National Institute of Allergy and Infectious Diseases

Efficacy of Filgrastim in the Treatment of Hematopoietic Syndrome of the Acute Radiation Syndrome

National Institute of Allergy and Infectious Diseases
Division of Allergy, Immunology and Transplantation

May 3, 2013

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Joint Meeting of the Medical Imaging Drugs Advisory Committee and Oncologic Drugs Advisory Committee

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Regulatory Overview of the NIAID Filgrastim Program

Jui Shah, PhD
Sr. Regulatory Affairs Officer
Division of Allergy, Immunology and Transplantation,
National Institute of Allergy and Infectious Diseases,
National Institutes of Health,
Department of Health and Human Services

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Background

- Project Bioshield Act authorized DHHS to procure countermeasures for public health emergencies
- Responsibility to develop countermeasures for radiation/nuclear incidents was delegated to NIAID
  - Clinical trials using toxic doses of radiation not ethical
  - Regulatory path to licensure: FDA Animal Rule with efficacy studies in animals
  - Contract awarded to University of Maryland to conduct these studies

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Hematopoietic Syndrome of the Acute Radiation Syndrome

- Hematopoietic Syndrome of the Acute Radiation Syndrome (H-ARS) is a consequence of exposure to toxic doses of radiation
  - Bone marrow suppression leading to neutropenia, thrombocytopenia and anemia resulting in infection, hemorrhage and death

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Why Filgrastim?

- **Neupogen® (filgrastim), Amgen, Inc**
  - Increases proliferation and differentiation of neutrophils
  - Approved in the U.S. for chemotherapy-induced neutropenia
  - Extensive clinical experience
  - Is likely to be used off label in a radiation/nuclear incident
  - FDA approval of filgrastim for treatment of H-ARS will facilitate access to this countermeasure

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Filgrastim Program Development Strategy

- NIAID defined scenario for filgrastim use
  - Administer as soon as possible
  - Continue dosing until post nadir absolute neutrophil count (ANC) >1000/µL for 3 consecutive days or when ANC exceeds 10,000/µL
  - Administer with medical management
- Establish regulatory strategy to meet requirements of FDA Animal Rule
  - NIAID designed animal study protocols
    - Well-characterized animal model predictive of human H-ARS
    - GLP-compliant efficacy study in the model

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Filgrastim Program – Key Events (1)

- Initial meeting with FDA (May 2005) to:
  - Confirm the Animal Rule as the appropriate regulatory pathway to licensure
  - Discuss proposed animal studies to demonstrate efficacy of filgrastim for H-ARS
- Proposed animal protocols submitted to FDA
- Continued dialogue with FDA regarding:
  - Study design
  - Medical management

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Filgrastim Program – Key Events (2)

- NIAID and University of Maryland conducted two studies in the nonhuman primate, rhesus macaque (NHP):
  - Study AXR01: NHP Model Characterization
  - Study AXG15: GLP Filgrastim Efficacy Study
- NIAID submitted Final Study Reports to FDA
- FDA reviewed and analyzed Study AXG15 data
- FDA audited University of Maryland GLP laboratory
  - AXG15 specific
- FDA scheduled Advisory Committee Meeting

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Agenda

Title	Speaker
Regulatory Overview of the NIAID Filgrastim Program	Jui Shah, PhD Sr. Regulatory Affairs Officer Division of Allergy, Immunology and Transplantation, NIAID, NIH
Characterization of a Rhesus Macaque Model of the Hematopoietic Syndrome of Acute Radiation Syndrome (H-ARS) and Correlation with the Human Syndrome	**Thomas J. MacVittie, PhD Professor and Principal Investigator, School of Medicine, University of Maryland**
Study AXG15: Efficacy and Statistical Analysis	Ann Farese, MS, MT (ASCP) Research Associate and Study Director, School of Medicine, University of Maryland
Summary	Jui Shah, PhD Sr. Regulatory Affairs Officer Division of Allergy, Immunology and Transplantation, NIAID, NIH

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Characterization of a Rhesus Macaque Model of the Hematopoietic Syndrome of Acute Radiation Syndrome (H-ARS) and Correlation with the Human Syndrome

