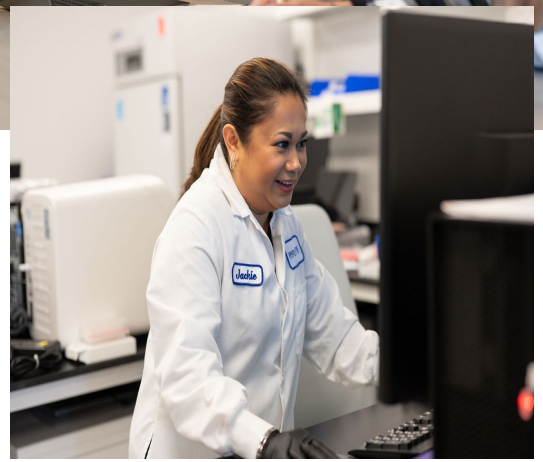
REPLICATE

Single and Low Dose Self Replicating RNA Vaccine Provides Effective Immune Protection Against Rabies in Healthy Volunteers

Zelanna Goldberg, MD, MAS
Chief Medical Officer
Replicate Bioscience
May 2024

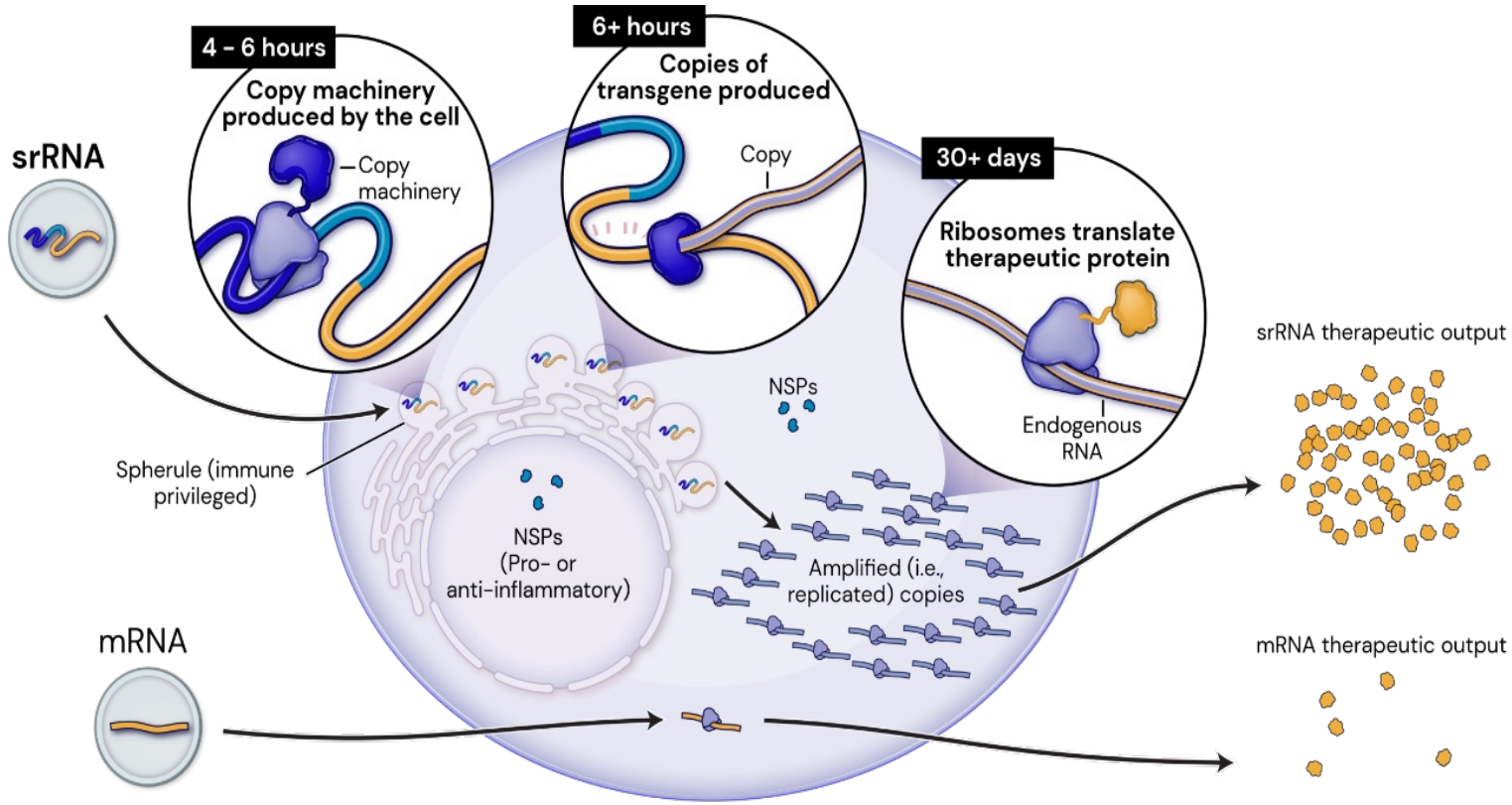
Disclosures and Acknowledgements

- I am an employee of Replicate Bioscience
- The study was funded by Replicate Bioscience and I will be discussing a vaccine that does not yet have FDA approval



srRNA: an instruction manual for your body's own cells to create fully natural mRNA

