EU Risk Management Plan (RMP) for Imreplys (sargramostim)

RMP version to be assessed as part of this application:

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QPPV name: Aylin Aydiner

QPPV signature:

Rationale for submitting an updated RMP: <Not applicable for initial marketing authorisation application submission>

Summary of significant changes in this RMP, other than those requested by EMA:

- Aligned description of the mode of action, indication and dosage to the current proposed summary of product characteristics (SmPC)
- Protocol submission date revised for the study PTX-01-001 from 31 December 2025 to 30 June 2025

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Abbreviations

ADA	Anti-Drug Antibody
ALC	Absolute Lymphocyte percent of normal in first 24 hours
ALL	Acute Lymphoblastic Leukaemia
AML	Acute Myeloid Leukaemia
ANC	Absolute Neutrophil Count
ARS	Acute Radiation Syndrome
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMT	Bone Marrow Transplantation
CBC	Complete Blood Count
DSUR	Development Safety Update Report
EDQM	European Directorate for the Quality of Medicines
EDTA	Ethylenediaminetetraacetic acid
EEA	European Economic Area (European Union plus Norway, Iceland and Liechtenstein)
FDA	Food and Drug Administration
GD	Gestation day
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
H-ARS	Haematopoietic Syndrome of Acute Radiation Syndrome
HLA	Human Leukocyte Antigen
HS	Haematopoietic Syndrome
HSV	Herpes simplex virus
ICH	The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INN	International Non-proprietary Name
LD	Lactation day
MAH	Marketing Authorisation Holder
NHP	Non-Human Primate
NOAEL	No-observed-adverse-effect-level
ORISE	Oak Ridge Institute for Science and Education
PSCT	Peripheral stem cell transplantation
REAC/TS	ORISE Radiation Emergency Assistance Centre/Training Site
rhu GM-CSF	Recombinant Human Granulocyte-Macrophage Colony-Stimulating Factor
RMP	Risk Management Plan
SC	Subcutaneous
SmPC	Summary of Product Characteristics
TBI	Total body irradiation
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation

Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Sargramostim, recombinant human granulocyte-macrophage colony-stimulating factor (rhu GM-CSF).
Pharmacotherapeutic group(s) (ATC Code)	Colony-stimulating factors, ATC code: L03AA09
Marketing Authorisation Applicant	Partner Therapeutics Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Imreplys 250 mcg powder for solution for injection
Marketing authorisation procedure	Centralised procedure, application under exceptional circumstances
Brief description of the product	Chemical class: Glycoprotein
	Summary of mode of action: Sargramostim is a recombinant human GM-CSF. The binding to GM-CSF receptors expressed on the surface of target cells (haematopoietic progenitors and mature immune cells), initiates an intracellular signalling cascade which induces the cellular responses (i.e., division, maturation, activation). GM-CSF is a multilineage factor and, in addition to dose-dependent effects on the myelomonocytic lineage, it can promote the proliferation and maturation of megakaryocytic and erythroid progenitors.
	Important information about its composition: Sargramostim is a human granulocyte-macrophage colony-stimulating growth factor (rhu GM-CSF) produced by recombinant DNA technology in a yeast (*S. cerevisiae*) expression system.
Hyperlink to the Product Information	Module 1.3.1 of the eCTD.
Indication(s) in the EEA	Current: Imreplys 250 mcg powder for solution for injection is indicated in patients of all ages acutely exposed to myelosuppressive doses of radiation Haematopoietic Sub-syndrome of Acute Radiation Syndrome (H-ARS).
	Proposed (if applicable): Not applicable

Dosage in the EEA	Current: Daily dose: administered once daily as a subcutaneous injection and dosing is based on body weight as follows: • 7 micrograms/kg in children and adolescents weighing more than 40 kg and in adults • 10 micrograms/kg in children and adolescents weighing 15 kg to 40 kg • 12 micrograms/kg in neonates, infants or children weighing less than 15 kg Treatment with Imreplys should be started as soon as possible in any adult, adolescent, child, or infant who has been acutely exposed to myelosuppressive doses (greater than 2 gray [Gy]) of radiation with suspected H-ARS based on clinical signs and symptoms or confirmed H-ARS based on laboratory tests. If possible, a baseline complete blood count (CBC) with differential should be obtained. Treatment should not be withheld if H-ARS is suspected or diagnosed even if the absorbed radiation dose is estimated as lower than 2 Gy. If possible, estimate a patient’s absorbed radiation dose (i.e., level of radiation exposure) based on information from public health authorities, biodosimetry if available, or clinical features and laboratory findings such as lymphocyte depletion kinetics. Imreplys should not delayed if a CBC is not readily available or absorbed radiation dose cannot be estimated. Imreplys is injected under the skin (subcutaneous injection), by a healthcare provider, or at home by patient or patient’s caregiver. If sargramostim is injected at home by patient or patient’s caregiver, detailed instructions are available in the patient information leaflet section 3.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current (if applicable): Powder for solution for subcutaneous injection, 250 mcg
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Incidence:

H-ARS is a serious and life-threatening condition which occurs in persons exposed to greater than 1 Gray (Gy) of total or partial body irradiation. The risk of death is strongly correlated with the levels of myelosuppression and pancytopenia that present in patients. Myelosuppression and pancytopenia present in a radiation dose-dependent fashion and are impacted by the radiation dose, volume of body irradiated, and duration of exposure. Patient age and gender, as well as co-morbidities and concomitant injuries, are believed to impact susceptibility to H-ARS, clinical outcomes, and ultimately risk of death (Goans and Flynn, 1989; Dainiak, 2018; Adams et al., 2017, WHO, 2023).

H-ARS would most likely occur after a radiological and/or nuclear incident with ability to cause mass casualties such as the detonation of a "dirty bomb" (i.e., radiological dispersal device), nuclear weapons attack, or deliberate sabotage or accidental release of radioactivity from a nuclear reactor. The estimate of effect from a Hiroshima-sized (i.e., approximate 10 kiloton) nuclear weapon over a heavily populated urban area indicates 100 000 to 500 000 casualties are likely to require immediate medical attention for treatment of potentially life-threatening radiation illness. The total number of casualties will be dependent on the surrounding urban architecture and/or natural environment, population density, height of the burst (e.g., ground burst versus air burst), and other factors (IoM, 2009; Buddemeier, 2018; NAS, 2019).

Some of the known historical incidents of radiological and/or nuclear catastrophe reporting H-ARS are described below.

Human data on the clinical course and pathological effects of H-ARS are largely derived from the atomic bombings of Hiroshima and Nagasaki during World War II, accidents at nuclear installations, and accidents involving industrial radiography or clinical radiation therapy sources. The number of casualties from Hiroshima and Nagasaki are estimated at 366 000 with 213 000 deaths. Approximately one-third of deaths occurred immediately, while 90 percent of subsequent deaths occurred within three weeks (Jones et al., 2014). Mortality was 97 percent within in one-half kilometre of ground zero, and injuries and mortality were reported up to 5 kilometres from ground zero (Jones et al., 2014). While overall death rates were greater than 90 percent within 1 kilometre of ground zero, mortality among victims who were in reinforced buildings, was reported to be less than 50% due to shielding provided by intact/semi-intact structures (Shirabe, 2006).