Thomas J. MacVittie, MS, PhD

School of Medicine, University of Maryland

Definition of Terms for H-ARS

- **Radiation dose response relationship (DRR):** determine mortality vs. radiation dose over the time course that defines the H-ARS – 60 days
- **LD50 at 60 days**: the dose of radiation that results in 50% mortality over the 60 day time course for the H-ARS
- **Natural history:** the time course of morbidity, mortality and recovery post-radiation exposure

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Presentation Objectives

- Define the human radiation DRR for the H-ARS
- Define the nonhuman primate (NHP) DRR for the H-ARS
- Compare the DRRs and the natural history for the H-ARS in human and NHP
  - Focus on the neutrophil parameters

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Key Data Sets that Define the Human H-ARS

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Key Data Sets that Define the Human H-ARS

- **Nuclear weapon exposures:** Hiroshima, Nagasaki
  - Nagasaki school students/personnel (75 people)
- **Radiation accidents:**
  - Pre Chernobyl and Chernobyl (238 people)
  - Others (42 people) include:
    - Tokai-mura
    - Samut Prakarn
    - Goiania
    - Meet Halfa
    - Istanbul
    - Others
- **Clinical data**: chemotherapy, stem cell transplant

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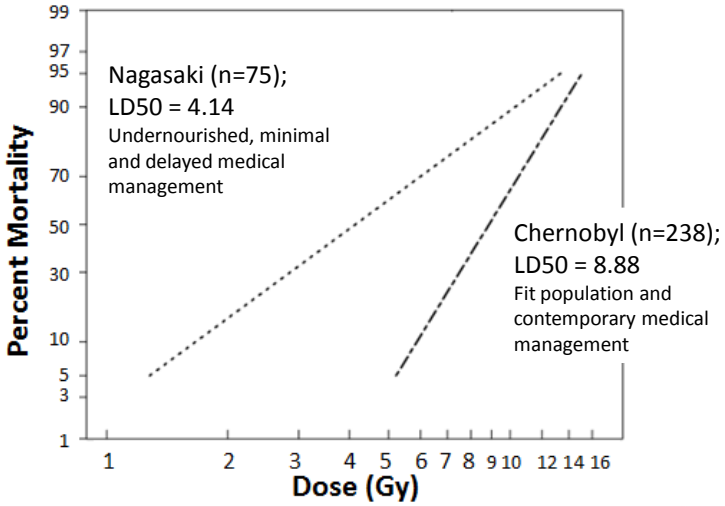
Human H-ARS Lethality Radiation Dose-Response Curves With Variable Medical Management



Anno, et al. *Health Phys* 84(5): 565-575; 2003

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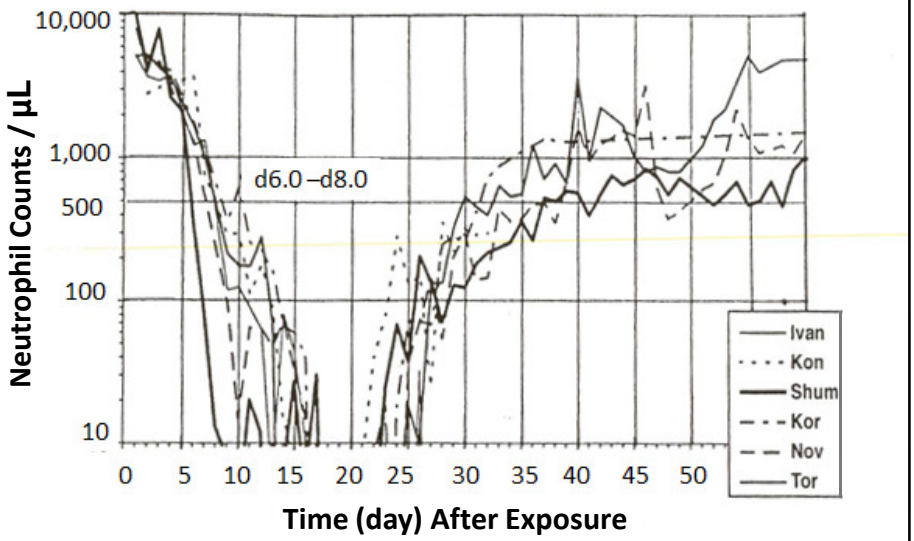
Absolute Neutrophil Counts in Chernobyl Victims



Stem Cells 1997;15(suppl 2):275-285 *Reproduced from* Baranova et al. *with permission.*

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Key Data Sets that Define the NHP H-ARS