Mechanism for protein expression

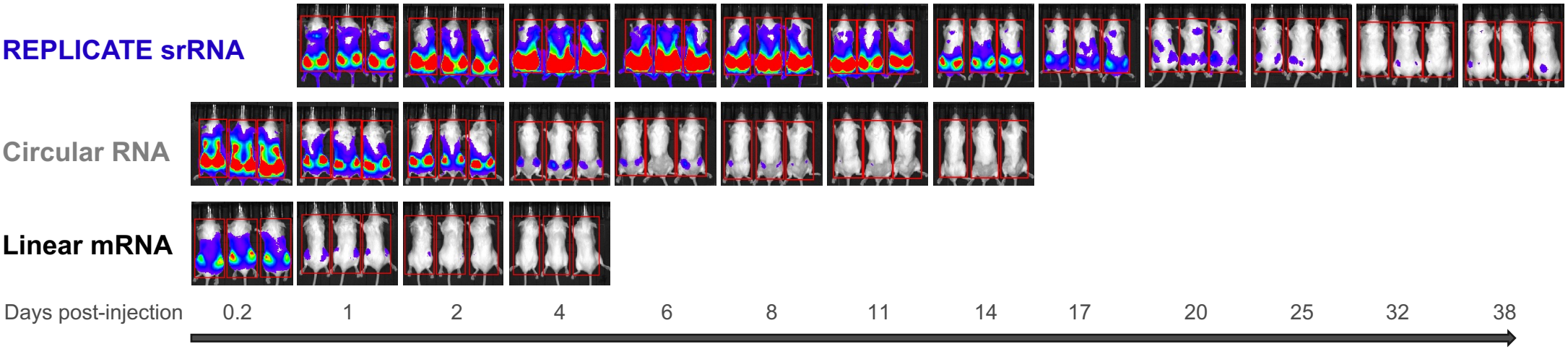


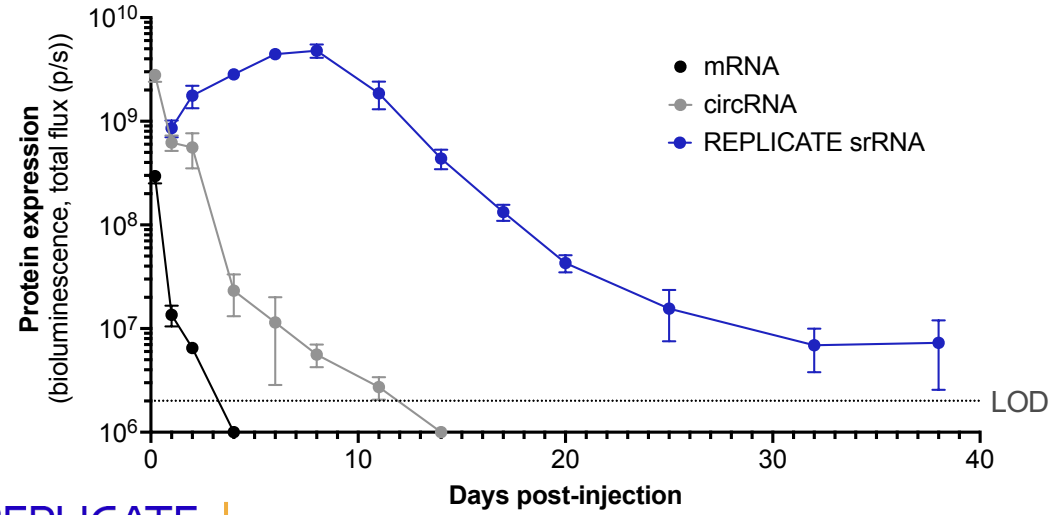
Replication machinery is only created the first few hours; mRNA production is a self-limiting process

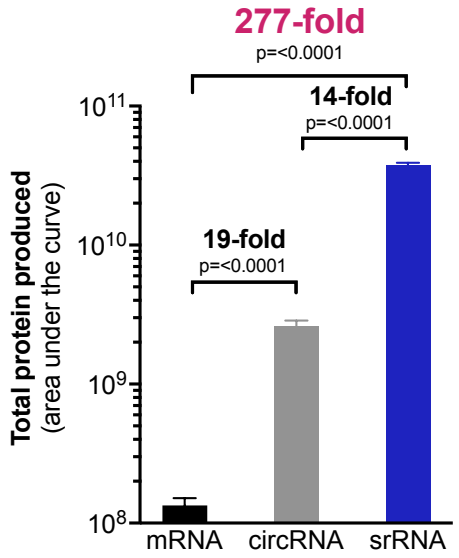
Blakney A., et al., Vaccines 2021

REPLICATE srRNA outperforms circRNA and linear mRNA

Luciferase expression (bioluminescence)







Novel Self-Replicating RNA Vectors Broaden Therapeutic Window and Expand Use Outside of Vaccines

Session Title: Emerging Viral Vectors

Location and Time: Ballroom 4, Thursday, May 9, 5:15 PM - 5:30 PM ET

Abstract: 204

Presenter: Dr. P. Aliahmad

Data produced by Credo Casmil in Anna Blakney lab, UBC

RBI-4000 is a rabies srRNA vaccine

Rationale: Why Rabies?

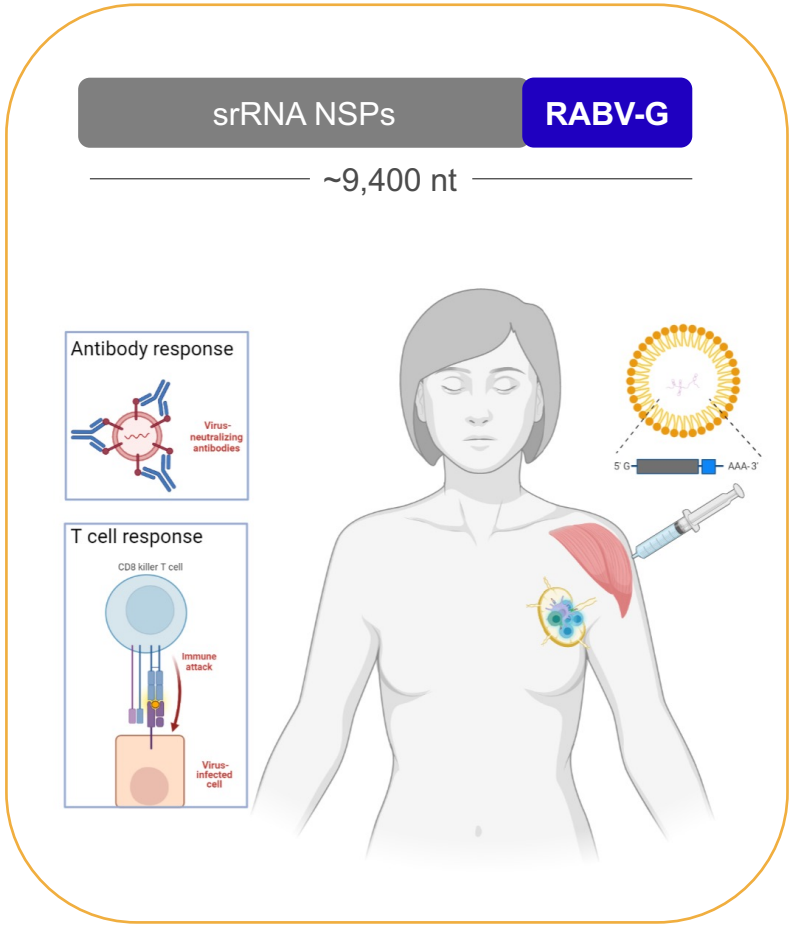
(1) Clean participant population: no prior exposure