The incidence of casualties and risk of mortality is expected to be directly related to absorbed radiation dose and the presence of combined injuries (wound or burn). In Hiroshima, out of a population of 255 000 people there were 136 000 estimated casualties, including 45 000 victims who died within 24 hours, leaving a total of 91 000 survivors who would have benefitted from treatment. Unfortunately, treatment was severely limited, and 16 340 people died between day 2 and day 21 and an additional 2,660 victims died between day 21 and day 120 (Oughterson and Warren, 1956; Woodruff et al., 2012).

Since 1945, approximately 417 radiological incidents have been reported according to the Oak Ridge Institute for Science and Education (ORISE) Radiation Emergency Assistance Centre/Training Site (REAC/TS). Each of these accidents involved significant radiation exposure of at least one person (when the absorbed dose to the whole-body exceeded 0.25 Gy, or 6 Gy to skin, or 0.75 Gy to any other organ). Among 3000 exposed persons 127 fatalities have been registered in 57 years (Turai and Veress, 2001). The lower reported mortality in these cases compared to Hiroshima and Nagasaki reflects both that personalised care was provided in these cases and that many accident victims experienced only partial body exposure (Woodruff et al., 2012).

The most significant radiation accident was the 1986 reactor incident at Chornobyl. It was reported that 237 people onsite and involved with the clean-up were hospitalised and 134 of these people were diagnosed with H-ARS. Of these, 28 people died as a result of H-ARS within four (4) months of the accident. Nineteen more workers subsequently died between 1987 and 2004, but their deaths could not be definitively attributed to radiation exposure (Turai and Veress, 2001).

While the number of cases of reported H-ARS since 1945, the threat of radiological/nuclear incidents is increasing. Development of tactical nuclear weapons that might be used in the battlefield make a nuclear exchange more plausible compared to the past when there were only strategic nuclear weapons. Additionally, the threat of nuclear terrorism and of damage to nuclear power facilities has increased substantially (Kendall *et. al.,* 2023; Lazarus et al*.,* 2022; Ryan, 2023).

In addition, there have been several reports in the published literature reporting industrial radiological accidents and radiation exposure through orphaned sources and accidental exposures. On 5 February 1989, at an industrial irradiation facility near San Salvador, El Salvador the source rack became stuck in the irradiation position and the operator bypassed the irradiator's degraded safety systems and entered the radiation room with two (2) other workers to free the source rack manually. The three (3) men were exposed to high radiation doses and developed H-ARS. The worker who had been most exposed died six and a half months after the accident with his death being attributed to residual lung damage due to irradiation, exacerbated by injury sustained during treatment (International Atomic Energy Agency, 1990). On 21 June 1990 at an industrial irradiation facility at Soreq, Israel an operator entered the irradiation room by circumventing safety systems and was acutely exposed, with an estimated whole-body dose of 10–20 Gy. He presented signs and symptoms indicative of severe haematological and gastrointestinal phases of ARS and died 36 days after the accident (International Atomic Energy Agency, 1993). On 26 October 1991, in the town of Nesvizh, Belarus on entering the facility the operator bypassed a number of safety features and left the controls in a position such that exposure was imminent. At some stage, the source rack became exposed, and the operator was irradiated for about 1 minute. It was estimated that he had received a whole-body dose of 11 Gy, with localised areas of up to 20 Gy. Despite intensive medical treatment, he died 113 days later (International Atomic Energy Agency, 1996). On 24 July 1996 at the combined cycle fossil fuel power plant in Gilan, Islamic Republic of Iran, a worker picked up a 192Ir industrial radiography source and put it in his chest pocket, where it remained for approximately 1.5 h. He survived the acute radiation disease without very severe complications, and fortunately he has a good prognosis for survival (International Atomic Energy Agency, 2002). In February 1999 in Yanango, Peru, a welder picked up an 192Ir industrial radiography source and put it in his pocket for several hours which led to the amputation of one leg. His wife and children were also exposed, but to a much less extent (International Atomic Energy Agency, 2000). On 26 April 1999, three (3) people were accidentally exposed to high dose (60)Co irradiation in Henan Province of China and suffered from severe (1 case) or moderate (2 cases) H-ARS. As part of the comprehensive treatment, strict reverse isolation and GM-CSF therapy was initiated and all the patients recovered after an appropriate treatment for 83 days (Liu et al*.*, 2008). In late January and early February 2000, in Samut Prakarn, Thailand, a disused Co-60 teletherapy head was partially dismantled, taken from an unsecured storage location and sold as scrap metal. Altogether, 10 people received high doses from this source, out of whom three (3) died within two (2) months of the accident as a consequence of their exposure (International Atomic Energy Agency, 2002).

Prevalence:

There is limited data available on the prevalence of H-ARS in humans. The prevalence for ARS, based on available data on incidence discussed above, is estimated to be 3,000 since 1945. The prevalence for H-ARS would be less than this. For the intended use, the prevalence could be as high as 250,000 per event.

In addition to the increased rate of mortality, level of radiation exposure and incidence of combined injury associated with proximity to ground zero, the risk of death or radiation/combined injury would be highest in persons outdoors at detonation, who go outside within two (2) hours of the detonation, or suffer combined injury (Woodruff et al*.,* 2012; Jones et al*.,* 2014; NAS, 2019). Mortality and injury data from Hiroshima were analysed (Oughterson and Warren, 1956) to develop estimates of distance and mechanism of injury leading to 50 percent lethality at radiation detonation levels, which is shown in Table 1 (Jones et al., 2014; Woodruff et al., 2012) and Table 2 (Jones *et. al.*, 2014) below.

Table 1: Casualty Estimates by Mechanism of Injury for 1 to 1 000 Kiloton (KT) Detonations

Mechanism of Injury	1 KT	10 KT	100 KT	1 000 KT
Indirect Blast (50% Lethality)	0.43 km	1.0 km	2.1 km	4.4 km
Direct Blast (50% Lethality)	0.14 km	0.3 km	0.7 km	1.4 km
Radiation Burn (50% 2^{nd} Degree Burns)	0.86 km	2.5 km	6.5 km	14 km
Radiation - 450 cGy (50% Lethality)	0.77 km	1.2 km	1.7 km	2.6 km

Table 2: Predicted Distribution of Injuries Sustained from a Nuclear Detonation

Injury Types	Percentage of Total Injuries
Radiation Only	15
Radiation Combined Injury	62
Burn or Wound Only	23

Demographics of the population in the proposed indication and risk factors for the disease:

Imreplys 250 mcg powder for solution for injection is indicated for use in both adult and paediatric patients from birth.

The clinical presentation of H-ARS is dependent upon the type, rate, and dose of radiation absorbed. Generally, persons experiencing an exposure of greater than 2 Gy will develop H-ARS (Waselenko et al., 2004; Koenig et al., 2005; Sugarman et al., 2017; Lazarus *et. al*, 2021). Persons exposed to radiation with combined injuries are at risk of H-ARS at approximately 1.2 Gy (Flynn and Goans, 2012).