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Key Data Sets that Define the NHP H-ARS

- Historical radiation studies to determine H-ARS in NHP
  - Established DRRs and natural history in the **absence** of medical management
- Contemporary radiation studies, single radiation dose, low lethal, myelosuppressive
  - Studies conducted **with** medical management

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Develop a NHP Model for H-ARS

- Radiation dose response relationship
  - Two parameters: LD50 at 60 days, slope
- Define the natural history
  - Time course: morbidity, mortality and recovery
- Define medical management criteria

Goal: establish a well-characterized NHP model that is predictive of human H-ARS

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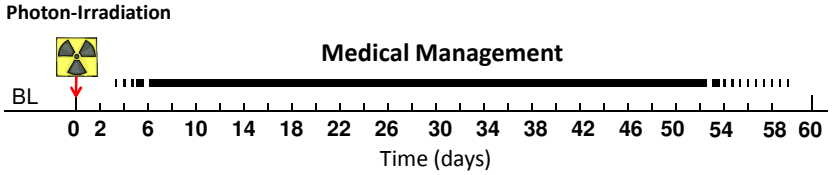
Protocol AXR01: Model Characterization

Species:	Rhesus macaque, 4 - 6.5 kg, n = 48 males
Protocol:	Irradiate on Day 0
Radiation:	6 MV photon, bilateral, TBI, mid-line tissue exposure at 0.80 Gy/min
Radiation Dose:	7.20, 7.55, 7.85, 8.05, 8.40, 8.90 Gy (n=8 each, randomized)
Medical Mgmt:	Fluids, antibiotics, irradiated whole blood, nutritional support, pain management, anti-diarrheals, anti-ulcerative, anti-inflammatories, anti-emetics, anti-pyretics
Primary Endpoint:	60 day survival



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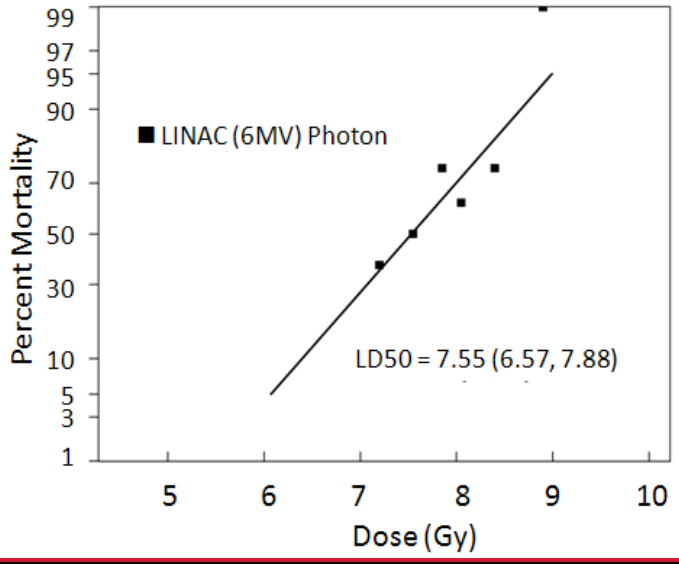
Hematopoietic Syndrome Dose Range NHP



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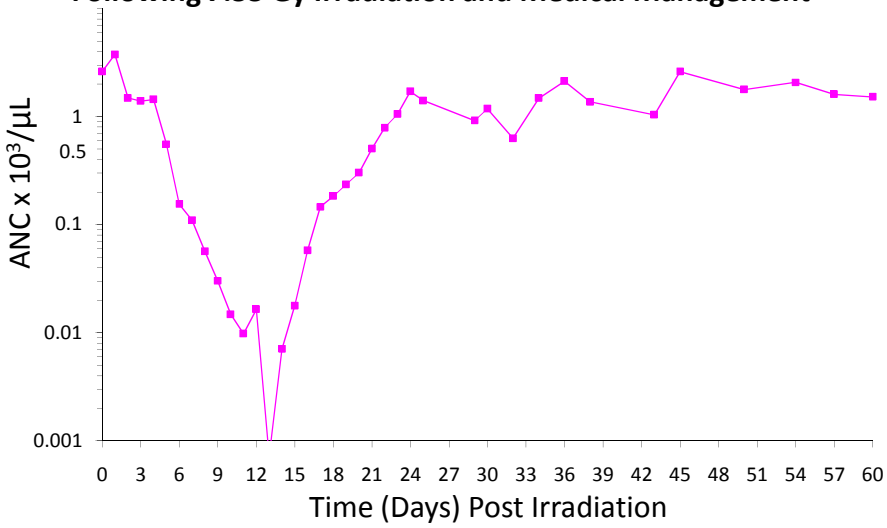
AXR01 NHP Mean Absolute Neutrophil Counts (ANC) Following 7.55 Gy Irradiation and Medical Management



