A Novel Therapeutic Vaccine (GEN003) for Genital Herpes Reduces HSV-2 Shedding

Initial Results of Clinical Trial GEN003-001

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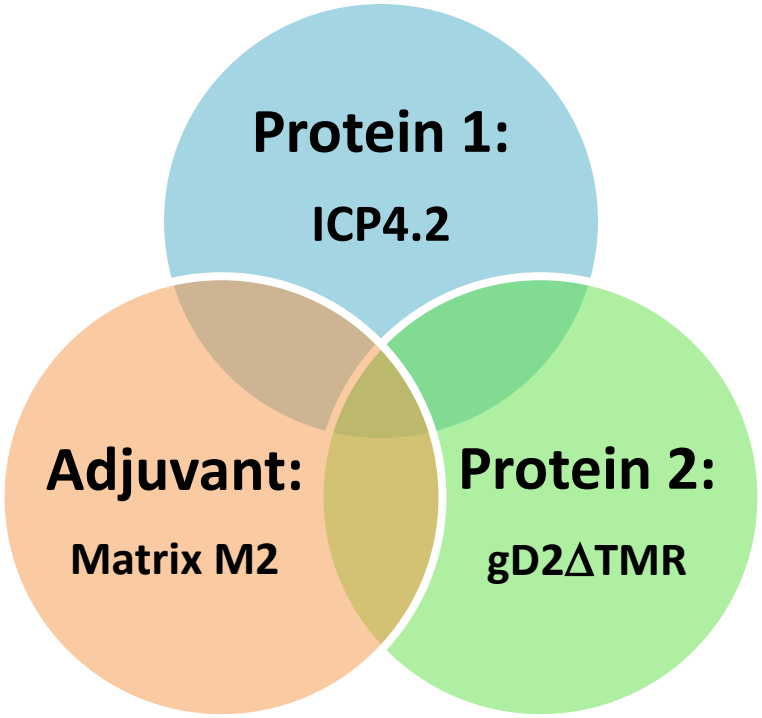
Conflict of interest

- Genocea Biosciences, the developer of GEN003, provided funding for the trial & my trip to ICAAC
- University of Washington has a clinical trials agreement with Genocea to conduct the study, in part, at the UW Virology Research Clinic

Introduction

- Genital HSV-2 affects 1 in 6 adults in the US between ages of 14 and 49
  - 500 million people worldwide
- Viral shedding from genital mucosa
  - Highest during recurrent outbreaks
  - Transmission occurs primarily during asymptomatic shedding
- T cell immunity is likely needed for immune control and prophylaxis
- Therapeutic vaccines could reduce shedding and thus:
  - Provide relief from recurrences
  - Reduce risk of transmission

GEN003 (Genocea Biosciences): Investigational Therapeutic Vaccine



GEN003	= ICP4 + gD2 + Matrix M2
"No Adjuvant"	= ICP4 + gD2
Matrix M2	= Proprietary adjuvant from Isconova, now part of Novavax

- **ICP4: Immediate early protein**
  T cell target; identified by Genocea by T cell screening platform
- **gD2**
  Target of neutralizing antibodies
  Also a T cell target
- **Matrix M2 adjuvant**
  Saponin derived
  Promotes T cell responses

- **Preclinical studies** GEN003:
  Reduced shedding (GP)
  Reduced severity of disease (GP)
  Generated $CD4^+$ and $CD8^+$ T cell responses (mice)

Clinical Trial Objectives

- **Primary Objective**

  To assess the safety and tolerability of a 3 dose vaccine regimen of GEN003 when administered to HSV-2 seropositive adults

- **Secondary Objectives**

  To evaluate:

  - Effect of GEN003 on HSV-2 shedding
  - Humoral and cellular immune responses
  - Ability of Matrix M2 to promote T cell responses directed against HSV-2 antigens