Paediatrics

Adams and colleagues estimated LD_{50}s of H-ARS for children between 6 months old and 18 years old using a blend of weight and number of stem cells transplanted in peripheral blood stem cell transplants. Their estimates indicate that children below the age of 5 years old are almost twice as sensitive to H-ARS as adults. This means that younger children would likely require care at radiation exposure levels of 1 Gy or potentially lower (Waselenko et al., 2004; Adams et al., 2017).

Elderly

Differences in sensitivity between the elderly and younger persons have been observed in the context of radiation therapy, but there is little data in the context of H-ARS. It is expected that a diminishing ability to effectively repair or replace damaged cells, including those damaged by radiation, that is associated with ageing, will maker older persons more susceptible to acute radiation exposure. This may potentially shift the level of radiation exposure causing H-ARS that requires treatment lower than the 2 Gy estimated threshold for healthy adults (Waselenko et al., 2004; Krasin et al., 2010, Stricklin et al., 2012, Narendran et al., 2019).

Populations at Higher Risk

Generally, poor health status and obesity is associated with increased risk for H-ARS. Immune compromised people, including persons with HIV, diabetes, cancer, and other conditions characterised by suppressed immune response and those taking immunosuppressive therapies will be at higher risk of infection and sepsis after radiation exposure (Farrell et al., 2008; Winfield et al., 2010).

Blood thinners and anti-coagulants are known to significantly increase the risk of haemorrhage, and since haemorrhage is a consequence of radiation-induced pancytopenia, patients on these treatments with H-ARS will likely be at risk at a lower level of radiation exposure than healthy adults (Mettler et al., 2001; International Atomic Energy Agency, 1996; Bereznicki et al., 2006; Mountain et al., 2010; Stricklin et al., 2012).

Cytomegalovirus, herpes simplex virus (HSV) 1 and HSV 2 are prevalent in the general population in their dormant state, and reactivation due to the immune-suppression from H-ARS would likely cause complications in affected patients (Staras et al., 2006, Stricklin et al., 2012). Reactivation of HSV in several Chornobyl patients with H-ARS caused significant complications and was reported to be a contributing factor to mortality in four (4) patients (Gale, 1987; Baranov et al., 1989).

Biological Sex Differences

Human data on biological sex differences in persons with H-ARS is very limited. There is some evidence of differences in an analysis of 4 406 survivors from Hiroshima and Nagasaki. These data suggest that a larger percentage of male survivors closest to ground zero experienced H-ARS than women in the same exposure group, and that males had a higher rate of sepsis than females. Additional data collected on 20-day survivors showed no difference based on biological sex (Oughterson et al., 1951; Stricklin et al., 2012). The findings are not considered adequate for making conclusions about biological sex related mortality and morbidity risk from acute radiation exposure.

The main existing treatment options:

There are currently no approved treatments in the EU for H-ARS in adults or paediatric patients (Stenke et al., 2022).

Prophylactic Measures

There are no known or approved prophylactic therapies for prevention of H-ARS. Avoiding exposure, minimising the length of exposure, or delaying the time post-detonation/incident to exposure are effective mitigation measures. For persons in affected areas that are in or can get into intact or safe, semi-intact buildings, sheltering in-place for up to 24 hours is recommended. Sheltering in-place would be particularly effective as distance from ground zero increases and in areas effected by fallout. It is estimated that being in the basement of a single-story wood-frame house can be 10 times more protective than being outside. In the fallout zone, sheltering in a shallow basement, wood-frame house or two (2)- or three (3)- story brick structure for 12 hours would reduce the number of persons with significant exposure by an estimated two-thirds (Buddemeier, 2018; NAS, 2019).

Supportive Care

Given the number of casualties, infrastructure damage and impact of post-event radiation exposure, intensive supportive care will not be available. Moderate supportive care can increase survival but will be difficult to provide after a mass casualty radiological/nuclear incident.

After exposure, patients should be decontaminated and first aid should be administered for any conventional injuries including wounds, blast injuries, and thermal burns. Supportive care would be based upon the severity of radiation exposure and resource availability and would be expected to include antimicrobials, IV fluids, transfusions, and anti-emetics (Waselenko et al., 2004; Wolbarst et al., 2010; Goans and Flynn, 1989; Jones et al., 2014; Sugarman et al., 2017). Supportive care includes the following:

All exposures (as needed):

- Antiemetic agents for nausea and emesis, which are symptoms of radiation damage to epithelial tissue in the gastrointestinal tract: selective 5-HT3 receptor antagonists (ondansetron, granisetron)
- Fluid and electrolyte replacement
- Analgesic agents
- Anxiolytic agents
- Topical burn creams
- Sedatives

Exposures greater than 2 Gy:

- Antifungal agents: fluconazole
- Antibiotic therapy: if ANC< 0.5 x 10^9cells per litre administer fluoroquinolones
- Antivirals: for persons with a history of HSV (acyclovir)

Exposures greater than 3 Gy:

- Antidiarrheal agents including anticholinergics, psyllium, aluminium hydroxide, and loperamide.
- Targeted antibiotics
- Transfusions: Packed red blood cells and platelets (leuko-reduced and irradiated to 25 Gy) may be needed but typically not for 2 to 4 weeks after exposure.
- Anticonvulsant agents

Therapies recommended but not approved in the EU

The treatment of H-ARS is focused primarily on reducing the risk of infection and sepsis by restoring immune response, treating and preventing infections and haemorrhage, and maintaining hydration, as well as options to restore bone marrow.

Treatments for use in paediatric and adult patients with H-ARS that are recommended for use by World Health Organisation (WHO), REAC/TS and other response agencies and are approved for use by the United States Food and Drug Administration include: granulocyte colony-stimulating factor (G-CSF) such as filgrastim and lenograstim and pegylated granulocyte colony-stimulating factor (PEG-G-CSF) such as pegfilgrastim, for neutrophil recovery; GM-CSF such as sargramostim for pancytopenia (leukopaenia, neutropaenia, thrombocytopaenia, lymphopenia and monopaenia) and lastly romiplostim, a thrombopoietin receptor agonist for thrombocytopaenia, which is also used in combination with the other cytokines (Goans and Flynn, 1989; Waselenko et al., 2004; Dainiak, 2018; WHO, 2023; Lazarus et al., 2021; Lazarus et al., 2022).

While all four (4) products are recommended by the WHO, there are significant differences in their practical and operational utility in a mass casualty radiological or nuclear incident. Sargramostim enhances survival from H-ARS when treatment is initiated up to 96 hours post-radiation exposure in the setting of minimal supportive care (i.e., fluids and antimicrobials) (Clayton et al., 2021; Zhong et al., 2020). Minimal supportive care conditions (i.e., absence of whole blood transfusions) mimic the expected limited resource environment following a radiological or nuclear mass casualty event. Data demonstrate G-CSF (i.e., filgrastim, pegfilgrastim) is not effective in the absence of whole blood transfusions (Gluzman-Poltorak et al., 2014). Further, the treatment window for filgrastim, pegfilgrastim, and romiplostim is short. Treatment with these products must be administered within 24-hours of exposure to enhance survival (Farese et al., 2014; Hankey et al., 2015; Bunin et al., 2023). This is unlikely to be feasible in a mass casualty setting. Finally, data supporting the efficacy of the G-CSF products was generated only in male non-human primate (NHP), while sargramostim was studied in both male and female NHP and significantly improved survival in both.