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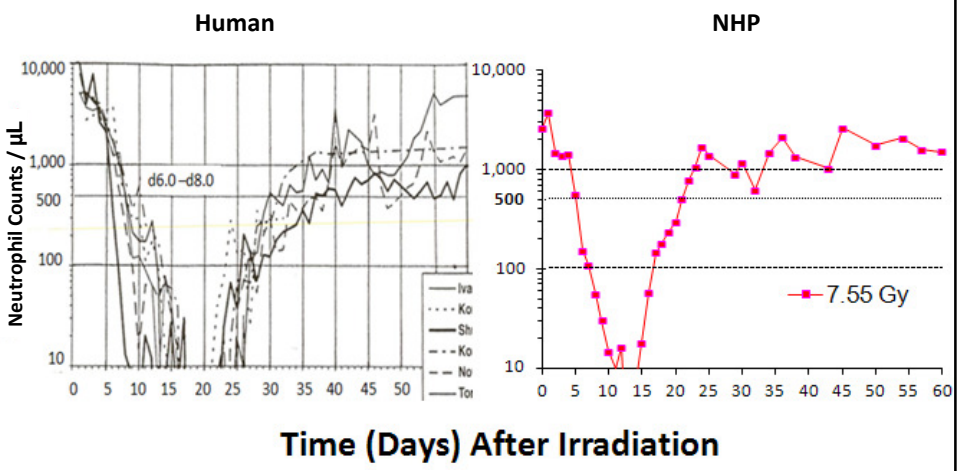
Absolute Neutrophil Count After Irradiation



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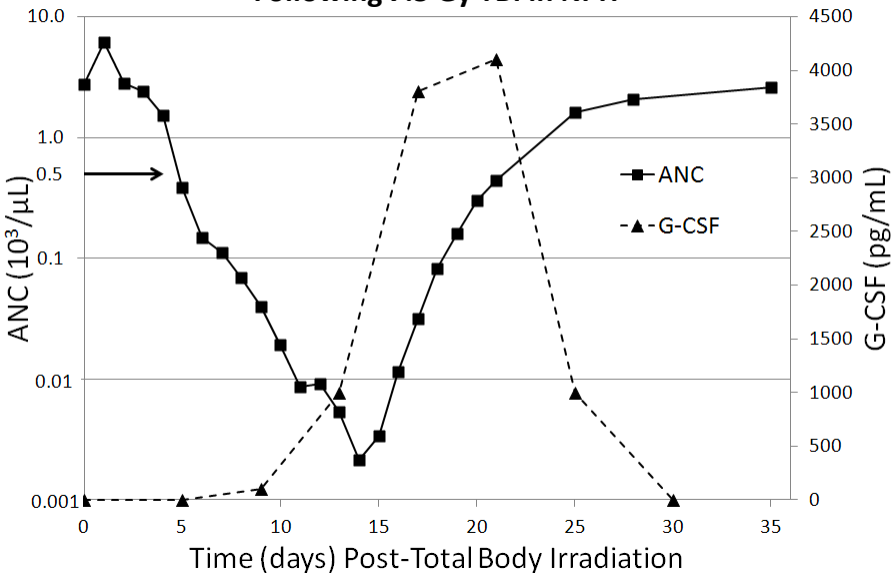
Absolute Neutrophil Count vs. Endogenous G-CSF Following 7.5 Gy TBI in NPH



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AXR01 Findings

- Established a well-characterized NHP model of H-ARS that is predictive of the human response. Comparable with respect to:
  - Mechanism of injury of the radiation
  - Clinical signs and symptoms
  - Response to medical management
  - Neutrophil loss and recovery

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Neutrophil Recovery

- Radiation: Depletion of hematopoietic progenitor cells in bone marrow
- Endogenous G-CSF: The physiologic regulator of granulopoiesis
  - Receptor-mediated action
  - Stimulates proliferation and differentiation of hematopoietic progenitor cells
  - Decrease maturation/transit time of neutrophils in bone marrow
  - Increase neutrophil viability and function

