Clinical Food Effect and Murine Efficacy Supporting BIO 300 Development as a Pre-Exposure Prophylactic Radiation Countermeasure

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Disclosure

- The speaker, Artur Serebrenik, is an employee of Humanetics Corporation, which is developing a prophylactic radiation medical countermeasure (MCM) with the Department of War (DOW) via a contract with the Capability Program Executive for Chemical, Biological, Radiological and Nuclear Defense (CPE CBRND) supported by Fiscal Year (FY) 2023 and FY24 Defense Appropriations Act funding.

- The views, opinions or assertions expressed herein are the private views of the presenter and are not necessarily those of the Uniformed Services University of the Health Sciences, or the U.S. DOW. Reference to any specific commercial products, process, or service by trade name, trademark, manufacturer, or otherwise do not necessarily constitute or imply endorsement, recommendation, or favoring by the United States government and shall not be used for advertising or product endorsement purposes.

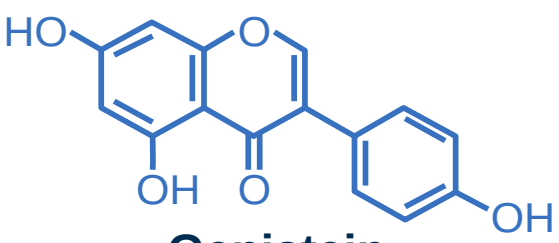
Enhanced preparedness necessary for operations in radiological/nuclear environments



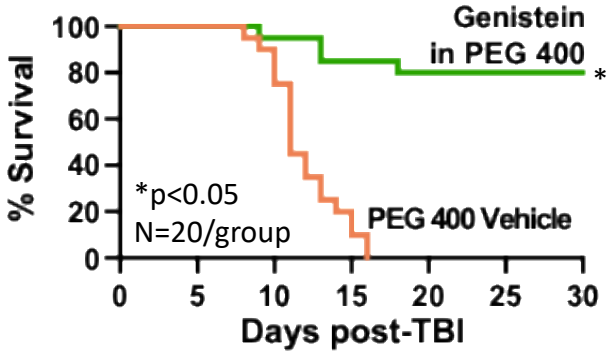

- Warfighters, first responders and civilians are at risk of developing acute radiation syndrome (ARS) in the event of a radiological/nuclear (R/N) incident
- R/N defense capabilities can be enhanced through implementation of pre-exposure prophylaxis (PrEP) radiation medical countermeasures (MCMs)
- Development of PrEP radiation MCMs is governed by the U.S. Food and Drug Administration (FDA) Animal Rule

Genistein discovered as a potent radioprotectant by the DOW

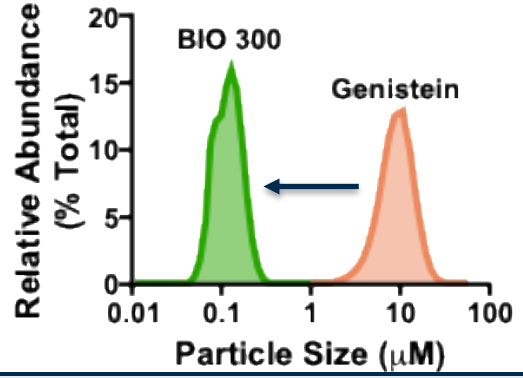
- Early studies evaluated genistein dissolved in PEG 400 given as PrEP to mice exposed to lethal total body irradiation
- Genistein is insoluble in water and has sub-therapeutic bioavailability when administered orally neat
- Oral bioavailability challenges overcome by wet-milling synthetic genistein into a nanosuspension (BIO 300)



Genistein



Mice pre-treated with Genistein prior to 9.3 Gy Total Body Irradiation (TBI)



