dose (7 months of age). Infants randomized to the control group participated until blood was drawn 1 month after the second catch-up immunization (10 months of age).

Monitored Parameters and Endpoints

Signs and symptoms of local and systemic reactions were recorded by caretakers for 3 days following each dose. Prompted local reactions included erythema, induration, and tenderness. The worse local reaction on each leg will be recorded. Prompted systemic reactions included irritability, change in sleep patterns, vomiting, diarrhea, hives, wheezing, change in skin tone, lethargic/limp, loss of consciousness and fever. Parents were also queried about whether fever medication was given.

IgG antibody concentration (GMC) to 7VPnC vaccine serotypes was measured before the first dose and one month after the third dose. Responses to polio and hepatitis B were assessed at 7 months of age.

The study had 2 co-primary immunogenicity endpoints for all 7 vaccine serotypes: 1) GMCs, and 2) response rates above defined threshold antibody concentrations. Threshold values for each serotype were determined by the maximal difference in serum antibody concentrations between immunized and unimmunized children at the 7-month bleed observed in previous studies using lots of vaccine from clinical scale production (i.e., studies D118-P12 and D118-P8). See section 12.3 for graphical illustration of threshold determination.

Manufacturing Bridging Study 118-16:
Threshold Serum Antibody Concentrations Used to Determine Percent Responders

Serotype	Threshold Concentration Level (µg/mL)
4	0.15
6B	0.25
9V	0.28
14	0.38
18C	0.21
19F	0.26
23F	0.18

Pre-defined criteria demonstrating acceptable bridging were: 1) [redacted]fold difference in GMTs between pilot and manufacturing lot ; 2) [redacted]difference in response rate between pilot and manufacturing lot at the defined threshold values for each serotype. Thus, successful demonstration of bridging in this study required 14 different comparisons, due to the multivalent nature of the vaccine. The sponsor identified the preferred manufacturing lot for initial comparisons as lot N.

Results: Bridging

Successful bridging of lot N to the pilot lot was demonstrated for all 7 serotypes, as shown in tables in section 12.3.

Safety

Local and systemic reaction rates among infants receiving vaccine from the pilot lot, or the preferred manufacturing lot, were similar for each dose. The sponsor pooled reactogenicity data from all 3 lots for presentation in the clinical summary. The pooled reactogenicity data from this study provided an important source of safety data in the context of co-administration of DTaP, IPV, and Hep B vaccines (selected tables shown with discussion of safety, above).

One death occurred during the study, 47 days after the first dose of 7VPnC; reported cause of death was Sudden Infant Death Syndrome (SIDS).

No seizures or other significant or unusual adverse reactions were reported for any vaccine group.

Study Conclusions

Bridging of manufacturing scale to pilot scale based on pre-defined immunogenicity criteria was successfully demonstrated. The manufacturing scale lot showed a similar reactogenicity profile as vaccine produced as a pilot lot. No new safety concerns were identified.

D118-P12: A randomized double-blind trial of the safety and immunogenicity of three lots of heptavalent (4, 6B, 9V, 14, 18C, 19F, 23F) pneumococcal conjugate vaccine administered to healthy infants at 2, 4 and 6 months of age

The primary objective of this study was to evaluate 3 independently produced pilot scale lots of 7VPnC for consistency of manufacture by comparing their safety and immunogenicity. Demonstration of consistency of production is required for vaccine licensure. Assessment of compatibility of 7VPnC with HbOC and DTaP when co-administered was a secondary objective. This multi-center study was initiated in September, 1996 and completed in March, 1998.

Approximately 300 subjects were randomized to one of four treatment groups (75 per group). Subjects in three groups received one of three lots of the 7-valent conjugate pneumococcal vaccine at 2, 4, and 6 months of age, administered concurrently with HbOC, DTaP, and IPV/OPV. Subjects in the 4th group received only HbOC, DTaP and IPV/OPV. The study was double-blind with respect to vaccine lots, however, unvaccinated control subjects could be identified.

Lot Consistency Study 118-12: Design and Subject Allocation

Vaccine group	Vaccine lot (lower left thigh @ 2, 4, 6 mos)	N	Concurrent vaccines & schedule (all groups)
1	Lot A 7-5018-011A	75	ACEL-IMUNE (right thigh) @ 2, 4, 6 mos) HibTITER (upper left thigh) @ 2, 4, 6 mos) OPV @ 2, 4, and 6 mos, or IPV right thigh or upper extremity @ 2 and 4 mos
2	Lot B 7-5018-010A	75	
3	Lot C 7-5018-008A	75	
4	Control group (no control vaccine or placebo administered)	75	

Subjects in the control group were re-enrolled and administered two doses of the 7VPnC vaccine at 7 and 9 months of age, with a boost at 15 - 18 months of age. Serological data from these subjects contribute to the data to support regimens for "catch-up" immunizations.

