GEN-003 Phase 2 Interim Results: Therapeutic Vaccine for Genital Herpes Significantly Reduces Viral Shedding and Genital Lesions

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INTRODUCTION

Herpes simplex virus type 2 (HSV-2) is a common sexually transmitted infection that may cause recurrent, painful genital lesions. Affecting over 400 million people worldwide, it is transmitted through viral shedding from the genital tract during clinical recurrences and more commonly during episodes of subclinical shedding.[1]

GEN-003 is a therapeutic vaccine for genital herpes consisting of two protein antigens identified by Genocea's proprietary screening platform ATLAS™: ICP4, an immediate early protein of HSV-2, and glycoprotein gD2. These two antigens are combined with Matrix M2, a saponin derived adjuvant (Novavax, Gaithersburg, MD) which promotes both B and T cell responses.

In a first-in-human study presented at IDWeek 2014, GEN-003 was associated with significant reductions in viral shedding and genital lesions, and durable humoral and cellular immune responses that persisted for the length of the 1 year study.[2] Non adjuvanted doses were ineffective and ranked efficacy of protein dose was 30µg>100µg>>10µg. GEN-003-002 is a Phase 2 study designed to confirm the antiviral activity of GEN-003 in HSV-2 infected patients and to select the best dose combination of antigen and adjuvant for future clinical trials.

STUDY DESIGN

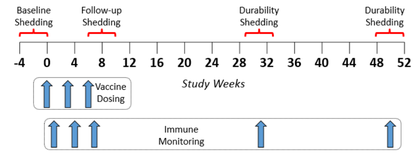

Figure 1: GEN-003 Phase 2 Study Design

RESULTS: Patient Demographics

Table 1: Patients Demographics & Disposition

	Placebo	30 µg/ 25 µg	30 µg/ 50 µg	30 µg/ 75 µg	60 µg/ 25 µg	60 µg/ 50 µg	60 µg/ 75 µg
N	45	44	45	44	44	44	44
Median Age	35	36.5	35	37.5	35	35	38
Percent Female	71.1	81.8	68.9	72.7	68.2	59.1	65.9
Percent White	57.8	50.0	57.8	59.1	70.5	68.2	63.6
Median annual outbreaks	5.0	5.0	5.0	5.5	4.0	5.0	4.5
Media duration of infection (yrs)	5.0	7.0	6.0	6.5	7.5	6.0	9.0
Received all doses	44	44	40	43	42	41	41
Data available Day 43	45	43	40	43	44	42	41
Data available Month 6	N/A	40	38	41	40	38	39

METHODS

The GEN-003-002 study (Clinical Trial number NCT02114060) was designed to confirm the results of GEN-003-001 and to titrate the adjuvant dose of Matrix M2. Three hundred and ten otherwise healthy HSV-2 seropositive subjects with at least 1 year history of 3-9 herpes outbreaks/year were randomized to saline placebo vs one of six dose combinations of GEN-003: either 30 or 60 µg of each antigen combined with either 25, 50 or 75 µg of Matrix M2. Three doses were given intramuscularly at 3 week intervals (Figure 1).

Prior to randomization and dosing, subjects obtained twice daily genital swabs for 28 days to measure viral shedding as measured by type-specific HSV PCR (limit of detection was 2 DNA copies/20 µL reaction with linearity over 5 logs of genomic DNA content)[3] and kept a diary recording days with genital lesions. Twice daily genital swabs were obtained immediately after dosing and at six months post-vaccination. After the initial post-vaccination swabbing period, placebo recipients were unblinded and rolled over to active treatment in a separate sub-study. The study is ongoing and the planned 12 month timepoint has not yet been reached.

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. The model has the total positive swabs as the dependent variable and includes terms for treatment group, visit, treatment group by visit interaction, log of total swabs collected (offset) and a random intercept. The regression analysis included data up to 6 months for both shedding and lesion data. Thirty subjects per treatment was sufficient to detect a 30% reduction in HSV-2 genital viral shedding from baseline, with a power of 80% and a 2-sided α of 0.05, and assuming a 20% shedding rate at baseline.