In a radiological or nuclear mass casualty incident, medical resources including supportive care will be limited. Given shelter-in-place orders, infrastructure damage, logistical challenges in deploying medical personnel and treatments, and the need to wait for radiation levels to subside, it is unlikely that H-ARS treatments could be deployed before 24 hours (ASPR/SNS, 2023).

Stem cell transplantation therapy for exposures between 8 and 10 Gy

Bone marrow transplants were generally unsuccessful in Chornobyl victims. Two (2) accident victims in Japan received G-CSF and haematopoietic cell transplants, both died of multi-organ failure. A victim in China received G-CSF followed by a transplant and infusion of mesenchymal stem cells. He died of multi-organ failure. A fourth (4th) victim in Israel received GM-CSF and a transplant. He died from presumed graft-versus-host disease (Goans and Flynn, 1989; Lazarus et al., 2022). In hindsight, it is thought that these poor results were, at least partially, due to the survival of some host stem cells in the bone marrow. As a result, as surviving marrow was regenerated, it rejected the transplanted marrow cells.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

ARS, also known as radiation sickness or radiation toxicity, occurs when individuals are exposed to high doses of total body irradiation (TBI) that causes multi-organ injury. The first signs of injury appear in organ systems with high cell turnover rates, such as the haematopoietic system and gastrointestinal tract. Without medical intervention, death from ARS can occur within days to weeks. Significant causes of death among patients with ARS include overwhelming infection and sepsis, uncontrollable bleeding, and severe acute anaemia, all of which contribute to multi-organ dysfunction and failure (MOD/MOF) (Wolbarst et al., 2010; Dainiak 2018). Over time, delayed effects of acute radiation exposure may be seen in the heart, lungs, kidneys, and skin. At extremely high exposure levels (i.e., supralethal exposures), death occurs within twenty-four to forty-eight hours due to cerebrovascular collapse and shock (i.e., cerebrovascular syndrome) (Wolbarst et al., 2010).

The earliest symptoms of ARS (i.e., prodromal phase) typically include nausea, vomiting, headache, and diarrhoea that can begin within minutes of exposure. This is often followed by a period where symptoms subside (i.e., latent phase). Patients will then often become sick again with previous symptoms returning plus fever, loss of appetite, infection, bleeding, and anaemia (i.e., manifest illness phase). Hair loss and skin damage including swelling, itching, redness, blisters, or ulcers may also occur. Mild symptoms may occur at radiation exposures as low as 0.5 Gy. The severity of symptoms and shortness of the period where symptoms subside generally correspond with the level of exposure. Depending on the dose of exposure and extent of medical intervention, mortality can occur within hours to months after exposure.

Haematopoietic Syndrome of Acute Radiation Syndrome occurs after whole-body or partial-body (>60%) exposure to radiation of doses >0.7 Gy, causing damage to rapidly dividing tissues, including bone marrow, spleen, thymus, lymph nodes and blood cells, resulting in pancytopenia (severely low levels of white blood cells, platelets, and red blood cells). Low white blood cell counts, including lymphocytes, eosinophils, monocytes, and neutrophils, culminate in immunosuppression that leads to the development of bacterial, viral, and fungal infections and ultimately sepsis. Low platelet counts, or thrombocytopenia, leads to haemorrhage and severe acute anaemia.

Data from NHP studies suggests that the $LD_{50/60}$ after TBI is between 3.25 and 4 Gy without supportive care (Waselenko et al., 2004; Jones et al., 2014). Given the massive numbers of victims and the impact of a detonation on hospitals, infrastructure and medical and first responder personnel within and around the blast zone, supportive care (targeted antibiotics and blood transfusions) will not be available for most, if any, H-ARS patients (NAS, 2019; Jones et al., 2014; Lazarus et al., 2022; ASPR/SNS, 2023). Therefore, absent treatment, the life expectancy of those exposed to more than 3.25 Gy would be days to weeks. Persons exposed to 2 to 3.25 Gy would also be at risk, particularly those with concomitant injury (e.g., blast, trauma, etc.) or who are immune compromised or have other conditions which would be exacerbated by the effects of radiation (Mettler et al., 2001; Staras et al., 2006; Farrell et al., 2008; Winfield et al., 2010; Jones et al., 2014).

The clinical presentation of ARS is dependent upon the type, rate, and dose of radiation absorbed. Generally, persons experiencing an exposure of greater than 2 Gy will develop H-ARS (Waselenko et al., 2004; Koenig et al., 2005; Sugarman et al., 2017; Lazarus et al., 2021). Persons exposed to radiation with combined injuries are at risk of H-ARS at approximately 1.2 Gy (Flynn and Goans 2012). The four (4) phases of H-ARS (and ARS), timelines and symptoms are shown in Table 3 (Jones et al., 2014).

Table 3: Four phases of H-ARS

Phase	Time after Exposure	Symptoms	Implications
Prodromal	Hours	Nausea, vomiting, malaise	Time to onset associated with exposure level
Latent	Days to 2 weeks	Relatively symptom-free; pancytopenia	The shorter duration the higher the exposure level
Manifest	2 to 3 weeks	Infection, bleeding, anaemia, sepsis	Time to onset associated with exposure level
Recovery	Few weeks to 2 years	Improve; bone marrow cells repopulate	Patients recover or die

Currently, there are no biodosimeters approved in the EU for practical use in a mass casualty radiological/nuclear event. However, time to nausea and vomiting and/or lymphocyte depletion kinetics are widely considered reliable surrogates for estimating radiation exposure in patients with H-ARS (Waselenko et al., 2004; Flynn and Goans, 2006; Garau et al., 2011; Sugarman et al., 2017; Lazarus et al., 2021). Table 4 describes the presenting symptoms and/or lymphocyte depletion kinetics observed during the prodromal phase that would be used to estimate the level of radiation exposure in victims of a radiation/nuclear mass casualty incident (Sugarman et al., 2017; Garau et al., 2011; Flynn and Goans, 2006; Waselenko et al., 2004).