(2) WHO-established surrogate metric for protection (RVNA ≥ 0.5 IU/mL)

(3) Cross trial comparisons in linear mRNA and srRNA

- RBI-4000 composed of **proprietary srRNA** vector encoding validated antigen, rabies glycoprotein, encapsulated in a **novel LNP composition**

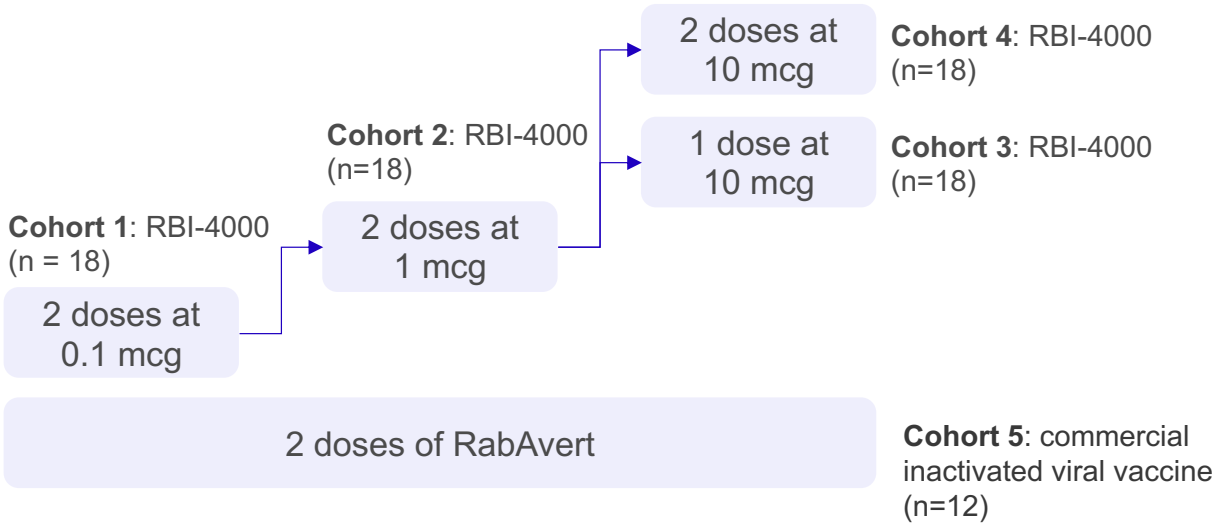
- **Preclinical testing showed:**
  - Durable rabies virus neutralizing antibodies (RVNA) above the WHO-defined surrogate metric for protection down to 0.0015 mcg
  - Robust T cell activity
  - 100% protection from a lethal challenge
  - Detectable RNA out to 60+ days
  - Strong safety profile consistent with a typical prophylactic vaccine



RBI-4000-101 phase 1 study design

Phase 1 (n = 84 healthy volunteers)

Regimen: mcg intramuscular injection x1 or x2 (8-week interval)



KEY OBJECTIVES	PHASE 1
Primary	Safety, reactogenicity, RP2D
Secondary	Surrogate metric for protection (RVNA (RFFIT))
Exploratory	T cells

Key Inclusion

- 18-45 y.o.
- Seronegative for hep B, hep C, HIV, rabies virus neutralizing antibodies
- Normal hematologic and biochemical parameters
- No pre-existing medical conditions

Key Exclusion

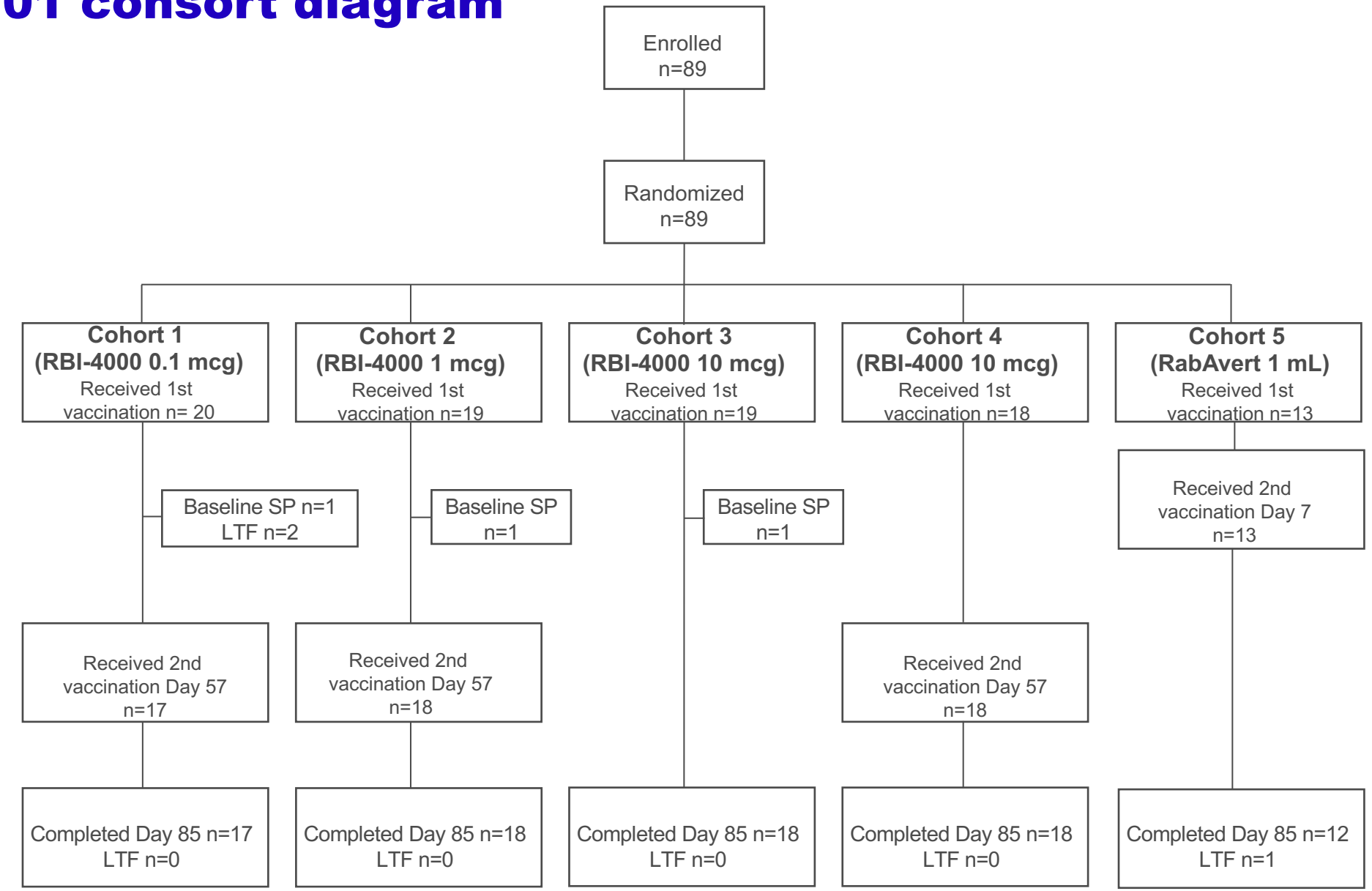
- Prior rabies vaccination or exposure
- Any immunosuppressive or immunodeficient condition or immunosuppressant medications
- Any history of myocarditis and/or pericarditis
- Lymphoproliferative disorder or malignancy within 5 yr

