatory and respiratory systems, as well as to enhance adherence.

PMDA's view:

The applicant's explanation about the study population, primary endpoint evaluation timepoints, and dosage regimen is acceptable.

The applicant explained that the primary endpoint is related to a reduction in gas exchange disturbance. Furthermore, the change from baseline in A-a$DO_2$ was established as the primary endpoint in other clinical studies of inhaled rhGM-CSF in patients with aPAP (*Orphanet J Rare Dis.* 2020;15:174, *N Engl J Med.* 2020;383:1635-44), which was reported after the completion of the PAGE study. Taken together, the primary endpoint is acceptable. However, the PAP Clinical Practice Guidelines released after the completion of the PAGE study state that efficacy evaluated using A-a$DO_2$ is generally defined as a change of ≥10 mmHg. Additionally, the Guidelines mentioned that in some cases, measures such as diffusing capacity of the lung for carbon monoxide % predicted (%$DL_{CO}$) or change in quality of life (QOL) are used for efficacy evaluation. Given this, it was decided to evaluate the efficacy of Sargmalin in a comprehensive manner based on the results for secondary endpoints such as response rate, %$DL_{CO}$, and change in QOL, in addition to the results for the primary endpoints [see Section 10 for the definitions of endpoints].

The duration of the post-study treatment/follow-up period was changed to 18 weeks, which is not favorable for the evaluation of the long-term safety and efficacy of Sargmalin. Although there were problems in drug development, including the preparation of the study drug, given the limited number of patients in the study population, it was decided to evaluate efficacy as much as possible based on the obtained results.

### 7.R.2 Efficacy

#### 7.R.2.1 Concerning the methods used to analyze the primary endpoint in the PAGE study

Based on the following discussions concerning the methods used to analyze the primary endpoint in the PAGE study and effects on the interpretation of results, the applicant explained its view that the efficacy of Sargmalin can be evaluated using the results from the primary analysis in the PAGE study.

- Regarding the primary analysis methods for the primary endpoint, the statistical analysis plan ver.1.1.0 (created on August 17, 2017), which was locked before unblinding, states that "when data in each group can be assumed to have a normal distribution (i.e., parametric distribution), a t-test should be used, conversely, when data cannot be assumed to have a normal distribution (i.e., nonparametric distribution), a Wilcoxon (Mann-Whitney) U-test should be used." However, because it was planned to assess the probability distribution for normality in a comprehensive manner taking various factors into account, the criteria for the normality of a probability distribution were not clearly stated in the statistical analysis plan or other documents. In accordance with the provisions in the statistical analysis plan ver.1.1.0, efficacy was evaluated based on the analysis results of data after unblinding. The box-and-whisker plot for the change from baseline in A-a$DO_2$ at Week 24 in the placebo group showed an outlier, with an absolute value of the skew number being ≥1 and greater than twice the standard error. Furthermore, a Smirnov-Grubbs test for outlier detection identified a significant *P*-value. Therefore, the applicant considered that a normal distribution cannot be assumed and decided to perform a Mann-Whitney U-test. The two-sided *P*-values for the primary endpoint were 0.062 for a Student t-test and 0.064 for a Welch t-test, respectively, suggesting a trend similar to that for the primary analysis.

- A deterministic minimization method was used for random allocation of patients. Of the baseline demographics and disease characteristics of patients other than the allocation factors,[11)] it became apparent that an imbalance existed between the treatment groups in terms of the proportion of subjects in the "never smoker" category (54.5% [18 of 33] of subjects in the Sargmalin group and 38.7% [12 of 31] of subjects in the placebo group). Accordingly, an analysis was performed for the primary endpoint using the multiple regression analysis model shown below. The result adjusted by smoking history showed a trend similar to that for the primary analysis. To reduce the predictability of allocation, the details of allocation ratios and allocation factor categories for the deterministic minimization method were specified only in the written allocation specification, and were not to be disclosed to researchers.
  - ✓ The analysis results using the multiple regression model with treatment and smoking history as covariates showed a two-sided *P*-value of 0.079 for the test for the regression coefficient for treatment.

- In the primary analysis for the primary endpoint, the impact of exclusion from the primary analysis of 1 subject in the placebo group, who was discontinued from the study by Week 24 and had no A-a$DO_2$ measurement data after administration of the study drug was evaluated. The results of sensitivity analysis in which missing data were imputed using the baseline observation carried forward (BOCF) approach tended to be similar to those of the primary analysis.

PMDA's view:

In the PAGE study, although the analysis for normality of the probability distribution for the primary endpoint was planned in advance, the criteria for the assessment were not specified in detail. In general, a study plan in which the primary analysis method for the primary endpoint is selected after unblinding could raise doubts about the way the analysis method was selected, namely, that a favorable analysis method may have been selected after obtaining the result; in addition, multiplicity of hypothesis testing cannot be controlled. Therefore, in the PAGE study, the applicant should have defined the details of the criteria for assessment in advance so that a unique analysis method could be determined. Based on the results from the PAGE study, it was confirmed that the applicant's assumption that normal distribution cannot be assumed for the probability distribution for the primary endpoint is reasonable.

The deterministic minimization method used for random allocation is a method that cannot assure probabilistic control of an imbalance in factors between treatment groups, except for the allocation factors; in addition, the predictability of treatment group allocation is prone to increase with this method; therefore, when such randomization methods are used, the results should be interpreted cautiously.

The analysis results for the primary endpoint of the PAGE study were evaluated, taking the above issues into account. The primary analysis showed a statistically significant difference between the Sargmalin and placebo groups, and trends in all sensitivity analyses similar to those in the primary analysis. Therefore, PMDA concluded that the evaluation of the efficacy of Sargmalin in the treatment of aPAP can be performed based on the results for A-a$DO_2$, the primary endpoint of the PAGE study.

### 7.R.2.2 Efficacy of Sargmalin

The applicant's explanation about the efficacy of Sargmalin in the treatment of aPAP:
In the PAGE study conducted in patients with aPAP, the difference in change from baseline in A-a$DO_2$ at Week 24, the primary endpoint, between the Sargmalin and placebo groups was statistically significant, demonstrating the superiority of Sargmalin over placebo [see Section 7.1.1].

Table 13 shows the results for the primary endpoint and secondary endpoints in the double-blind period. At Week 24, the parameters for secondary endpoints, i.e. response rate, dyspnea scale, %$DL_{CO}$, and $PaO_2$, as well as A-a$DO_2$, the primary endpoint, tended to improve in the Sargmalin group compared with the placebo group.

