GEN-003, a Genital Herpes Immunotherapy, Showed Significant Reduction in Viral Shedding and Lesion Rates in a Phase 2b Study Interim Analysis

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Abstract

Background: GEN-003 is an investigational genital herpes immunotherapy containing gD2ΔTMR, a primary target antigen for neutralizing antibodies and T cells, ICP4.2, an HSV-2 T cell antigen selected through human T cells screens, and Matrix-M2™, a saponin-based adjuvant.

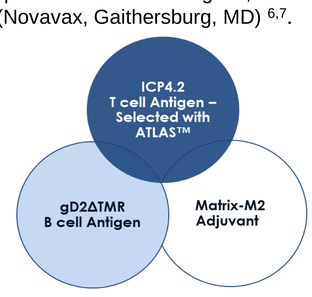
Methods: Healthy individuals, age 18-50 years, with 3-9 HSV-2 genital herpes outbreaks annually were randomized to three groups: placebo, or 60 µg of each antigen combined with either 50 µg (60/50 group) or 75 µg (60/75 group) of adjuvant, administered 3 times 21 days apart. Endpoints included safety, immunogenicity, HSV-2 shedding frequency, genital herpes lesion rate and recurrence-free rate at 6 and 12 months. Viral shedding was measured from participant-collected swabs using a quantitative PCR assay.

Results: 131 participants were enrolled. In the 28-day period following the last dose, viral shedding was reduced by 40% and 27% among the 60/50 and 60/75 dose recipients, respectively, compared to a 5% increase in placebo group. Six months after the last dose, median genital herpes lesion rates were significantly lower in the 60/50 and 60/75 dose recipients (2.7% and 1.9%, respectively) versus placebo (5.6%, P<0.05). Median recurrence frequency was lowest in the 60/50 group (1.0 recurrence/6 months) compared to placebo (2.0) and 60/75 (1.5). The median average duration of recurrences among 60/50 recipients (2.8 days) was lower than that among placebo recipients (4.2 days). The most commonly reported adverse events (AEs) following GEN-003 were injection site pain/tenderness (97%), fatigue (82%), headache (82%) and myalgia (80%). No vaccine-related serious AEs, autoimmune events or other adverse events of special interest were reported.

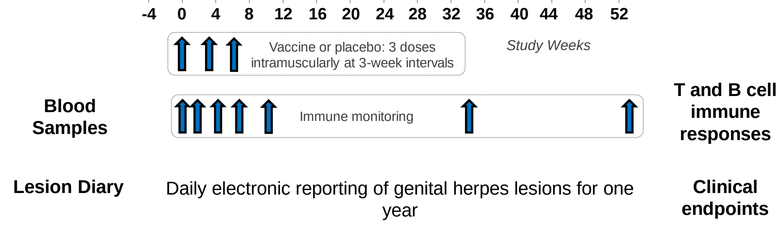
Conclusions: Three doses of GEN-003 significantly reduced viral shedding, lesion rates, frequency and duration of recurrences among participants with frequently recurrent genital herpes. Local and systemic symptoms were common in GEN-003 recipients, but 3-dose compliance was high, and no safety issues were identified during the study.

Introduction

- Genital herpes, which is characterized by recurrent painful ulcers, is primarily caused by HSV-2 and affects more than 500 million people worldwide [1].
- HSV-2 infection increases the risk of HIV-1 transmission [2] and causes severe disease in infants and in immunocompromised individuals [3].
- Prior attempts to develop prophylactic and therapeutic HSV-2 vaccines have failed.
- The effective control of primary and recurrent HSV-2 disease is likely to require T and B cell immunity [4,5].
- GEN-003 is a candidate subunit vaccine comprised of two viral antigens, ICP4.2 and gD2ΔTMR, and the adjuvant Matrix-M2 (Novavax, Gaithersburg, MD) [6,7].
  - ICP4.2 is an internal fragment of HSV-2 immediate early protein ICP4 and was identified as a target T cell antigen by Genocea Biosciences' ATLAS™ screening platform.
  - gD2ΔTMR is HSV-2 gD lacking the transmembrane domain and is a T and B cell antigen.



