THERAPEUTIC HSV-2 VACCINE (GEN-003) RESULTS IN DURABLE REDUCTION IN GENITAL LESIONS AT 1 YEAR

Phase 1/2a Clinical Trial: GEN-003-001

Anna Wald, MD, MPH
University of Washington
annawald@u.washington.edu

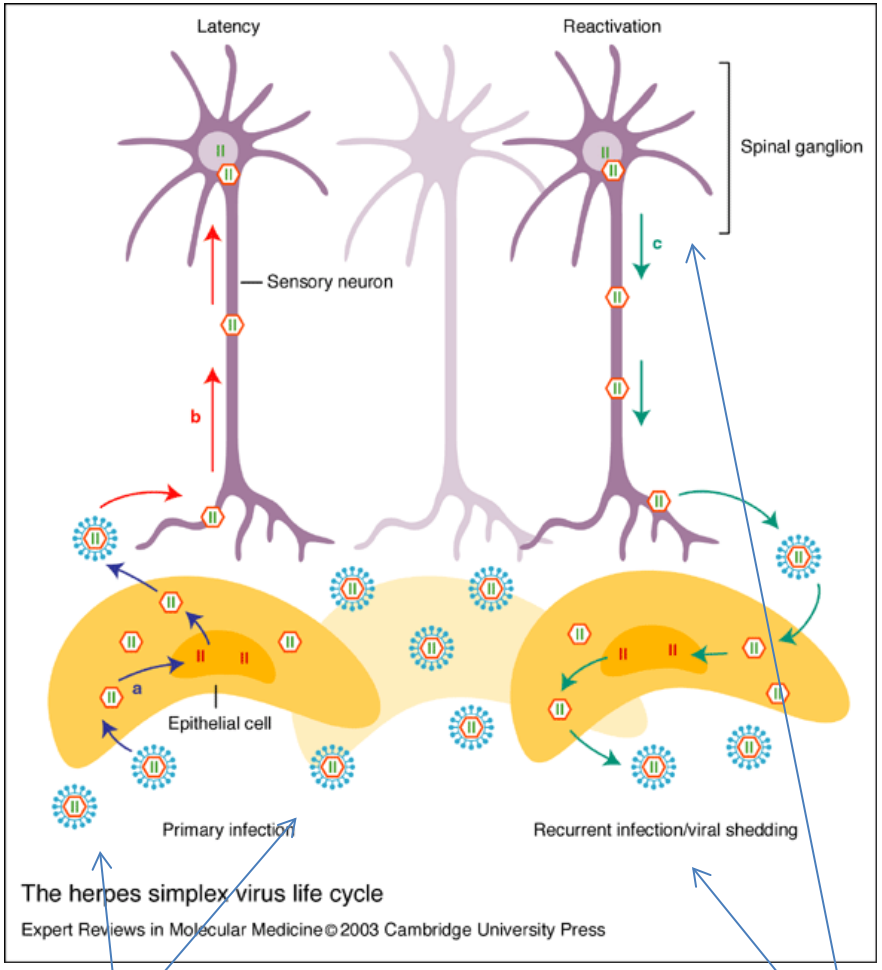
Conflict of interest

- Genocea Biosciences, the developer of GEN-003, provided funding for the trial
- PI at University of Washington for clinical trials with Genocea; also PI for trials with candidate HSV-2 vaccines with Agenus and Vical
- AW is a consultant for Aicuris, Eisai and Amgen

Need for vaccine

- Genital HSV-2 affects 1 in 6 adults in the US between ages of 14 and 49
  - 500 million people worldwide
- Reactivation of latent virus results in
  - Painful genital lesions
  - Viral shedding from genital mucosa, even in the absence of lesions
  - Transmission occurs
- HSV-2 infection fuels the HIV epidemic in subSaharan Africa