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Conclusions

- Established a NHP model that is predictive of the human response to radiation
- H-ARS model is appropriate to assess the efficacy of agents such as filgrastim

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Agenda

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Study AXG15: Efficacy and Statistical Analysis	**Ann Farese, MS, MT (ASCP) Research Associate and Study Director, School of Medicine, University of Maryland**
Summary	Jui Shah, PhD Sr. Regulatory Affairs Officer Division of Allergy, Immunology and Transplantation, NIAID, NIH

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Study AXG15: Efficacy and Statistical Analysis

Ann Farese, MS, MT (ASCP)
School of Medicine, University of Maryland

AXG15 Protocol Design

Protocol AXG15: Design

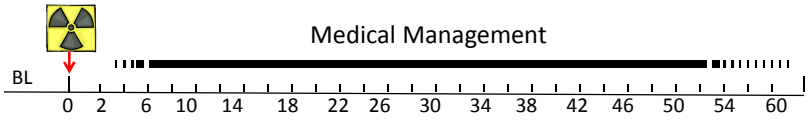
Species and Number: Rhesus macaques, 4-6 kg
Planned maximum n=62, (Male/Female)

Randomization: Filgrastim : Control = 1:1

Radiation: 6 MV Linear Accelerator, photon irradiation
Bilateral exposure, at 0.80 Gy/min
Total body irradiation (TBI) to 7.50 Gy at midline tissue

Time of Irradiation: Mornings

Photon-Irradiation



Time (days) After Irradiation

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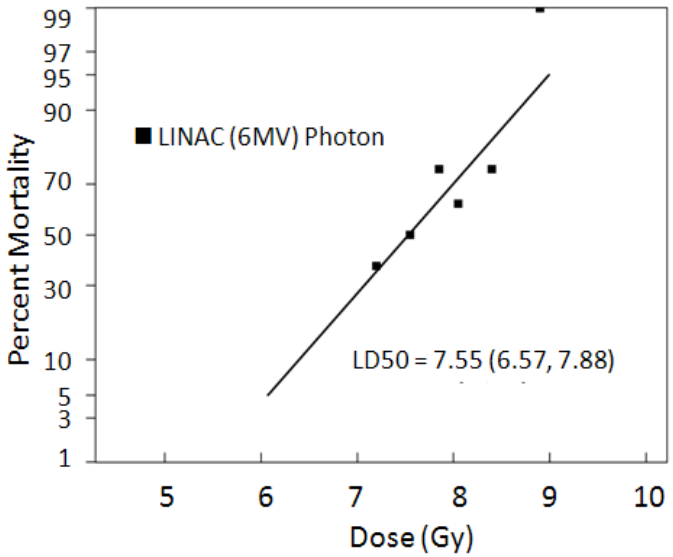
Hematopoietic Syndrome Dose Range NHP



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Protocol AXG15: Animal Facility

The University of Maryland, School of Medicine (UM-SOM)

- USDA registered research facility
- Office of Laboratory Animal Welfare (OLAW) Assurance
- Public Health Service Policy on Humane Care and Use of Laboratory Animals and the Guide for the Care and Use of Laboratory Animals
- The Association for Assessment and Accreditation of Laboratory Animal Care international (AAALACi)
- All procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of UM-SOM

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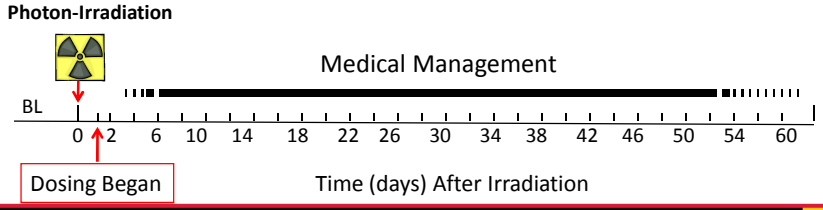
Protocol AXG15: Drug, Dose & Justification

Filgrastim:	Neupogen® (Amgen, Inc.) (obtained from commercial vendor)
Filgrastim Dose:	10 µg/kg/day
Dose Justification:	Published PK data showed that C_{max} and area under the curve (AUC) in NHP approximates human approved doses
Controls:	5% Dextrose in Water (D5W) (0.154 mL/kg/day)



