Safety and Immunogenicity of a Novel 24-Valent Pneumococcal Vaccine in Healthy Adults

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INTRODUCTION

- *Streptococcus pneumoniae* (*S. pneumoniae*) infection continues to be a major cause of morbidity and mortality in young children and the elderly[1]
- Despite the global availability of pneumococcal conjugate vaccines (PCVs) and a pneumococcal polysaccharide vaccine (PPSV), invasive pneumococcal disease (IPD) caused by nonvaccine serotypes remains prevalent[1,2]
  - There is a medical need for a vaccine that provides both B-cell– and T-cell–dependent immunity against a broad range of serotypes of *S. pneumoniae*
- ASP3772 is a novel 24-valent pneumococcal vaccine that was developed based on a multiple antigen-presenting system (MAPS) platform, which induces comprehensive B-cell and T-cell immunity[3]
  - ASP3772 serotypes are 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F (these serotypes are shared with PCV13) plus 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20B, 22F, and 33F
  - The MAPS platform takes advantage of the high-affinity noncovalent binding between biotin and rhizavidin, a biotin-binding protein that has no significant predicted homology with human proteins
  - The current study is the first clinical study to evaluate the safety/tolerability and immunogenicity of ASP3772, compared with PCV13, in healthy adults (NCT03803202)

METHODS

Study Design, Endpoints, and Assessments

- This was a phase 1 study conducted in healthy participants aged 18-64 years who had never received a pneumococcal vaccine
- Participants were randomly assigned 3:1 at each dose to receive a single intramuscular injection of ASP3772 (1, 2, or 5 µg of each polysaccharide) or PCV13
- The primary objective was to evaluate the safety and tolerability of three different dose levels of ASP3772, compared with PCV13
- The secondary objective was to evaluate the immunogenicity of three different dose levels of ASP3772
- Safety and tolerability were assessed for each cohort through Day 30 postimmunization
- Reactogenicity was assessed using solicited adverse reactions recorded daily for 7 days and included:
  - Local reactions of pain, tenderness, redness/erythema, and swelling/induration
  - Systemic reactions of nausea/vomiting, diarrhea, headache, fever, fatigue, and muscle discomfort or pain/myalgia
- Immunological response assessments included:
  - Functional opsonophagocytic activity (OPA) for each serotype characterized by an OPA titer[1] response and pneumococcal serotype–specific anticapsular polysaccharide immunoglobulin G (IgG) for each serotype on Day 1 before immunization and on Day 30 postimmunization
- Vaccine-related adverse events (AEs) included nausea, myalgia, general erythema, and conditions specific to the injection site (erythema, pain, and swelling)

Statistical Methods

- The safety analysis set comprised all participants who received an immunization with either ASP3772 or PCV13
- The full analysis set (FAS) comprised all participants who received an immunization with either ASP3772 or PCV13 and had at least one postimmunization measurement
  - The FAS was used for the summary of immunogenicity data
  - This phase 1 study was not powered for a formal statistical analysis of the immunogenicity data
- Continuous data were summarized with descriptive statistics and categorical data were summarized with frequency and percentage

RESULTS

Participants

- Baseline characteristics were generally balanced across the ASP3772 cohorts and between the total ASP3772 group and the PCV13 group (**Table 1**)
  - Most participants were female and white
  - Median age was 29 years (range, 18-64) in the total ASP3772 group and 28 years (range, 18-63) in the PCV13 group

Table 1. Baseline Characteristics

		ASP3772 1 µg (n=30)	ASP3772 2 µg (n=31)	ASP3772 5 µg (n=32)	ASP3772 Total (N=93)	PCV13 (N=33)
Sex, n (%)	Female	19 (63.3)	20 (64.5)	21 (65.6)	60 (64.5)	23 (69.7)
	Male	11 (36.7)	11 (35.5)	11 (34.4)	33 (35.5)	10 (30.3)
Median age, years (range)		34 (24-58)	31 (18-64)	27 (19-61)	29 (18-64)	28 (18-63)
Race, n (%)	White	25 (83.3)	26 (83.9)	29 (90.6)	80 (86.0)	28 (84.8)
	Black	4 (13.3)	4 (12.9)	2 (6.3)	10 (10.8)	5 (15.2)
	Native Hawaiian	1 (3.3)	0	0	1 (1.1)	0
	Other	0	1 (3.2)	1 (3.1)	2 (2.2)	0
Median weight, kg (range)		90.0 (57.5-133.3)	79.0 (42.2-132.3)	82.2 (52.2-127.0)	83.9 (42.2-133.3)	82.7 (53.2-132.8)
Median BMI, kg/m^2 (range)		31.1 (22.2-45.8)	27.4 (17.0-37.6)	27.1 (20.4-45.1)	28.6 (17.0-45.8)	29.6 (20.1-43.3)

Abbreviations: BMI, body mass index; PCV, pneumococcal conjugate vaccine.