Particle size by laser diffraction

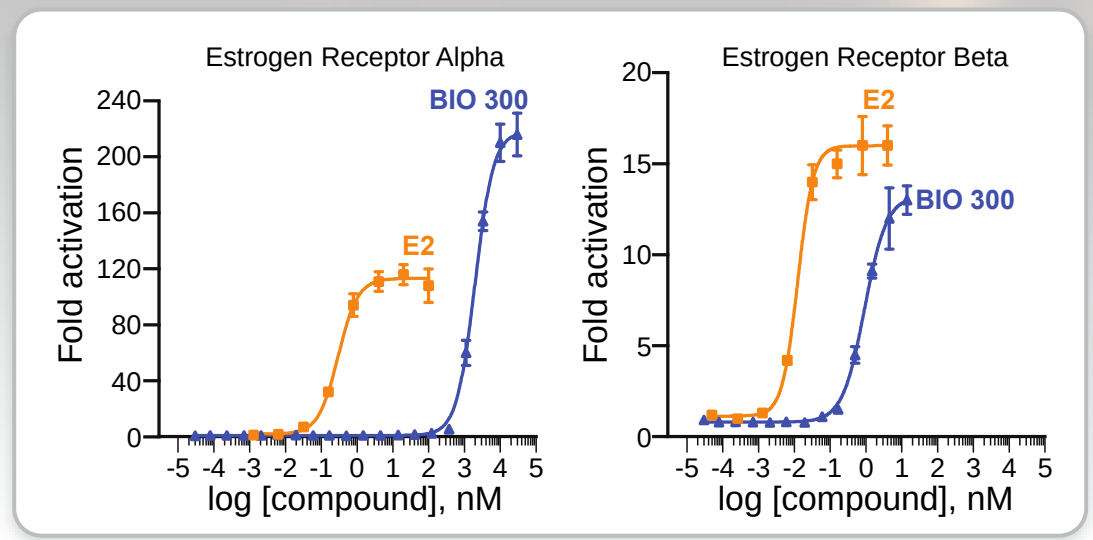
BIO 300 (genistein nanosuspension) is under advanced development as a PrEP radiation MCM

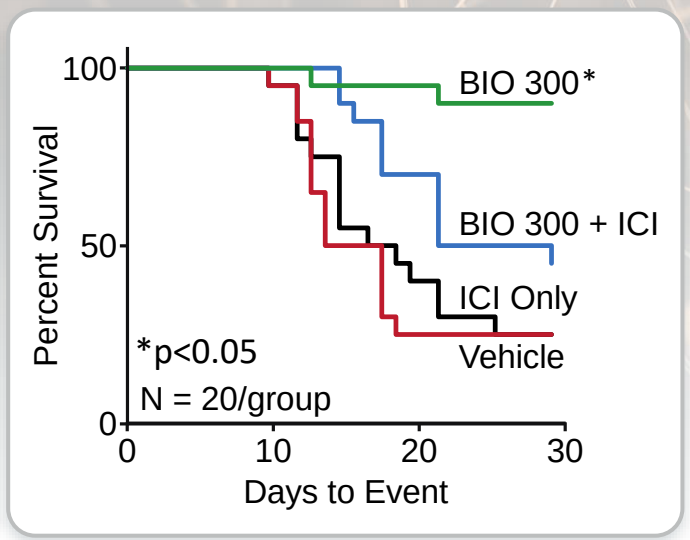
- Two nanosuspension formulations of genistein developed suitable for oral and parenteral administration
- Pharmaceutical formulations of genistein developed by Humanetics are collectively known as BYOGRAYZ™ aka BIO 300
- **Key attributes:** ease of use, shelf-stable, favorable safety profile, domestic manufacturing, broad indications (military relevant, not military specific)
- **Regulatory status:** Four (4) open Investigational New Drug applications (INDs) and FDA Fast Track and Orphan Drug designations for ARS

Oral daily dose is less than a tablespoon

Genistein-mediated activation of estrogen receptor beta promotes whole-body radioprotective effects

- ERβ counteracts ERα and has anti-proliferative and anti-inflammatory effects
- Genistein has a 2000-fold higher selectivity for ERβ vs ERα[1]
- Genistein's radioprotective mechanism was demonstrated to require estrogen receptor activation[1]