Although the change from baseline in %$DL_{CO}$ and $PaO_2$ at Week 24 was smaller than the changes after whole lung lavage in patients with aPAP reported in the literature[12)] (%$DL_{CO}$, 8-11; $PaO_2$, 6-20 mmHg), given that Sargmalin can be administered at home and is less invasive than whole lung lavage, Sargmalin treatment has a certain clinical advantage.

12) *Eur Respir J.* 2004;23:526-31, *J Korean Med Sci.* 2010;25:393-8, *Annals of the Japanese Respiratory Society*. 2011;49:569-76 [in Japanese], *Chin Med J (Engl).* 2015;128:2714-9, *Am J Respir Crit Care Med*. 2002;166:215-35, *Respiration.* 2017;93:198-206, *J Thorac Dis.* 2021;13:3539-48

The secondary endpoints that did not show clear trends towards improvement at Week 24 in the Sargmalin group do not deny that Sargmalin shows efficacy based on the following discussions:

- In the PAGE study, patients with aPAP with $PaO_2$ ≥50 mmHg and <70 mmHg, corresponding to PAP severity 3 and 4, were eligible for enrollment regardless of clinical symptoms such as cough and sputum, and a certain number of subjects without such symptoms at baseline were enrolled.[13)] It was considered that this decreased baseline cough score and sputum score tended to affect the change from baseline.

- There are no established questionnaires for QOL assessment of patients with aPAP, and the chronic obstructive pulmonary disease (COPD) assessment test (CAT) questionnaire was used. The CAT questionnaire consists of domains such as cough, sputum, shortness of breath, and exertional dyspnea. Although the majority of subjects experienced symptoms of cough, sputum, or dyspnea at baseline,[14)] the baseline CAT scores were lower than the mean values for patients with COPD (16-21; *Eur Respir J.* 2009;34:648-54), suggesting that a reliable evaluation of the effects on the QOL due to symptoms of aPAP may not be possible using the CAT questionnaire.

- The percentage of vital capacity (%VC) was ≥80%, the normal range, in approximately half of the subjects,[15)] and the mean %VC at baseline in each group was approximately 80%. Therefore, it is considered that detection of any improvement brought about by Sargmalin based on %VC was difficult.

- Because of major interindividual variability in the improvement of exercise tolerance in patients with aPAP, it is considered that change from baseline in the 6-minute walk distance was not a reliable indicator of the degree of improvement.

[13)] No cough, 54.5% (18 of 33) of subjects in the Sargmalin group and 58.1% (18 of 31) of subjects in the placebo group; no sputum, 36.4% (12 of 33) of subjects in the Sargmalin group and 48.4% (15 of 31) of subjects in the placebo group
[14)] 97.0% (32 of 33) of subjects in the Sargmalin group and 100% (31 of 31) of subjects in the placebo group
[15)] 48.5% (16 of 33) of subjects in the Sargmalin group and 51.6% (16 of 31) of subjects in the placebo group

Table 13. Main efficacy endpoint results in the double-blind period (PAGE study; FAS, OC)

| | | | Sargmalin (N = 33) | Placebo (N = 31) |
|---|---|---|---|---|
| A-a$DO_2$ | Baseline (Week 0) | | 37.52 ± 9.99 (33) | 35.22 ± 11.38 (31) |
| | Change from baseline | Week 12 | −3.24 ± 8.68 (33) | −3.09 ± 9.60 (30) |
| | | Week 24 | −4.50 ± 9.03 (33) | 0.17 ± 10.50 (30) |
| Response rate | | Week 12 | 21.2 (7/33) | 20.0 (6/30) |
| | | Week 24 | 21.2 (7/33) | 13.3 (4/30) |
| Cough score | Baseline (Week 0) | | 0.6 ± 0.8 (33) | 0.5 ± 0.7 (31) |
| | Change from baseline | Week 12 | −0.3 ± 0.7 (33) | −0.1 ± 0.7 (30) |
| | | Week 24 | −0.1 ± 0.8 (33) | −0.1 ± 0.7 (30) |
| Sputum score | Baseline (Week 0) | | 0.8 ± 0.7 (33) | 0.7 ± 0.7 (31) |
| | Change from baseline | Week 12 | 0.0 ± 0.4 (33) | −0.1 ± 0.7 (30) |
| | | Week 24 | −0.2 ± 0.7 (33) | −0.1 ± 0.7 (30) |
| Dyspnea scale | Baseline (Week 0) | | 1.5 ± 0.9 (33) | 1.4 ± 1.0 (31) |
| | Change from baseline | Week 12 | −0.5 ± 0.8 (33) | −0.1 ± 0.8 (30) |
| | | Week 24 | −0.5 ± 0.8 (33) | 0.0 ± 0.9 (30) |
| QOL | Baseline (Week 0) | | 13.5 ± 8.5 (33) | 14.5 ± 8.0 (31) |
| | Change from baseline | Week 24 | −0.5 ± 6.9 (33) | −3.4 ± 7.2 (30) |
| %VC | Baseline (Week 0) | | 77.19 ± 17.64 (33) | 82.30 ± 14.98 (31) |
| | Change from baseline | Week 24 | 1.89 ± 6.24 (32) | −0.74 ± 7.42 (30) |
| %$DL_{CO}$ | Baseline (Week 0) | | 64.79 ± 22.17 (32) | 64.16 ± 19.57 (30) |
| | Change from baseline | Week 24 | 4.70 ± 15.57 (31) | 0.37±14.46 (30) |
| $PaO_2$ (mmHg) | Baseline (Week 0) | | 66.38 ± 8.66 (33) | 68.82 ± 8.96 (31) |
| | Change from baseline | Week 12 | 3.83 ± 7.85 (33) | 3.09 ± 10.75 (30) |
| | | Week 24 | 4.77 ± 9.43 (33) | −0.05 ± 9.48 (30) |
| 6-minute walk distance (m) | Baseline (Week 0) | | 391.4 ± 159.1 (31) | 352.3 ± 164.0 (28) |
| | Change from baseline | Week 24 | 19.2 ± 71.8 (28) | 5.6 ± 178.6 (27) |

Mean ± standard deviation (N); response rate, % (n/N)

Table 14 shows change from baseline in A-a$DO_2$ at Week 24 in subgroups based on baseline demographics and disease characteristics of patients. Although interpretation of results based on subgroup analysis requires caution, except for the subgroups “smoking history: former smoker” and “previous whole lung lavage: yes,” the results showed trends towards greater improvement in the Sargmalin group compared with the placebo group. No trend towards improvement was shown in the subgroups “smoking history: former smoker” and “previous whole lung lavage: yes,” and the reason for this result could not be identified.