- **Exploratory**

  - Effect on clinical recurrences

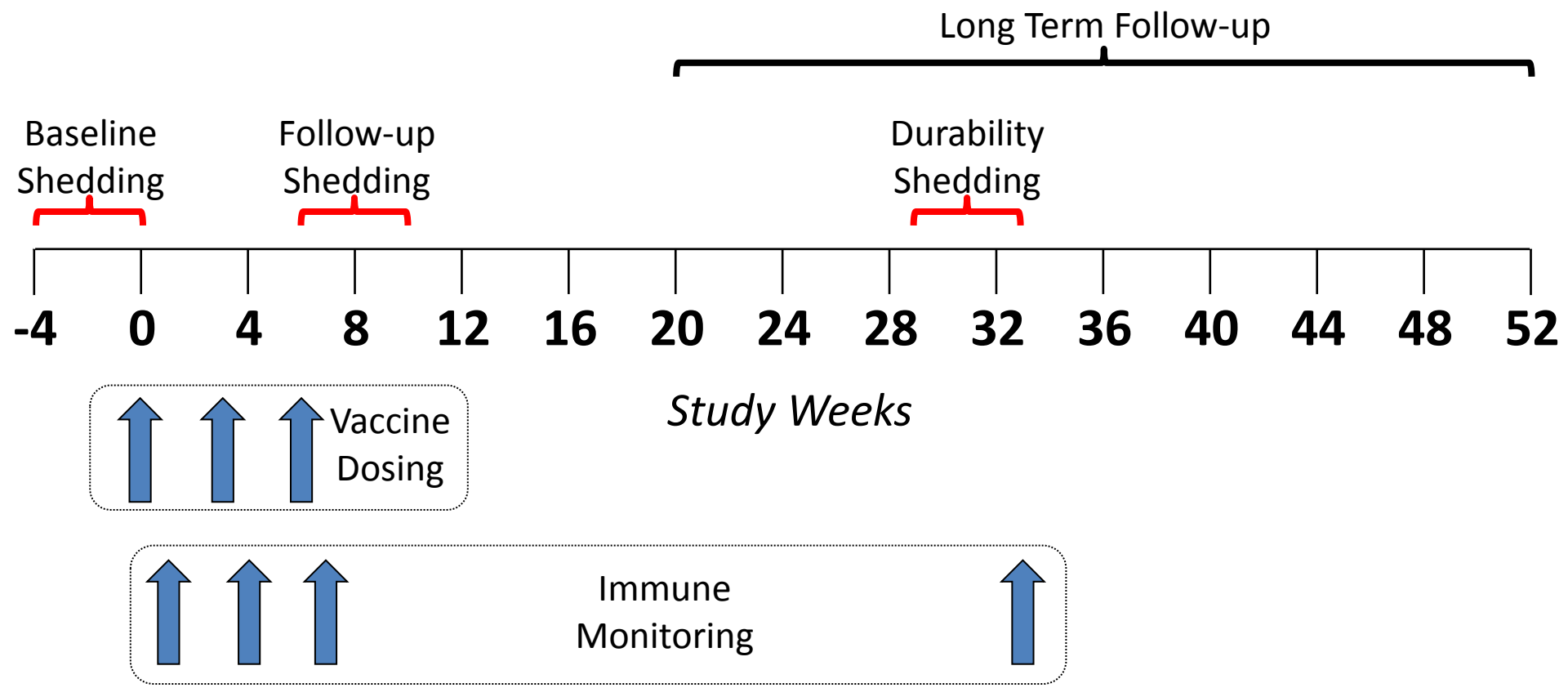
Entry Criteria

- Men and women, ages 18 to 50 years
- Documented genital infection with HSV-2 for > 1 year
- History of 3 to 9 recurrent episodes per year in the absence of antiviral suppression
- General good health