Enrolled at 2 US sites

- Miami (Dr. Somodevilla)
- Omaha (Dr. Essink)

** RBI 4000 data as of March 21, 2024*

RBI-4000-101 consort diagram



** RBI 4000 data as of March 21, 2024*

RBI-4000-101 demography: groups are well balanced

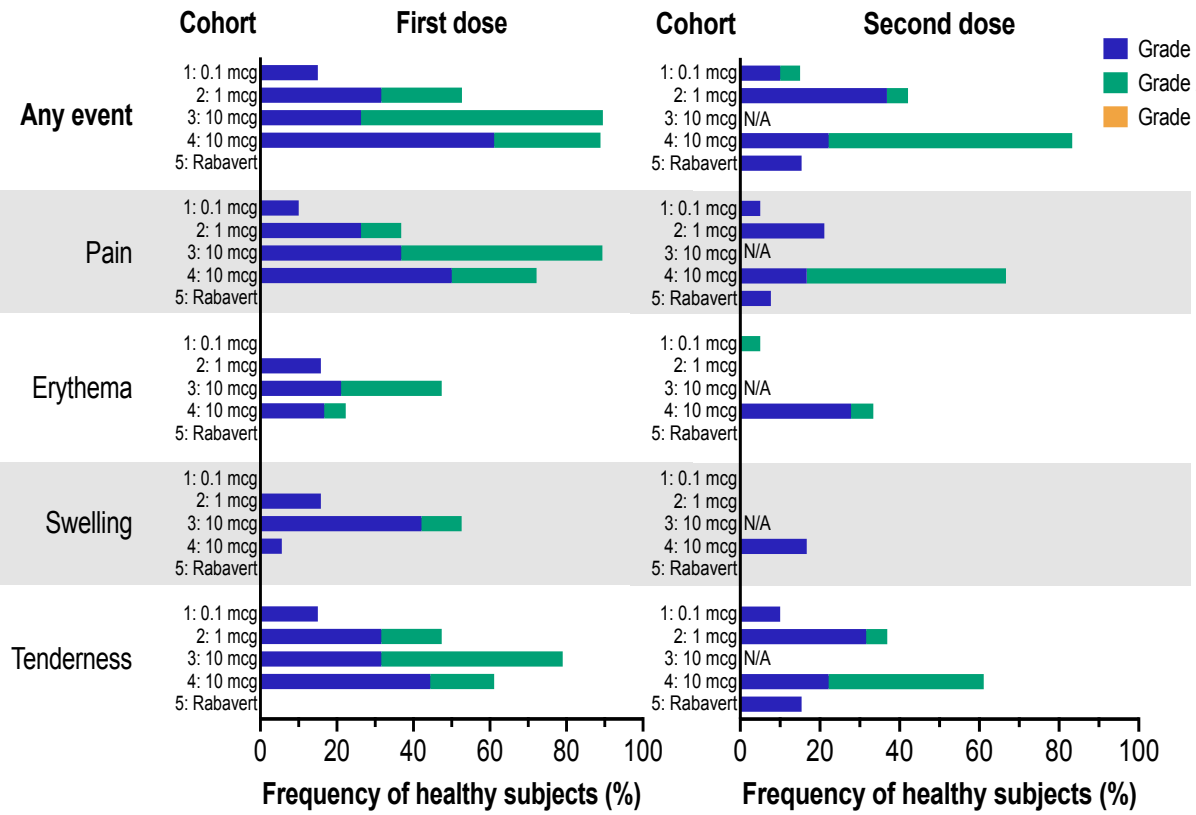
	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Total
Mean age in yrs (range)	35.6 (23-45)	34.4 (25-45)	36 (22-45)	32.5 (20-43)	36.7 (27-44)	35 (20-45)
Sex (M/F)	10/10	10/9	3/16	8/10	7/6	38/51
Race (B/W/O)	5/15	4/15	2/17	4/12/2	4/8/1	19/67/3
Ethnicity (Hispanic or Latino / other)	10/10	9/10	10/9	10/8	6/7	45/44
Total Enrolled	20	19	19	18	13	89
Replaced	1 RVNA+ 2 lost to FU	1 RVNA+	1 RVNA+		1 lost to FU	

