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PW-039

GEN-003, a Therapeutic Vaccine for Genital Herpes, Significantly Reduces Viral Shedding and Lesions for at Least 6 Months

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Abstract

Background: GEN-003 is a candidate therapeutic vaccine containing recombinant herpes simplex virus (HSV) antigens glycoprotein D2 (gD) and infected cell polypeptide 4 (ICP4) with Matrix M-2 (MM) adjuvant. This Phase 2 study was designed to confirm GEN-003 antiviral activity and select the best dose combination for future trials. We previously reported an immediate reduction in virus shedding and lesions. We now present durability of effect.

Methods: Healthy adults with genital herpes were randomized to receive 30 or 60 µg of each protein antigen and 25, 50, or 75 µg MM, or saline placebo, 3 times 3 weeks apart. Participants collected twice-daily genital swabs for HSV-2 DNA polymerase chain reaction (PCR) for 28 days prior to dosing, after the third vaccination, and at 6 and 12 months following immunization and recorded stop and start dates of every outbreak. Placebo recipients were unblinded and re-randomized to one of the 6 active arms after post-vaccination swabbing period.

Results: 310 participants were evaluable. Six months after immunization, HSV-2 shedding was significantly reduced in all vaccine groups containing 60 µg of HSV-2 antigens compared to baseline, with the highest reduction in the 60/75 µg group (58%, p<0.0001). In subjects receiving 30 µg of antigens, only the 30/50 µg group had a significant reduction in shedding (50%, p<0.0001). All active groups (except 30/25 µg group) had a reduction in lesions, ranging from 43% to 69% (p<0.0001 vs. baseline). Common side effects included injection-site discomfort, fatigue and myalgia. No Grade 4 reactogenicity or related serious adverse events (SAEs) were observed.

Conclusion: GEN-003 had a significant antiviral activity persisting at least 6 months post dosing with an acceptable safety profile.

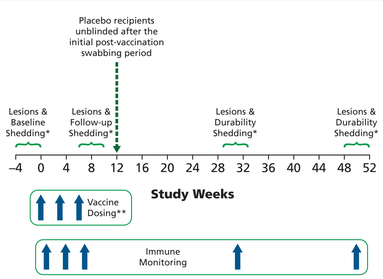
Introduction

- Current therapy of genital HSV type 2 (HSV-2) does not fully abrogate shedding or transmission.[1]
- GEN-003 is a therapeutic vaccine consisting of 2 viral antigens: a transmembrane deletion mutant of glycoprotein D (gD2ΔTMR), and a large fragment of infected cell protein 4 (ICP4.2; a T cell antigen) prioritized through Genocea's proprietary screening platform, ATLAS™.[2] These 2 antigens are combined with Matrix-M2 (MM, a saponin derived adjuvant, Novavax, Gaithersburg, MD).
- In a preclinical study of HSV-2 infected guinea pigs GEN-003 reduced the prevalence and severity of lesions and decreased shedding frequency and viral titer of HSV-2 compared to controls.[3]
- Here we report the durability of the virologic and clinical effects to 12 months after the last dose of the GEN-003-002 Phase 2 study in patients with HSV-2 (clinicaltrials.gov number NCT02114060).

Methods and Study Design

- Randomized, double-blind, factorial study enrolled 310 HSV-2 seropositive subjects with ≥1-year history of 3–9 herpes outbreaks/year who were not on suppressive antiviral therapy at the time of enrolment.
- Dosing groups of GEN-003: either 30 or 60 µg of each antigen combined with 25, 50 or 75 µg MM; OR placebo.
- At 3 months, placebo recipients were unblinded and rolled over to active treatment in a separate sub-study (**Figure 1**).

Figure 1. GEN-003 Phase 2 study design



*For 28 days prior to dosing, subjects performed twice-daily genital swabs to measure viral shedding (measured by type-specific HSV PCR). Twice-daily genital swabs were also obtained for a 28-day period immediately after dose 3 and at 6 and 12 months post-vaccination. Lesion days were recorded during the 28 day observation periods.

**Three doses of placebo or GEN-003 were given intramuscularly at 3 week intervals.

Objectives

- Primary – to identify the best dose combination by impact on viral shedding.
- Secondary – to confirm impact on clinical disease (lesion rate and proportion of subjects recurrence free at 6 and 12 months), safety and immunogenicity.