Table 4: Signs and Symptoms of Radiation Exposure Level During Prodromal Phase

Signs and Symptoms	Mild (1-2 Gy)	Moderate (2-4 Gy)	Severe (4-6 Gy)	Very Severe (6-8 Gy)	Lethal (>8 Gy)
Vomiting					
Onset	4 hours post exposure	2-4 hours post exposure	1-2 hours post exposure	<30 minutes post exposure	<10 minutes post exposure
Incidence	20-35%	35-72%	72-100%	90-100%	100%
Diarrhoea	None	None	Mild	Heavy	Heavy
Onset	-	-	3-8 hours	1-3 hours	Minutes
Incidence	-	-	<10%	>10%	100%
Headache	Slight	Mild	Moderate	Severe	Severe
Onset	-	-	4-24 hours	3-4 hours	1-2 hours
Incidence	-	-	50%	80%	80-90%
Body Temp.	Normal	Increased	Fever	High Fever	High Fever
Onset	-	1-3 hours	1-2 hours	<1 hour	<1 hour
Incidence	-	10-80%	80-100%	100%	100%
ALC	88-78%	78-60%	60-47%	<47%	<47%

ALC = Absolute Lymphocyte percent of normal in first 24 hours

The signs and symptoms of H-ARS from the prodromal through final phase vary based upon the type and amount of radiation exposure and portion of the body exposed (partial vs. TBI). Individual sensitivity to radiation, on-going or recent use of immunosuppressive therapies and pre-existing medical conditions can also impact the risk and exposure level at which a person develops H-ARS (Baranov et al., 1989; Mettler et al., 2001; Staras et al., 2006; Farrell et al., 2008; Stricklin et al., 2012, Jones et al., 2014). Typical symptoms, latency periods, illness manifestations and probable based on estimated absorbed dose are shown in Table 5 (Garau et al., 2011; Jones et al., 2014).

Table 5: Time Course and Severity of Clinical Signs and Symptoms across Four Phases of H-ARS at Radiation Exposures

Absorbed Dose (Gy)	Prodromal Phase	Latent Phase	Manifest Illness	Recovery / Final Phase
0.5 to 1.5	No symptoms, or nausea and vomiting for one day, temporary hair loss	1 day – several weeks	No symptoms or weakness, nausea and vomiting	Recovery
1.5 to 4	Nausea, vomiting, fatigue, weakness, diarrhoea for up to two days, hair loss	1 – 3 weeks	H-ARS: Leukopaenia and thrombocytopaenia	Recovery possible with supportive care
4 to 6	Nausea, vomiting, weakness, diarrhoea for up to two days	< 1-3 weeks	H-ARS: Leukopaenia and thrombocytopaenia, immune-suppression and sepsis, bleeding	Death without treatment

Absorbed Dose (Gy)	Prodromal Phase	Latent Phase	Manifest Illness	Recovery / Final Phase
6 to 15	Severe nausea and vomiting, diarrhoea	Several days	H-ARS: Pancytopenia, immune-suppression and sepsis, bleeding, Gastrointestinal: bleeding, diarrhoea, fluid loss and electrolyte imbalance	Variable with supportive care and treatment

Note: patients exposed to more than 15 Gy would be expected to die within days of exposure from neurovascular effects of ARS and no treatments are currently available to address injuries in this population.

The treatment of H-ARS is focused primarily on reducing the risk of infection by restoring immune response, treating infections, maintaining hydration, and facilitating bone marrow recovery. Without medical intervention, death from ARS can occur within days to weeks. The lethal dose at 60 days (The $LD_{50/60}$ is defined as the dose necessary to cause death in 50% of an irradiated population in 60 days) for humans not receiving supportive care has been estimated to be approximately 3.25–4.0 Gy. It is estimated that the administration of targeted antibiotics, blood transfusions, anti-emetics and IV fluids could move the $LD_{50/60}$ to a range of 5 to 7 Gy (Waselenko et al., 2004; Jones et al., 2014), however, it is unlikely that this level of supportive care would be available for a mass casualty nuclear incident.

After the detonation in Hiroshima, approximately 80 percent of the areas doctors and nurses were dead or incapacitated. Most hospitals and clinics within a two (2)-mile radius of the detonation zone were damaged or destroyed. Only three (3) of the city's 45 hospitals could be used and none had functioning blood banks. It has been reported that very few patients were able to receive blood transfusions. Bandages, antibiotics, lactated Ringer's, blood products and other supportive care were in severely short supply (Flynn and Goans, 2012). Based on blood supply limitations, expected infrastructure damage and the number persons requiring treatment, is not anticipated that the availability of blood or blood products after a radiation mass casualty event would be substantially different than after Hiroshima.

In Chornobyl, the 134 victims hospitalised and diagnosed with H-ARS were treated by over 2 000 medical personnel, equating to a greater than 10 to 1 medical provider to patient ration. These patients also received heroic supportive care consisting of precision antibiotics, blood transfusions, and in some cases bone marrow and/or stem cell transplantation. In a mass casualty radiological or nuclear event, the ratio will be significantly lower and, quite likely would be inverted (1 to 10) (Flynn and Goans, 2012).

Absent treatment for H-ARS and given the impossibility of intensive supportive care, hundreds of thousands of treatable patients would likely die (NAS, 2019). Those who survive into the manifest illness phase would require hospitalisation. The inability to provide immediate care (supportive care within a day or two of exposure) would result in many in-hospital deaths. In Hiroshima, there were no survivors among persons exposed to greater than 3 Gy (Waselenko et al., 2004). Given the immune system damage and sepsis-induced immune-suppression that would be experienced by many patients receiving this level of radiation exposure, they would be at significant risk for secondary infections through the recovery phase (Akashi, 2005; Sugarman et al., 2017; Dainiak, 2018). Even after recovery and discharge, patient immune systems remain dysregulated putting them at high risk for infection and autoimmune disorders and they are prone to chronic rehospitalisation (Sugarman et al., 2017; Dainiak, 2018). Persons surviving H-ARS also experience higher rates of leukaemia, breast, thyroid, colon, stomach, lung and ovarian cancer, cardiovascular disease, respiratory disease and disorders, autoimmune disorders, and cataracts (Lopez et al., 2011; Sugarman et al., 2017).

Important co-morbidities:

Concurrent combined injury – wounding, burns, and/or blast – will impact the threshold level of radiation exposure that will cause H-ARS and lethality. The burden of early healing and damage control systems further deplete an already deficient haematopoietic system and damage to bone marrow and precursor cells limits the system's ability to regenerate leading to severely deficient immune response. The loss of blood cells from radiation and depletion of reserves without adequate regeneration leads to more rapid and severe pancytopenia than what is seen from radiation exposure alone (Jones et al., 2014). Persons exposed to radiation with combined injuries are at risk of H-ARS at approximately 1.2 Gy (Flynn and Goans, 2012).

Part II: Module SII - Non-clinical part of the safety specification

The safety of sargramostim was evaluated in cynomolgus monkeys following a single IV administration (study 2423-103) and repeated IV daily dosing up to 14 days in duration (study 2423-105), and repeated subcutaneous (SC) daily dosing up to 42-days in duration (studies 2423-111, A24993, and A27294). Additionally, fertility and toxicities on reproductive organs was evaluated as part of the 42-day toxicity study in sexually mature monkeys (study A27294), and fertility, embryo-foetal and pre- and post-natal toxicities were evaluated in New Zealand White rabbits (studies A28816, A31774, A39389, A38192, A33918, A38193, A43883). All toxicity studies were conducted between 1987 to 2010. Sargramostim was administered via daily SC injections in all studies except the single-dose and 14-day toxicity studies in which daily intravenous (IV) injections were administered to support early clinical trials with that route of administration.

