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Pneumococcal protein vaccine GEN-004 reduces experimental human pneumococcal carriage in healthy adults

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INTRODUCTION

- *Streptococcus pneumoniae* is the leading cause globally of respiratory tract infections among young children. Pneumococcal polysaccharide-conjugate vaccines are effective against vaccine-type strains, but their high manufacturing costs, compounded by increases in the rates of disease caused by pneumococci not covered by current vaccines, have made the production of universal inexpensive vaccine a high global health priority.
- GEN-004 vaccine, developed with Genocea's ATLAS™ technology, is based on stimulation of T cell responses to three universal pneumococcal protein antigens, SP2108, SP0148 (both lipoproteins) and SP1912. The vaccine is designed to protect against colonization of nasopharynx, a prerequisite step to pneumococcal disease. It was highly protective in pre-clinical animal model studies (1), and has been shown to be safe and immunogenic in humans (2).
- The goal of this Phase 2 study (3) was to evaluate the effect of immunization with GEN-004 on the rate and density of pneumococcal colonization, using the human challenge model (4).

STUDY DESIGN (3)

- Double blind, placebo controlled trial, powered to observe >50% reduction in acquisition of carriage
- Healthy adult subjects were randomized at 1:1 ratio into placebo (saline) or GEN-004 vaccine groups
- Subjects received 3 i.m. doses of vaccine at approximately 4-week intervals. 2 weeks post last vaccine dose the subjects were inoculated intranasally with live *S.pneumoniae* 6B
- Blood for immune monitoring and nasal washes for assessment of colonization were collected as indicated in Figure 1.

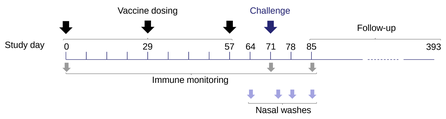


Figure 1: GEN-004 Phase 2 Study Design

RESULTS: Patient Demographics and completed procedures

Table 1: Patient Demographics, Disposition, Inoculation Dose & Completed Procedures

	GEN-004	Placebo
Demographics		
N	46	50
Age Range	18-52	18-50
Median Age	21	22
Percent Female	58.7	58.0
Percent White	87.0	88.0
Percent Asian	6.5	2.0
Median BMI	23.7	23.4
Disposition		
Discontinued from study	0	0
Discontinued from treatment	1	1
…due to intolerable AE or lab abnormality	1	0
..withdrew consent for reason other than AE	0	1
Completed procedures		
Received 1 dose	0	1
Received 2 doses	1	0
Received 3 doses	45	49
Received inoculation	42	49
Completed all nasal washes	41	47
Actual inoculation dose (CFU)		
Median	77167	76833
Min	70000	66834
Max	90333	90333

RESULTS: Safety

Table 2: Safety & Discontinuation

n (%)	GEN-004	Placebo
Solicited Systemic Symptoms (within 7 days post dose)		
Any grade, any timepoint		
Muscle Aches	18 (39.1)	3 (6)
Fatigue	16 (34.8)	14 (28)
Nausea	8 (17.4)	1 (2)
Diarrhea	4 (8.7)	3 (6)
Fever	2 (4.3)	1 (2)
Vomiting	1 (2.2)	1 (2)
Grade 3 per timepoint		
Dose 1	0	0
Dose 2	2 (4.3)	0
Dose 3	0	0
Solicited Local Symptoms (within 7 days post dose)		
Any grade, any timepoint		
Tenderness	46 (100)	9 (18)
Injection site pain	41 (89.1)	4 (8)
Swelling	29 (63)	2 (4)
Redness	22 (47.8)	0
Grade 3 per timepoint		
Dose 1	0	0
Dose 2	2 (4.3)	0
Dose 3	2 (4.3)	0
D/C due to reactogenicity/AE	1 (2.2)	0

- No hematological events ≥ Grade 3 were reported. One Grade 3 AST event was reported in GEN-004 group. Five and two elevated creatine kinase events ≥ Grade 3 were reported in GEN-004 and placebo groups, respectively. One Grade 3 elevated bilirubin event was reported in placebo group.
- One AESI has been reported (moderate psoriasis), likely related to vaccine.

RESULTS: Immunogenicity

Figure 2: Percent Responders Post Three Vaccine Doses

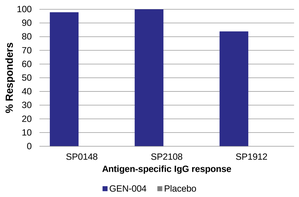
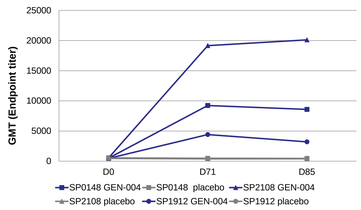


Figure 3: Endpoint IgG Titers to Vaccine Antigens



RESULTS: Efficacy

Figure 4: GEN-004 Reduces Number of Colonized Subjects

Figure 5: GEN-004 Reduces Median Density of Colonization Among All Subjects

Figure 6: No Difference In Mean Density of Colonization Among Those Colonized

Figure 4: GEN-004 Reduces Number of Colonized Subjects

Figure 5: GEN-004 Reduces Median Density of Colonization Among All Subjects

Figure 6: No Difference In Mean Density of Colonization Among Those Colonized

The top plot in each figure shows data from culturing nasal washes; the lower plot shows results of qPCR for *lytA* gene
In Figure 4, the numeral within each column indicates the number of colonized subjects

METHODS

- **Immunization** 96 healthy participants aged 18–52 years received either GEN-004 (n = 46) or placebo (n = 50) in 3 intramuscular doses at 4-week intervals. Blood samples were collected before and after immunization and after pneumococcal challenge to assess immunogenicity. Immunogenicity was assessed by antibody response in vaccine antigen-specific ELISAs. Responders were defined as those subjects with ≥ 4 fold increase of endpoint antibody titers over baseline (D0).
- **Experimental infection (4)** Immunized subjects were inoculated with 80,000 CFU of *S. pneumoniae* 6B per naris. Nasal washes were collected two (D73), 7 (D78), and 14 days (D85) after inoculation to measure pneumococcal carriage by microbiological culture and *lytA* qPCR. Fisher's exact test was used to compare number of colonized subjects between treatment groups and Wilcoxon's rank sum test was used to assess comparability of colonization densities between the treatment groups. Subjects were followed for safety throughout the study.

SUMMARY & CONCLUSIONS

- GEN-004 vaccine was generally well tolerated and was immunogenic as measured by antibody response to the vaccine antigens
- Fewer vaccinated subjects than control subjects developed carriage
  - Compared across multiple time points and methods, acquisition of carriage was consistently between 18 and 36 percent lower in vaccine group than in placebo group. However, none of the individual endpoints was statistically significant.
  - The reduction was lower than observed in preclinical studies, which may be explained by pre-existing T_H17 immunity in healthy adults but not animals. The target population is immunologically naïve infants.
- Data are result of an interim analysis (post Study day 85). The study is currently in a long-term follow-up period and final analysis is pending.
- Lack of statistical significance for the findings may have been the result of Type II error
- The data are promising and support further development of GEN-004

References

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