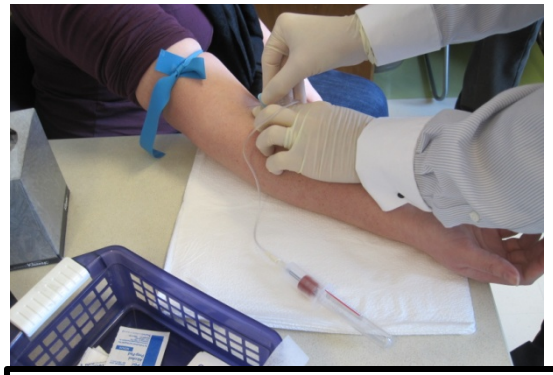
Protocol GEN003-001 Trial Design

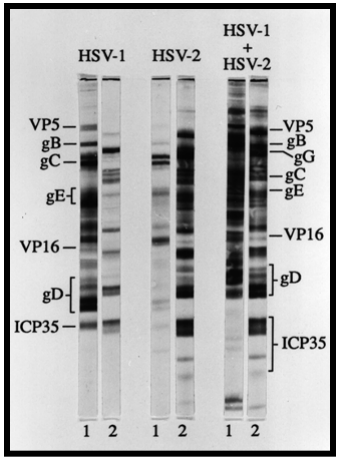
- Double blind, placebo controlled
- 3 Dose Cohorts (10, 30 and 100 µg of each protein)
  - Approximately 50 Subjects per Dose Cohort
  - Within each Dose Cohort, subjects randomized to
    - GEN003 n=30
    - No Adjuvant n=10
    - Placebo n=10
  - Dose of Matrix M2 adjuvant constant for all groups (50 µg)
- Safety monitored by an independent Data Safety Monitoring Board