The toxicology programme identified the lympho-haematopoietic system as the primary target of toxicity, which is expected based on the pharmacology of sargramostim. While these toxicities were apparent at dose levels starting at 20 µg/kg/day with a formulation containing ethylenediaminetetraacetic acid (EDTA), the toxicities were considerably less at 200 µg/kg (with 30 days of dosing) with lyophilised sargramostim without EDTA, and there was minimal to no effect at 20 µg/kg/day when formulated without EDTA (lyophilised).

The reproductive and developmental studies in rabbits were performed with modified dosing paradigms (i.e., collectives limited to two (2)-week durations of daily SC administration) to cover the targeted developmental period without complete loss of sargramostim systemic exposure or pharmacological activity.

No genotoxicity studies were performed with sargramostim in compliance with ICHS6(R1). Sargramostim is a recombinant protein that exerts its pharmacological activity through a membrane bound receptor. It is not expected to reach the nucleus nor directly interact with DNA or other chromosomal material. Moreover, since sargramostim will not be administered chronically, a carcinogenicity assessment was not required [ICH S1(A)].

Toxicology

In a repeated-dose toxicity study, sargramostim was administered subcutaneously daily to cynomolgus monkeys at doses of 20 and 200 mcg/kg/day for 30 days. The lympho-haematopoietic system was identified as the primary target of toxicity: an increase in white blood cells and platelets as well as splenic inflammatory and lymphoid cell infiltration were observed at ≥ 20 mcg/kg/day.

Moderate to moderately severe bone marrow myeloid hyperplasia and mononuclear cell infiltrates in the heart and other organs were observed at 200 mcg/kg/day at terminal sacrifice, and moderate to moderately severe thymic atrophy was observed at 200 mcg/kg/day in both terminal and recovery animals. All findings were considered related to the pharmacology of sargramostim and therefore are potentially clinically relevant; however, the majority of the findings were observed at a dose that is approximately 17 to 29-fold greater than clinical exposure at the recommended human doses (7 to 12 mcg/kg/day) based on body weight scaling.

A similar pattern of toxicity but at a lower dose (20 mcg/kg/day) was observed in a 42-day repeated-dose toxicity study in which cynomolgus monkeys were subcutaneously administered 20, 63 and 200 mcg/kg/day with a sargramostim formulation containing EDTA, different from Imreplys. In this study, the systemic exposure (AUC) at 20 mcg/kg/day was approximately 2-fold greater than the clinical exposure at the recommended human doses (7 to 12 mcg/kg/day).

Reproductive and developmental toxicity

All reprotoxicity studies were carried out with a sargramostim formulation containing EDTA, different from Imreplys.

In the fertility and early embryonic development study, sargramostim was administered subcutaneously to rabbits at doses of 25, 70 and 200 mcg/kg/day from 6 days prior to artificial insemination and continuing through gestation day (GD) 7. Maternal toxicity was evident at ≥ 70 mcg/kg/day. A decrease in implantation sites and an increase in preimplantation loss and reduction in viable embryos was observed at 200 mcg/kg/day. The AUC at the no-observed-adverse-effect-level (NOAEL) for female reproductive and early embryonic developmental toxicity of 70 mcg/kg/day was initially (at the start of the dosing period) approximately 7.2-fold the clinical exposure at the recommended adult clinical dose (7 mcg/kg/day).

In the embryo-foetal developmental study, pregnant rabbits were administered subcutaneously doses of sargramostim during the period GD 6 to GD19 or GD19 to GD28 at 25, 70, and 200 mcg/kg/day.

Maternal toxicity was evident at ≥ 25 mcg/kg/day. An increase in late resorptions and reduced foetal weights were observed at ≥ 70 mcg/kg/day. An increase in spontaneous abortions and post-implantation loss, a reduction in viable foetuses and a reduced gravid uterine and placental weight were evident at 200 mcg/kg/day. The AUC at the NOAEL for embryo-foetal toxicity of 25 mcg/kg/day was initially (at the start of the dosing period) approximately 2.9-fold the clinical exposure at the recommended adult clinical dose (7 mcg/kg/day).

In the pre- and postnatal development study, rabbits were administered SC doses of sargramostim during GD6 to GD19, GD19 to parturition, or lactation day (LD)1 to LD14 at 25, 70, and 200 mcg/kg/day. Maternal toxicity was observed at ≥ 25 mcg/kg/day. At doses ≥ 25 mcg/kg/day, a reduction in postnatal offspring survival was observed when rabbits were dosed during lactation. The high-dose of 200 mcg/kg caused a decreased pup body weight when rabbits were dosed during lactation and from GD19 to parturition. Treatment from GD6-GD19 and GD19-parturition at 200 mcg/kg/day resulted in abortions, while after GD6-GD19 treatment with 200 mcg/kg/day total litter loss, early resorptions, reduced number of kits born and reduced live litter size on Post Natal Day 0 were also observed. There is no NOAEL for neonatal toxicity. The AUC of 25 mcg/kg/day dose was initially (at the start of the dosing period) approximately 2.6-fold the clinical exposure at the recommended adult clinical dose (7 mcg/kg/day).

By the end of the dosing periods, the systemic exposures decreased due to the production of anti-sargramostim antibodies reaching 1-fold, 0.2-fold and 0.2-fold the clinical exposure in the fertility and early embryonic development, embryo-foetal developmental and pre- and postnatal development studies, respectively.

Part II: Module SIII - Clinical trial exposure

Sargramostim has been under clinical investigation since 1987. The safety and efficacy of sargramostim has been studied in humans and it has been approved by the US Food and Drug Administration (FDA) (Approval Package for Application Number 103362Org1S5240) for the following indications:

- to shorten time to neutrophil recovery and to reduce the incidence of severe, life-threatening, or fatal infections following induction chemotherapy in adult patients 55 years and older with acute myeloid leukaemia (AML).
- in adult patients with cancer undergoing autologous haematopoietic stem cell transplantation for the mobilisation of haematopoietic progenitor cells into peripheral blood for collection by leukapheresis.
- for the acceleration of myeloid reconstitution following autologous peripheral blood progenitor cell (PBPC) or bone marrow transplantation in adult and paediatric patients 2 years of age and older with non-Hodgkin's lymphoma, acute lymphoblastic leukaemia (ALL) and Hodgkin's lymphoma.
- for the acceleration of myeloid reconstitution in adult and paediatric patients 2 years of age and older undergoing allogeneic bone marrow transplantation from Human Leukocyte Antigen (HLA)- matched related donors.
- for the treatment of adult and paediatric patients 2 years and older who have undergone allogeneic or autologous bone marrow transplantation in whom neutrophil recovery is delayed or failed.
- to increase survival in adult and paediatric patients from birth to 17 years of age acutely exposed to myelosuppressive doses of radiation (H-ARS).