The potential of therapeutic HSV vaccine



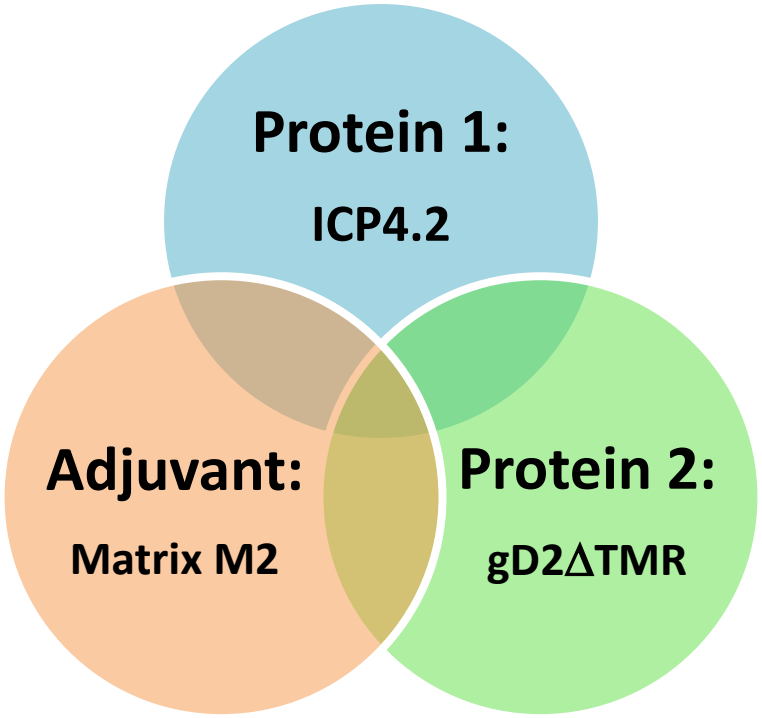
- Both T and B cell immunity are likely needed for immune control and prophylaxis
- Therapeutic vaccines potentially offer :
  - Relief from recurrences
  - Reduction in HSV-2 shedding/risk of transmission
  - Novel mechanism of action

Antibodies[1]

T cells[2,3]

[1]*Muggeridge (2000) J Gen Virol*
[2]*Koelle et al., (1998) JCI*
[3] *Knickelbein et al., (2008) Science*

GEN-003 (Genocea Biosciences): Investigational Therapeutic Vaccine



GEN-003	= ICP4 + gD2 + Matrix M2
"No Adjuvant"	= ICP4 + gD2

- **ICP4: Immediate early protein**
  T cell target identified by ATLAS ™
- **gD2**
  Target of neutralizing antibodies
  T cell target
- **Matrix M2 adjuvant**
  Saponin derived
  Promotes T-cell responses
  Developed by Isconova, now Novavax

- **Preclinical studies** GEN-003:
  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 GEN-003 when administered to HSV-2 seropositive adults

- **Secondary Objectives**

  To evaluate:

  - Effect of GEN-003 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 HSV-2 genital lesions