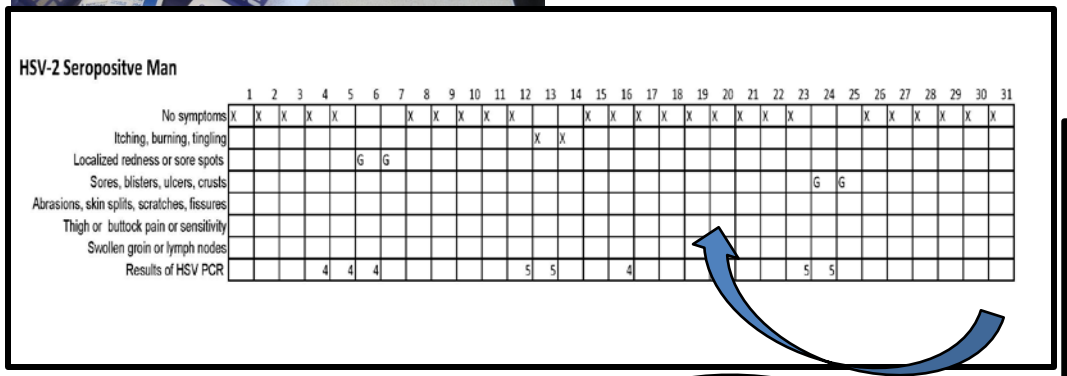
Clinical Trial Schedule of Events

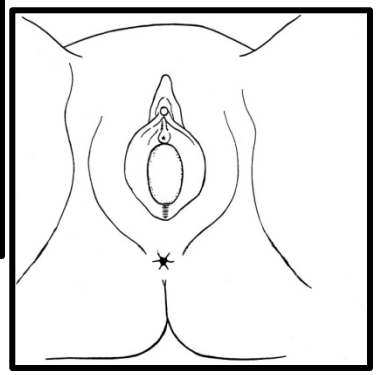


Genital HSV Shedding









HSV DNA PCR

Tronstein et al, JAMA 2011

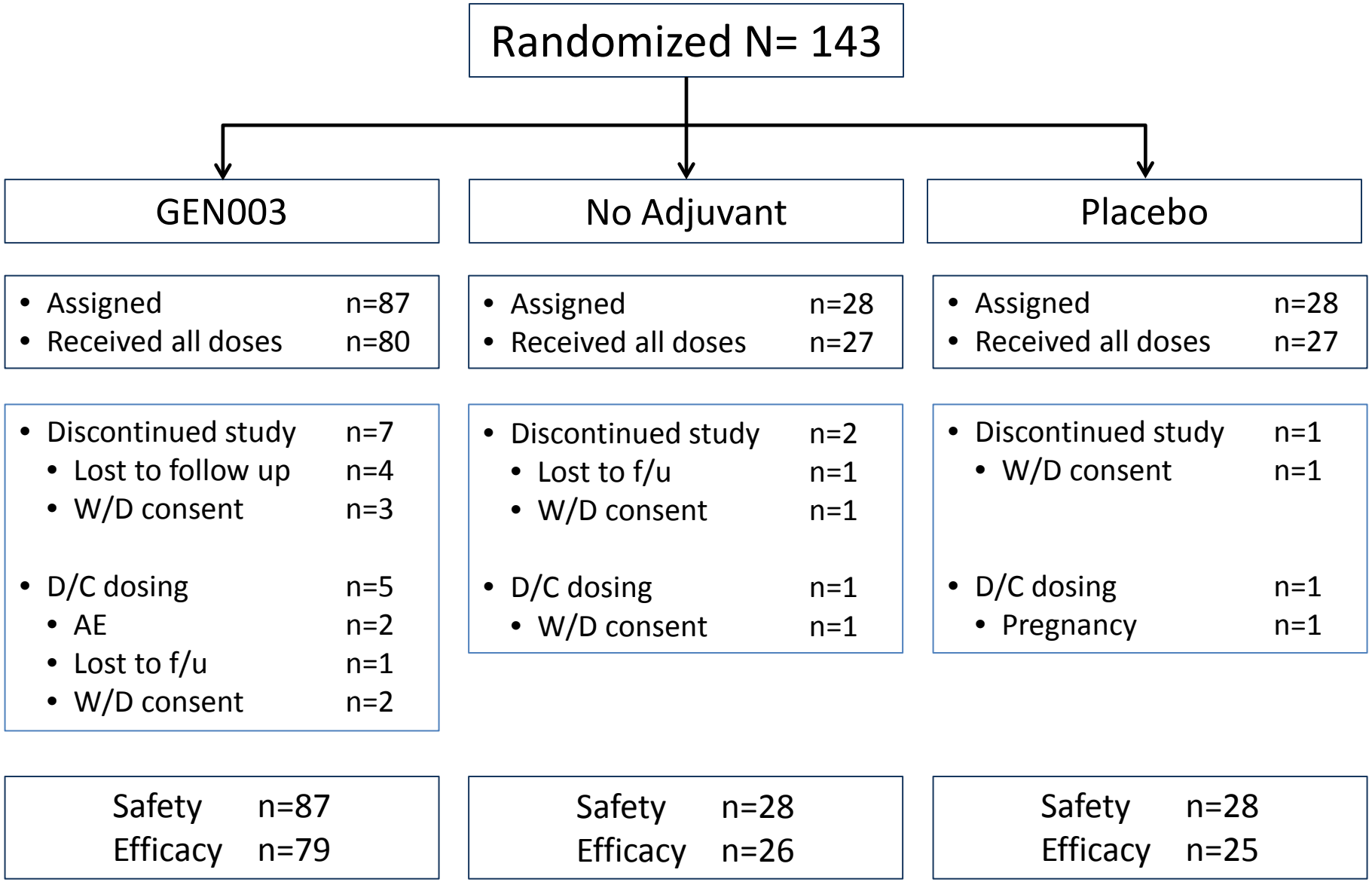
Methods

- Safety
  - Solicited AEs from day of each dose through 7 days
  - All AEs throughout the course of the trial
- Immunologic responses to vaccine proteins
  - **IgG antibody** by ELISA
  - **Neutralizing antibody** by colorimetric assay
  - **Cellular immune responses** by IFN-γ ELISpot
- Virology
  - Genital swabs for HSV-2 DNA collected twice daily for 28 days
  - Change from baseline analyzed by Poisson model