Safety

- The overall incidence of AEs ranged from 16.1% to 36.7% in the ASP3772 dose cohorts and was 18.2% in the PCV13 group; participants in the lowest ASP3772 dose cohort had the highest incidence of AEs (**Table 2**)
- Five (5.4%) participants experienced seven AEs that were considered related to ASP3772 by the investigator; all were mild to moderate in severity
  - ASP3772 1-µg group: nausea and myalgia (n=1 each)
  - ASP3772 2-µg group: erythema (n=1)
  - ASP3772 5-µg group: injection-site erythema (n=2), injection-site swelling (n=1), and injection-site pain (n=1)
- There were no AEs considered related to PCV13 by the investigator
- Six (6.5%) participants experienced eight medically attended AEs in the total ASP3772 group; none were related to ASP3772
  - ASP3772 1-µg group: hemorrhoids, upper respiratory tract infection, and arthralgia (n=1 each)
  - ASP3772 2-µg group: viral gastroenteritis, tooth abscess, procedural pain, pain in extremity, and oropharyngeal pain (n=1 each)
- One (3.0%) participant in the PCV13 group experienced a medically attended AE (tooth infection)

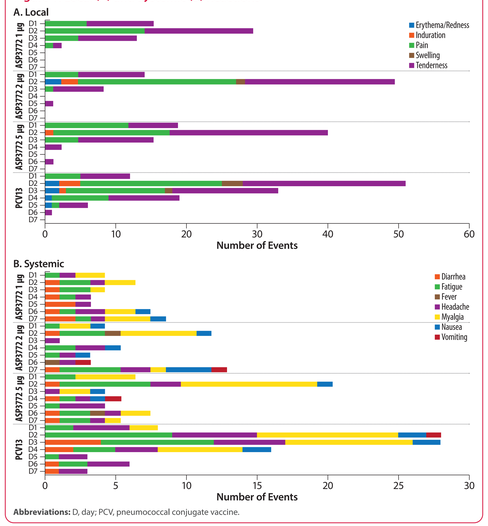
Table 2. Treatment-Emergent AEs in ≥2 Participants in the Total ASP3772 Group or the PCV13 Group

	ASP3772 1 µg (n=30)	ASP3772 2 µg (n=31)	ASP3772 5 µg (n=32)	ASP3772 Total (N=93)	PCV13 (N=33)
Overall	11 (36.7)	5 (16.1)	6 (18.8)	22 (23.7)	6 (18.2)
Myalgia	2 (6.7)	1 (3.2)	0	3 (3.2)	0
Nausea	2 (6.7)	0	0	2 (2.2)	1 (3.0)
Fatigue	1 (3.3)	1 (3.2)	0	2 (2.2)	0
Injection-site erythema	0	0	2 (6.3)	2 (2.2)	0
Viral gastroenteritis	1 (3.3)	1 (3.2)	0	2 (2.2)	0
Pain in extremity	0	1 (3.2)	1 (3.1)	2 (2.2)	0
Headache	2 (6.7)	0	0	2 (2.2)	1 (3.0)

Abbreviations: AEs, adverse events; PCV, pneumococcal conjugate vaccine.

- Reactogenicity, in total, was higher with PCV13 than with ASP3772 on Day 2 and Day 3
  - In the ASP3772 dose groups and the PCV13 group, the most frequently reported local reactions were tenderness and pain after injection occurring within the first 2 days (**Figure 1A**)
  - The most frequently reported systemic reactions were fatigue, headache, and myalgia (**Figure 1B**)

Figure 1. Local (A) and Systemic (B) Reactions



Abbreviations: D, day; PCV, pneumococcal conjugate vaccine.

Immunogenicity

- Across ASP3772 cohorts, most participants (≥50%) had a ≥4-fold rise in OPA antibody titers relative to baseline for serotypes common to ASP3772 and PCV13 and unique to ASP3772 (**Table 3**)
- The percentage of participants with a ≥4-fold rise in OPA antibody titers to serotype 23F was lower for all ASP3772 doses than for PCV13
- For the serotypes unique to ASP3772, there was a strong response to ASP3772 compared to no response or a slight response to PCV13