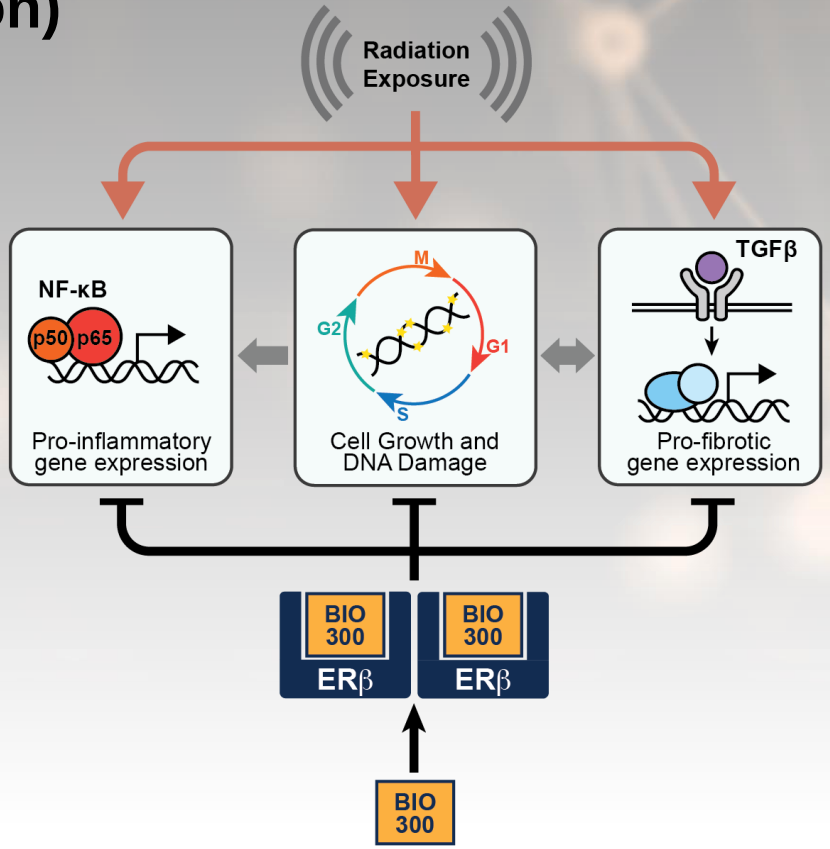




1) Landauer, et al. 2019. Journal of Radiation Research

ICI: ICI 182,780; Fulvestrant ER antagonist

Proposed mechanism of action for BIO 300 (genistein nanosuspension)



Translating Animal Efficacy into a Human Dose

FDA Animal Rule (21 CFR 314.600): Efficacy is established in animal models because human efficacy trials are neither ethical nor feasible. Instead, **human dose must be justified by translation from animal PK/PD**.

PK Exposure Matching

- Set the human dose to reproduce the systemic exposure (AUC, Cmax) tied to protection in the pivotal species.
- Preferred if full range of human exposures exceeds animal exposure.
- Ideal approach when the effect is exposure-driven.

BIO 300

PD Biomarker Bridging

- A translatable biomarker measured in both animals and humans anchors dose selection to a reproducible protective response.
- Biomarker should be related to the mechanism of action for radioprotection.

Safety and tolerability of the putative human dose are evaluated in human healthy volunteer trials

Today's Data: Human PK & Murine Dose Scheduling Efficacy

*Studies supporting the development of **BIO 300** as an oral, PrEP radiation MCM for ARS*

Human Multiple Ascending Dose PK/PD and Food Effect

- **Trial:**
  - Protocol: CL0111-01 (NCT06741345)
  - Status: **Complete**
  - Enrollment: 56 healthy male and female volunteers
- **Objective:**
  - Evaluate single and multi-ascending dose PK
  - Evaluate dose response PD
  - Evaluate single dose food effect on PK

➔ Informs approach for human dose selection

Murine Dose Scheduling Efficacy

- **Model:**
  - Male/Female CD2F1
  - Total-body irradiation (TBI); 9.2 Gy ($LD_{70/30}$)
- **Objective:**
  - Minimum doses needed for radioprotection
  - Efficacy with extended PrEP dosing
  - Time to radioprotection following an optimal schedule

➔ Results help define CONOPS for PrEP deployment

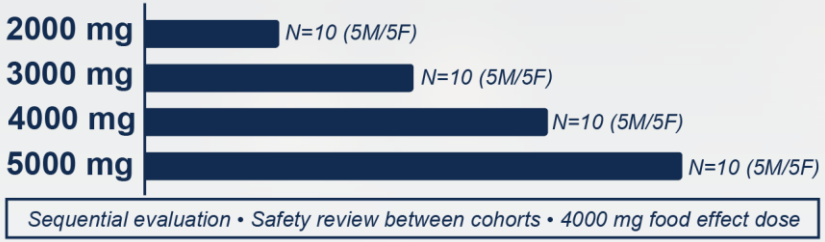
Phase 1 Trial Design: Multiple Ascending Dose (MAD) and Food Effect (FE)

Population	Test Article	MAD Design	FE Design	Endpoints
Healthy volunteers Male and Female	BIO 300 Oral Suspension (BIO 300 OS)	Open-label, 14-day ascending dose	Open-label, single dose, randomized, crossover	Safety, PK, PD

Part 1

What is the maximum tolerated dose?