Table 14. Change from baseline in A-a$DO_2$ at Week 24 in subgroups based on baseline demographics and disease characteristics of patients (PAGE study; FAS, OC)

| | | Sargmalin | Placebo | Difference from placebo |
|---|---|---|---|---|
| Overall population | | −4.50 [−7.70, −1.30] (33) | 0.17 [−3.75, 4.09] (30) | −4.68 [−9.60, 0.24] |
| Age | <65 years | −3.74 [−8.04, 0.56] (22) | 0.41 [−5.01, 5.83] (21) | −4.15 [−10.82, 2.52] |
| | ≥65 years | −6.04 [−11.21, −0.86] (11) | −0.39 [−5.54, 4.76] (9) | −5.65 [−12.51, 1.22] |
| Sex | Male | −2.02 [−5.69, 1.65] (19) | −1.34 [−6.78, 4.10] (18) | −0.68 [−6.95, 5.58] |
| | Female | −7.87 [−13.62, −2.13] (14) | 2.44 [−3.79, 8.68] (12) | −10.31 [−18.34, −2.29] |
| Smoking history | Current smoker | −5.53 [−20.64, 9.57] (3) | 17.80 (1) | −23.33 [−53.54, 6.87] |
| | Former smoker | 0.20 [−4.91, 5.31] (12) | −2.09 [−7.20, 3.02] (18) | 2.29 [−4.93, 9.52] |
| | Never smoker | −7.47 [−11.97, −2.96] (18) | 2.28 [−4.27, 8.83] (11) | −9.75 [−17.07, −2.43] |
| Dust exposure | Yes | −4.20 [−10.10, 1.70] (13) | 1.12 [−3.07, 5.31] (14) | −5.32 [−12.10, 1.46] |
| | No | −4.70 [−8.81, −0.59] (20) | −0.66 [−7.52, 6.21] (16) | −4.04 [−11.39, 3.31] |
| Previous whole lung lavage | Yes | 0.49 [−8.87, 9.85] (8) | −3.60 [−16.14, 8.94] (8) | 4.09 [−10.11, 18.28] |
| | No | −6.10 [−9.33, −2.87] (25) | 1.55 [−2.16, 5.25] (22) | −7.65 [−12.40, −2.89] |
| PAP severity | 1 ($PaO_2$ ≥70 mmHg, no symptoms) | — (0) | — (0) | — |
| | 2 ($PaO_2$ ≥70 mmHg, symptomatic) | −6.59 [−10.39, −2.78] (8) | 0.68 [−7.18, 8.53] (8) | −7.26 [−15.18, 0.66] |
| | 3 ($PaO_2$ ≥60 mmHg and <70 mmHg) | −4.78 [−9.68, 0.13] (17) | −1.64 [−7.74, 4.46] (16) | −3.13 [−10.60, 4.33] |
| | 4 ($PaO_2$ ≥50 mmHg and <60 mmHg) | −1.84 [−11.38, 7.70] (8) | 4.35 [−5.65, 14.35] (6) | −6.19 [−18.74, 6.37] |

Mean [95% CI] (N); individual value is shown if N = 1

The applicant’s explanation about the long-term efficacy of Sargmalin:

Table 15 shows the results for the main efficacy endpoints in the post-study treatment/follow-up period: In subjects whose improvement from baseline in A-a$DO_2$ at Week 24 was <10 mmHg and continued to receive Sargmalin during the post-study treatment/follow-up period (Sargmalin→Sargmalin group), change from Week 24 in A-a$DO_2$ tended to reflect an improvement, although there is no comparator group, and some subjects achieved response. The results suggest that there are some patients who require a treatment duration of >24 weeks to respond to Sargmalin treatment.

Table 15. Results for main efficacy endpoints in the post-study treatment/follow-up period (PAGE study; FAS, OC)

| | | | Sargmalin→Sargmalin | Sargmalin→observation | Placebo→Sargmalin | Placebo→observation |
|---|---|---|---|---|---|---|
| A-a$DO_2$ | Week 24 | | 35.07 ± 12.34 (26) | 25.43 ± 12.75 (7) | 37.29 ± 13.90 (26) | 23.48 ± 9.52 (4) |
| | Change from Week 24 | Week 36 | 0.60 ± 9.60 (26) | 1.81 ± 19.41 (7) | −5.93 ± 10.49 (25) | 2.63 ± 7.23 (4) |
| | | Week 42 | −0.26 ± 11.11 (25) | 1.70 ± 15.09 (7) | −4.54 ± 8.14 (25) | 5.83 ± 4.18 (4) |
| Response rate from baseline | | Week 36 | 7.7 (2/26) | 57.1 (4/7) | 32.0 (8/25) | 75.0 (3/4) |
| | | Week 42 | 16.0 (4/25) | 57.1 (4/7) | 20.0 (5/25) | 50.0 (2/4) |
| Cough score | Week 24 | | 0.5 ± 0.8 (26) | 0.4 ± 0.5 (7) | 0.3 ± 0.5 (26) | 0.5 ± 0.6 (4) |
| | Change from Week 24 | Week 36 | −0.1 ± 0.6 (26) | −0.1 ± 0.4 (7) | 0.0 ± 0.3 (26) | −0.3 ± 0.5 (4) |
| | | Week 42 | 0.0 ± 0.7 (26) | −0.1 ± 0.4 (7) | 0.0 ± 0.3 (26) | −0.3 ± 0.5 (4) |
| Sputum score | Week 24 | | 0.6 ± 0.7 (26) | 0.6 ± 0.8 (7) | 0.6 ± 0.7 (26) | 0.5 ± 0.6 (4) |
| | Change from Week 24 | Week 36 | −0.1 ± 0.5 (26) | −0.1 ± 0.4 (7) | −0.1 ± 0.7 (26) | 0.3 ± 0.5 (4) |
| | | Week 42 | −0.1 ± 0.7 (26) | 0.1 ± 0.4 (7) | −0.2 ± 0.8 (26) | 0.5 ± 0.6 (4) |
| Dyspnea scale | Week 24 | | 1.2 ± 1.0 (26) | 0.9 ± 1.1 (7) | 1.3 ± 0.9 (26) | 1.8 ± 0.5 (4) |
| | Change from Week 24 | Week 36 | 0.1 ± 0.6 (26) | −0.1 ± 0.4 (7) | −0.3 ± 0.6 (26) | −0.5 ± 0.6 (4) |
| | | Week 42 | 0.2 ± 0.6 (26) | −0.1 ± 0.4 (7) | −0.3 ± 0.6 (26) | −0.5 ± 0.6 (4) |
| QOL | Week 24 | | 14.0 ± 8.5 (26) | 9.6 ± 6.3 (7) | 11.5 ± 7.5 (26) | 6.8 ± 3.8 (4) |
| | Change from Week 24 | Week 42 | −1.1 ± 5.9 (26) | 3.1 ± 8.8 (7) | −0.3 ± 7.6 (26) | 1.0 ± 8.3 (4) |
| %VC | Week 24 | | 75.72 ± 20.08 (25) | 87.52 ± 16.79 (7) | 82.75 ± 16.41 (26) | 82.18 ± 9.83 (4) |
| | Change from Week 24 | Week 42 | −0.29 ± 6.17 (25) | 1.49 ± 3.89 (7) | 1.87 ± 6.14 (26) | 0.43 ± 1.10 (4) |
| %$DL_{CO}$ | Week 24 | | 68.26 ± 23.41 (24) | 70.45 ± 14.80 (7) | 63.77 ± 22.93 (26) | 69.46 ± 20.09 (4) |
| | Change from Week 24 | Week 42 | −4.94 ± 16.94 (24) | 6.98 ± 10.06 (7) | 6.92 ± 9.24 (26) | 3.06 ± 10.72 (4) |
| $PaO_2$ (mmHg) | Week 24 | | 68.77 ± 10.77 (26) | 80.00 ± 11.62 (7) | 66.58 ± 11.94 (26) | 81.33 ± 8.91 (4) |
| | Change from Week 24 | Week 36 | −1.88 ± 9.43 (26) | −2.59 ± 19.41 (7) | 5.07 ± 10.66 (25) | −1.10 ± 8.21 (4) |
| | | Week 42 | −0.74 ± 10.55 (25) | −2.16 ± 13.42 (7) | 2.05 ± 7.38 (25) | −7.55 ± 7.42 (4) |
| 6-minute walk distance (m) | Week 24 | | 398.7 ± 140.4 (23) | 532.0 ± 85.8 (7) | 367.2 ± 189.2 (26) | 369.5 ± 212.5 (4) |
| | Change from Week 24 | Week 42 | −25.2 ± 88.0 (21) | 37.1 ± 67.3 (7) | 96.1 ± 144.6 (25) | 95.2 ± 119.8 (3) |