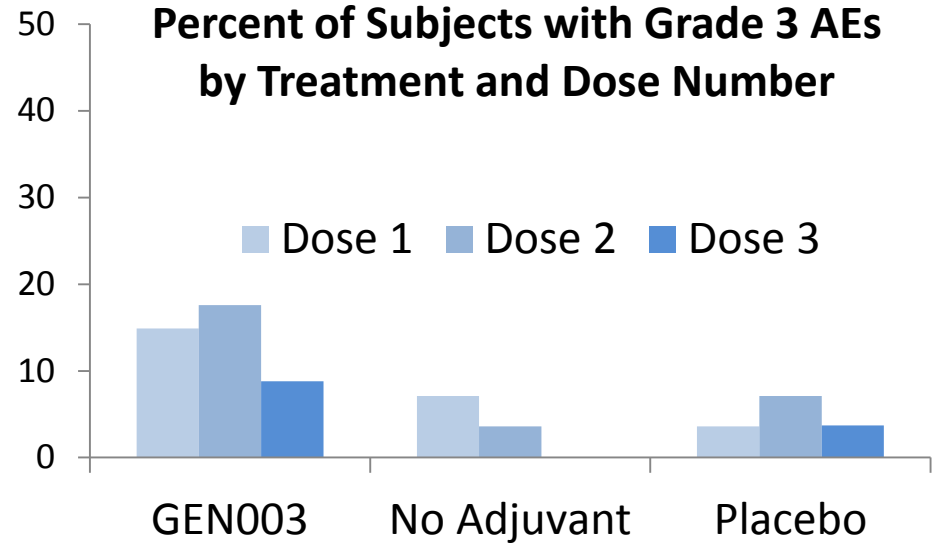
Demographics of Study Participants

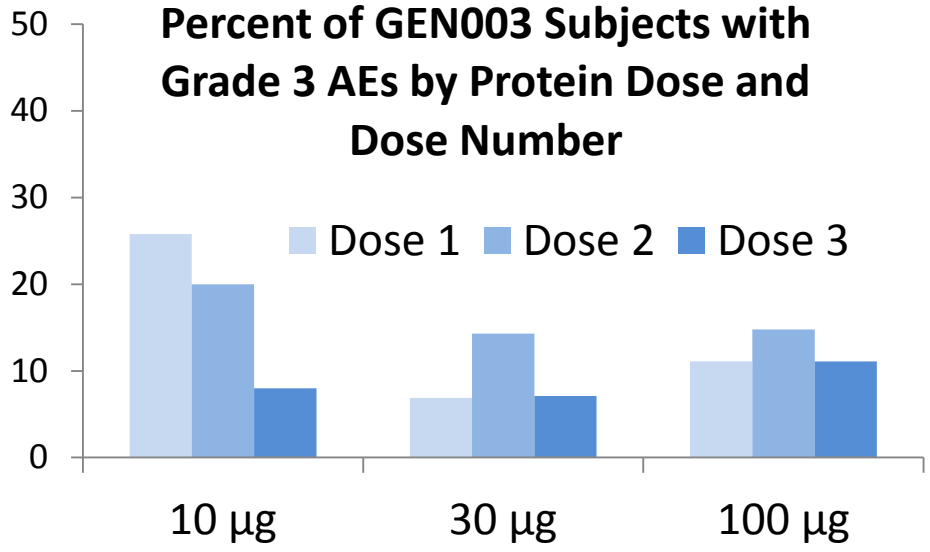
	GEN003 All Doses N=87	No Adjuvant All Doses N=28	Placebo N=28	Total N=143
No. of women (%)	54 (62)	17 (61)	17 (61)	88 (61)
Mean age	37	36	37	37
Race (%): White	56 (64)	15 (54)	17 (61)	88 (61)
Black	23 (26)	8 (29)	10 (36)	41 (29)
Asian	2 (2)	1 (4)	0	3 (2)
Multiracial	4 (5)	3 (11)	1 (4)	8 (6)
Other	2 (2)	1 (4)	1	4 (3)

Participant Disposition



Safety: Grade 3 or 4 AEs Day 0 to Day 7





- Reactogenicity driven by Matrix M2
- Among subjects receiving GEN003, most Grade 3 AEs appeared with earlier doses and lower protein content
- Safety after Day 7: similar among all groups (data not shown)
- 2 Grade 4 AEs: suicide attempt, temp >104, transiently

Number (%) of GEN003 Subjects with Grade 3 or 4 AEs Days 0-7 after Dose 1

	10 µg n=31	30 µg n=29	100 µg n=27	Placebo n=28
Total	8 (26)	2 (7)	3 (11)	1 (4)
Nausea	2 (7)	1 (3)	0	1 (4)
Vomiting	1 (3)	0	0	0
Diarrhea	0	0	0	0
Fatigue	**6 (19)**	**1 (3)**	**2 (7)**	**1 (4)**
Myalgia	**6 (19)**	**1 (3)**	**0**	**0**
Pain	**4 (13)**	**0**	**0**	**0**
Tenderness	**5 (16)**	**1 (3)**	**1 (4)**	**0**
Induration	1 (3)	1 (3)	0	0
Fever	1 (3)	0	1 (3)	0