4 sequential cohorts • N=5/sex/cohort • 14 days, QD dosing
PK evaluated following 1, 6 and 14 doses



Characterizes the **range of human exposures achievable** with BIO 300 OS following 1, 6 and 14 days of once-daily dosing.

Part 2

What is the effect of food on systemic exposure?

Randomized, balanced, single-dose (4000 mg), two-treatment (fed vs fasted), two-period, crossover design

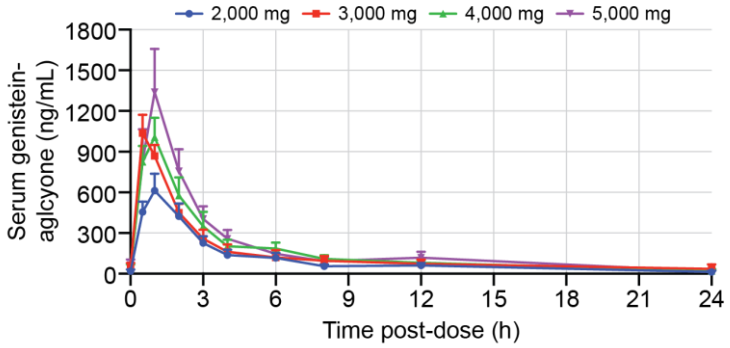
Defines **fed vs fasted** systemic drug exposure and safety/tolerability to inform dosing instructions and product labeling

Animal Rule relevance: the MAD study **defines the range of human exposures** achievable with BIO 300; the food effect study informs dosing instructions and expands the potential for a **PK approach for human dose translation**.

Phase 1 MAD Study Results

Pharmacokinetics

Day 14 mean serum genistein-aglycone conc. x time profiles



Key PK Finding: exposure increased with dose but was less than dose-proportional, which may reflect solubility-limited absorption

Pharmacodynamics

To bridge nonclinical biomarkers (mouse/NHP), human biomarkers were assessed on Day 1, 6 and 14 by whole blood RNA sequencing. Biomarker signal was most pronounced after 6-14 days of dosing.

Steady-State Mean PK Parameters

Day 14 serum genistein-aglycone, by dose cohort (N=9-10/cohort)

Dose (mg/day)	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24} (ng·h/mL)	t½ (h)	R_{acc}
2,000	640	1.1	2,201	8.9	0.9
3,000	1,087	0.7	3,027	6.3	0.8
4,000	1,001	0.9	3,524	5.4	0.9
5,000	1,380	1.2	4,031	5.5	0.8

Safety & Tolerability

BIO 300 OS was generally well-tolerated across all four cohorts through 14 days; **no SAEs or dose-limiting toxicities** (grade 3+ treatment emergent adverse events [TEAEs]); the **majority of TEAEs were Grade 1-2 gastrointestinal (GI) events.**

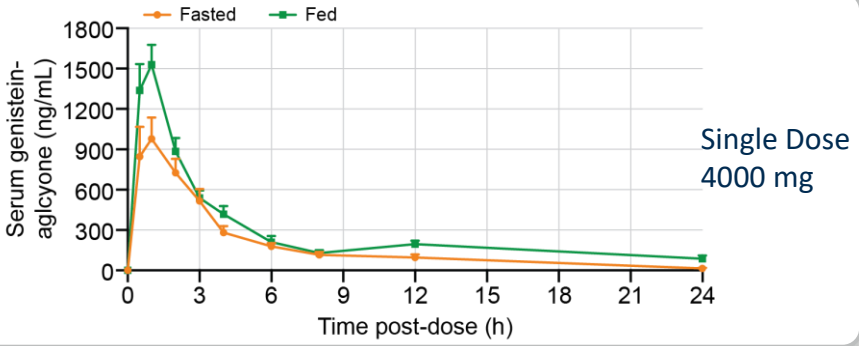
4,000 mg dose selected for food effect study based on tolerability (highest dose without grade 2 GI TEAEs)