Adverse events (AEs) were captured from the first immunization until 28 days after the last dose. Solicited AEs included those generally associated with immunization and were recorded by subjects on a 7-day diary card after each immunization. Serious AEs (SAEs), and Adverse Events of Special Interest (AESI), consisting of a pre-defined list of autoimmune disorders, will be recorded through the end of the study. All AEs are graded by severity according to specified criteria (http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm074775.htm)

RESULTS: Safety

Table 2: Safety & Discontinuation

(%)	Placebo	30 µg/ 25 µg	30 µg/ 50 µg	30 µg/ 75µg	60 µg/ 25µg	60 µg/ 50 µg	60 µg/ 75 µg
Solicited Systemic Symptoms							
Any grade, any timepoint							
Myalgia	24.4	84.1	93.3	90.9	88.6	86.4	88.6
Fatigue	48.9	70.5	80.0	72.7	79.5	88.6	81.8
Nausea	22.2	40.9	28.9	38.6	45.5	54.5	38.6
Diarrhea	26.7	18.2	22.2	15.9	27.3	25.0	27.3
Fever	0	13.6	6.7	15.9	13.6	13.6	18.2
Vomiting	2.2	6.8	2.2	2.3	2.3	13.6	4.5
Grade 3 per timepoint							
Dose 1	0	4.5	8.9	20.5	9.1	20.5	25.0
Dose 2	2.2	9.1	15.6	9.1	13.6	11.4	15.9
Dose 3	2.2	4.5	13.3	2.3	0	2.3	4.5
Solicited Local Symptoms							
Any grade, any timepoint							
Tenderness	31.1	93.2	97.8	95.5	90.9	95.5	93.2
Injection site pain	13.3	88.6	91.1	95.5	88.6	84.1	88.6
Swelling	4.4	40.9	53.3	54.5	47.7	45.5	54.5
Erythema	0	9.1	22.2	29.5	20.5	27.3	27.3
Grade 3 per timepoint							
Dose 1	0	6.8	4.4	15.9	6.8	13.6	11.4
Dose 2	0	9.1	11.1	9.1	9.1	18.2	13.6
Dose 3	0	9.1	8.9	9.1	0	6.8	11.4
Discont. due to reactogenicity/AE	1	0	2	1	2	1	2

- A total of 7 unrelated SAEs (bipolar disorder, cholecystitis, diverticulitis, femur fracture, myocardial infarction, pyelonephritis, and viral syndrome) were observed
- No AEs of special interest were observed

RESULTS: Sustained Reduction in Viral Shedding

Table 3: Viral Shedding Rates (% of Swabs Positive) per Treatment Group

	Baseline	Post dose 3 (43-71 days)					6 months		
	Rate (%)	Rate (%)	Rate ratio vs baseline (95% CI)	P-value	Rate ratio vs placebo (95% CI)	P-value	Rate (%)	Rate ratio vs baseline (95% CI)	P-value
Placebo	23.2	22.2	0.96 (0.85-1.08)	0.4788	N/A	N/A	N/A	N/A	N/A
30 µg/25 µg	13.6	11.3	0.83 (0.70-0.98)	0.0239	0.86 (0.71-1.06)	0.1579	11.8	0.87 (0.73-1.03)	0.0968
30 µg/50 µg	17.5	10.8	0.62 (0.52-0.72)	**<0.0001**	0.64 (0.53-0.78)	**<0.0001**	8.7	0.50 (0.42-0.59)	**<0.0001**
30 µg/75 µg	14.5	9.3	0.64 (0.54-0.76)	**<0.0001**	0.67 (0.55-0.83)	**0.0002**	13.7	0.95 (0.81-1.10)	0.4729
60 µg/25 µg	19.5	11.0	0.56 (0.48-0.66)	**<0.0001**	0.59 (0.48-0.71)	**<0.0001**	11.8	0.61 (0.52-0.71)	**<0.0001**
60 µg/50 µg	27.1	16.0	0.59 (0.52-0.67)	**<0.0001**	0.62 (0.52-0.73)	**<0.0001**	14.5	0.53 (0.47-0.61)	**<0.0001**
60 µg/75 µg	18.9	8.5	0.45 (0.38-0.53)	**<0.0001**	0.47 (0.38-0.58)	**<0.0001**	7.9	0.42 (0.35-0.50)	**<0.0001**