Sargramostim has also been evaluated in non-approved indications including sepsis-associated immune-suppression, sulphur mustard-induced myelosuppression, radiation combined injury, Crohn's disease, colorectal cancer, myelodysplastic syndrome, prostate cancer, breast cancer, biliary cancer, autoimmune pulmonary alveolar proteinosis, COVID-19 acute hypoxemia, acute respiratory distress syndrome, chemotherapy associated bone marrow suppression, chemoradiation in lung cancer, melanoma, peripheral arterial disease, Parkinson's disease, immunoparalysis in paediatric sepsis-induced multiple organ dysfunction syndrome, Alzheimer's disease, potentiation of antitumor response outside radiation field (abscopal effect), aplastic anaemia, blunt trauma, cystic fibrosis, lower extremity ulcers, human immunodeficiency virus infection, autoimmune disease, Down syndrome, stroke, spinal cord injury, traumatic brain injury and retinal degeneration.

No Partner Therapeutics, Inc. sponsored trials with sargramostim have been conducted to date in humans with H-ARS. Sargramostim efficacy studies cannot be conducted in humans with H-ARS as such studies to collect clinical safety and efficacy data would be contrary to generally accepted principles of medical ethics due to the harmful levels of radiation required to induce H-ARS. Of note, there is a US FDA post-approval requirement study (PMR 3363-1; PTX-01-001) for the H-ARS indication. This is a retrospective observational study to evaluate the efficacy and safety of Leukine (sargramostim) in the setting of Haematopoietic Syndrome (HS) following acute radiation exposure within the US. The protocol PTX-01-001 shall serve as a single master protocol applicable to all countries where the use of sargramostim in case of nuclear accident

The safety data evaluated in the RMP represents the Sponsor's best attempt to collate and interpret the most relevant available data, including:

- Clinical data supporting the use of sargramostim in adult and paediatric patients undergoing autologous bone marrow transplant (BMT) following myelosuppressive chemotherapy with or without TBI are provided to compliment non-clinical efficacy data and demonstrate the safety of the product in adults and paediatrics.

- Seven studies in healthy volunteers support the use of sargramostim in an otherwise healthy general population following a radiation exposure incident.
- Fifteen clinical studies with paediatric patients support the use of sargramostim in paediatric patients following a radiation exposure incident.

The safety data from 22 studies of sargramostim in the three (3) populations is provided below:

Exposure in haematological patients pertinent to H-ARS

A total of 153 adult and paediatric patients have been enrolled in 3 studies with haematological patients pertinent to H-ARS.

In studies of sargramostim in recipients of autologous BMT and peripheral stem cell transplantation (PSCT) indications, a total of 77 patients received daily infusions of 250 µg/m^2 IV lyophilised sargramostim for 21 days and 76 patients received placebo.

Exposure in healthy volunteer subjects

In the seven (7) healthy volunteer studies, a total of 317 subjects received sargramostim; several received more than 1 formulation, dose, or route of administration. Of the 317 healthy volunteer subjects exposed to sargramostim in these studies, 136 subjects received lyophilised sargramostim, 78 subjects received liquid sargramostim without EDTA, and 189 subjects received liquid sargramostim with EDTA.

A total of 244 healthy volunteer subjects received SC sargramostim (doses: 125 µg/m^2, 250 µg/m^2, 2 µg/kg, 6 µg/kg, 8 µg/kg, or 500 µg) and 38 subjects received IV Sargramostim (250 µg/m^2 or a fixed 500 µg dose). Of the 275 healthy volunteer subjects, approximately 45 subjects received sargramostim doses greater than or equal to the proposed dose for the H-ARS indication (7 µg/kg; all of the healthy volunteer subjects for whom weight data are available weighed >40 kg).

Exposure in paediatric patients

A total of 332 paediatric patients were exposed to sargramostim in 15 clinical studies completed between 1988 and 2006. However, it is important to note that the legacy data (prior to Partner Therapeutics, Inc. ownership), for paediatric patients is not complete.

In studies of sargramostim in recipients of BMT, PSCT, and patients with other oncology and bone marrow indications, a total of 120 paediatric patients received sargramostim. All but 6 of the paediatric patients receiving sargramostim in these studies were treated via the IV route; the other six (6) patients received sargramostim via the SC route. Although doses varied widely across studies and within some of the individual studies, most patients received sargramostim doses of approximately 250 µg/m^2/day. In all but one of these studies, patients received the lyophilised formulation of sargramostim (in the remaining study, the formulation administered is unknown).

Study 308001 was a study of sargramostim in paediatric patients with Crohn’s disease (age range: 8 to 16 years). A total of 22 children received liquid sargramostim with EDTA SC at doses of 4 or 6 µg/kg/day for eight (8) weeks in this study.

In studies of sargramostim in preterm neonates, 190 neonates received sargramostim. Sargramostim doses ranged from 0.05 µg/kg/day to 10 µg/kg twice daily. All neonates received the lyophilised formulation via the IV route.

Of the 332 paediatric patients exposed to sargramostim in the 15 studies, approximately 30 patients received sargramostim doses greater than or equal to those proposed for the H-ARS indication.

Part II: Module SIV - Populations not studied in clinical trials

Sargramostim efficacy studies cannot be conducted in humans with H-ARS as such studies would be contrary to generally accepted principles of medical ethics due to the harmful levels of radiation required to induce H-ARS. Safety was evaluated in human clinical studies in patients with cancers where white blood cells are affected similarly to what occurs during acute exposure to myelosuppressive doses of radiation. The use of sargramostim in special populations is described within the SmPC based on well-established use of sargramostim since first authorisation across licenced indications and populations.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Patient exposure from marketing experience is taken from the fifth (5th) annual Development Safety Update Report (DSUR) covering the period from 05 March 2022 up to and including 04 March 2024.

Sargramostim is marketed in the US under the trade name Leukine® and is currently approved for the following indications:

- to shorten time to neutrophil recovery and to reduce the incidence of severe, life-threatening, or fatal infections following induction chemotherapy in adult patients 55 years and older with AML.
- in adult patients with cancer undergoing autologous haematopoietic stem cell transplantation for the mobilisation of haematopoietic progenitor cells into peripheral blood for collection by leukapheresis.
- for the acceleration of myeloid reconstitution following autologous PBPC or bone marrow transplantation in adult and paediatric patients 2 years of age and older with non-Hodgkin's lymphoma, ALL and Hodgkin's lymphoma.
- for the acceleration of myeloid reconstitution in adult and paediatric patients 2 years of age and older undergoing allogeneic bone marrow transplantation from HLA- matched related donors.
- for the treatment of adult and paediatric patients 2 years and older who have undergone allogeneic or autologous bone marrow transplantation in whom neutrophil recovery is delayed or failed.
- to increase survival in adult and paediatric patients from birth to 17 years of age acutely exposed to myelosuppressive doses of radiation (H-ARS).

Sargramostim is currently manufactured for commercial, and Health Security uses in the lyophilised formulation of 250 mcg single-use vials.

In the first five (5) indications listed above, sargramostim is administered at the standard dose of 250 mcg/m^2/day. For the H-ARS indication, sargramostim dose is based on 7, 10 or 12 mcg/kg depending on patient age and weight.