** RBI 4000 data as of March 21, 2024*

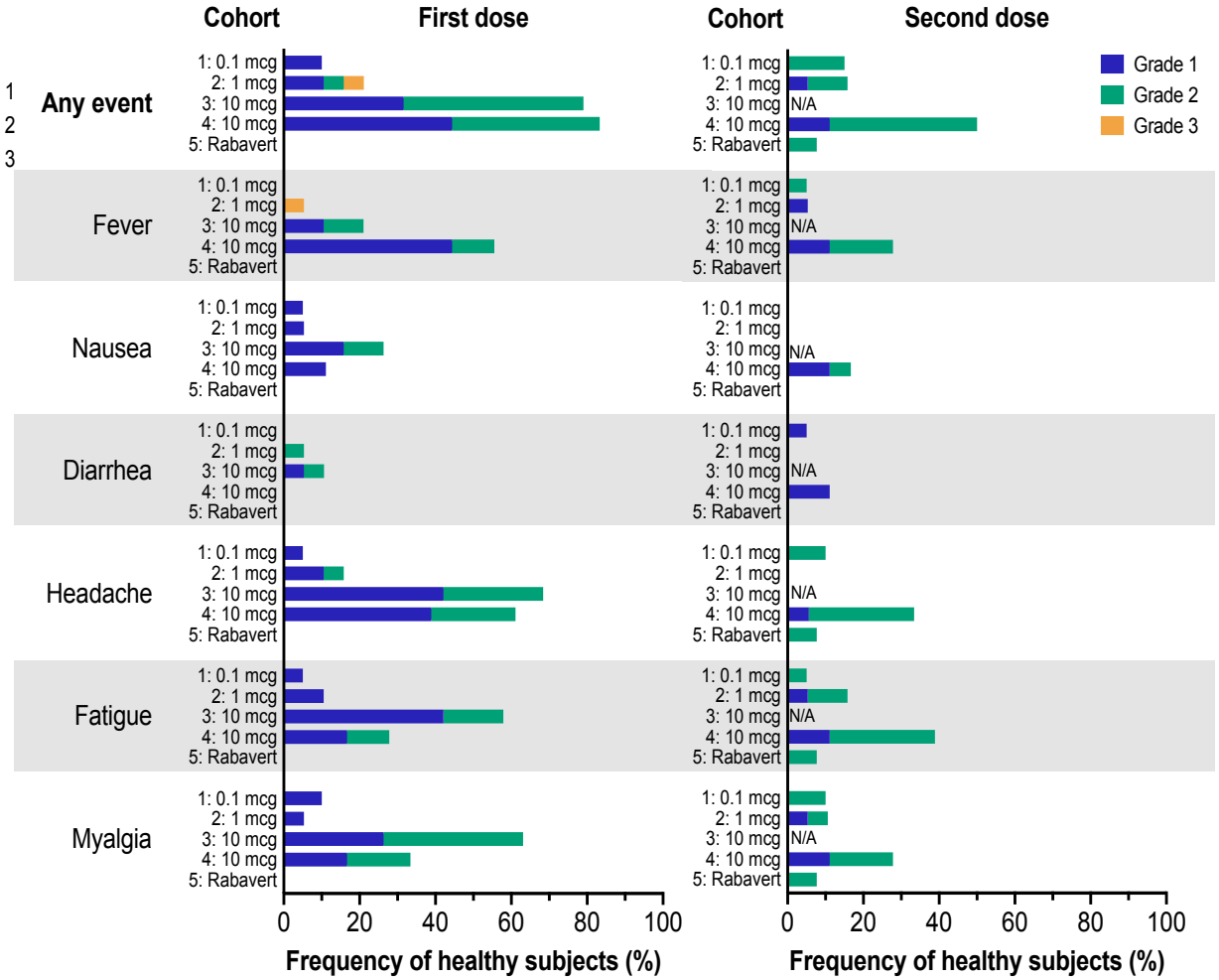
RBI-4000-101: low reactogenicity without any SAEs

Well tolerated. No DLT. No SAEs. MTD not reached.

