Expanding the Use of an FDA-Approved Host-Directed Therapy for Known and Unknown Threats: Treating Pancytopenia and Immune Dysregulation Due to Acute Radiation or Sulfur Mustard (HD) Exposure with Leukine® [sargramostim/Recombinant Human Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF)]

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There are no FDA-approved treatments for HD-induced myelosuppression and associated immune dysregulation. Leukine is FDA-approved to treat the myelosuppressive effects of acute radiation exposure (H-ARS). For HD, Leukine (rhu GM-CSF) is Technology Readiness Level 7B and a supplemental Biological License Application submission is planned in 2025.

Partner Therapeutics (PTx) is collaborating with the Joint Project Manager for Chemical, Biological, Radiological, and Nuclear Medical (JPM CBRN Medical) Countering Emerging Threats - Rapid Acquisition and Investigation of Drugs for Repurposing (CET RAIDR) program to expand Leukine's utility to protect warfighters against known and unknown, chemical, biological, radiological, and nuclear (CBRN) threats. CET RAIDR and PTx aim to generate data to inform DoD Clinical Practice Guidelines and expand the H-ARS label to include treatment of HD-induced myelosuppression.

Radiation or HD-induced myelosuppression drives infection, sepsis, and organ damage. Leukine has been shown to play a critical role in host defense, immune homeostasis, and tissue repair. While classically known for promoting differentiation of bone marrow (BM) precursor cells, and stimulating proliferation, differentiation, and maturation of myeloid cells, GM-CSF also plays important roles in antigen presentation, T-cell activation, and myeloid cell survival and function. It also promotes tissue repair, wound healing, and resolution of inflammation. These effects have shown benefit in H-ARS and may have similar benefit in HD exposure.

This CET RAIDR program seeks to expand warfighter protection against additional threats, to evaluate Leukine's potential to provide frontline defense and enable time for development of targeted therapies, and complements ongoing clinical development in sepsis, ARDS, and combined injury.

A Proof-of-Concept (PoC) study was conducted in a non-human primate (NHP) model of intravenous (IV) HD exposure of 0.75 mg/kg ($LD_{50/28}$) to investigate the potential benefit of Leukine in mitigating HD-induced mortality and injury for 28 days. Twelve male and female NHPs were divided equally into two groups and received either Leukine (6.1 µg/kg) or sterile water for injection subcutaneously once daily for 14 days beginning on Day 1 post HD exposure. Endpoints for this study included morbidity/mortality, body weights, hematology, clinical chemistry, pathology, and histopathology.

Day 28 Control group survival was 3 of 6 (50%), compared to 6 of 6 (100%) for the Leukine group. Decedents demonstrated lesions, crypt damage and epithelial denudation in the intestines and decreased BM cellularity. Absolute lymphocyte count (ALC) decreased markedly in all animals on Day 1 and remained below baseline. Leukine treatment resulted in earlier and higher ALC nadir and reduced duration of moderate and severe lymphopenia. Severe leukopenia was observed on Day 7 with nadir on Day 7 for the Leukine Group and Day 9 for the Control group.

Leukine treatment increased survival and generated signals of benefit on key measures of HD systemic toxicity in the NHP. Observed systemic toxic effects were similar to descriptions of human HD exposures. Results from a confirmatory study are expected by October.

Expanding CPGs and Leukine's label to include HD exposure will enhance warfighter protection by addressing the primary driver of prolonged hospitalization and mortality for a threat with no approved treatments.

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Disclosures:

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