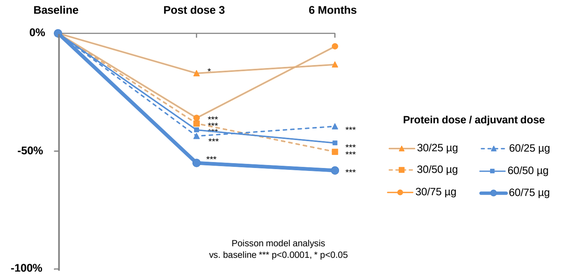

Figure 2: Reduction in Viral Shedding per Group

RESULTS: Sustained Reduction in Lesion Rate

Table 4: Lesion Rates (Percent of Days with Lesions) per Treatment Group

	Baseline	Post dose 3 (43-71 days)					6 months		
	Rate (%)	Rate (%)	Rate ratio vs baseline (95% CI)	P-value	Rate ratio vs placebo (95% CI)	P-value	Rate (%)	Rate ratio vs baseline (95% CI)	P-value
Placebo	16.2	6.2	0.38 (0.29-0.50)	**<0.0001**	N/A	N/A	N/A	N/A	N/A
30 µg/25 µg	9.4	5.0	0.53 (0.39-0.72)	**<0.0001**	1.37 (0.91-2.07)	0.1268	10.5	1.12 (0.86-1.45)	0.3939
30 µg/50 µg	9.0	6.2	0.69 (0.51-0.93)	0.0139	1.80 (1.21-2.67)	**0.0038**	3.9	0.43 (0.30-0.62)	**<0.0001**
30 µg/75 µg	14.4	7.4	0.51 (0.40-0.66)	**<0.0001**	1.33 (0.92-1.92)	0.1243	7.5	0.52 (0.40-0.67)	**<0.0001**
60 µg/25 µg	15.1	5.3	0.35 (0.26-0.47)	**<0.0001**	0.91 (0.62-1.35)	0.6513	4.7	0.31 (0.23-0.42)	**<0.0001**
60 µg/50 µg	12.7	3.9	0.31 (0.22-0.43)	**<0.0001**	0.80 (0.52-1.22)	0.2957	6.2	0.49 (0.37-0.65)	**<0.0001**
60 µg/75 µg	12.7	5.1	0.41 (0.30-0.55)	**<0.0001**	1.06 (0.71-1.57)	0.7862	7.2	0.57 (0.43-0.75)	**<0.0001**

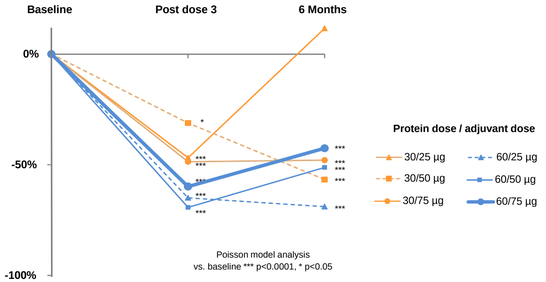

Figure 3: Reduction in Lesions per Group

SUMMARY

- GEN-003 was associated with over 50% reduction in HSV-2 shedding and up to 69% reduction in genital lesion rates that continued 6 months post vaccination.
- Placebo recipients also had a significant reduction in lesion rates, but no change in viral shedding.
- Common side effects after vaccination included injection site discomfort, fatigue and myalgia. Reactogenicity increased with increasing dose of Matrix-M2 adjuvant, but not with repeated dosing, and was not associated with increased rates of discontinuation.

DISCUSSION & CONCLUSIONS

- In this Phase 2 study, GEN-003, a therapeutic vaccine for genital herpes, demonstrated profound and durable effect on viral shedding and lesion rates, confirming results of a previous Phase 1/2 study.
- Safety was acceptable for a therapeutic vaccine.
- The placebo effect observed on lesion rates, had not been seen in the first study, and may reflect an expectation of benefit, 6:1 randomization scheme, and/or short follow-up for placebo recipients.
- Twelve month data will be available in early 2016.

References

1- Looker et al. Global Estimates of Prevalent and Incident Herpes Simplex Virus Type 2 Infections in 2012. *PLoS ONE, 10*(1), e114989. doi:10.1371/journal.pone.0114989
2- Wald. "Therapeutic HSV-2 vaccine (GEN003) results in durable reduction in genital lesions at 1 year." *IDWeek 2014*. IDSA, 2014.
3- Skoberne *et al*. An adjuvanted herpes simplex virus 2 subunit vaccine elicits a T cell response in mice and is an effective therapeutic vaccine in Guinea pigs. *J Virol* 2013;87:3930-42