Additionally, on 26 March 2024, sargramostim was approved in Japan by Pharmaceuticals and Medical Devices Agency (PMDA) for the treatment of autoimmune alveolar proteinosis. It will be marketed under the brand name of Sargmalin by Nobelpharma Co., Ltd. The sargramostim dose is 125 mcg inhaled twice daily using a nebuliser for seven (7) consecutive days, then paused for seven (7) days; this treatment course is then repeated.

[redacted]

SV.1.2 Exposure

Cumulative exposure is based on patient exposure reported in the last DSUR submitted by the previous MAH from 05 March 1991 through 12 September 2017) and, since the transfer of ownership of sargramostim to Partner Therapeutics (May 2018), for 01 September 2017 to 04 March 2024 (2024 DSUR) [redacted]

Post-marketing data by age group and gender is not available.

Since the first sargramostim marketing authorisation (05 March 1991), based on sales data through 04 March 2024, estimated cumulative patient exposure is 560,075 patients.

Given the multiple commercial uses of sargramostim, it is not possible to report exposure by indication (or disease), age group or gender.

[redacted]

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Sargramostim belongs to the class of drugs of colony-stimulating factors. Neither sargramostim nor its components are known to possess addictive properties. Sargramostim has not been reported as a drug of abuse. Sargramostim is a prescription only medicine.

Potential for transmission of infectious agents

Sargramostim is expressed in yeast fermentation (*S. cerevisiae*). Therefore, risks from mammalian viruses (i.e., transmissible spongiform encephalopathy) and non-viral adventitious agents (i.e., mycoplasma, fungi, and bacteria) are very low.

Any animal-derived raw materials are evaluated for origin, tissue type, and processing of the material to reduce risk from adventitious agents. Bacterial and fungal contamination are controlled by facility, process and environmental controls, autoclaving, SIP, and filtration; control is confirmed by testing throughout the process. Due to the selection of yeast as an expression system, being of non-animal origin, viral validation studies were not performed.

The sargramostim fermentation process utilises two (2) animal-derived raw materials, [redacted]. There are no additional animal-derived raw materials in either the downstream process or the drug product fill-finish process.

[redacted]

[redacted]

Sargramostim is expressed in yeast, which will not propagate mammalian viruses, and the animal-derived raw materials used in the fermentation process are of low risk of viral contamination. Through careful selection of raw materials, implementation of in-process controls, and process monitoring, there is minimal risk of adventitious agent contamination in the manufacture of sargramostim bulk drug substance.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded (SmPC section 4.4).

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Acute exposure to high doses of ionising radiation is a life-threatening condition. The potential benefit of sargramostim in reducing the risk of death should be considered relative to potential risks of taking the drug for patients with the conditions described below. Many of the adverse events listed here also are symptoms of radiation exposure.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers:

- Rapid increase in peripheral blood count (e.g., leucocytosis)
- Infusion-related reactions
- Myelosuppression during concomitant use with chemotherapy or radiotherapy
- Respiratory symptoms (e.g., gasping syndrome in neonates and low-birth-weight infants when administered drugs prepared with benzyl alcohol)
- Transmission of infectious agents

- Immunogenicity (no neutralising antibodies) were reported with short term exposure to sargramostim as proposed for the current indication)
- Hypersensitivity anaphylaxis
- Supraventricular arrythmias
- Haemodynamic oedema, effusions and fluid overload
- Potential effects on malignant cells

Missing Information:

- Use during pregnancy
- Use during lactation

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

Not applicable.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are not required for sargramostim.

III.2 Additional pharmacovigilance activities

Routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the product and detect any safety concerns. No additional pharmacovigilance activities have been proposed.

III.3 Summary Table of additional Pharmacovigilance activities

There are no on-going or planned additional pharmacovigilance activities.

Part IV: Plans for post-authorisation efficacy studies

Table Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study **Status**	**Summary of objectives**	**Efficacy uncertainties addressed**	**Milestones**	**Due Date**
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Retrospective, observational study to assess the clinical benefit and safety of sargramostim in individuals exposed to myelosuppressive doses of radiation following an ionising radiation event PTX-01-001 Planned	The objectives of this study are to evaluate the efficacy (survival rate), adverse events, and medical resource utilisation such as hospitalisation, supportive care, transfusions, antibiotics, etc. following acute exposure to myelosuppressive doses of radiation.	Clinical benefit and safety	The target date for submission of the updated protocol PTX-01-001 is 30 June 2025. Study to be initiated only after an ionising radiation event.	Final study results within 6 months after the use of the product in an incident.

The protocol PTX-01-001 shall serve as a single master protocol applicable to all countries where the use of sargramostim in case of nuclear accident, could occur. The protocol will be amended after sargramostim approval for H-ARS by EMA to allow for collection of data in any country where an ionising radiation event has occurred, and cooperation with non-government organisations or government organisations can be obtained. Details of the revised protocol will be agreed with the health authorities.

Additional updates to the protocol will include procedural guidance and instruction to maximise the collection of data in the setting of a nuclear event, including data to assess the impact of radiation dose a person was subjected to.

The MAH commits to provision of yearly updates on any new information concerning the safety and efficacy of sargramostim upon approval.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Not applicable.

V.2. Additional Risk Minimisation Measures

Not applicable.

V.3 Summary of risk minimisation measures

Not applicable.

Part VI: Summary of the risk management plan

Summary of risk management plan for Imreplys 250 mcg powder for solution for injection (Sargramostim)

This is a summary of the RMP for Imreplys 250 mcg powder for solution for injection (sargramostim). The RMP details important risks of Imreplys 250 mcg powder for solution for injection and how more information will be obtained about Imreplys 250 mcg powder for solution for injection's risks and uncertainties (missing information).

Imreplys 250 mcg powder for solution for injection's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Imreplys 250 mcg powder for solution for injection should be used.

This summary of the RMP for Imreplys 250 mcg powder for solution for injection should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Imreplys 250 mcg powder for solution for injection’s RMP.

I. The medicine and what it is used for

Imreplys 250 mcg powder for solution for injection is authorised in patients of all ages acutely exposed to myelosuppressive doses of radiation with Haematopoietic Sub-syndrome of Acute Radiation Syndrome (H-ARS). It contains sargramostim (recombinant human granulocyte-macrophage growth factor [rhu GM-CSF]) as the active substance, and it is given by subcutaneous injection.

Further information about the evaluation of Imreplys 250 mcg powder for solution for injection’s benefits can be found in Imreplys 250 mcg powder for solution for injection’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Imreplys 250 mcg powder for solution for injection, together with measures to minimise such risks and the proposed studies for learning more about Imreplys 250 mcg powder for solution for injection's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Imreplys 250 mcg powder for solution for injection are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Imreplys 250 mcg powder for solution for injection. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

II.B Summary of important risks

Not applicable.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

PTX-01-001

Purpose of the study: To assess the clinical benefit and safety of sargramostim in adults and children exposed to myelosuppressive doses of radiation following an ionising radiation.

The objectives of this study are to evaluate the efficacy (survival rate), adverse events, and medical resource utilisation such as hospitalisation, supportive care, transfusions, antibiotics, etc. following acute exposure to myelosuppressive doses of radiation.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Imreplys 250 mcg powder for solution for injection.

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.