GEN-003-003 Study Design



- **Study population:**
  - Immunocompetent adults 18-50 years of age with HSV-2 genital herpes and a history of 3-9 recurrences/year
  - Not receiving suppressive antiviral therapy for genital herpes
- **Safety monitoring**:
  - Solicited adverse events (AEs) for 7 days after each dose; Unsolicited AEs through Day 71; Serious AEs and AEs of special interest until study end

Methods

- Randomized, double-blind, placebo-controlled, dose-escalation study
- Three treatment groups:
  - 60 µg of each HSV-2 antigen + 50 µg of Matrix-M2 (60/50 group)
  - 60 µg of each HSV-2 antigen + 75 µg of Matrix-M2 (60/75 group)
  - Placebo
- **Endpoints:**
  - **Safety and tolerability**
  - **Virologic:**
    - Shedding rate (% of days on which HSV-2 DNA is detected in genital samples)
  - **Clinical:**
    - Lesion rate (% of days on which genital herpes lesions are present)
    - Recurrence rate
    - Duration of recurrences
    - % of subjects recurrence free at 6 and 12 months
- **Immunogenicity** *(Immunogenicity data presented in Poster 8.04)*

Table 1: Demographic and Baseline Characteristics

Variable	60/50	60/75	Placebo	Total
Age (years)				
n	43	44	44	131
Mean	38.4	35.5	36.0	36.6
Median	38.0	34.0	35.5	35.0
Sex				
Male	15 (34.9%)	16 (36.4%)	21 (47.7%)	52 (39.7%)
Female	28 (65.1%)	28 (63.6%)	23 (52.3%)	79 (60.3%)
Race				
American Indian or Alaska Native	0 (0%)	0 (0%)	1 (2.3%)	1 (0.8%)
Asian	2 (4.7%)	0 (0%)	2 (4.5%)	4 (3.1%)
Black	9 (20.9%)	14 (31.8%)	7 (15.9%)	30 (22.9%)
Hawaiian or Pacific Islander	0 (0%)	0 (0%)	1 (2.3%)	1 (0.8%)
White	32 (74.4%)	29 (65.5%)	32 (72.7%)	93 (71.0%)
Other	0 (0%)	1 (2.3%)	1 (2.3%)	2 (1.5%)
Ethnicity				
Hispanic or Latino	5 (11.6%)	6 (13.6%)	5 (11.4%)	16 (12.2%)
Not Hispanic or Latino	38 (88.4%)	38 (86.4%)	39 (88.6%)	115 (87.8%)
HSV-1 Serostatus				
Positive	17 (39.5)	15 (34.1)	16 (36.4%)	48 (36.6%)
Negative	26 (60.5)	29 (65.9)	28 (63.6%)	83 (63.4)

Solicited Local and Systemic Grade 3 Events by Treatment Group

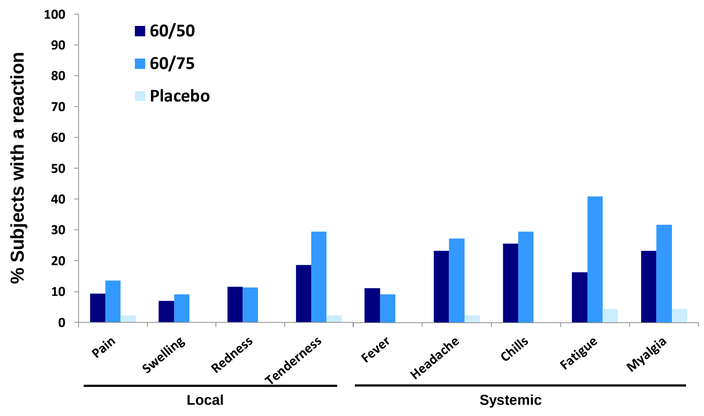


Figure 1. Percent of subjects reporting a Grade 3 solicited local or systemic reaction. Subjects reporting the same event more than once are counted only one time.

Safety

- 7 serious AEs were reported in 5 subjects. None were considered to be treatment-related by the investigator; one death, attributed to an accidental drug overdose, was reported.
- No autoimmune diseases or other AEs of special interest were reported.
- Five subjects discontinued dosing for safety reasons: 2 in each active group and 1 in the placebo group.