Mean ± standard deviation (N); response rate, % (n/N)

PMDA's view:

In the PAGE study, in which the efficacy and safety of Sargmalin were evaluated in patients with aPAP, the results demonstrated the superiority of Sargmalin over placebo for the primary endpoint, and showed trends towards improvement in secondary endpoints, namely, response rate, dyspnea scale, %$DL_{CO}$, and $PaO_2$ at Week 24 in the Sargmalin group. In addition, while these are results from the open-label period without comparator, some subjects who had not achieved response at Week 24 achieved response by continuing treatment with Sargmalin. Taken together, although the results for some secondary endpoints and the results for the primary endpoint in subgroups based on baseline demographics and disease characteristics of patients did not show a trend towards greater improvement in the Sargmalin group compared with placebo, these results do not necessarily deny the efficacy of Sargmalin in the treatment of aPAP. Therefore, it is considered that Sargmalin is expected to have a certain level of efficacy in the treatment of Japanese patients with aPAP. Whether Sargmalin should be used over a long period of time will be discussed in Section 7.R.6.3.

The PMDA's conclusion above will be discussed in the Expert Discussion.

### 7.R.3 Safety

The applicant's explanation about the safety of Sargmalin in patients with aPAP:
In the NTU study, a phase I study [see Section 6.2.1], adverse events occurred in 40.0% of patients with aPAP who received a single inhaled dose of Sargmalin 125 μg (2 of 5 subjects; headache and red rash in 1 subject each). There were no reports of death, serious adverse events, adverse events leading to treatment discontinuation, or adverse reactions.

The summary of safety data and reported main adverse events in the PAGE study, a phase III study, are presented in Table 16 and Table 11, respectively. Overall, Sargmalin was well tolerated and the data demonstrated that there are no safety concerns when administering Sargmalin at the proposed dosage to patients with aPAP.

Table 16. Summary of safety data (PAGE study; safety analysis set)

| | Double-blind | | Overall period[a)] |
|---|---|---|---|
| | Sargmalin | Placebo | Sargmalin-treated subjects[b)] |
| N | 33 | 31 | 60 |
| Total exposure duration (person-years) | 7.55 | 6.92 | 16.47 |
| Summary of adverse events | | | |
| Adverse events | 30 (90.9)<br>913.8 | 23 (74.2)<br>636.0 | 43 (71.7)<br>783.1 |
| Serious adverse events | 3 (9.1)<br>39.7 | 1 (3.2)<br>14.5 | 6 (10.0)<br>42.5 |
| Death | 0 | 0 | 0 |
| Adverse events leading to treatment discontinuation | 0 | 1 (3.2)<br>14.5 | 0 |
| Adverse reactions | 3 (9.1)<br>79.5 | 4 (12.9)<br>57.8 | 5 (8.3)<br>78.9 |
| Adverse events of special interest | | | |
| Breakdown of adverse events | | | |
| Adverse events related to increased leukocytes | 0 | 2 (6.5)<br>28.9 | 2 (3.3)<br>12.1 |
| White blood cell count increased (PT) | 0 | 2 (6.5)<br>28.9 | 1 (1.7)<br>6.1 |
| Eosinophil count increased (PT) | 0 | 0 | 1 (1.7)<br>6.1 |
| Hypersensitivity | 2 (6.1)<br>26.5 | 1 (3.2)<br>14.5 | 4 (6.7)<br>30.4 |
| Pruritus (PT) | 1 (3.0)<br>13.2 | 1 (3.2)<br>14.5 | 1 (1.7)<br>6.1 |
| Conjunctivitis (PT) | 1 (3.0)<br>13.2 | 0 | 1 (1.7)<br>6.1 |
| Pruritus generalised (PT) | 0 | 0 | 1 (1.7)<br>6.1 |
| Rash (PT) | 0 | 0 | 1 (1.7)<br>6.1 |
| Eosinophil count increased (PT) | 0 | 0 | 1 (1.7)<br>6.1 |
| Anaphylactic reaction | 1 (3.0)<br>13.2 | 2 (6.5)<br>28.9 | 4 (6.7)<br>30.4 |
| Pruritus (PT) | 1 (3.0)<br>13.2 | 1 (3.2)<br>14.5 | 1 (1.7)<br>6.1 |
| Cough (PT) | 0 | 1 (3.2)<br>14.5 | 1 (1.7)<br>12.1 |
| Pruritus generalised (PT) | 0 | 0 | 1 (1.7)<br>6.1 |
| Rash (PT) | 0 | 0 | 1 (1.7)<br>6.1 |
| Malignant tumors | 0 | 0 | 1 (1.7)<br>6.1 |
| Breast cancer (PT) | 0 | 0 | 1 (1.7)<br>6.1 |
| Cardiovascular events | 1 (3.0)<br>13.2 | 0 | 1 (1.7)<br>6.1 |
| Cardiac failure congestive (PT) | 1 (3.0)<br>13.2 | 0 | 1 (1.7)<br>6.1 |
| Arrhythmia | 0 | 0 | 0 |
| Effusion and capillary leak syndrome | 1 (3.0)<br>13.2 | 0 | 1 (1.7)<br>6.1 |
| Cardiac failure congestive (PT) | 1 (3.0)<br>13.2 | 0 | 1 (1.7)<br>6.1 |