Viral Shedding by Treatment Group

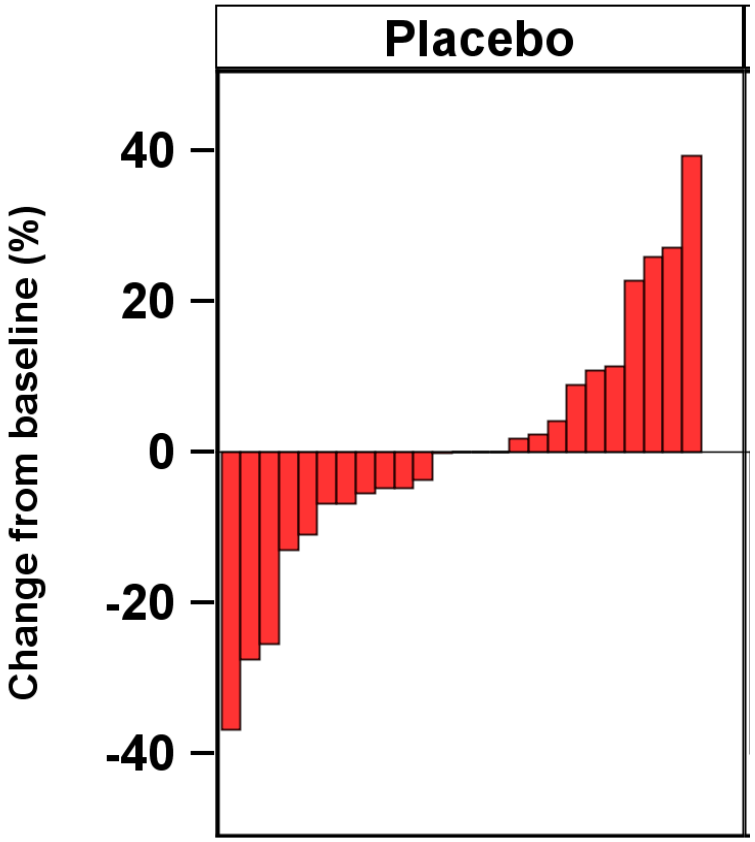
Treatment Group	N	Mean Baseline Rate	Mean Post-Treatment Rate	Mean Relative Change from Baseline	p-value	Reduction, Log HSV-2 DNA copies/mL	% Reduction
Placebo	28	11.8	13.2	12%	0.8	-0.03	7%
Vaccine: No adjuvant	28	7.5	8.8	17%	0.07	-0.01	2%
GEN003 (10 µg)	31	11.5	11.3	-2%	0.75	-0.05	0%
GEN003 (30 µg)	29	**13.5**	**6.6**	-51%	<0.001	-0.33*	41%
GEN003 (100 µg)	27	**14.8**	**10.4**	-30%	<0.001	-0.25†	49%

- Statistically significant reduction in viral shedding
- Reduction in magnitude of viral shedding
- Study not designed to test differences between vaccine doses