Reduction in Viral Shedding Immediately after Dose 3

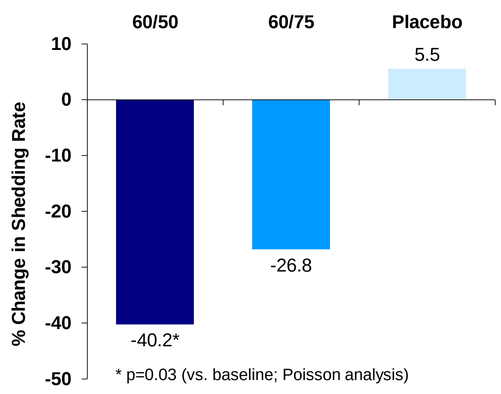
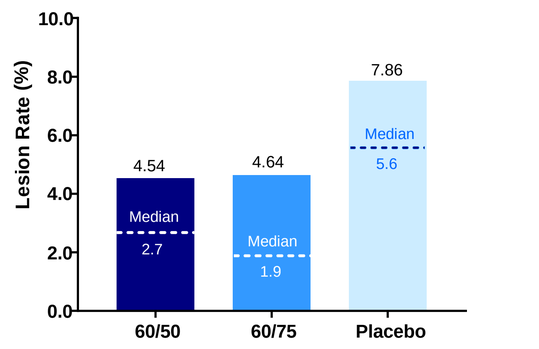


Figure 2. Change from baseline in HSV-2 shedding rates by treatment group. Shedding was evaluated by quantitative PCR analysis of anogenital swabs collected twice daily 28-days before dosing and during the 28-day period immediately after Dose 3. Then mean absolute change in shedding rate from baseline is shown.

(Additional HSV-2 shedding data presented in Poster 8.31)

Genital Herpes Lesion Rate Reduction in the 6 Month Period after the Last Dose

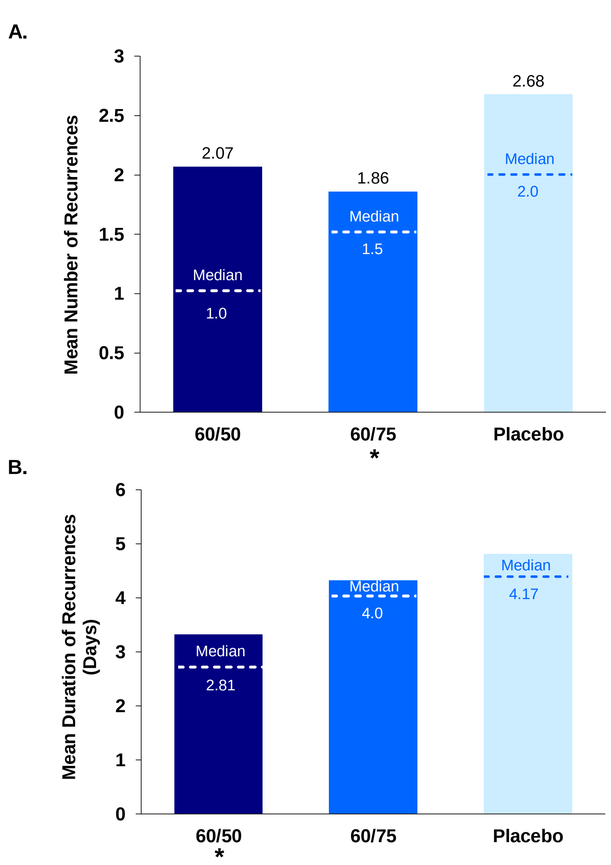


Treatment group	60/50	60/75
Reduction vs. placebo in mean lesion rate	42%	41%
Reduction vs. placebo in median lesion rate	52%*	66%*

* p<0.05 (Wilcoxon Rank Sum test vs. placebo)

Figure 3. Genital herpes lesion rate by treatment group. Bars depict mean lesion rates; median lesion rates are shown by the dotted white lines.

Reduction in Number and Duration of Genital Herpes Recurrences in the 6 Month Period after the Last Dose



* p<0.05 (Wilcoxon rank sum test vs. placebo)

Figure 4. Number and Duration of Recurrences. Mean and median number **(A)** and duration **(B)** of genital herpes recurrences over the 6 months following the last GEN-003 dose. For duration, subjects with no recurrences were excluded from the analysis. Bars depict the means and the dotted lines depict the medians.