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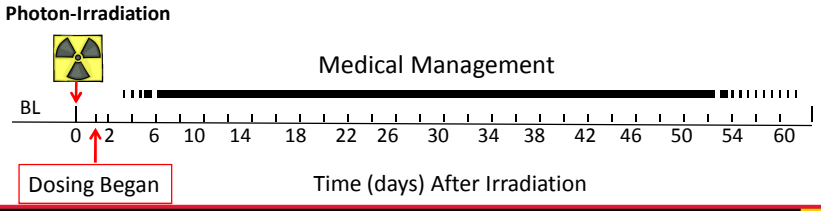
Protocol AXG15: Drug Administration

Filgrastim Dilution:	Diluted daily to 65 µg/mL with D5W
Dosing Volume:	Dose volume ranged between 0.6 mL to 1.0 mL
Route:	Subcutaneous injection
Dosing Schedule:	Beginning at 24 hours (range 20-26 hours) after TBI until post-nadir ANC ≥ 1,000/µL for 3 consecutive days



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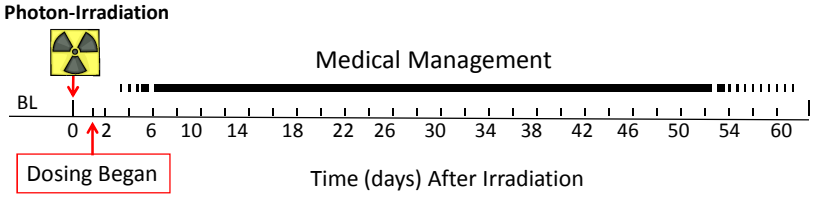
Protocol AXG15: Medical Management

Medical Mgmt:

Analgesics	Anti-pyretics
Antibiotics	Anti-ulceratives
Anti-diarrheals	Fluids
Anti-emetics	Irradiated whole blood
Anti-inflammatories	Nutritional support



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Protocol AGX15: Blinding Assignments

Blinded Personnel	Unblinded Personnel
Veterinarians, Technicians	Statisticians
Husbandry Staff	Quality Assurance Unit
Research Staff	Drug Managers
Radiation Physicist	Study Director
Microbiologist	
Histologist	
Pathologist*	

*Pathologist unblinded upon submission of preliminary contributing scientist report

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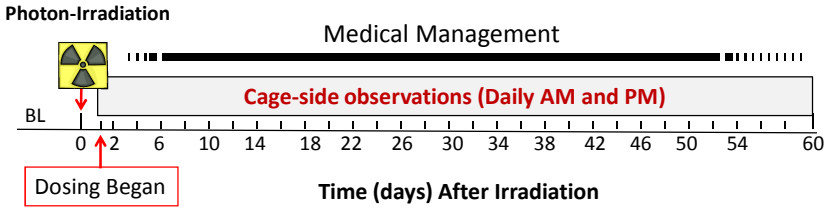
Protocol AXG15: Cage-Side Observations

Cage-Side Observations: Performed 2X daily by veterinarians blinded to drug treatment, antibiotic administration and hematopoietic values

Treatment-blinded veterinarians made decision to euthanize prior to study endpoint



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Protocol AXG15: Euthanasia Criteria

Any one of the following:	Two or more of the following:
• Seizure	• Abnormal appearance
• Hemorrhage	• Abnormal activity
• Hyperthermia	• Deteriorating clinical condition
• Weight Loss (≥ 25%)	• Weight Loss (≥ 20%)
• Hypothermia	
• Severe injury or condition	

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Protocol AXG15: Study End Points and Statistics

Primary End Point:	Overall survival at 60 days
Secondary End Points:	Hematologic parameters Signs of morbidity
Statistical Design:	Randomized, blinded, one-sided $P \leq 0.05$ 30% increase in survival
Planned Interim Analysis:	Evaluate efficacy or futility when ≥ 50% of the animals are 60 days past irradiation

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AXG15 Results

AXG15 Interim Analysis of Primary Outcome (60-day Survival)