Local AEs



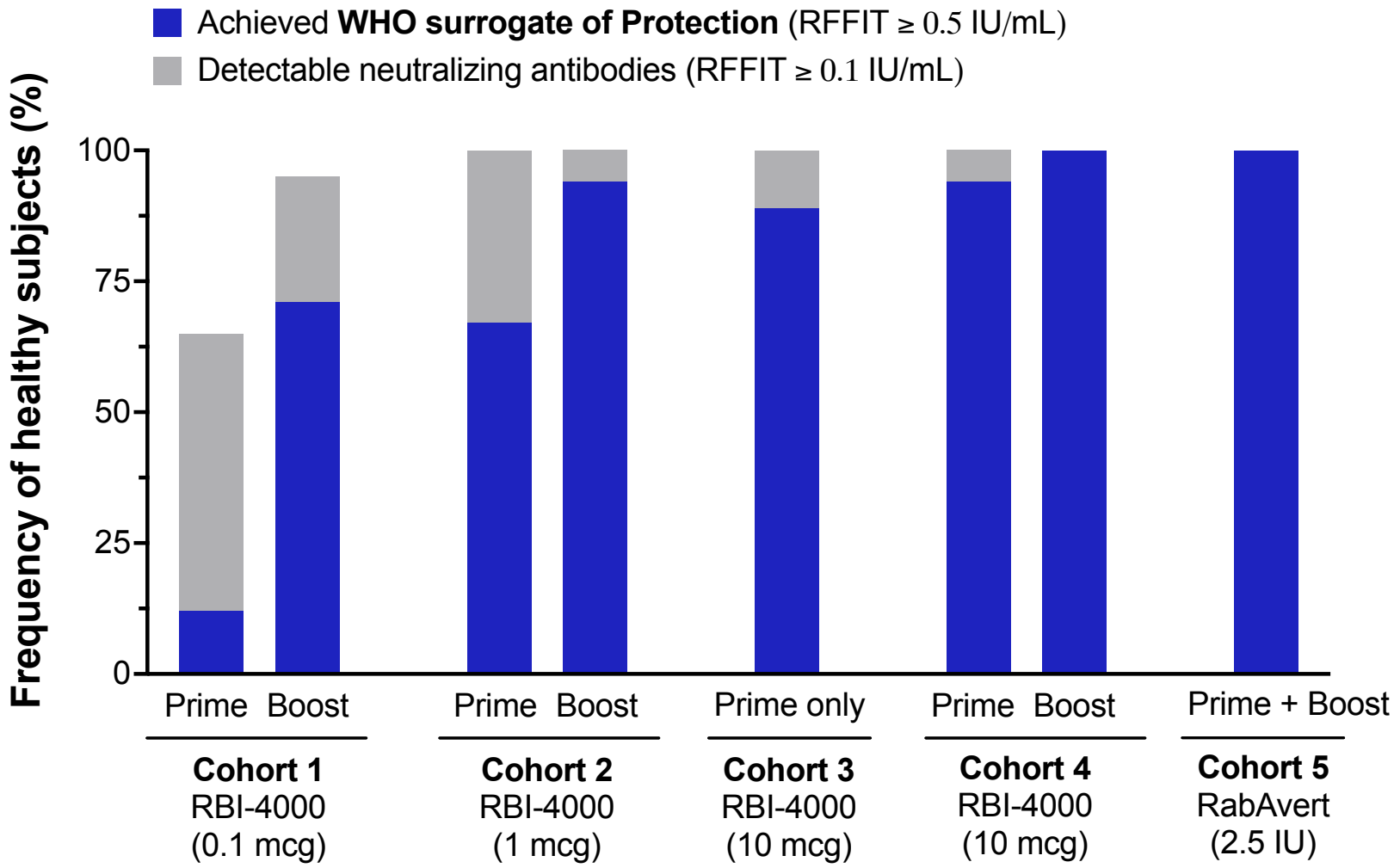
Systemic AEs



DLT=dose limiting toxicity. SAE=serious adverse event. MTD=maximally tolerated dose.
NA = not applicable; AE = adverse event. Data as of March 21, 2024.

Immunogenicity: 300-1000x lower dose than other mRNA vaccines

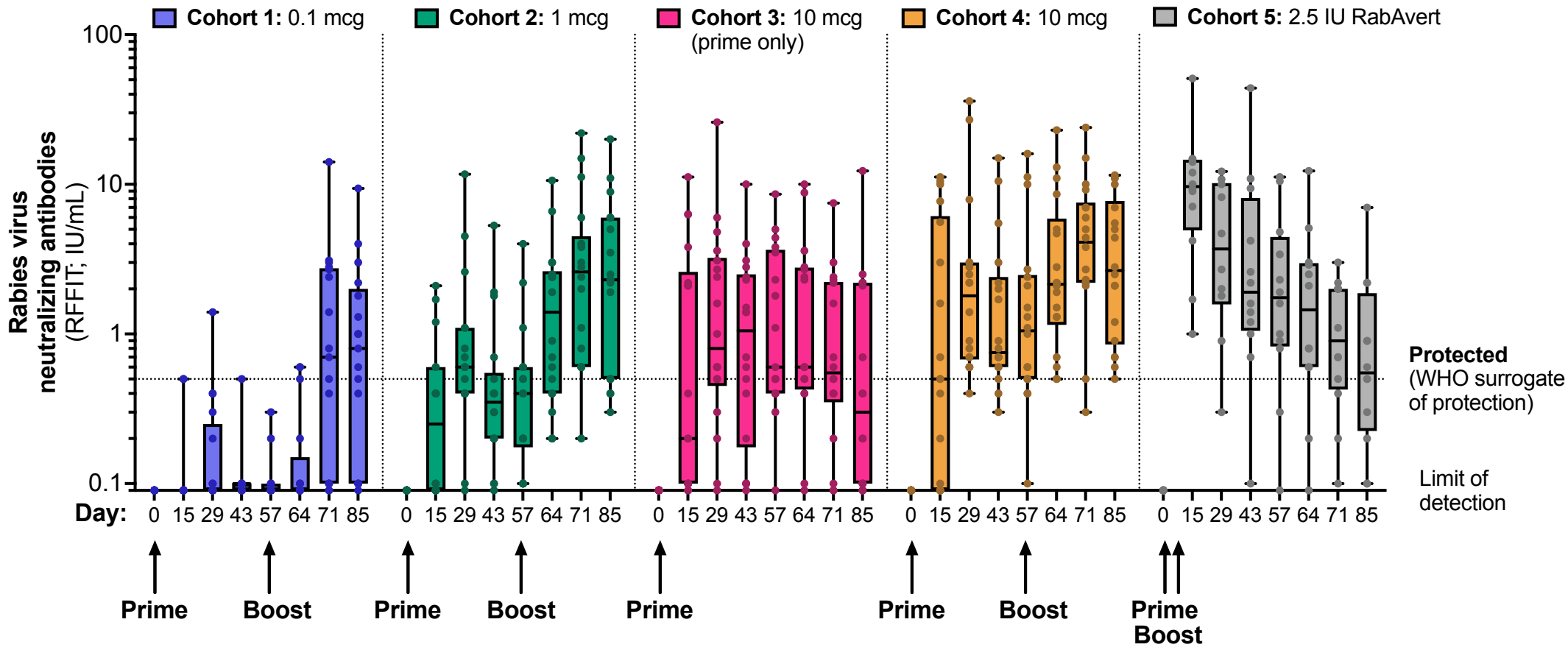
Clinical bioactivity at 0.1 mcg, and with a single dose