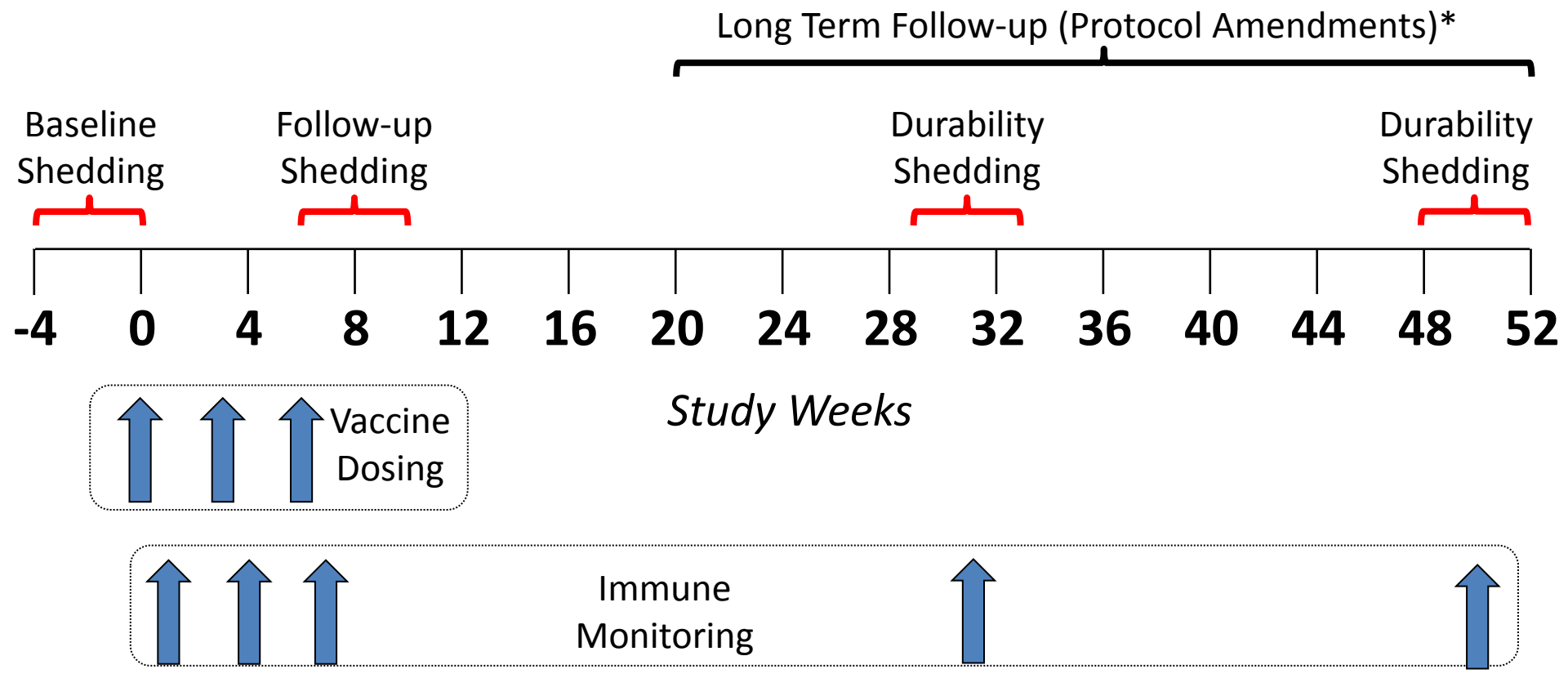
Study Participants

- 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
- Willing to forgo antiviral treatment during HSV-2 shedding assessment periods

Protocol GEN-003-001 Trial Design

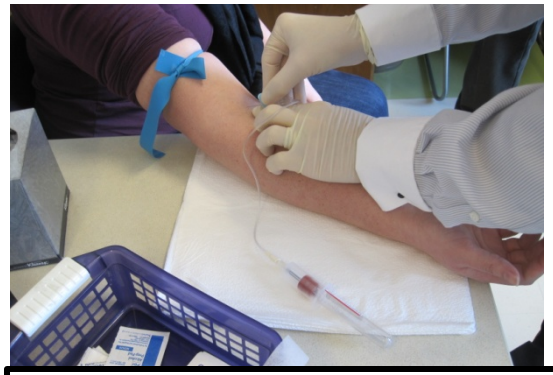
- Double blind, placebo controlled
- 3 dose cohorts (10, 30 and 100 µg of each protein)
  - Approximately 50 subjects per dose cohort
  - Within each dose cohort, subjects randomized to
    - GEN-003 n=30
    - Antigen, No Adjuvant n=10
    - Placebo n=10
  - Dose of Matrix M2 adjuvant constant for all groups (50 µg)
- Safety monitored by an independent Data Safety Monitoring Board
- Protocol later amended to extend follow up for shedding and immunogenicity

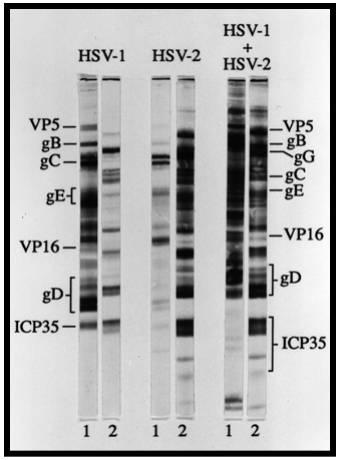
Clinical Trial Schedule of Events

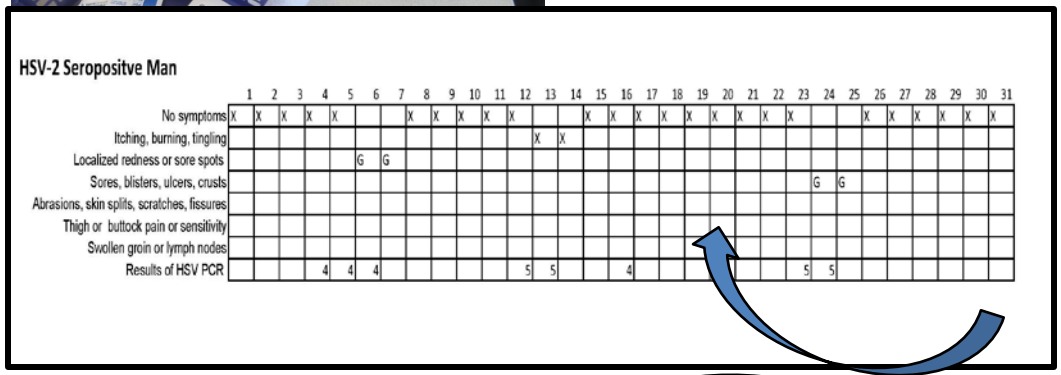


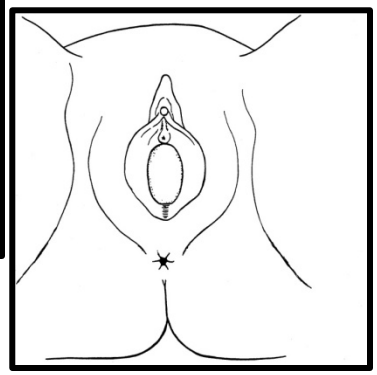
*Initial data was presented at ICAAC 2013. Protocol amended to allow additional data collection at 6 months (all subjects) and 12 months (30 and 100 µg subjects only)