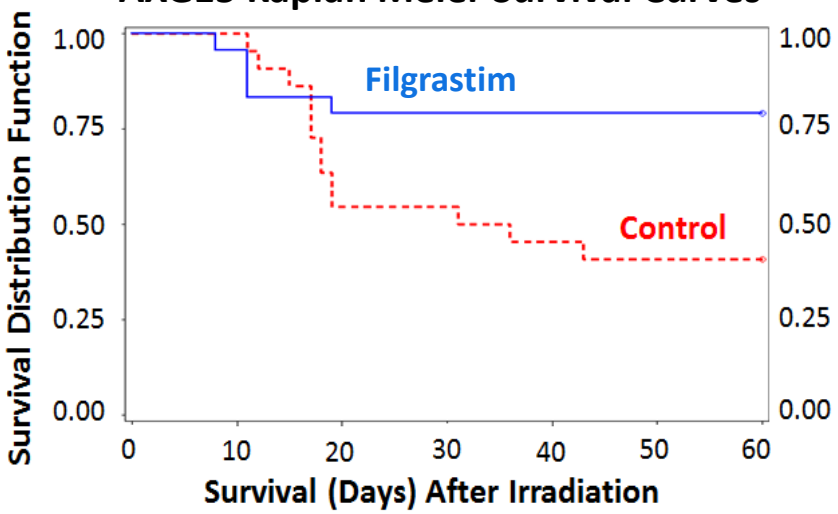
Treatment	Total	Survived	Percent Survived
Control	22	9	**41**
Filgrastim	24	19	**79**
P value (one-sided)			***0.004***

Two-sided P value = 0.008

Study was **terminated early for efficacy** based on DMC recommendation; **therefore, these are the final data**

Rad Res 197, 87-100 (2013)

AXG15 Kaplan Meier Survival Curves



P = 0.018 (log rank test)

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AXG15 Secondary Endpoints

Indices of Hematopoietic Recovery:

- Neutrophil-related parameters
  - Nadir
  - ANC Duration: number of days <500/µL, <100/µL
  - Day of recovery ANC ≥1,000/µL

Other:

- Incidence of febrile neutropenia (FN)
- Incidence of documented infection (confirmed by culture of blood or tissues)

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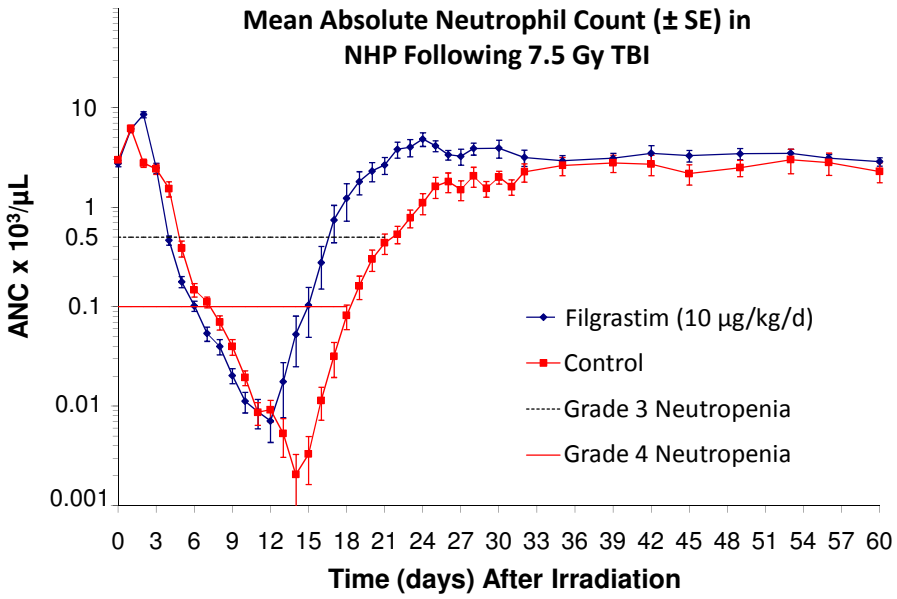

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AXG15 Mean (±SE) Neutrophil-related Parameters in NHP Following 7.50 Gy TBI

	Duration of Neutropenia* (days and range) ANC < 500/µL	Duration of Neutropenia* (days and range) ANC < 100/µL	Recovery to ANC ≥ 1000µL*	ANC Nadir (µL)
Control	18.6 (±0.8)	12.3 (±0.6)	25.8 (±0.9)	1.5 (±1.0)
Filgrastim	14.3 (±0.5)	10.4 (±0.6)	19.7 (±0.6)	5.0 (±2.0)
P value	*<0.0001*	*0.009*	*<0.0001*	*0.115*