Statistical analysis

- Analyses of viral shedding and lesion rate change from baseline were performed using a longitudinal Poisson mixed model with a random intercept using a log link to test for differences within treatment group.

Results

- In total, 310 participants were randomized (mean age 35–38 years; 70% were women; **Table 1**).

Viral shedding and lesion rate

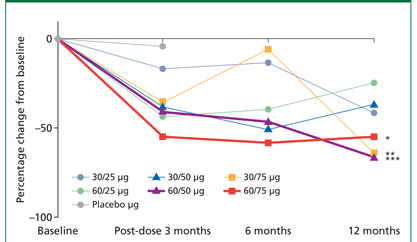
- Statistically significant reductions from baseline in viral shedding were observed in all GEN-003 dose groups immediately after the third dose. Reductions remained significant 12 months after the last dose for the 60/50, 30/75 and 60/75 µg groups (**Figure 2**).
- Statistically significant reductions from baseline in lesion rate were recorded for all dose groups at 3 months and maintained for up to 12 months for all groups except the 30/25 µg group (**Figure 3**).
- At 3 months, placebo recipients had a significant reduction in lesion rates, but no change in viral shedding, compared with baseline.
- **Table 2** shows the viral shedding and lesion rate ratios over time for each dosing group.
- Ranking analysis was performed for the 6 dose groups and placebo based on change from baseline in viral shedding rates. The 60/50 µg and 60/75 µg dosing groups experienced the most consistent and durable reductions in viral shedding.

Table 1. Patient demographics

	Antigen/adjuvant (µg)						
	30/25 (N=44)	30/50 (N=45)	30/75 (N=44)	60/25 (N=44)	60/50 (N=44)	60/75 (N=44)	Placebo (N=45)
Women, n (%)	36 (82)	31 (69)	32 (73)	30 (68)	26 (59)	29 (66)	32 (71)
Mean age, (years)	36	36	37	36	35	38	36
Race, n (%)							
White	22 (50)	26 (58)	26 (59)	31 (71)	30 (68)	28 (64)	26 (58)
Black	19 (43)	16 (36)	15 (34)	12 (27)	13 (30)	13 (30)	16 (36)
Other	3 (7)	3 (7)	3 (7)	1 (2)	1 (2)	3 (7)	3 (7)
Mean number of recurrences in last 12 months*	5.1	5.3	5.4	4.6	5.5	4.9	5.2

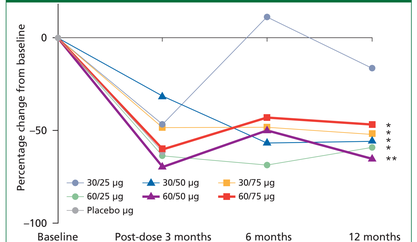
*or in the 12 month period prior to initiating suppressive therapy.

Figure 2. Reduction in viral shedding from baseline per dosing group



*p<0.05, **p<0.001, ***p<0.0001 compared with baseline

Figure 3. Reduction in lesion rate from baseline per dosing group



*p<0.05, **p<0.01 compared with baseline

Table 2. Viral shedding and lesion rate ratios per dosing group

	Antigen/adjuvant (µg)	12-month time point
Viral shedding rate ratio vs baseline, (95% CI)	30/25	0.64 (0.35–1.17)
	30/50	0.69 (0.37–1.31)
	30/75	0.34 (0.19–0.61)
	60/25	0.79 (0.50–1.25)
	60/50	0.38 (0.25–0.57)
	60/75	0.43 (0.23–0.82)
Lesion rate ratio vs baseline, (95% CI)	30/25	0.95 (0.54–1.66)
	30/50	0.42 (0.18–0.96)
	30/75	0.46 (0.23–0.92)
	60/25	0.42 (0.21–0.83)
	60/50	0.35 (0.18–0.71)
	60/75	0.53 (0.31–0.89)

CI, confidence interval

Subjects who were recurrence free

- At 6 months following the last dose, 30–46% of GEN-003-treated subjects were recurrence free. Additionally, 16–32% were recurrence free at 12 months following the last dose.
- At both time points, the 60/25 µg dose group had the highest proportion of recurrence free subjects (46% at 6 months and 32% at 12 months).
- None of the differences across doses were statistically significant.
- No comparisons were made with the placebo group since patients in that arm were followed for 3 months only.

