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G-291

Safety and Immunogenicity of a Novel Lipidated Protein Subunit *Streptococcus pneumoniae* Vaccine

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Introduction

Current PCVs effectively prevent most invasive pneumococcal disease caused by strains covered by the vaccine, but serotype replacement and limited efficacy on mucosal disease, such as otitis media, necessitate development of additional vaccines. In infants and young children, pneumococcal colonization of the nasopharynx is common, is the primary source of pneumococcal transmission, and is required prior to development of mucosal or invasive disease. GEN-004 vaccine contains 3 conserved *S. pneumoniae* proteins. In preclinical experiments, GEN-004 reduced or prevented colonization by a T_H17-mediated mechanism [1,2].

GEN-004 was tested in a Phase 1 study to evaluate safety and tolerability when administered with and without aluminum hydroxide. As a secondary objective, we measured T_H17 and IgG immune responses [3].

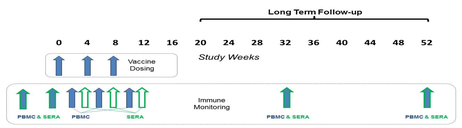
Methods

VACCINE
GEN-004 is comprised of three protein antigens SP0148 (GB104), SP2108 (GB144) and SP1912 (GB152) and was administered with or without aluminum hydroxide adjuvant.

CLINICAL TRIAL ENTRY CRITERIA
- Males and females, ages 18 to 55 years
- General good health
- Have not previously received pneumococcal vaccine

GEN-004-001 CLINICAL TRIAL DESIGN
- Randomized placebo controlled dose escalation study
- 90 healthy adults, randomized 3:1:1 to GEN-004 + aluminum hydroxide (adjuvant), GEN-004 antigens alone and placebo groups
- 3 doses at 28 day intervals (56 days)
- 10, 30 or 100 µg of each antigen ± adjuvant, 350 µg aluminum hydroxide, in 0.5 mL administered by intramuscular injection

OVERVIEW OF SCHEDULE OF EVENTS



SAFETY AND TOLERABILITY
We recorded: number and proportion of subjects with solicited local and systemic adverse events (AE) between 1 hour and 7 days following each dose, AE and clinical laboratory abnormalities from study day 1 through study day 85, serious adverse events (SAE), adverse events of special interest (AESI), and new onset of chronic medical conditions from study day 1 through 12 months following the last dose. We present data through study day 85.
AE were reported in a manner consistent with the FDA Guidance for Industry and Investigators[4].

IL-17 ELISPOT
Peripheral blood mononuclear cells (PBMC) were stimulated with SP0148, SP2108 and SP1912 proteins in IL-17 ELISpot plates for 3 days. Responding antigen-specific cells were enumerated (spot forming units - SFU) and absolute differences in SFU and fold increases over pre-vaccination baseline were calculated. Baseline was calculated by averaging two pre-vaccination time points.

IgG ELISA
IgG against each vaccine antigen was measured by ELISA, and expressed as an endpoint titer. Percent of subjects with greater than 4-fold increase over pre-vaccination baseline was determined. Baseline was calculated by averaging two pre-vaccination time points.

STATISTICAL ANALYSIS
Descriptive statistics were used for safety, tolerability and IgG response data. T cell responses were compared by 2 sided Fisher exact test.

DEMOGRAPHICS
Baseline characteristics were generally comparable across all treatment groups.

TABLE 1: DEMOGRAPHICS

Treatment group	GEN-004 w adjuvant			GEN-004 alone			Placebo
	10µg	30µg	100µg	10µg	30µg	100µg	
N	18	18	18	6	6	6	18
Age, mean	38	39	35	40	46	33	32
Women, %	56	44	67	67	50	50	56
White, %	94	94	83	67	67	83	100

SAFETY AND TOLERABILITY

TABLE 2: PERCENT OF SUBJECTS REPORTING MOST COMMON AE

Treatment group	GEN-004 w adjuvant			GEN-004 alone			Placebo
	10µg	30µg	100µg	10µg	30µg	100µg	
N	18	18	18	6	6	6	18
Muscle aches (%)	50	50	67	33	83	67	17
Fatigue (%)	44	33	67	33	50	50	28
Pain (%)	83	83	100	100	100	83	6
Tenderness (%)	78	100	100	100	83	100	22