Genital HSV-2 Shedding









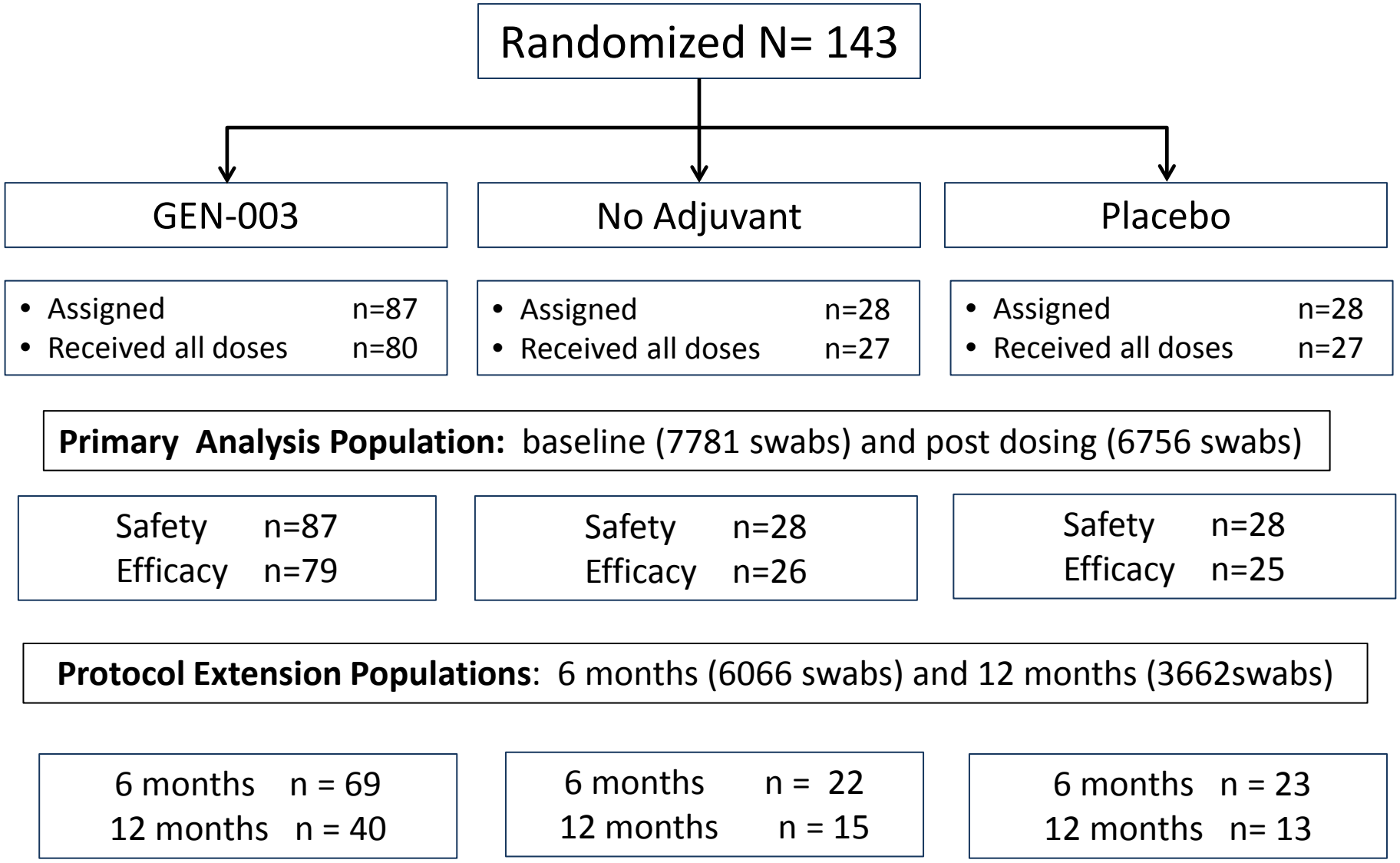
HSV-2 DNA PCR

Tronstein et al, JAMA 2011

Demographics of Study Participants

	GEN-003 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)	4 (3)