Parents were asked to monitor their children for local reactions (induration, erythema, and tenderness), systemic events (fussiness, drowsiness, decreased appetite, and temperature), and use of antipyretics on the day of each immunization and for three days following each immunization, and to record such information on a symptom report form.

Blood was collected from each subject prior to the first immunization (at 2 months of age), prior to the third immunization (at 6 months of age), and one month after the third dose (at 7 months of age). Serum samples were analyzed for IgG antibodies to all seven pneumococcal vaccine serotypes by standard ELISA methods. Sera were also analyzed for antibody responses to the components of DTaP and Hib-PRP.

Post dose 3 antibody concentration (GMC) for each of the 7 vaccine serotypes was the primary immunogenicity endpoint. Two-fold difference between GMCs in pairwise comparisons between lots was the pre-specified primary immunogencity criteria for determining consistency of antibody responses among lots.

See **section 12.2** for lot-to-lot comparisons of immunogenicity data and discussion of lot consistency.

Kinetics of the immune response to pneumococcal antigens were also studied in this trial. Antibody responses post dose 2 and post dose 3 are found in section **12.2.**

Safety

The power of the present study to identify safety concerns and to describe the reactogenicity profile of 7VPnC was increased by pooling subjects who received one of the three 7VPnC lots for making comparisons to the control group. This approach was justified based on the similar immunogenicity and safety profiles of the three vaccine lots.

Vaccine reactogenicity data from this trial were presented in **sections 10.3 and 10.4**, above.

Serious adverse events were reported for 18 (7%) of 256 subjects in the pooled 7VPnC groups and 4 (4.7%) of 84 subjects in the control group. The most common serious adverse event was bronchiolitis or RSV bronchiolitis, accounting for 9 of the 22 serious adverse events. No statistical analysis of serious significant events was provided or performed by the sponsor, due to the small number of events in each treatment group.

No deaths occurred during the study period.

Two seizures events were recorded during the study period, both in subjects who received 7VPnC.

Another subject who received 7VPnC was terminated from the study for inconsolable crying on the day of receiving dose 2, considered by the investigator as moderate in severity, and possibly related to immunization.

118-12: Healthy Infants Previously Enrolled as Control Group were Immunized with Heptavalent Pneumococcal Conjugate Vaccine Administered at 7, 9, and 15-18 Months of Age

Amendments 2 and 4 to 118-12 provided for immunization of control subjects at 7 and 9 months of age, with a 4th dose to be administered at 15-18 months of age. This part of the trial, completed in December 1998, was intended to provide safety and immunogenicity data to support catch-up immunization schedules.

The trial was conducted open-label. Of the 54 control subjects enrolled, 38 were analyzed for immunogenicity after 2 doses, and 22 after a 3rd dose at 15-18 months.

Results of immunogenicity assessments are included in the summary tables for immunizations of previously unvaccinated older children.

Study 92-05: A randomized, controlled, blinded, multicenter trial of the safety and immunogenicity of 2 models of pentavalent (6B, 14 18C, 19F, 23F) pneumococcal conjugate vaccine at 3 dose levels as a primary immunization series in infants at 2, 4, and 6 months of age with a booster dose of polysaccharide vaccine at 15-18 months of age

This study of pentavalent pneumococcal conjugates was initiated in May 1993 and completed in January 1996. The purpose of the study was to determine the optimal formulation (oligosaccharide vs. polysaccharide) and saccharide dose level (5, 2, or 0.5 μg) of a vaccine for use in infants. The 5 vaccine serotypes studied were among those chosen for inclusion in Prevnar.

A protocol amendment provided for a booster dose of PNU-IMUNE®23 to be given at 15-18 months of age to children who had completed the primary series. This is the only study in the PLA that provides safety and immunogenicity for a dose of pneumococcal polysaccharide vaccine following a vaccination series with pneumococcal conjugate vaccines. Another protocol amendment provided for a dose of 7-valent pneumococcal conjugate vaccine at 12-15 months of age to be given at one of the centers.

Subjects were randomized equally to one of 6 treatment groups, or a 'no vaccine' control group (N=60/group). Investigational vaccines were inoculated into the left thigh at 2, 4, and 6 months of age. All subjects also received DTP-HbOC (Tetramune) in the right thigh.