** RBI 4000 data as of March 21, 2024*

RBI-4000 primes RVNA in dose dependent manner

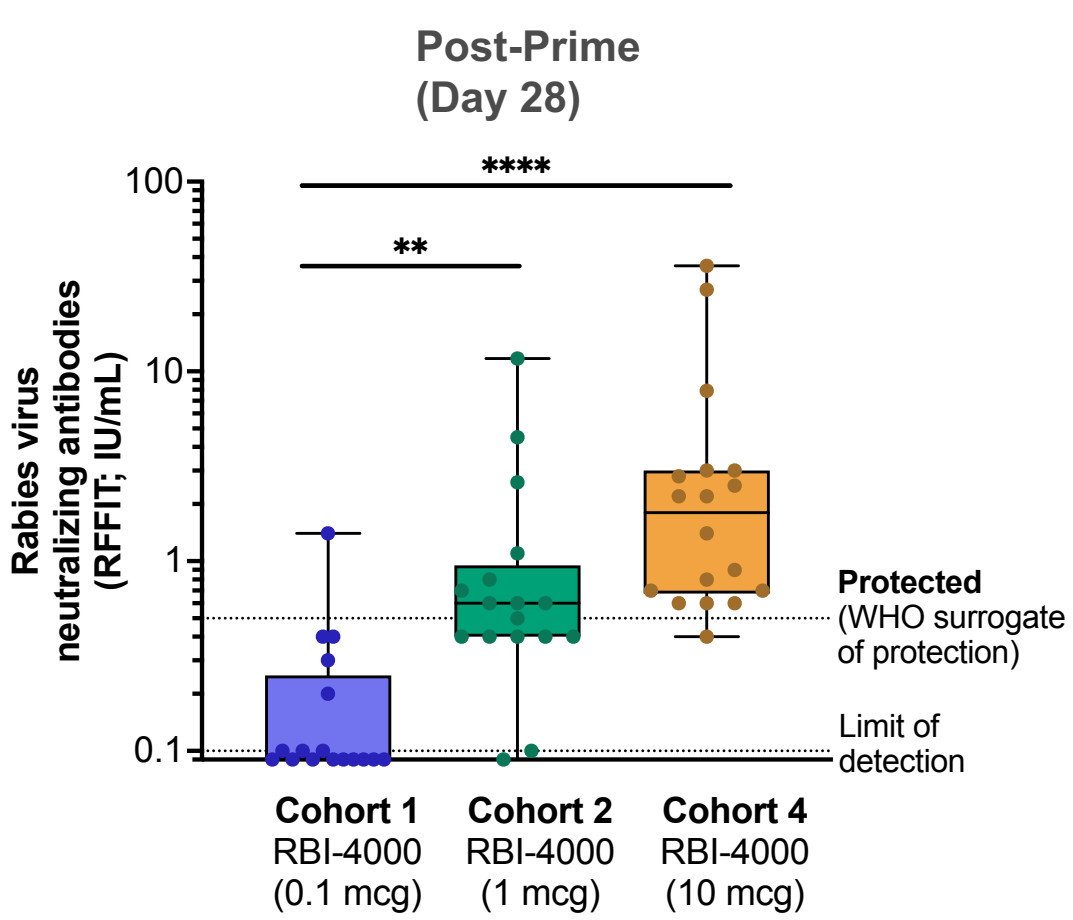
Single 10 mcg dose results in 3 months of protection, similar to approved vaccine

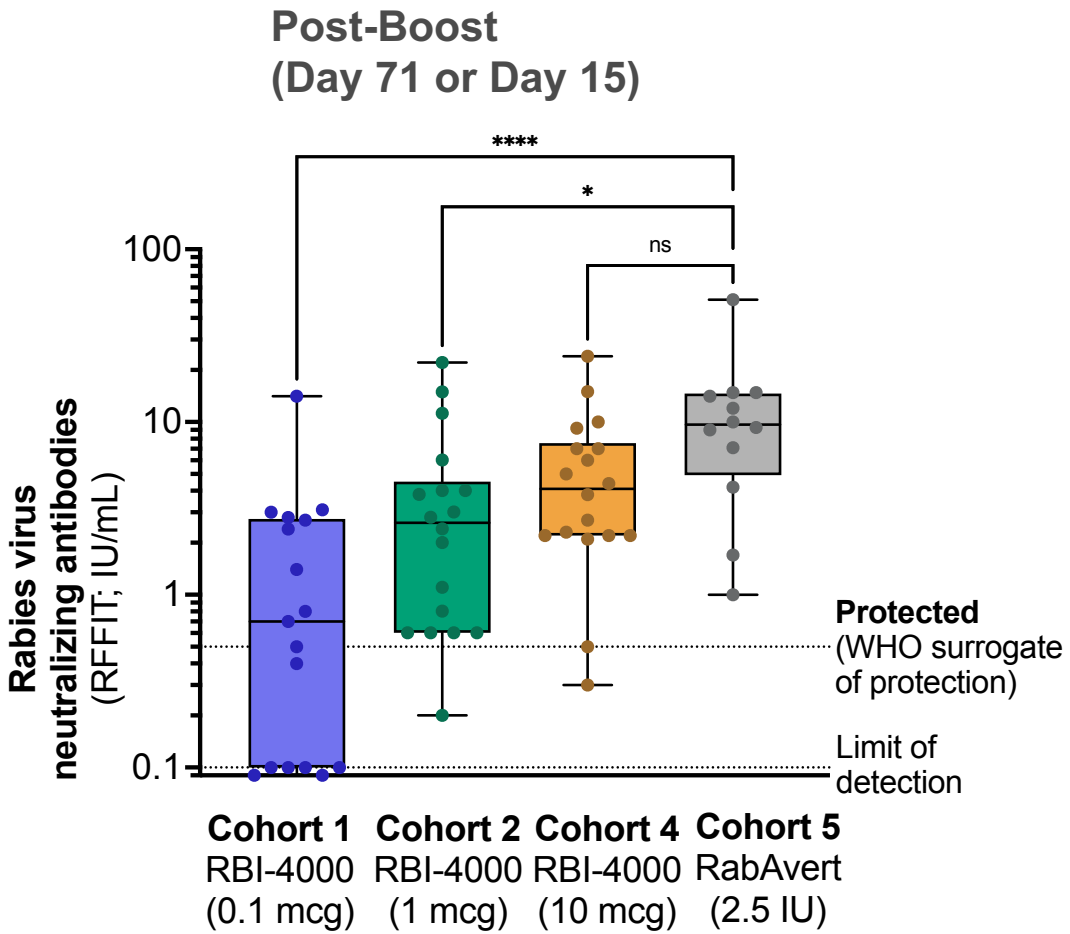


** RBI 4000 data as of March 21, 2024*

RBI-4000 can achieve similar peak levels of RVNA to RabAvert

Strong Prime and Boost Responses.

