Poster 1023

Sustained Lesion and Shedding Rate Reductions in Genital Herpes Patients 24 Months after Immunization with GEN-003, a Genital Herpes Immunotherapy

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ABSTRACT

Background: Herpes simplex viruses (HSVs) are the main cause of genital ulcers worldwide. GEN-003 is an investigational genital herpes immunotherapy composed of HSV-2 antigens gD2ΔTMR and ICP4.2, and the saponin-based adjuvant Matrix-M2TM (MM2). In a Phase 2 dose-ranging study (GEN-003-002), 3 doses of GEN-003 reduced HSV-2 lesion rate (percent of days with genital lesions) and anogenital HSV-2 shedding rate (percent of days with detectable virus). The antiviral effect of GEN-003 persisted to 12 months after the 3-dose vaccination regimen. We report here the results of an extension study to evaluate efficacy and immunogenicity of GEN-003 at 24 months post-vaccination.

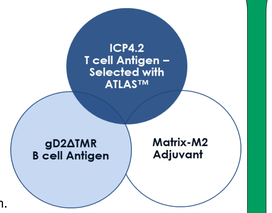
Methods: GEN-003-002 subjects who received at least 1 dose of GEN-003 (dose groups: 30 or 60 µg of antigens combined with 25, 50 or 75 µg of MM2) were eligible to enroll in the extension study. At 24 months post-vaccination, anogenital swabs were collected twice daily for 28 days for HSV-2 DNA detection by quantitative PCR. During this period, subjects also reported genital herpes lesion data via a daily reporting tool. Blood samples were collected at the end of the swab collection period to evaluate humoral and cellular immune responses. HSV-2 immunoglobulin G (IgG) was measured by ELISA, and HSV-2 neutralizing antibodies were measured by a colorimetric assay. Cellular responses were evaluated in peripheral blood mononuclear cells using an interferon-γ/granzyme B Fluorospot assay.

Results: 140 subjects were enrolled. At 24 months, those in the two best-performing GEN-003-002 study groups, 60 µg antigens combined with either 50 or 75 µg MM2 (60/50 and 60/75, respectively), recorded decreased mean viral shedding rates of 58% and 69% below baseline, similar to the 12-month shedding rate reductions, and mean anogenital lesion rates of 77% and 39% below baseline, respectively. In all dose groups, mean IgG titers to ICP4.2 and gD2ΔTMR and mean neutralizing antibody titers were sustained from 12 to 24 months. In addition, cellular immune responses were stable from month 12 to month 24.

Conclusions: GEN-003 induces reductions in HSV-2 shedding and genital herpes lesion rates that persist to 24 months following treatment. Humoral immune responses to GEN-003 are maintained at 24 months after immunization.

INTRODUCTION

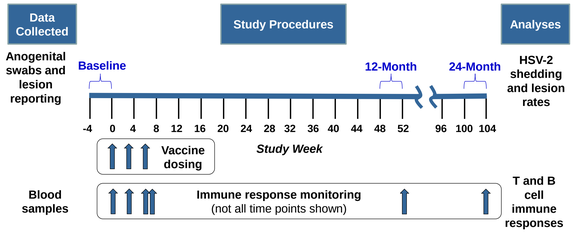
- Genital herpes, which is most commonly cause by HSV-2, affects more than 500 million people worldwide[1].
- Prevention and control of primary and recurrent HSV-2 disease is believed to require T and B cell immunity[2,3].
- Prior attempts to develop prophylactic and therapeutic genital herpes vaccines have failed.
- GEN-003 is a candidate therapeutic vaccine for genital herpes. It contains two HSV-2 antigens, ICP4.2 and gD2ΔTMR, and Matrix-M2 adjuvant (Novavax, Gaithersburg, MD)[4,5].
  - ICP4.2 was identified as a T cell antigen by Genocea Biosciences' ATLAS™ screening platform.
  - gD2ΔTMR is a T and B cell antigen.
- In study GEN-003-002, 3 doses of GEN-003 reduced the % of days with genital lesions (lesion rate) and the % of days with HSV-2 shedding (shedding rate) through 12 months following vaccination.



GEN-003 candidate therapeutic genital herpes vaccine

Here we report the results of an extension study to evaluate GEN-003 efficacy and immunogenicity at 24 months following vaccination.