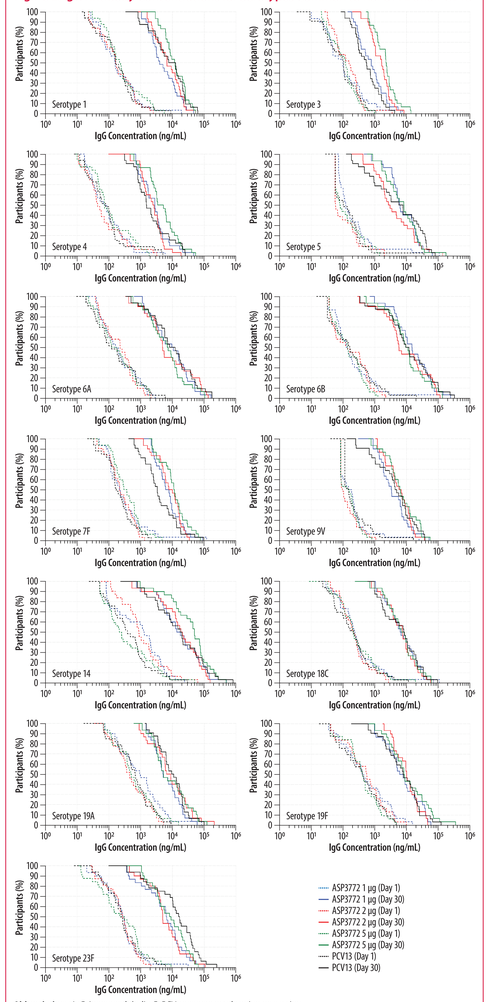
Table 3. Proportion of Participants with ≥4-Fold Rise in OPA Antibody Titers Relative to Baseline by Serotype

		ASP3772 1 µg (n=30)		ASP3772 2 µg (n=31)		ASP3772 5 µg (n=32)		PCV13 (N=33)	
		n/N[a]	%[b] (95% CI)[c]	n/N[a]	%[b] (95% CI)[c]	n/N[a]	%[b] (95% CI)[c]	n/N[a]	%[b] (95% CI)[c]
Serotypes common to ASP3772 and PCV13	1	28/29	96.6 (82.2-99.9)	25/28	89.3 (71.8-97.7)	28/30	93.3 (77.9-99.2)	27/30	90.0 (73.5-97.9)
	3	15/26	57.7 (36.9-76.6)	10/17	58.8 (32.9-81.6)	13/14	92.9 (66.1-99.8)	16/22	72.7 (49.8-89.3)
	4	22/26	84.6 (65.1-95.6)	19/23	82.6 (61.2-95.0)	15/17	88.2 (63.6-98.5)	19/22	86.4 (65.1-97.1)
	5	27/29	93.1 (77.2-99.2)	27/29	93.1 (77.2-99.2)	30/30	100.0 (88.4-100.0)	29/30	96.7 (82.8-99.9)
	6A	24/26	92.3 (74.9-99.1)	25/27	92.6 (75.7-99.1)	22/27	81.5 (61.9-93.7)	27/28	96.4 (81.7-99.9)
	6B	25/28	89.3 (71.8-97.7)	21/24	87.5 (67.6-97.3)	23/24	95.8 (78.9-99.9)	21/22	95.5 (77.2-99.9)
	7F	15/24	62.5 (40.6-81.2)	14/28	50.0 (30.6-69.4)	17/25	68.0 (46.5-85.1)	15/25	60.0 (38.7-78.9)
	9V	17/29	58.6 (38.9-76.5)	22/29	75.9 (56.5-89.7)	24/29	82.8 (64.2-94.2)	21/28	75.0 (55.1-89.3)
	14	16/26	61.5 (40.6-79.8)	17/26	65.4 (44.3-82.8)	23/25	92.0 (74.0-99.0)	22/28	78.6 (59.0-91.7)
	18C	25/29	86.2 (68.3-96.1)	22/27	81.5 (61.9-93.7)	25/28	89.3 (71.8-97.7)	23/29	79.3 (60.3-92.0)
	19A	14/27	51.9 (31.9-71.3)	16/26	61.5 (40.6-79.8)	24/28	85.7 (67.3-96.0)	21/29	72.4 (52.8-87.3)
	19F	17/29	58.6 (38.9-76.5)	18/27	66.7 (46.0-83.5)	23/29	79.3 (60.3-92.0)	21/29	72.4 (52.8-87.3)
	23F	13/22	59.1 (36.4-79.3)	11/15	73.3 (44.9-92.2)	10/13	76.9 (46.2-95.0)	15/16	93.8 (69.8-99.8)
Serotypes unique to ASP3772	2	22/27	81.5 (61.9-93.7)	23/29	79.3 (60.3-92.0)	26/30	86.7 (69.3-96.2)	1/30	3.3 (0.1-17.2)
	8	20/26	76.9 (56.4-91.0)	26/28	92.9 (76.5-99.1)	30/30	100.0 (88.4-100.0)	3/29	10.3 (2.2-27.4)
	9N	19/25	76.0 (54.9-90.6)	21/29	72.4 (52.8-87.3)	20/30	66.7 (47.2-82.7)	10/29	34.5 (17.9-54.3)
	10A	19/28	67.9 (47.6-84.1)	20/26	76.9 (56.4-91.0)	19/27	70.4 (49.8-86.2)	0/27	0 (0.0-12.8)
	11A	12/25	48.0 (27.8-68.7)	12/26	46.2 (26.6-66.6)	18/26	69.2 (48.2-85.7)	0/24	0 (0.0-14.2)
	12F	18/22	81.8 (59.7-94.8)	12/17	70.6 (44.0-89.7)	20/24	83.3 (62.6-95.3)	4/15	26.7 (7.8-55.1)
	15B	10/24	41.7 (22.1-63.4)	12/21	57.1 (34.0-78.2)	15/22	68.2 (45.1-86.1)	2/22	9.1 (1.1-29.2)
	17F	23/28	82.1 (63.1-93.9)	22/28	78.6 (59.0-91.7)	24/29	82.8 (64.2-94.2)	5/27	18.5 (6.3-38.1)
	20B	17/25	68.0 (46.5-85.1)	22/28	78.6 (59.0-91.7)	23/29	79.3 (60.3-92.0)	1/29	3.4 (0.1-17.8)
	22F	10/23	43.5 (23.2-65.5)	13/20	65.0 (40.8-84.6)	8/19	42.1 (20.3-66.5)	0/18	0 (0.0-18.5)
	33F	22/29	75.9 (56.5-89.7)	21/25	84.0 (63.9-95.5)	23/27	85.2 (66.3-95.8)	1/21	4.8 (0.1-23.8)