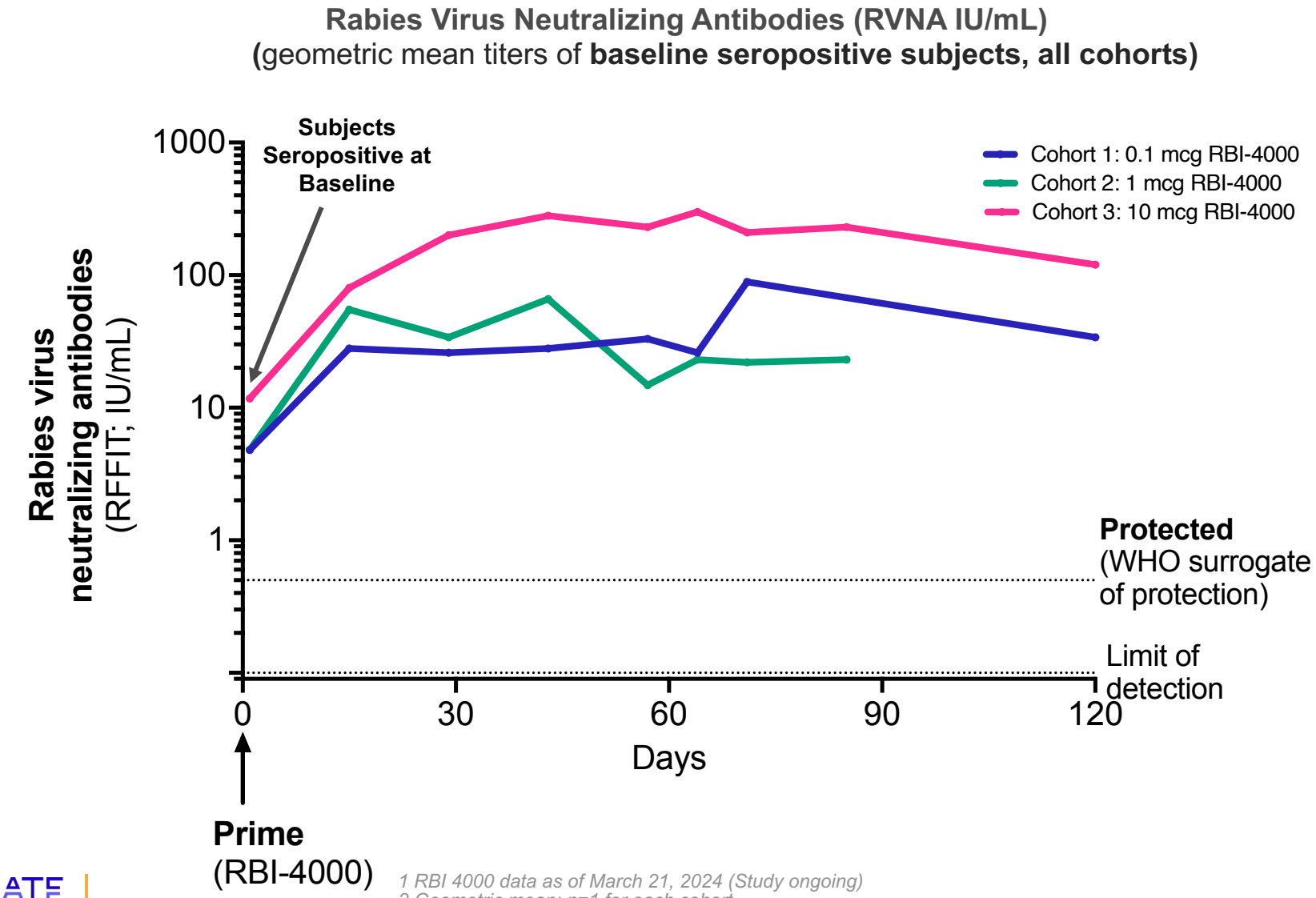




1 RBI 4000 data as of March 21, 2024 (Study ongoing)
2 Geometric mean with 95% confidence intervals

Subjects seropositive at baseline exhibit a strong, durable boost

>13-fold increase in geometric mean of Rabies Viral Neutralizing Antibodies (RVNA) over baseline



1 RBI 4000 data as of March 21, 2024 (Study ongoing)
2 Geometric mean; n=1 for each cohort

RBI-4000-101 conclusions

- **Clean safety profile**: RBI-4000 was well tolerated at all doses tested with no DLTs or SAEs
  - MTD was not reached in this study enabling further dose escalation if desired
  - Adverse events were mild or moderate, self-limiting and usually required no treatment
  - Low reactogenicity/high tolerability *derives from improved manufacturing of long RNA*
- **Improved bioactivity**: RBI-4000 RVNA titers above surrogate of protection in majority of subjects
  - Down to lowest dose evaluated (Cohort 1: 0.1 mcg)
  - Following a single dose (Cohort 3 and Cohort 4 prime; 10 mcg)
  - The high bioactivity *derives from propriety vector engineering and optimization*
- **The high bioactivity/low reactogenicity combination represents a platform improvement and constitutes a step up from existing approaches**
  - **Broad potential applications across many areas of medicine**

REPLICATE

Thanks and Acknowledgement

All the study volunteers and their families

Site personnel at the study centers

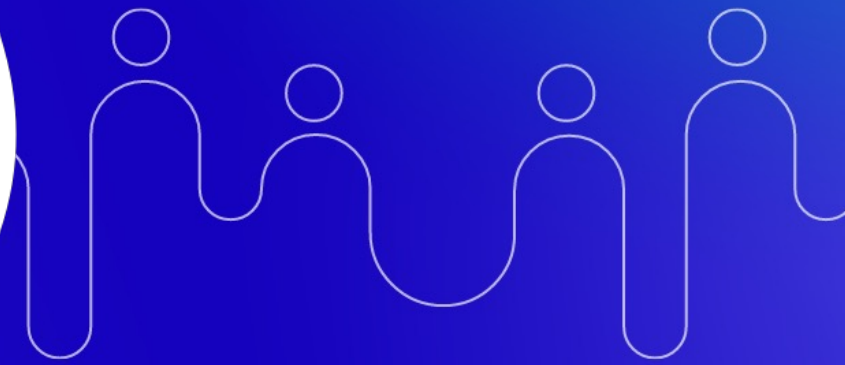
Dr. Anna Blakney, UBC

Credo Casmil

Replicate Team: Drs. C. Maine, P. Aliahmad, A. Geall and N. Wang and all of Replicate CMC, discovery and preclinical teams

Clinical operations support from Halloran: Jessica Fowler and Rebecca Shorin

THANK YOU



REPLICATE