*p= 0.01

†p=0.047

Shedding Rate Changes from Baseline by Treatment Arm



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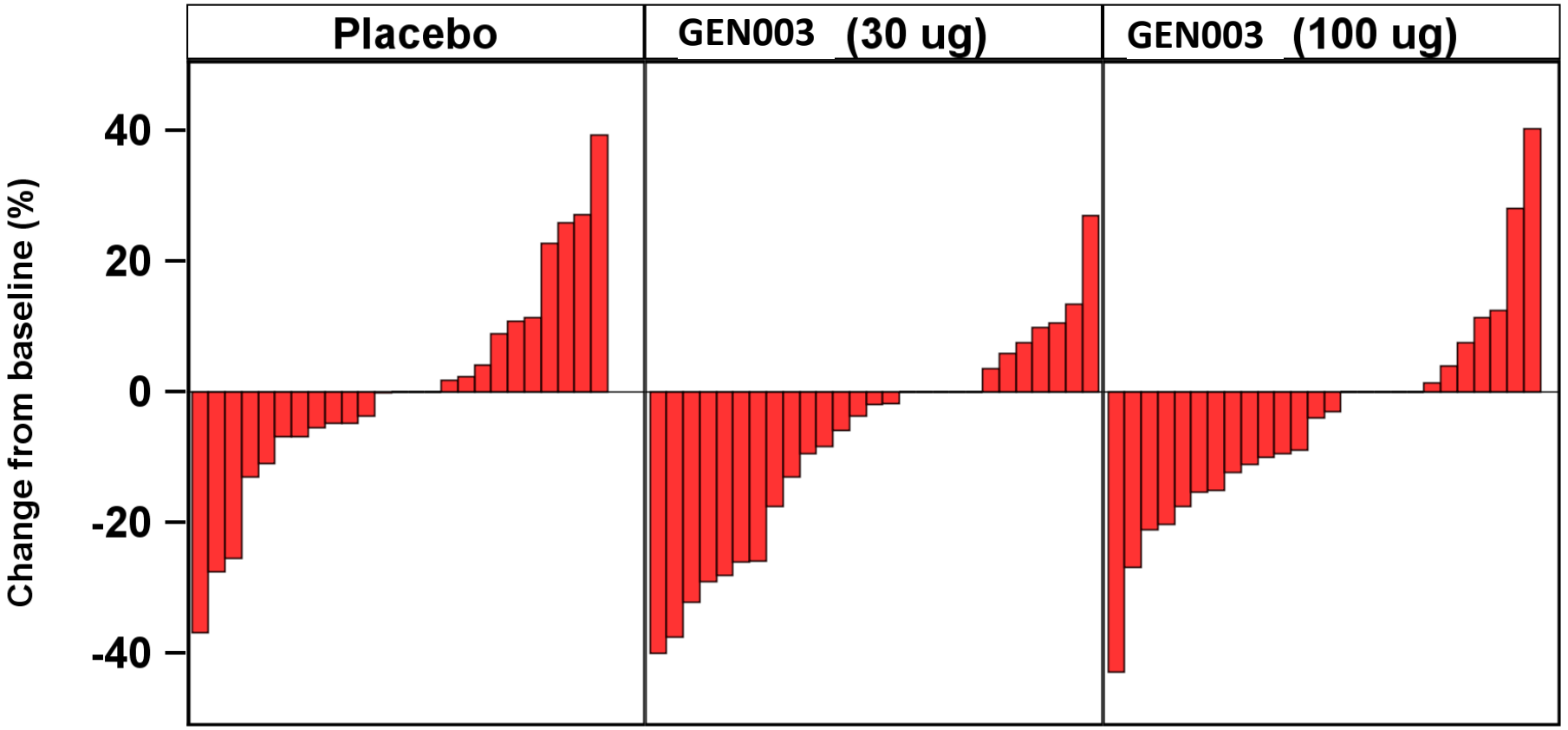
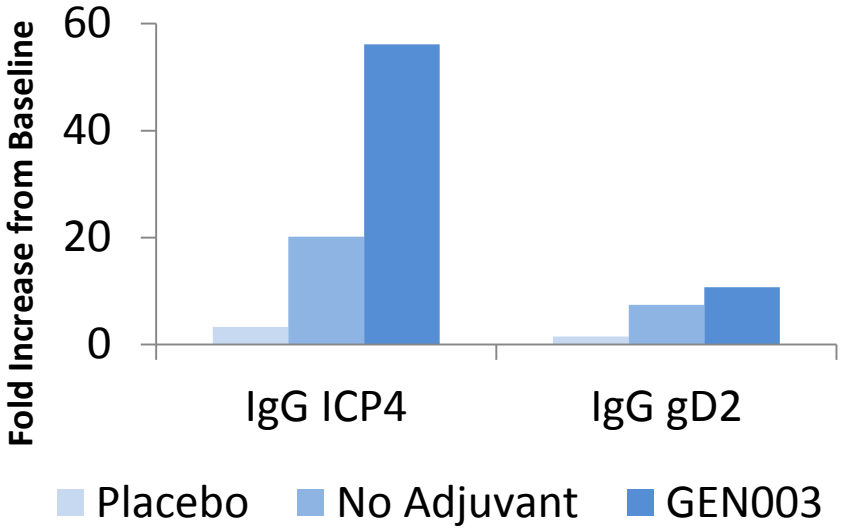