[a]n/N=number of participants with an antibody titer ≥4-fold increase from baseline/number of participants with a determinate OPA antibody titer for the specified serotype.
[b]Percentages are based on paired samples.
[c]Exact 2-sided CI based on the observed proportion of participants.
Abbreviations: CI, confidence interval; OPA, opsonophagocytic activity; PCV, pneumococcal conjugate vaccine.

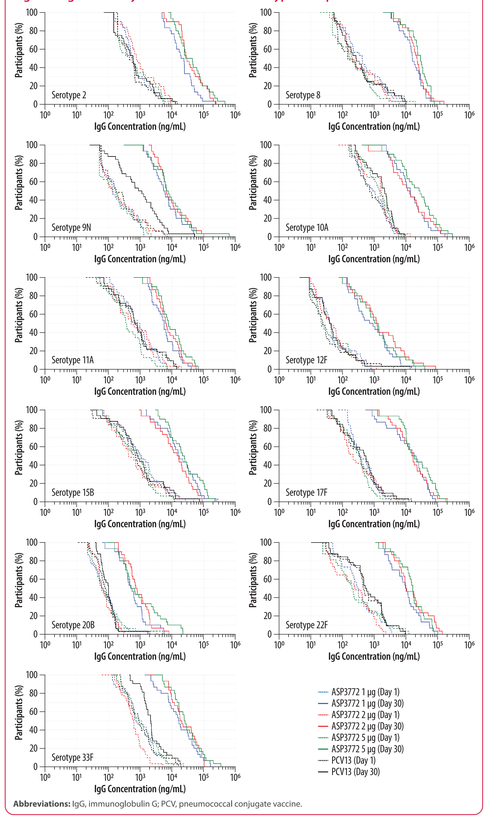
- Across the ASP3772 dose groups, robust IgG responses were observed for serotypes shared with PCV13, and were similar to or greater than the IgG responses to PCV13, with the exception of serotype 23F (**Figure 2**)
- IgG responses at day 30 to the serotypes unique to ASP3772 were greater with all doses of ASP3772 than with PCV13 (**Figure 3**)

Figure 2. IgG Antibody Concentrations for Serotypes Common to ASP3772 and PCV13



Abbreviations: IgG, immunoglobulin G; PCV, pneumococcal conjugate vaccine.

Figure 3. IgG Antibody Concentrations for Serotypes Unique to ASP3772



Abbreviations: IgG, immunoglobulin G; PCV, pneumococcal conjugate vaccine.

CONCLUSIONS

- ASP3772 vaccine is safe and well tolerated in healthy adults aged 18-64 years
- ASP3772 is highly immunogenic and induces both serotype-specific IgG concentrations and OPA antibody titers to all 24 serotypes included in the vaccine at all three dose levels tested
- These results support the continued development of ASP3772
  - The safety and immunogenicity of ASP3772 in elderly participants (≥65 years) is being assessed in the phase 2 part of this study
  - Results of this study should be interpreted with caution due to the small sample size

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