Participant Disposition



Viral shedding by treatment group over 1 year

Treatment group	Baseline	2 months			6 months			12 months*	
	Rate	Rate	% change	P	Rate	% change	P	Rate	% change
Placebo	12.4	12.8	3%	0.64	16.6	**34%**	**0.01**	12.3	-1%
Antigen no adjuvant	**7.4**	**10**	**35%**	**0.02**	**8.6**	**16%**	**<0.001**	14.4	95%
GEN-003									
10 µg	10.8	10.8	0%	0.62	**17.3**	**60%**	**<0.001**	ND	
30 µg	**13.4**	**6.4**	**-52%**	**<0.001**	**8.0**	**-40%**	**<0.001**	12.3	-8%
100 µg	**15.0**	**10.3**	**-31%**	**<0.001**	12.4	-17%	0.22	11.1	-26%

Bold indicates P<0.05
Analysis by Poisson mixed effects model,
*12 months dosing model unstable, descriptive statistics only

Lesion rates by treatment group over 1 year

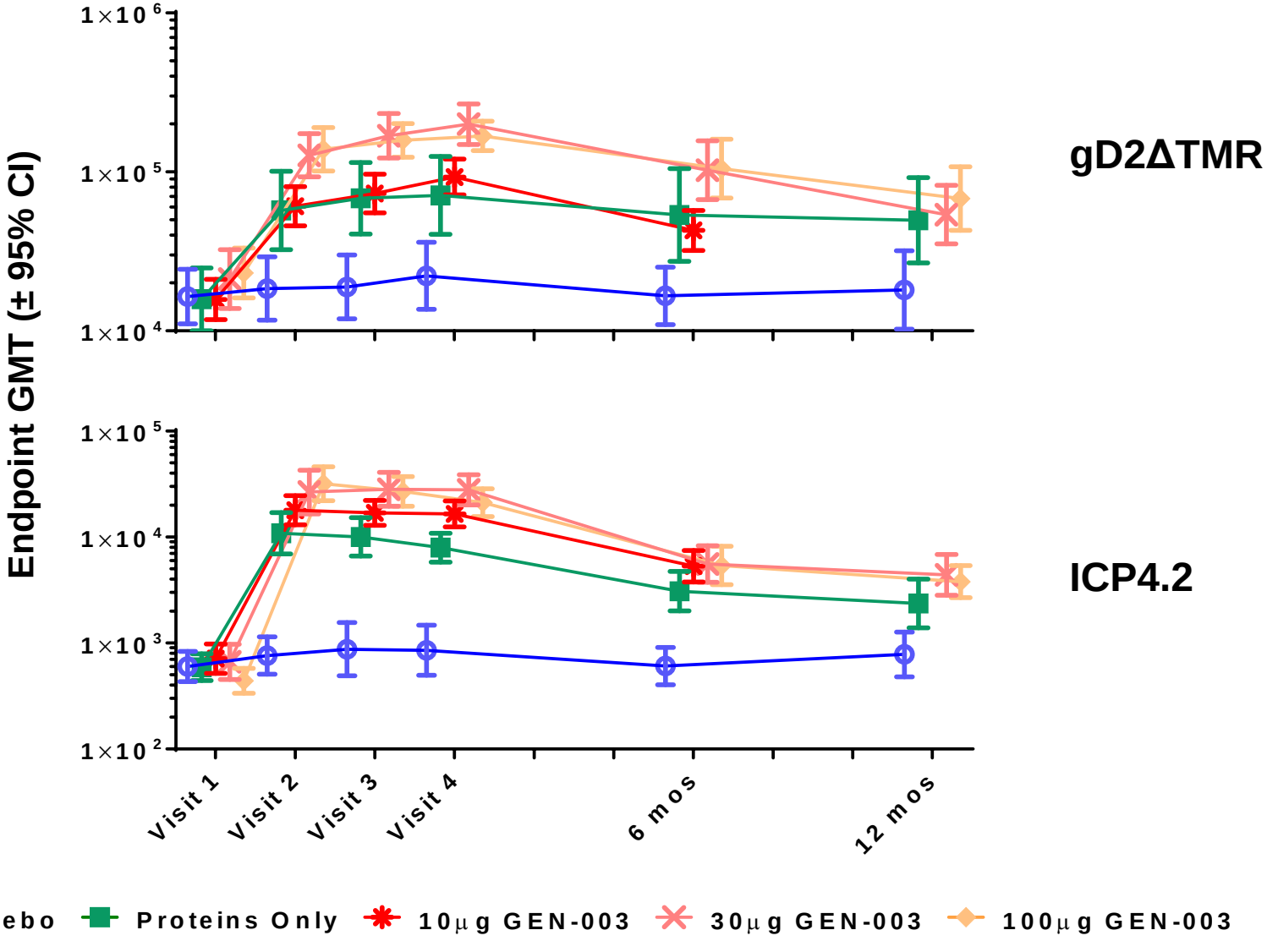
Treatment group	Baseline	2 months			6 months			12 months*	
	Rate	Rate	% change	P	Rate	% change	P	Rate	% change
Placebo	7.2	9.1	26%	0.28	9.2	28%	0.15	4.0	-44%
Antigen no adjuvant	9.5	6.7	-29%	0.67	6.7	-29%	0.42	2.6	-73%
GEN-003									
10 µg	14.7	9.0	-38%	0.09	11.2	-24%	0.53	ND	
30 µg	9.7	**5.0**	**-48%**	**0.001**	**3.4**	**-65%**	**<0.001**	5.6	-42%
100 µg	6.8	**3.7**	**-46%**	**0.009**	4.6	-32%	0.49	5.8	-15%