Exploratory Analysis: Time to First Recurrence*

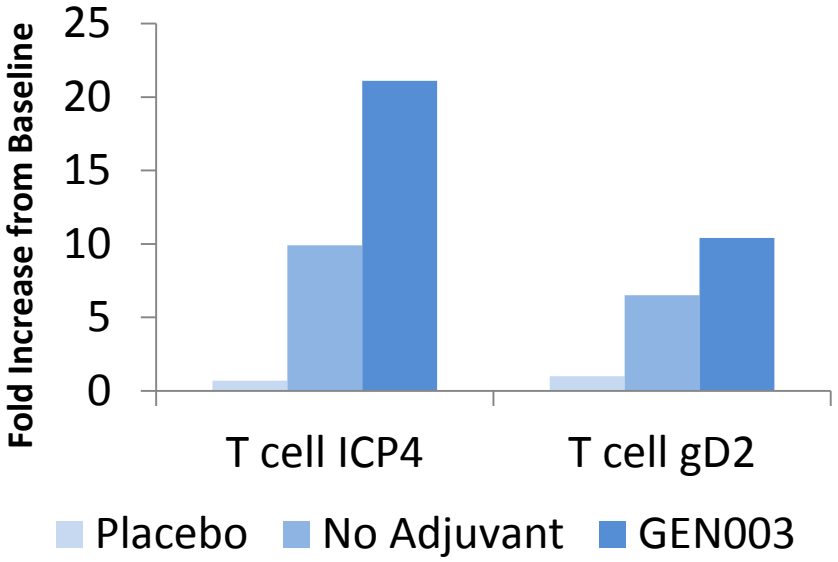
	GEN003 10 µg (n = 31)	GEN003 30 µg (n = 29)	GEN003 100 µg (n = 27)	Placebo (n = 28)
Median days	67	60	Not Reached	45
95% confidence interval	*(23, 152)*	*(20, 92)*	*(92, NR)*	*(18, 93)*

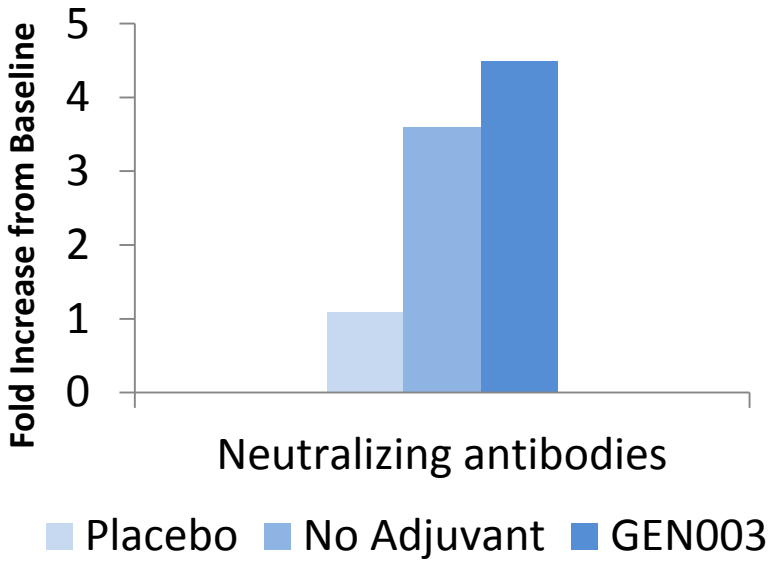
*** Measured from 1st injection**
NR = not reached

Immune Responses



- All measures of immunity increase with immunization
- Matrix M increases responses





Conclusions

- First demonstration of reduced viral shedding by therapeutic vaccine
- Immune responses to both antigens in the vaccine
  - Augmented by Matrix M adjuvant
  - Correlation between immune response and anti-viral effect under investigation
- Safety profile acceptable for intended use as a therapeutic vaccine
- Further studies are planned to optimize dose for maximum clinical and virologic response
- Viral shedding assessment is an efficient approach to measure efficacy of antiviral interventions.

Acknowledgements

- University of Washington
  - Anna Wald MD, MPH
  - Amalia Margaret, PhD
  - Emma Robinson
- Westover Heights Clinic
  - Terri Warren RN, ANP
  - Basak Gokcora
- Indiana University School of Medicine
  - Kenneth Fife MD
  - Elisha Eppes NP
- Clinical Study Center of Texas
  - Stephen Tyring MD
  - Farhan Khan MD, MBA
- Webster Texas
  - Patricia Lee MD
  - Deborah Yetman
- University of Alabama Birmingham
  - Nick Van Wagoner MD
  - Aeryn Peck
- Cincinnati Children's Medical Center
  - David Bernstein MD
  - Tara Foltz RN
- Genocea Biosciences
  - Seth Hetherington MD
  - Jessica Flechtner PhD
  - Alexander Lee
- Rho, Inc. (statistics and database)
  - Karen Kessler, PhD

And the patients who participated in this study.