*For ANC duration and recovery parameters decedent animals were censored at time of death

TBI = total body irradiation; ANC = absolute neutrophil count; SE = standard error

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AXG15 Febrile Neutropenia Incidence, Mean (± SE) First Day and Number of Days in NHP Following 7.50 Gy TBI

Treatment	Incidence (n/N)	First day FN† ±(SE)	Number of days FN*±(SE)
Control	90.0% (20/22)	11.7 ±0.8	6.2 ±1.5
Filgrastim	79.1% (19/24)	10.7 ±0.7	3.8 ±0.8
P value	*0.418*	*0.3882*	*0.2206*

† Includes all animals
*Includes only survivors

FN= febrile neutropenia = ANC <500/µL AND body temperature ≥103°F; SE = standard error

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AXG15 Summary of Blood Culture Results in NHP Following 7.50 Gy TBI

	Number of NHP With at Least One Bacteria-Positive Blood Culture	
Treatment	**Number**	**%**
Control (n=22)	19	86
Filgrastim (n=24)	14	58
P value		*0.035*

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AXG15 Cage-Side Observations (1)

Observations were made twice daily for the following signs in NHP following 7.5 Gy TBI:

- Activity
- Posture
- Hemorrhage
- Respiration
- Stool Consistency
- Alopecia
- Emesis

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AXG15 Cage-Side Observations (2)

Summary

- Cage-side observations were generally unremarkable and with no marked difference between treatment groups
- There was a slight trend for worse outcomes for activity, posture, respiration, and stool consistency in the control animals and alopecia in the filgrastim animals

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AXG15 Percent of Animals with Lesions at Necropsy

	Control (%)	Filgrastim (%)	*P* Value
Bone Marrow	50	21	0.06
Liver	27	8	0.13
Heart	41	21	0.20
Lung	50	29	0.23
Thymus	55	21	0.03
Spleen	45	25	0.22
Mesenteric Lymph Node	77	63	0.35
Skin	27	17	0.48
Kidney	50	29	0.23
Small Intestine	86	91	0.67
Large Intestine	32	54	0.15

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AXG15 Primary Endpoint Conclusions

- Filgrastim significantly improved overall 60 day survival **79% (filgrastim) vs. 41% (control)**; represents an approximate doubling of survival
  - **One-sided *P = 0.004* (Two-sided *P = 0.008*)**
- The study results were overwhelmingly positive; therefore, the **study was terminated early for efficacy**

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AXG15 Secondary Endpoint Conclusions

- Secondary parameters significantly improved in filgrastim-treated vs. controls:
  - Earlier recovery of neutrophil counts
  - Decreased duration of neutropenia
  - Fewer documented infections (positive blood culture)

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Summary

Jui Shah, PhD
Sr. Regulatory Affairs Officer
Division of Allergy, Immunology and Transplantation,
National Institute of Allergy and Infectious Diseases,
National Institutes of Health,
Department of Health and Human Services

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Filgrastim for H-ARS Development Program Summary (1)

- Currently, no FDA-approved countermeasure for H-ARS
- U.S. licensure path for filgrastim for H-ARS must use FDA Animal Rule with efficacy studies in animals
- Data from the filgrastim development program (AXR01 and AXG15) met the efficacy requirements of the Animal Rule

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Filgrastim for H-ARS Development Program Summary (2)

- **AXR01**
  - **Mechanism of radiation injury:**
    - Radiation of NHPs led to mortality and a depression in neutrophil counts similar to human
  - **Predictive model:**
    - The H-ARS induced in NHPs was similar in time course to human H-ARS
- **AXG15:**
  - **Efficacy (clinically relevant endpoint) in a predictive model of the human syndrome**:
    - Demonstrated that filgrastim significantly improved survival at 60 days
  - **Mechanism of filgrastim action:**
    - Filgrastim also improved neutrophil parameters and decreased incidence of infection
  - **Selection of human dose:**
    - Filgrastim dose used approximates the approved human dose based on published data
  - **Human safety data**:
    - Manufacturer's labeling for filgrastim

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Conclusion

- The data from the NIAID program as presented today support the use of filgrastim for the treatment of H-ARS and meet the NIAID's goal of developing medical countermeasures for radiation/nuclear incidents

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BACKUP SLIDES

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