Bottom line: BIO 300 OS produced **increasing systemic exposures (AUC) with minimal accumulation and an acceptable safety profile**; however, fasted exposure may not support PK-based dose translation under Animal Rule

Phase 1 FE Study Results

Pharmacokinetics

Mean serum genistein-aglycone conc. x time profiles



Key PK Finding: Dosing with food resulted in a significant food effect on genistein-aglycone absorption and bioavailability

Safety & Tolerability

Dosing under fasted vs fed conditions was well-tolerated. No SAEs occurred. All TEAEs were Grade 1-2, and most were GI events. **No diarrhea events occurred under fed dosing** conditions.

Single Dose Mean PK Parameters

Serum genistein-aglycone, fed vs fasted (N=14-15/condition)

Dose (mg)	Condition	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng·h/mL)	t½ (h)
4,000	Fasted	1175	1.6	4240	6.9
4,000	Fed	1662	1.1	7221	8.9

Parameter	Fed-to-Fasted Ratio (%)	90% CI
C_{max}	157%	100% – 247%
AUC_{0-t}	180%	118% – 275%

Adverse Events

Treatment-emergent adverse events in fasted vs fed (N=15-16)

Condition	% Participants reporting TEAE	# TEAEs	% Diarrhea
Fasted	31% (5/16)	8	25%
Fed	20% (4/15)	4	0%

Bottom line: Dosing with **food significantly increases systemic drug exposure** and may improve tolerability; fed dosing provides an **opportunity for potential human dose translation** using a PK approach under the Animal Rule

How Phase 1 PK Supports Human Dose Conversion

1 Define the target exposure

From the **animal efficacy studies**, identify the systemic exposure (AUC) associated with survival benefit / the **exposure to be matched** in humans.

2 Map the human exposure range

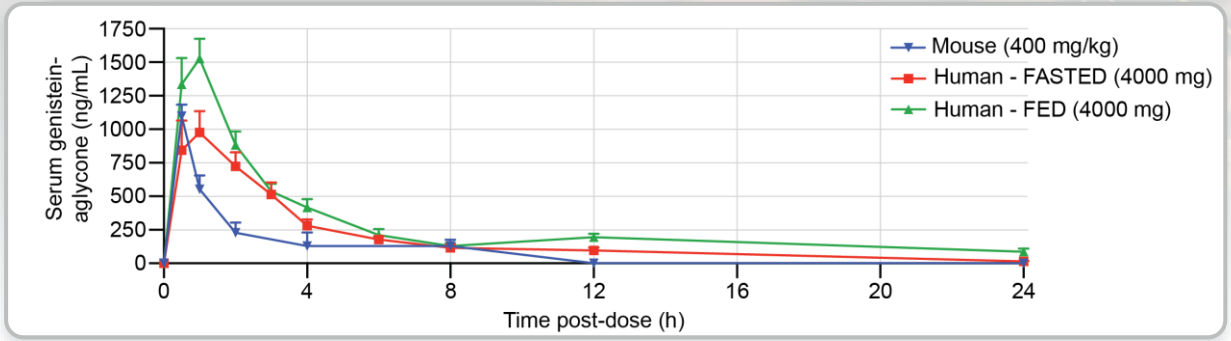
The **MAD study** defined achievable human exposures, increasing with dose but **less than dose-proportionally**, while tolerability decreases with higher doses under fasted conditions

3 Close the gap with food

The **FE study** shows fed dosing raises exposure (AUC +80%, C_{max} +57%) and improves GI tolerability, **extending the reachable exposure range**.

Safety enables dose headroom

No SAEs or DLTs through 14 days and **MTD not reached at 5,000 mg;** room to dose to the exposure needed, especially under fed conditions.