Upper row, n (%); lower row, number of cases per 100 person-years adjusted by overall exposure duration
See Section 10 for adverse events of special interest
a) Adverse events occurring after the start of administration of Sargmalin were included.
b) Subjects who were in the Sargmalin group in the double-blind period, and subjects who were in the placebo group during the double-blind period and received Sargmalin in the post-study treatment/follow-up period.

Based on the adverse events that occurred in the clinical studies, pharmacology of Sargmalin, and safety profiles of Leukine®, a sargramostim formulation for injection marketed in the US, PMDA evaluated the adverse events that may be associated with Sargmalin treatment in the following sections in detail.

### 7.R.3.1 Adverse events related to increased leukocytes

The applicant's explanation:

Eosinophil count increased and white blood cell count increased were reported in 1 subject each treated with Sargmalin. These events were mild in severity, and there were no adverse events sufficient to raise concerns about the safety of Sargmalin; therefore, it is not considered necessary to include these events in the safety specification of the risk management plan (RMP) based on the results of the PAGE study.

PMDA's view:

Based on the currently available clinical study data, no clear relationship has been identified between Sargmalin treatment and adverse events related to increased leukocytes; therefore, the applicant's explanation of not including this group of events in the safety specification of the RMP is reasonable. However, data on the occurrence of adverse events related to increased leukocytes after administration of Sargmalin should be gathered in post-marketing settings, including data from published literature. If new information becomes available, the applicant should provide information to healthcare professionals as necessary.

### 7.R.3.2 Hypersensitivity and anaphylactic reaction

The applicant's explanation:

The adverse events related to hypersensitivity and anaphylactic reaction reported in Sargmalin-treated subjects were all mild in severity except for moderate cough in 1 subject. Although there were no adverse events sufficient to raise concerns about the safety of Sargmalin, there have been reports of anaphylaxis after subcutaneous or intravenous administration of Leukine® for injection marketed in the US, and anaphylactic reaction is a critical event that may have serious outcomes; therefore, it was decided to include anaphylactic reaction as the important potential risk in the RMP, and include a cautionary statement in the package insert.

PMDA's view:

The currently available clinical study data, albeit limited, do not strongly suggest the occurrence of hypersensitivity and adverse events related to anaphylactic reaction associated with Sargmalin treatment. However, although it is rare for a preparation containing a protein as an active ingredient like Sargmalin to be administered by inhalation, in general, preparations containing a protein as an active ingredient may cause serious hypersensitivity. In fact, there have been reports of anaphylaxis associated with Leukine®. The applicant plans to include a cautionary statement in the package insert to the effect that anaphylaxis has been reported with an injection containing sargramostim as an active ingredient, and include anaphylaxis as an important potential risk in the RMP. PMDA considers the applicant's actions are appropriate. The applicant is required to gather data through post-marketing surveillance, and provide the information to healthcare professionals in an appropriate manner.

### 7.R.3.3 Malignant tumors

The applicant's explanation:

Serious breast cancer was reported in 1 Sargmalin-treated subject and a causal relationship to the study drug was denied. Currently, no clear relationship has been identified between Sargmalin treatment and malignant tumors. However, although there is no information that suggests a relationship with carcinogenesis based on the pharmacological mechanism of action of GM-CSF, from the perspective of pharmacological action, the possibility that sargramostim could act as a growth factor for tumor cells cannot be ruled out. In addition, malignant tumors are critical events that may have serious outcomes; therefore, it was decided to include malignant tumors as an important potential risk in the RMP.

PMDA's view:

Because of the small number of patients treated and limited treatment duration in the currently available clinical study data, it is difficult to conclusively determine the risk of developing malignant tumors associated with Sargmalin treatment. Given that the prescribing information of Leukine® cautions that the possibility of an effect on tumor cells cannot be excluded, the applicant's action to include malignant tumors as an important potential risk in the RMP is appropriate. The applicant is required to gather data on the incidence of malignant tumors in patients receiving long-term Sargmalin treatment through post-marketing surveillance, and provide the obtained information, including that from published literature, to healthcare professionals.

### 7.R.3.4 Other adverse events that may be related to Sargmalin treatment

The applicant's explanation:

Serious cardiac failure congestive, an adverse event included in the category of cardiovascular events and the category of effusion and capillary leak syndrome, occurred in 1 subject, and a causal relationship to the study drug was denied. No arrhythmia-related adverse events were reported. There were reports of serious arrhythmia supraventricular and capillary leak syndrome that may be serious in Leukine®-treated patients, although no clear relationship to Sargmalin treatment has been identified at present. However, given the clinical importance of these events, it was decided that arrhythmia supraventricular and capillary leak syndrome will be included in the important potential risks in the RMP.

PMDA's view:

While there are no clear relationships between Sargmalin treatment and the reported cardiovascular events, arrhythmia, effusion, and capillary leak syndrome based on the currently available clinical study data, given that serious events were reported in patients receiving Leukine®, the applicant will include arrhythmia supraventricular and capillary leak syndrome as important potential risks in the RMP. PMDA considers the applicant's action is appropriate. The applicant is required to gather data through post-marketing surveillance, and provide the information to healthcare professionals in an appropriate manner.