Bold indicates $p<0.05$

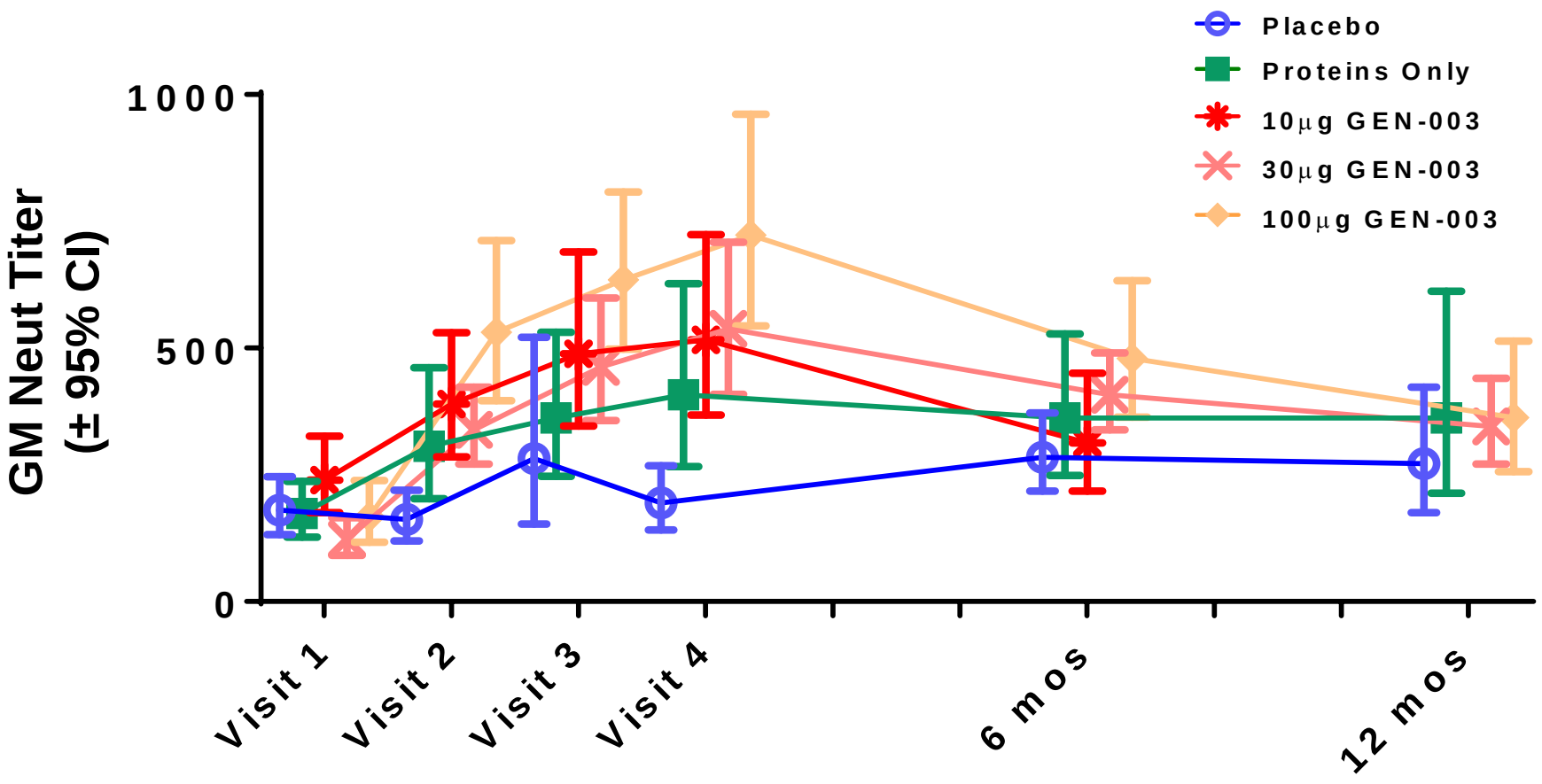
Analysis by Poisson mixed effects model,