Safety

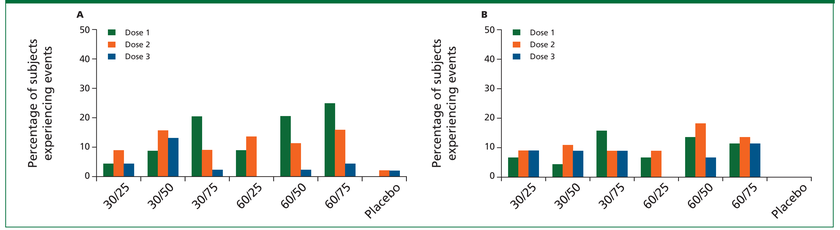
- The most frequent side effects after vaccination included injection-site tenderness (any Grade: 91–98%; Grade 3: 9–20%), injection-site pain (any Grade: 89–95%; Grade 3: 9–18%), myalgia (any Grade: 86–93%; Grade 3: 16–27%) and fatigue (any Grade: 70–89%; Grade 3: 11–25%) (**Table 3**).
- No Grade 4 reactogenicity, related SAEs or adverse events of special interest (AESI) were observed.
- Nine subjects discontinued secondary to reactogenicity or adverse event (AE) (**Table 3**).
- Reactogenicity increased with increasing dose of MM adjuvant, but not with repeated dosing (**Figures 4A** and **4B**).

Table 3. Local reactions and systemic events occurring within 7 Days post-dose and discontinuations due to reactogenicity or AE

		Antigen/adjuvant (µg)						
	Grade	30/25 (N=44)	30/50 (N=45)	30/75 (N=44)	60/25 (N=44)	60/50 (N=44)	60/75 (N=44)	Placebo (N=45)
Systemic symptoms (%)								
Myalgia	Any	84	93	91	87	86	87	24
	Grade 3	16	16	20	16	27	18	0
Fatigue	Any	70	80	73	80	89	89	49
	Grade 3	11	11	18	16	20	25	0
Nausea	Any	41	29	39	45	55	39	22
	Grade 3	5	0	2	2	7	9	0
Diarrhea	Any	18	22	16	27	25	27	27
	Grade 3	2	2	0	0	0	7	4
Fever	Any	14	7	16	14	14	18	0
	Grade 3	0	4	2	0	0	2	0
Vomiting	Any	7	2	2	2	14	5	2
	Grade 3	0	0	0	0	5	5	0
Local symptoms (%)								
Tenderness	Any	93	98	95	91	95	93	31
	Grade 3	14	13	16	9	20	20	0
Injection-site pain	Any	89	91	95	89	84	89	13
	Grade 3	9	13	18	9	11	11	0
Swelling	Any	41	53	55	48	45	55	4
	Grade 3	5	7	2	0	7	5	0
Erythema	Any	9	22	30	20	27	30	0
	Grade 3	0	0	2	2	5	7	0
Discontinuations of immunizations due to reactogenicity or AE (n)								
		0	2	1	2	1	2	1

AEs were monitored from dose 1 until 28 days after the last dose. Solicited AEs, including those generally associated with immunization, were recorded by subjects on a 7-day diary card after each immunization. SAEs, and AESI, consisting of a pre-defined list of autoimmune disorders, were recorded throughout the study period. All AEs were graded by severity according to specified criteria.[4]

Figure 4. Percentage of subjects experiencing systemic (A) and local (B) Grade 3 reactogenicity or AEs



Conclusions

- GEN-003, demonstrated significant, clinically meaningful and durable effects on viral shedding and recurrence rates for up to 12 months.
- The safety profile of GEN-003, at all doses, was acceptable for a therapeutic vaccine and reactogenicity was transient and self-limiting.
- The antigen/adjuvant combinations of 60/50 µg and 60/75 µg produced the most consistent and durable reductions in viral shedding, and are being evaluated in additional trials.

Acknowledgments

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