Absolute Change from Baseline in Genital Herpes Lesion Rates

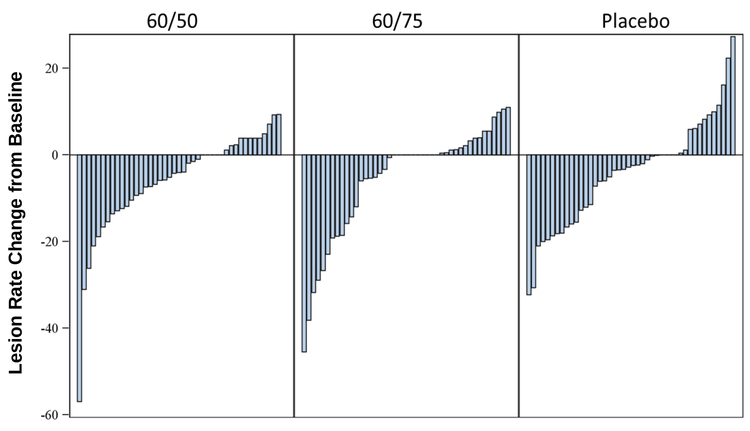


Figure 5. Waterfall plots of the absolute change from baseline in genital herpes lesion rates. Data shown are for 6 months following the first GEN-003 vaccination. Bars represents individual subjects, and the baseline lesion rate for each subject is set at 0. Bars extending above and below the line indicate genital herpes lesion rates higher or lower than baseline, respectively. The length of the bars depicts the magnitude of the change from baseline.

Time to First Recurrence After the First Dose of GEN-003

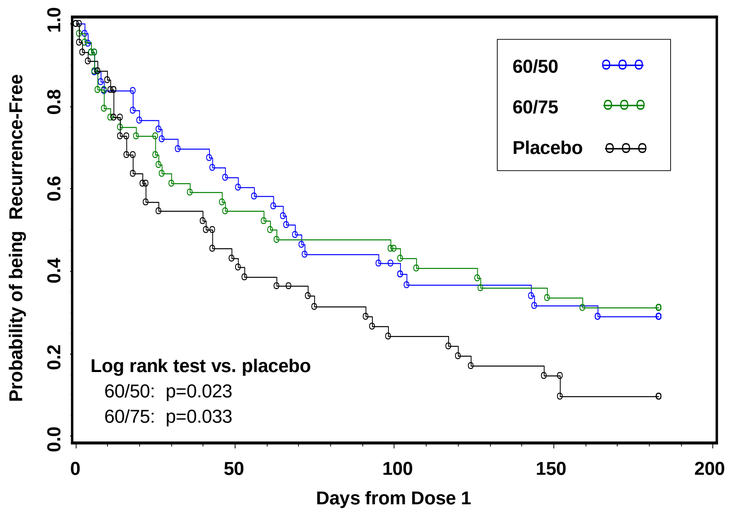


Figure 6. Probability of being genital herpes recurrence-free following the first dose of GEN-003. The probability of being recurrence-free is depicted for 6 months following the first dose of GEN-003.

Conclusions

- **GEN-003 reduces the rate of genital HSV-2 shedding following vaccination in people with recurrent genital herpes.**
  - The 60/50 dose appears more effective than the 60/75 dose in reducing the HSV-2 shedding rate.
  - The shedding rate reduction for the 60/50 dose is similar to that observed in previous GEN-003 clinical trials [8,9].
- **The 60/50 and 60/75 doses of GEN-003 have similar efficacy against recurrent HSV-2 disease.**
  - Lesion rate: Median reductions 52-66%
  - Recurrence frequency: Median reduction up to 50%
  - Duration of recurrences: Median reduction of 33%
- **GEN-003 has an acceptable safety and reactogenicity profile:**
  - Local and general reactions to GEN-003 are common.
  - The frequency of solicited systemic reactions appears to be adjuvant dose-related.
  - No vaccine-related serious adverse events or adverse events of special interest have been reported in this or prior GEN-003 clinical trials.
  - Few study discontinuations were caused by an adverse event.
- **Based on these results, the 60/50 dose of GEN-003 has been selected for further development.**

References

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Acknowledgments

The authors wish to thank the study participants and study personnel who made this trial possible. This work was funded by Genocea Biosciences, Inc.