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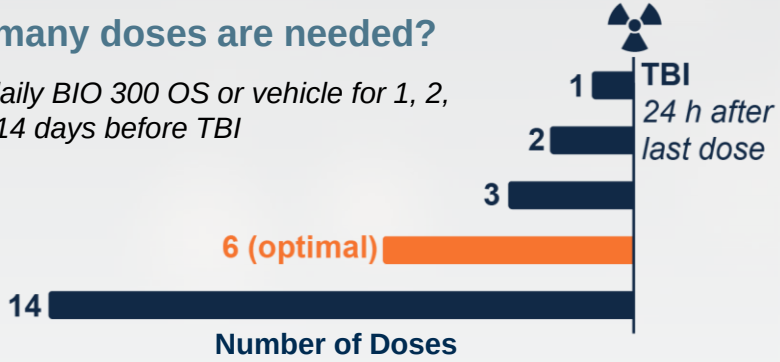
Murine Study Design: Dose Number and Durability of BIO 300 Radioprotection

Model	Group Size	Challenge	Endpoint	Design
CD2F1 Mice Male and Female	N = 20 /sex / group	9.2 Gy ^{60}Co TBI (~$LD_{70/30}$)	30-day survival	8 dosing groups Paired vs vehicle control

Part 1

How many doses are needed?

Once-daily BIO 300 OS or vehicle for 1, 2, 3, 6 or 14 days before TBI



Defines the **minimum effective schedule** and tests **extended dosing**. 6-days is the established optimal schedule (positive control).

Part 2

How long does protection last?

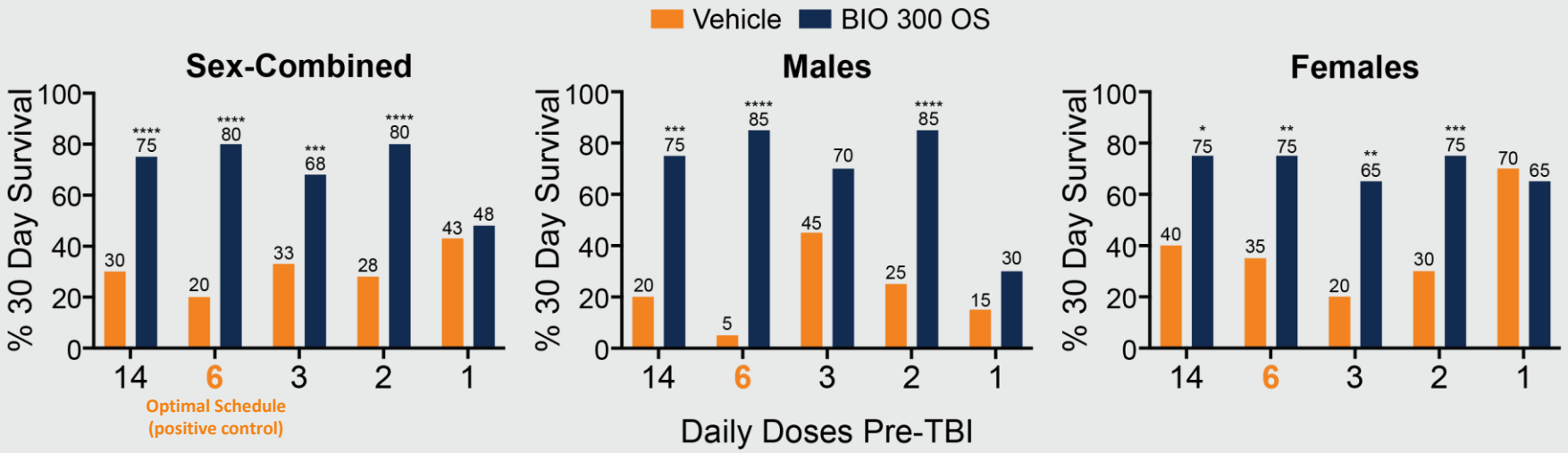
Fixed 6-day schedule followed by TBI at 12, 24, 36 or 48 h after the last dose

Characterizes the **protective window**; how long are individuals protected after dosing stops. 24 h is the established positive control.

CONOPs relevance: together the two parts of this study define the **dosing flexibility** (minimum effective course through extended dosing) and the **protective window** (how long protection persists after last dose).