#### 7.R.3.5 Long-term safety

PMDA's view on the long-term safety of Sargmalin:

In the PAGE study, there are no trends towards an increase in the incidence of adverse events, serious adverse events, death, adverse events leading to treatment discontinuation, or adverse reactions in subjects receiving Sargmalin in the overall treatment period compared with that in the Sargmalin group in the double-blind period (Table 16); in addition, there are no trends towards an increase in the incidence of specific adverse events (Table 11). At present, therefore, there has been no observable increase in safety risks with an increase in Sargmalin treatment duration. The necessity of long-term treatment of Sargmalin will be discussed in Section 7.R.6.3.

PMDA's view on the safety of Sargmalin on the basis of discussions in Sections 7.R.3.1 through 7.R.3.5:

As a result of reviewing the submitted clinical study data, at present, there are no significant safety concerns associated with Sargmalin in patients with aPAP, and the safety of Sargmalin is acceptable. It is considered that the reported adverse events are manageable through implementation of appropriate safety measures.

The PMDA's above conclusion will be discussed at the Expert Discussion.

### 7.R.4 Clinical positioning

PMDA's view:

On the basis of submitted data and the results of discussions in Sections 7.R.2 and 7.R.3, Sargmalin is a drug that can be expected to improve the clinical symptoms of aPAP requiring therapeutic intervention, given the current status of aPAP treatment [see Section 1]. However, given that there were patients who did not respond adequately to Sargmalin in the PAGE study, and that the efficacy of Sargmalin was evaluated at Week 24, use of whole lung lavage or other existing treatments should be considered as necessary in patients who do not adequately respond to Sargmalin treatment. The choice of lavage or other treatments depends on the patient's condition, such as where early improvement of respiratory function is necessary or where there has been a rapid deterioration in respiratory function.

The PMDA's conclusion above will be discussed in the Expert Discussion.

### 7.R.5 Indication

On the basis of submitted data and discussions in Sections 7.R.2, 7.R.3, and 7.R.4, the proposed indication of Sargmalin "autoimmune pulmonary alveolar proteinosis" is acceptable.

The PMDA's conclusion above will be discussed in the Expert Discussion.

### 7.R.6 Dosage and administration

#### 7.R.6.1 Appropriateness of the proposed dosage regimen

On the basis of submitted data and discussions in Sections 7.R.2 and 7.R.3, the proposed dosage regimen of Sargmalin in the treatment of aPAP is acceptable.

#### 7.R.6.2 Interruption of Sargmalin treatment and whether treatment can be resumed

The applicant's explanation:

In the PAGE study, subjects whose improvement from baseline in A-a$DO_2$ at Week 24 was ≥10 mmHg and who did not receive Sargmalin during the post-study treatment/follow-up period (Sargmalin→observation group) showed a trend towards a deterioration in A-a$DO_2$ after Week 24; however, the response rate was maintained at Week 42. The results suggest that observation of clinical course can begin in the majority of patients who achieved response after Sargmalin treatment and that Sargmalin doses can be interrupted. According to the PAP Clinical Practice Guidelines and opinions of medical specialists, whether Sargmalin doses can be interrupted should be determined by physicians in a comprehensive manner based on the results of arterial blood gas test, pulmonary function test, clinical symptoms, findings from high-resolution computed tomography (HRCT) imaging, and other data.

The resumption of treatment after dose interruption of Sargmalin was not evaluated in the clinical studies. However, in the follow-up survey (*Chest.* 2014;145:729-37) of the clinical research on inhaled Sargmalin therapy (reference B in Table 12), an additional inhaled Sargmalin therapy was performed in 5 of 12 subjects whose PAP status corresponding to Severity 3 or 4 with aggravated symptoms, or Severity 5 during the follow-up period of 30 months after completion of Sargmalin treatment using the treatment algorithm in the PAP Clinical Practice Guidelines as a reference. The results showed no particular problems. Based on the above, it is considered that Sargmalin treatment can be resumed using the treatment algorithm in the PAP Clinical Practice Guidelines as a reference.

PMDA's view:

Based on the results of the PAGE study, it is considered possible to interrupt Sargmalin doses and start monitoring of clinical course in patients who were treated with Sargmalin and showed improvement in clinical symptoms of aPAP. However, there is not sufficient knowledge on the criteria used to determine dose interruption, and therefore it should be determined carefully by physicians based on the results of arterial blood gas test, pulmonary function test, clinical symptoms, and other data. The resumption of treatment after dose interruption of Sargmalin was not evaluated in the clinical studies. While only limited data on the resumption of Sargmalin treatment are available at present, no data have suggested that Sargmalin treatment should not be resumed; therefore, resumption of Sargmalin treatment should be carefully determined by physicians using the PAP Clinical Practice Guidelines as a reference. It is recommended for the criteria for dose interruption and resumption of Sargmalin to be

further discussed by the relevant academic societies taking into account post-marketing information that become available in the future.

#### 7.R.6.3 Necessity of long-term treatment of Sargmalin

PMDA's view:

As discussed in Sections 7.R.2.2 and 7.R.3.5, data from the PAGE study suggest that in order to elicit a response to Sargmalin, some patients require a treatment duration of >24 weeks. Given that increase in safety risk has not been reported in long-term treatment, PMDA concluded that there is no compelling reason to place a limit on the duration of long-term treatment. However, Sargmalin has not been administered for >42 weeks before; in addition, Sargmalin doses are interrupted in the majority of subjects who achieved response after the treatment, and observation of clinical course is considered possible in these subjects [see Section 7.R.6.2]. Based on the above, the need for long-term Sargmalin treatment should be carefully determined depending on the patient's condition. Because only a small number of patients with aPAP were evaluated in the clinical studies with an evaluation period of ≤42 weeks, the applicant is required to gather long-term safety and efficacy data of Sargmalin treatment through post-marketing surveillance, and provide the information to healthcare professionals in an appropriate manner.

The PMDA's above conclusion will be discussed at the Expert Discussion.

### 7.R.7 Post-marketing investigations

PMDA's view:

As discussed in Section 7.R.3, the safety of Sargmalin is acceptable based on the clinical study data. However, there is paucity of data on Sargmalin in patients with aPAP in the clinical studies; in particular, there is only limited data on the long-term treatment and safety after resumption of Sargmalin treatment. To gather more data, the applicant is required to conduct a use-results survey covering all patients who will be receiving Sargmalin and carefully evaluate the safety and other aspects of Sargmalin treatment.

The PMDA's above conclusion will be discussed at the Expert Discussion.

## 8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

### 8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

### 8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, it was confirmed that the study was generally conducted in compliance with the GCP, and PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following findings at some of the study sites. Although the issues had no significant impact on the overall assessment of the studies, the heads of the relevant medical institutions were notified of the issues as the findings requiring improvement.