*12 months dosing model unstable, descriptive statistics only

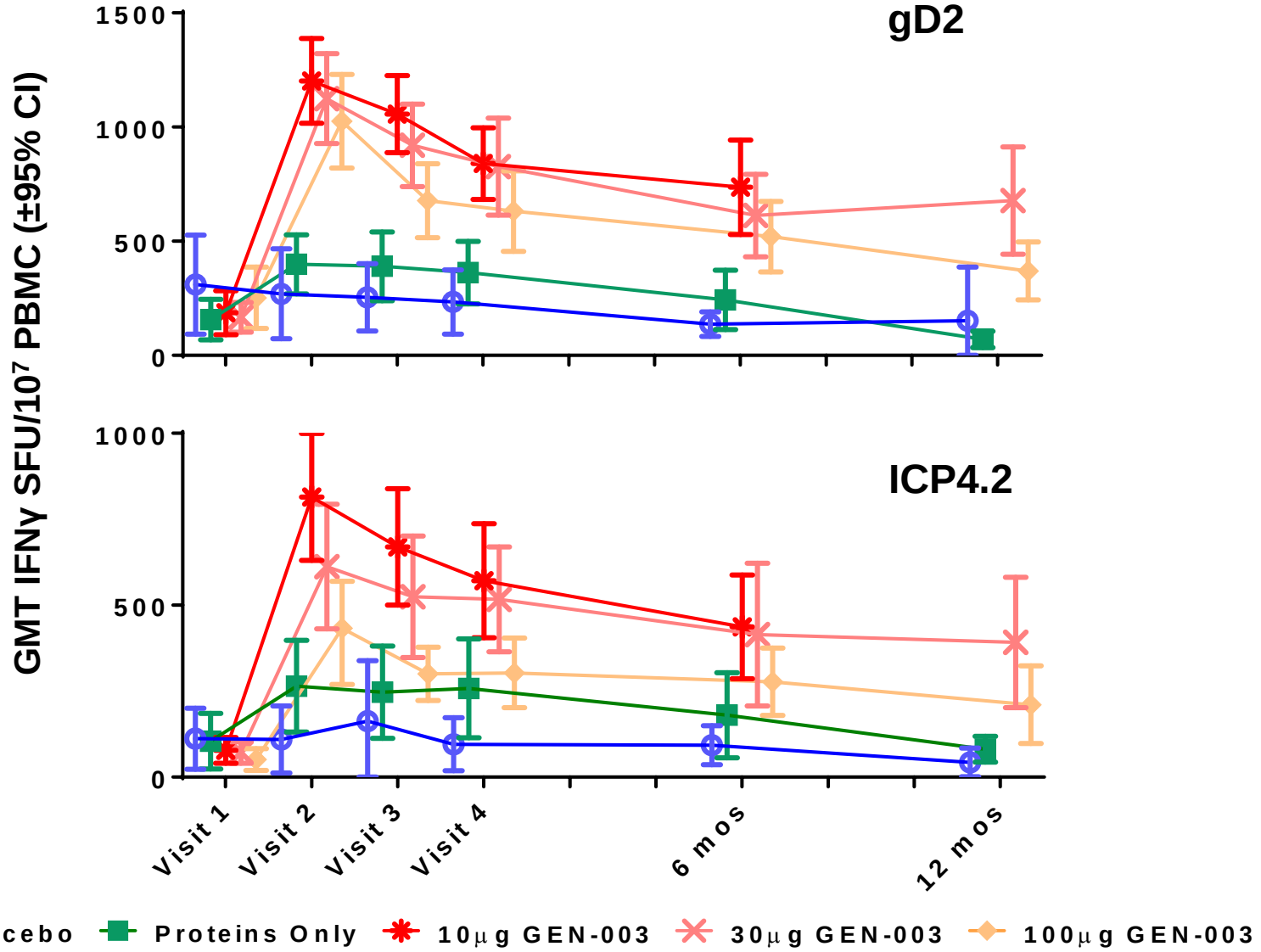
IgG Titers are Dose-Dependent, Durable, with Modest Adjuvant Benefit