(Part 1) Murine Dose Scheduling Survival Results

Model	Group Size	Challenge	Endpoint	Design
CD2F1 Mice Male and Female	N = 20 /sex / group	9.2 Gy ^{60}Co TBI (~$LD_{70/30}$)	30-day survival	4 irradiation schedules Paired vs vehicle control

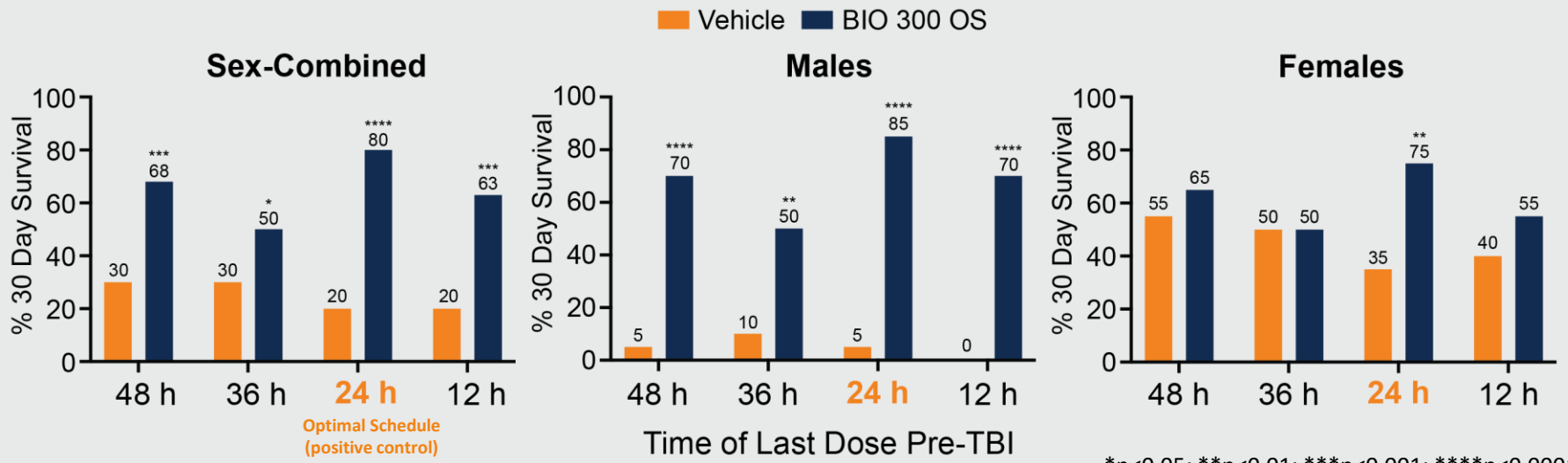


*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001

Conclusion: BIO 300 OS significantly improved 30-day survival across schedules. In males and females, protection was significant from as few as 2 daily doses through extended 14-day dosing; a single dose was insufficient. This defines a **wide effective dosing window**; as little as 2 doses are required and extended dosing does not diminish efficacy.

(Part 2) Murine Duration of Response Survival Results

Model	Group Size	Challenge	Endpoint	Design
CD2F1 Mice Male and Female	N = 20 /sex / group	9.2 Gy ^{60}Co TBI (~$LD_{70/30}$)	30-day survival	5 dosing schedules Paired vs vehicle control



Conclusion: In males, BIO 300 OS conferred significant **protection through 48 h** after the last dose. In females, high and variable vehicle survival (35–55%) confounded statistical comparisons. The female comparisons may reflect **model variability and sex-differences in radiosensitivity**; additional assessments of the lethality profile are planned.

Conclusion

Phase 1 human PK and murine efficacy data support BIO 300 development under the Animal Rule

Human PK, Food Effect and Safety

- Tolerated at daily doses of 2,000-5,000 mg through 14 days; **MTD not reached**.
- No DLTs or SAEs. Majority of TEAEs were Grade 1-2 GI events.
- **Significant food effect** (AUC +80%, C_{max} +57%) increases systemic exposure and improves GI tolerability.

Murine Efficacy

- **Minimum of 2 once-daily doses** needed to significantly improved 30-day survival
- Extended dosing up to 14 days maintains efficacy
- **Durability of protection lasts 48 h** after the last dose (in male model); significant variability in female animal model confounded survival analysis

FDA Animal Rule Path Forward

- Food effect expands exposure range for dose selection under the PK approach
- Murine survival data defines dosing flexibility and protective window
- **Next steps:** confirm target exposure range for efficacy in NHPs and re-evaluate female murine model

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