Finding requiring corrective action

Study sites

- The heads of the medical institutions received an audit report as stipulated in Article 26-9, Paragraph 3 of the Ministerial Ordinance on Good Clinical Practice for Drugs, but failed to hear the opinions of the members of the Institutional Review Board as to whether the trial was conducted in an appropriate manner at the medical institutions.

## 9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that sargramostim is expected to have a certain level of efficacy in the treatment of aPAP, and that sargramostim has acceptable safety in view of its benefits. Sargramostim is clinically meaningful because it offers a new treatment option for patients with aPAP. Because only a small number of patients were evaluated in the clinical studies of sargramostim, PMDA considers that safety and other aspects of sargramostim in clinical use including long-term treatment should be further investigated through a post-marketing use-results survey or by other means.

PMDA has concluded that sargramostim may be approved if sargramostim is not considered to have any particular problems based on comments from the Expert Discussion.

## 10. Others

The method of efficacy evaluation and definitions of endpoints in the clinical studies of sargramostim are shown below.

| Item | Definition |
|---|---|
| A-aDO$_2$ | Calculate using the following equation.<br>$$A\text{-}aDO_2 = \left(PB - P_{H_2O}\right) \times FiO_2 - \frac{PaCO_2}{R} + PaCO_2 \times FiO_2 \times \frac{1-R}{R} - PaO_2$$<br>$A\text{-}aDO_2$ = alveolar-arterial oxygen difference; $PB$ = barometric pressure (measured); $P_{H_2O}$= partial pressure of water vapor in the air (47 mmHg); $FiO_2$ = fraction of inspired oxygen (0.21); $PaCO_2$ = partial pressure of arterial carbon dioxide (measured); $R$ = respiratory quotient (0.8); $PaO_2$ = partial pressure of oxygen in arterial blood (measured) |
| Response rate | Proportion of subjects whose A-aDO$_2$ at Week 24 improved from baseline by ≥10 mmHg |
| Cough score | Score on a 4-point scale to rate the severity of cough symptoms as shown below<br>0 = no cough<br>1 = mild; treatment with over-the-counter cough medication is required<br>2 = moderate; medical treatment is required; limitations in daily living activities (except self-care)<br>3 = severe; limitations in daily self-care activities |
| Sputum score | Score on a 4-point scale to rate the severity of sputum: 0 = no sputum; 1 = mild; 2 = moderate; 3 = severe |
| Dyspnea scale | Score on a 5-point scale to rate the severity of dyspnea symptoms using the Modified British medical research council (mMRC) scale<br>0 = Dyspnea only with strenuous exercise<br>1 = Dyspnea when hurrying or walking up a slight hill<br>2 = Walk slower than people of the same age because of dyspnea or has to stop for breath when walking at own pace<br>3 = Stop for breath after walking approximately 100 m or after a few minutes<br>4 = Too dyspneic to leave house or breathless when dressing |
| QOL | QOL was evaluated using COPD assessment test (CAT), COPD disease-specific questionnaire<br>CAT is a questionnaire comprising 8 items: cough, sputum, chest tightness, exertional dyspnea, daily activities, confidence leaving home, sleep, and energy. Each item is presented on a 6-point scale, ranging from 0 (no impairment) to 5 (greatest impairment), with a score ranging from 0 to 40 (higher score representing lower QOL) |

The definitions for the events described in Section 7.R.3 are shown below.

| Item | Definition |
|---|---|
| Adverse events related to increased leukocytes | PTs: leukocytosis, white blood cell count increased, hyperleukocytosis, neutrophilia, neutrophil count increased, neutrophil percentage increased, band neutrophil count increased, band neutrophil percentage increased, lymphocytosis, lymphocyte count increased, lymphocyte percentage increased, allergic eosinophilia, drug reaction with eosinophilia and systemic symptoms, eosinophilia myalgia syndrome, eosinophilia, hypereosinophilic syndrome, angiolymphoid hyperplasia with eosinophilia, eosinophil count increased, eosinophil percentage increased, basophilia, basophil count increased, basophil percentage increased, monocytosis, monocyte count increased, monocyte percentage increased |
| Hypersensitivity | SMQ: hypersensitivity |
| Anaphylactic reaction | SMQs: anaphylactic reaction, anaphylactic/anaphylactoid shock conditions (narrow) |
| Malignant tumors | SMQ: malignant tumours |
| Cardiovascular events | SOC: cardiac disorders |
| Arrhythmia | SMQ: cardiac arrhythmia |
| Effusion and capillary leak syndrome | PTs: capillary leak syndrome, hypotension, hypoalbuminaemia, blood albumin abnormal, blood albumin decreased, hypoproteinaemia, haematocrit increased, oedema, generalised oedema, pulmonary oedema, pleural effusion, ascites, volume blood decreased, haemoconcentration, hypovolaemia, hypovolaemic shock, protein total decreased, effusion, capillary leak syndrome, pericardial effusion, fluid retention, oedema peripheral, lung infiltration, cardiac failure congestive, weight increased, weight fluctuation, weight abnormal, abnormal weight gain, overweight |

**Review Report (2)**

February 21, 2024

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | Sargmalin for Inhalation 250 μg |
| **Non-proprietary Name** | Sargramostim (Genetical Recombination) |
| **Applicant** | Nobelpharma Co., Ltd. |
| **Date of Application** | June 30, 2023 |

**List of Abbreviations**

See Appendix.

## 1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

### 1.1 Efficacy, safety, clinical positioning, indication, dosage and administration, post-marketing investigations, and risk management plan (draft)

At the Expert Discussion, the expert advisors supported the PMDA's conclusion on the efficacy, safety, clinical positioning, indication, dosage and administration, and post-marketing investigations of Sargmalin presented in Review Report (1), and the following comments were made:

- When determining as to whether a treatment period of >24 weeks is necessary for patients to respond to Sargmalin treatment, if the size of the standard deviation for the change from baseline in A-a$DO_2$ is taken into account, the possibility of natural fluctuation cannot be ruled out; therefore, it is difficult to draw a clear conclusion based on the results from the PAGE study.
- Since there is paucity of data on the use of Sargmalin, information obtained from post-marketing surveillance, including the following information, should be provided to healthcare professionals promptly and in an appropriate manner.
  - ✓ Use-results data from patients with severe aPAP with resting $PaO_2$ <50 mmHg, a patient population that has not been evaluated, and patients in the subgroups based on baseline demographic and disease characteristic factors (Table 14) that did not show trends towards greater improvement compared with the placebo group.