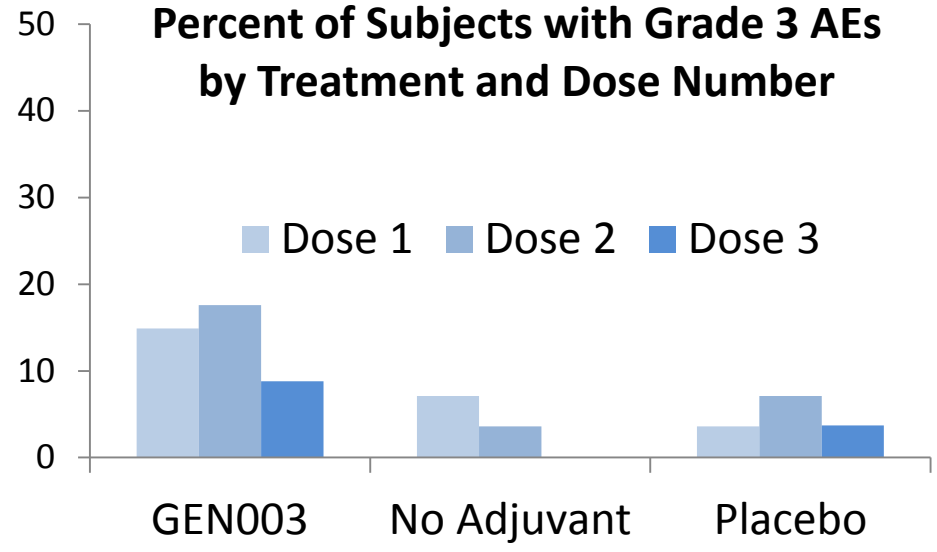
50% Neutralization Titers are Dose-Dependent, Durable, with Modest Adjuvant Benefit

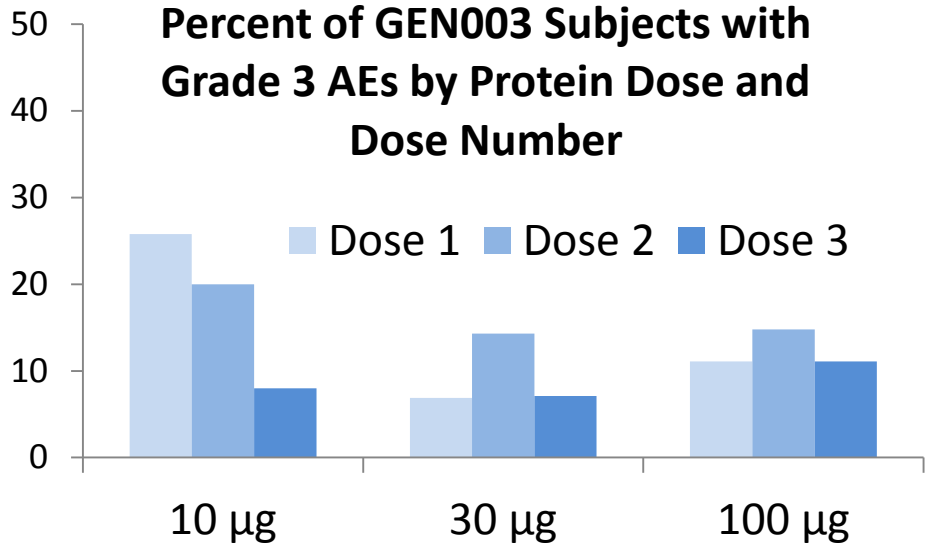


T cell Responses are Durable and Adjuvant-Dependent; Dose Relationship?



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





- Fatigue, myalgia, pain and tenderness most common AE's
- Reactogenicity driven by Matrix M2, higher with lower protein content
- 1 Grade 4 (transient fever to 104^{o} F)
- 3 participants discontinued secondary to reactogenicity

Serious AEs and AEs of Special Interest

- 5 unrelated SAEs
  - Femur fracture
  - Suicide attempt
  - Spontaneous miscarriage
  - Complex migraine
  - Myocardial infarction (d 370)
- No AEs of special interest

Conclusions

- First demonstration of reduced viral shedding by a therapeutic HSV vaccine
- Durable decrease in genital lesions
- Immune responses to both antigens in the vaccine
  - Both neutralizing antibody and T cell
  - Augmented by Matrix M adjuvant, especially T cell response
  - Durable to 12 months
- Safety profile acceptable for intended use as a therapeutic vaccine
- Further studies are planned to optimize dose for maximum clinical and virologic response

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