GEN-003-002 and GEN-003-002b STUDY DESIGNS



GEN-003-002 (parent study) was a 12-mo randomized, blinded study:

- *Population:* Adults ≥18 years with 3-9 HSV-2 recurrences/year (N=310; 44-45/group)
- *Dose regimen:* 3 intramuscular doses of GEN-003 at 21 day intervals
- *Data collection:* Genital herpes lesion reporting, anogenital swabs for HSV-2 shedding and blood for immune response assessment

GEN-003-002b: We evaluated the durability of shedding and lesion rate reductions at 24 months following GEN-003 administration

METHODS

Subjects: Subjects who completed the parent study, GEN-003-002, and had received at least 1 dose of GEN-003 were eligible. The GEN-003-002b study groups are:

Study Groups	N	Dose of antigens	Dose of adjuvant
30/25	24	30 µg	25 µg
30/50	25	30 µg	50 µg
30/75	20	30 µg	75 µg
60/25	25	60 µg	25 µg
60/50	21	60 µg	50 µg
60/75	25	60 µg	75 µg

Procedures:

- Conducted at 17 centers in the US.
- Anogenital swabs were collected twice daily for 28 days at 24 months after last vaccine dose and tested for HSV-2 DNA by a quantitative PCR assay.
- During the anogenital swab collection period, subjects also reported the presence or absence of genital herpes lesions using a daily reporting tool.
- Blood was collected at Day 1 (pre-vaccination) and at various post-vaccination time points including Week 7 (1-week post-dose 3), Week 10 (4 weeks post-dose 3), Month 12 and Month 24 to evaluate humoral and cellular immune responses:
  - Humoral: HSV-2 IgG (ELISA) and HSV-2 neutralizing antibodies (colorimetric assay)
  - Cellular: HSV-2-specific CD4 and CD8 T cells (interferon-γ/granzyme B fluorospot assay)

Genital Herpes Lesion Rate

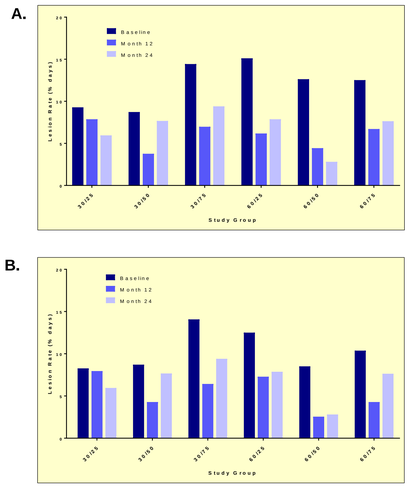


Figure 1. Lesion rate is defined as the number of days with lesions divided by the number of days in the reporting period. Bars depict mean lesion rates for each GEN-003 dose combination at Baseline (pre-vaccination), and at 12 and 24 months following the last dose. **A.** Analysis includes Baseline and 12-month data from subjects enrolled in the parent study (GEN-003-002; N=36-45). **B.** Analysis includes only subjects who continued in the follow-up study, GEN-003-002b (N=19-25). [In both **A.** and **B.**, 24-month data is from GEN-003-002b.]

Genital Herpes Shedding Rate

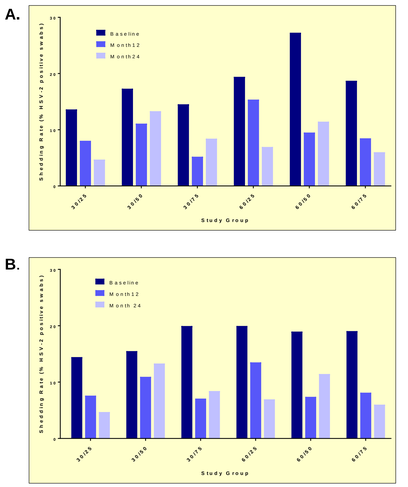


Figure 2. Shedding rate is defined as the number of HSV-2 positive anogenital swabs divided by the total number of swabs collected. Bars depict mean shedding rates for each GEN-003 dose combination at Baseline (pre-vaccination), and at 12 and 24 months following the last dose. **A.** Analysis includes Baseline and 12-month data from subjects enrolled in the parent study (GEN-003-002; N=34-45). **B.** Analysis includes only subjects who continued in the follow-up study, GEN-003-002b (N=19-25). [In both **A.** and **B.**, 24-month data is from GEN-003-002b.]