- ✓ Safety information on patients who have comorbid pulmonary conditions accompanied by inflammation, such as bronchial asthma and interstitial pneumonia, i.e. patient populations that have not been evaluated. In such patients, there is a possibility that the leukocytic proliferation effect of Sargmalin could cause an exacerbation of comorbidities.

In view of the discussion presented in Section "7.R.7 Post-marketing investigations" in Review Report (1) and comments at the Expert Discussion, PMDA considers that post-marketing surveillance should be conducted covering all patients who will be treated with Sargmalin to evaluate the safety and efficacy of Sargmalin in the treatment of aPAP. In addition, the applicant should provide obtained information to healthcare professionals in an appropriate and timely manner. PMDA has concluded that the risk management plan (draft) for Sargmalin should include the safety specification presented in Table 17, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Table 18. PMDA instructed the applicant to conduct post-marketing surveillance that allows evaluation of these issues.

Table 17. Safety and efficacy specifications in the risk management plan (draft)

| Safety specification | | |
|---|---|---|
| Important identified risks | Important potential risks | Important missing information |
| None | • Anaphylaxis<br>• Capillary leak syndrome<br>• Arrhythmia supraventricular<br>• Malignant tumors | None |
| Efficacy specification | | |
| None | | |

Table 18. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

| Additional pharmacovigilance activities | Efficacy survey and studies | Additional risk minimization activities |
|---|---|---|
| • Early post-marketing phase vigilance<br>• General uses-results survey | None | • Disseminate data gathered during early post-marketing phase vigilance |

The applicant explained that as shown in Table 19, a general use-results survey will be conducted covering all patients treated with Sargmalin until data from a certain number of patients are accrued.

Table 19. Outline of general use-results survey (draft)

| | |
|---|---|
| Objective | To investigate safety and efficacy in clinical practice |
| Survey method | All-case surveillance |
| Population | Patients with aPAP |
| Observation period | For 96 weeks from administration of the first dose of Sargmalin |
| Planned sample size | 170 patients (safety analysis set) |
| Main survey items | • Safety specification: anaphylaxis, capillary leak syndrome, arrhythmia supraventricular, malignant tumors<br>• Baseline demographics and disease characteristics of patients (e.g., age, sex, smoking history, dust exposure, medical history, comorbidities)<br>• Disease duration, severity, and prior therapy for aPAP<br>• Status of Sargmalin treatment<br>• Co-administered drugs/therapies<br>• Laboratory tests<br>• Adverse events<br>• Efficacy evaluation |

PMDA accepted the applicant's actions.

## 2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below with the following approval conditions. Since the product is designated as an orphan drug, the re-examination period is 10 years. The product is classified as a biological product. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

**Indication**

Autoimmune pulmonary alveolar proteinosis

**Dosage and Administration**

The usual adult dosage is 125 μg/dose of inhaled sargramostim (genetical recombination) administered twice daily for 7 consecutive days using a nebulizer, followed by a 7-day rest period. The treatment cycle is repeated.

**Approval Conditions**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product, until data from a certain number of patients are accrued and to promptly obtain safety and efficacy data on the product. On the basis of the obtained data, the applicant should take necessary actions for the proper use of the product.

**Appendix**

**List of Abbreviations**

| | |
|---|---|
| A-a$DO_2$ | Alveolar-arterial oxygen difference |
| A/G | Albumin/Globulin ratio |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| aPAP | Autoimmune pulmonary alveolar proteinosis |
| APTT | Activated partial thromboplastin time |
| $AUC_{last}$ | Area under the concentration-time from time 0 to the last observed concentration |
| $AUC_{0-t}$ | Area under the concentration-time curve from zero to t hours |
| BALF | Bronchoalveolar lavage fluid |
| BID | Twice daily |
| CAT | COPD assessment test |
| CBB | Coomassie brilliant blue |
| CI | Confidence interval |
| COPD | Chronic obstructive pulmonary disease |
| CQA | Critical quality attribute |
| $\%DL_{CO}$ | Diffusing capacity of the lung for carbon monoxide % predicted |
| EDTA | Ethylenediaminetetraacetic acid |
| EFD | Embryo fetal development |
| ELISA | Enzyme-linked immunosorbent assay |
| EMA | European medicines agency |
| EMA Guidelines | Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products – Revision 3 (EMA/410/01 rev.3) |
| EOPC | End of production cell |
| FAS | Full analysis set |
| FEED | Fertility and early embryo development |
| GALT | Gut-associated lymphoid tissue |
| GM-CSF | Granulocyte-macrophage colony-stimulating factor |
| HPLC | High performance liquid chromatography |
| HRCT | High-resolution computed tomography |
| ICH | International council for harmonisation of technical requirements for pharmaceuticals for human use |
| ICH Q5B Guidelines | “Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products” (PMSB/ELD Notification No. 3, dated January 6, 1998) |
| ICH Q5D Guidelines | “Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products” (PMSB/ELD Notification No. 873, dated July 14, 2000) |
| MCB | Master cell bank |
| MCH | Mean corpuscular hemoglobin |
| MCHC | Mean corpuscular hemoglobin concentration |
| MCV | Mean corpuscular volume |
| MedDRA/J | Medical dictionary for regulatory activities Japanese version |
| ME ratio | Myeloid/Erythroid ratio |
| OC | Observed case |

| | |
|---|---|
| $PaO_2$ | Partial pressure of oxygen in arterial blood |
| PAP | Pulmonary alveolar proteinosis |
| PAP Clinical Practice Guidelines | The JRS Clinical Practice Guideline for Pulmonary Alveolar Proteinosis 2022, edited by the Japanese Respiratory Society PAP Clinical Practice Guideline Committee. |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PPND | Pre- and postnatal development |
| PPQ | Process performance qualification |
| PT | Preferred term |
| QOL | Quality of life |
| rhGM-CSF | Recombinant human granulocyte-macrophage colony-stimulating factor |
| RMP | Risk management plan |
| RP-HPLC | Reverse phase high-performance liquid chromatography |
| Sargmalin | Sargmalin for Inhalation 250 μg |
| Sargramostim | Sargramostim (genetical recombination) |
| SDS-PAGE | Sodium dodecyl sulfate-polyacrylamide gel electrophoresis |
| SEC | Size exclusion liquid chromatography |
| SMQ | Standardized MedDRA query |
| SOC | System organ class |
| Standards for Biological Raw Materials | Standards for Biological Raw Materials (MHLW Notification No. 210, enacted on May 20, 2003) |
| TSE | Transmissible spongiform encephalopathy |
| %VC | % vital capacity |
| WCB | Working cell bank |