TABLE 3: NUMBER OF SUBJECTS REPORTING GRADE 3 AE

Treatment group	GEN-004 w adjuvant			GEN-004 alone			Placebo
	10µg	30µg	100µg	10µg	30µg	100µg	
N =	18	18	18	6	6	6	18
Diarrhea	1	0	0	0	0	0	0
Muscle Aches	1	0	0	1	1	1	0
Fatigue	1	0	1	0	0	0	0
Tenderness	0	1	2	0	0	1	0

- All but 6 subjects received all 3 doses of Investigational Product
- No subjects discontinued Investigational Product prematurely due to intolerable side effects
- No alternations in laboratory values compared to placebo were observed (data not shown)
- To date, there have been no reports of AESI (autoimmune disease)
- One subject reported SAE which was not related to Investigational Product

Results

ANTIBODY IMMUNE RESPONSE

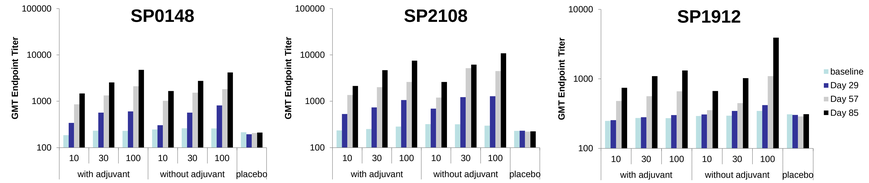


FIGURE 1: ENDPOINT TITERS TO SP0148, SP2108 AND SP1912.

TABLE 4: PERCENT OF SUBJECTS WITH GREATER THAN 4-FOLD IgG ENDPOINT TITER INCREASE

Treatment group/ ELISA specificity	GEN-004 w adjuvant			GEN-004 alone			Placebo
	10µg	30µg	100µg	10µg	30µg	100µg	
SP0148	88	100	89	60	100	100	0
SP2108	88	94	94	80	80	100	0
SP1912	25	39	50	20	40	83	0

Preliminary analysis of immunogenicity through day 85 of follow-up showed that IgG titers to each GEN-004 antigen increased with increasing doses of GEN-004 in both presence and absence of the aluminum hydroxide adjuvant.

T CELL IMMUNE RESPONSE

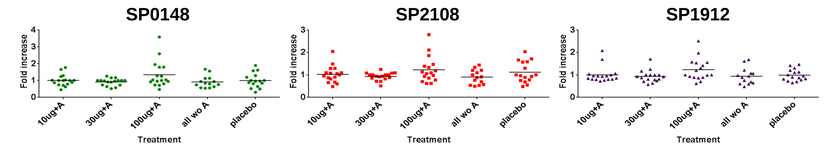


FIGURE 2: FOLD INCREASES FROM BASELINE IN IL-17 SECRETION BY PBMC AT DAY 15 (2 WEEKS AFTER THE FIRST DOSE).
Each dot represents a subject in either one of the adjuvanted GEN-004 groups (10 µg+A, 30 µg+A, or 100 µg+A), placebo or combined subjects from all 3 unadjuvanted groups (all wo A).

In an IL-17 ELISpot assay, we have observed a trend ($p>0.05$) towards increased response to *in vitro* stimulation with each of the individual GEN-004 antigens in immunized subjects. Because of relatively high pre-existing immune responses and relative insensitivity of the assay method to detect changes in frequency of rare cells such as T_H17, the number of responders may be underestimated.

Conclusions

- Preliminary data indicate that GEN-004 is safe and tolerable at all doses tested through day 85 of follow-up
  - There were more AE in treated groups compared to placebo
  - No consistent trend by dose or presence of adjuvant was observed
- IgG immune response was observed at all doses tested, regardless of presence of the adjuvant
- IL-17 response was only observed in 100 µg with aluminum hydroxide treatment group
- Future immunologic studies are ongoing to assess the effect of vaccine on multifunctional T cell phenotypes

Bibliography

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