Change from Baseline in Lesion and Shedding Rates at Month 24

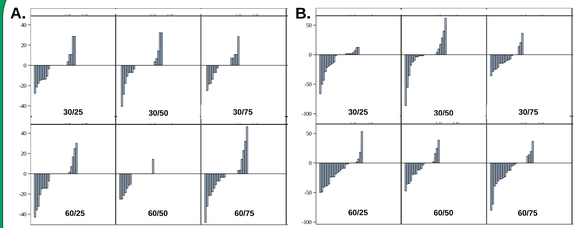


Figure 3. Waterfall plots of the absolute change from baseline in genital herpes lesion rates (A) and shedding rates (B). Data shown are for 24 months following the last GEN-003 vaccination for each of the 6 dose groups. Bars represents individual subjects, and baseline lesion and shedding rates for each subject are set at 0. Bars extending above and below the line indicate genital herpes lesion or shedding rates higher or lower than baseline, respectively. The length of the bars depicts the magnitude of the change from baseline.

Durability of Humoral Immune Responses to GEN-003

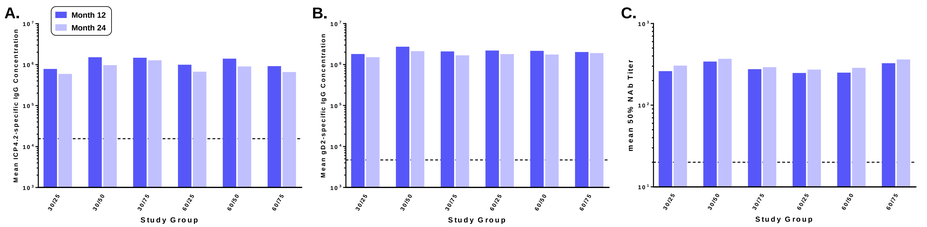


Figure 4. Humoral immune responses to GEN-003 at 12 and 24 months post-vaccination. Bars depict the geometric mean antibody titers for each GEN-003 dose combination at 12 (dark blue) and 24 (light blue) months following the last dose. **A.** ICP4.2- specific IgG concentrations. **B.** gD2ΔTMR-specific IgG concentrations. **C.** 50% HSV-2 neutralizing antibody titers. The dashed lines indicate the limit of quantification (LOQ) for each assay. Note that at 12 months, ICP4.2 and gD2ΔTMR mean antibody titers were 6.1 to 9.7-fold and 2.3 to 3.5-fold above baseline levels, respectively, and neutralizing antibody titers were 1.84 to 2.89-fold above baseline levels (data not shown).

SUMMARY AND CONCLUSIONS

1. GEN-003 durably reduces mean genital herpes lesion rates and HSV-2 shedding rates for 24 months.
2. GEN-003 elicits robust humoral and cellular immune responses to GEN-003, and these responses persist to 24 months after immunization.
3. Based on data from this and other clinical trials[6,7], the best performing dose groups are 60 µg HSV-2 antigens (ICP4.2 and gD2ΔTMR) combined with either 50 or 75 µg of MM2 adjuvant (60/50 and 60/75, respectively).
4. These results support the selection of the 60/50 GEN-003 dose for evaluation in future Phase 3 clinical trials.

Durability of Cellular Immune Responses to GEN-003

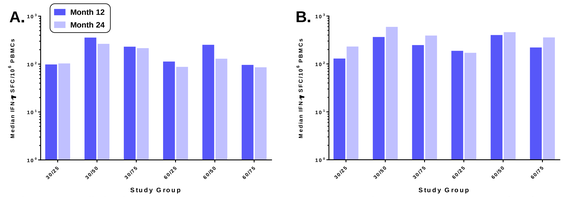


Figure 5. Cellular immune responses to GEN-003 at 12 and 24 months post-vaccination. Bars depict the median IFN-γ SFC/10^6 PBMCs for each GEN-003 dose combination at 12 and 24 months following the last dose. **A.** ICP4.2-specific T cell responses **B.** gD2ΔTMR-specific T cell responses. Note that at 12 months, median IFN-γ fold increases above baseline were 1.7-7.2 and 2.2-7.0 for ICP4.2 and gD2ΔTMR, respectively, using an intracellular cytokine staining assay.

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