Local and systemic symptoms during the first 3 days post-inoculation were recorded by the parent/guardian on symptom report forms that were returned to the investigator. Subjects were monitored for adverse events for the entire study duration (7 months).

Serum antibody concentration to each of the 5 serotypes contained in the vaccine were determined by ELISA, at 2, 4, 6, and 15 months of age, and one month after inoculations following the 6 and 15 month inoculations, and at 24 months of age. Antibody to Hib PRP was assessed for all groups. Antibodies to diphtheria, tetanus, pertussis antigens (PT, pertactin, FHA, and Fim 2) were assessed only for the 2 μg polysaccharide model, as this was the model chosen for subsequent development.

In the primary series, local reactions did not differ substantially among the 5-valent conjugates, and local reactions were no more common at the sites of 5-valent PnC than at the HbOC injection sites. Rates of systemic reactions among groups receiving the different 5-valent PnC conjugates were similar. However, when compared to the control group, fever ≥38°C, and fever >39 °C occurred with greater frequency among the 5-valent PnC treated groups with each dose of the primary series. The highest fever rates were reported for the 5μg PS conjugate: 39% with ≥38°C; 9% with >39 °C after the 3rd dose, compared to 19% and 0% for the control group. These data suggest that febrile reactions may be related to polysaccharide antigen content of the vaccine formulation.

No deaths were reported during the study period. No convulsions were reported within 3 days following any dose. One hypotonic-hyporesponsive (HHE) episode was recorded after the 1st dose in a recipient of 2 μg OS; this episode was considered probably related to study vaccine. Four episodes of high-pitched crying and six episodes of persistent crying were reported in the study vaccine groups; all were considered definitely or probably study vaccine related. No such episodes occurred in the control group. All occurred after the first dose, and none received subsequent study vaccines. No clear dose effect was apparent, although 2 infants with high-pitched cries received 5μg PS.

Results of the immunogenicity assessments supported the manufacturer's choice of the polysaccharide model and the 2 μg polysaccharide dose.

Overall, the safety profile of the 5VPnC formulations, whether oligosaccharide or polysaccharide, appeared to be within acceptable limits, such that larger clinical trials were justified.

GMC's to Hib PRP post dose 3 were significantly enhanced by co-administration of all 5VPnC formulations, and particularly so for the chosen 2 μg dose group. No interference with responses to diphtheria, tetanus, pertussis antigens was observed after the 3rd dose.

Pre and post dose sera for the 23V-polysaccharide booster were available for 16 to 20 subjects per group. Pre dose antibody concentrations were significantly lower for the control group, which did not receive 5VPnC with the primary series. Following boost, the 5VPnC treated groups achieved a substantial increase in GMCs to all serotypes. Little appreciable response to polysaccharide vaccine was observed among the "unprimed" control group, as might be expected among children under 2 years of age.

[redacted]

Supporting Study 92-05: Antibody Responses to Vaccine Serotypes following Administration of 23-Valent Polysaccharide Vaccine (PNU-IMUNE®23) as 4th Dose at 15-18 months of Age, GMCs (μg/mL) and 95% CI

Vaccine Serotype		P5VPnC (PS) 5 μg N=18	P5VPnC (PS) 2 μg N=17	P5VPnC (PS) 0.5 μg N=20	Control N=16
6B	Pre	0.9 (0.5, 1.7)	1.4 (0.7, 3.2)	0.4 (0.2, 0.8)	0.1 (0.1, 0.3)
	Post	18.0 (9.1, 35.6)	16.6 (7.4, 37.4)	18.9 (9.5, 37.4)	0.2 (0.1, 0.6)
14	Pre	0.7 (0.5, 1.2)	0.6 (0.3, 1.5)	0.6 (03, 0.9)	0.0 (0.0, 0.0)
	Post	10.4 (5.5, 19.6)	11.4 (5.5, 23.5)	21.0 (11.3, 39.0)	0.0 (0.0, 0.1)
18C	Pre	0.3 (0.2, 0.5)	0.3 (0.2, 0.5)	0.2 (0.1, 0.2)	0.0 (0.0, 0.1)
	Post	4.5 (3.0, 6.9)	6.3 (3.6, 10.9)	10.3 (7.4, 14.4)	1.2 (0.6, 2.3)
19F	Pre	0.7 (0.5, 1.1)	1.1 (0.4, 2.7)	0.9 (0.3, 2.5)	0.1 (0.0, 0.2)
	Post	18.7 (9.6, 36.3)	29.6 (15.0, 58.3)	13.7 (9.2, 20.5)	0.2 (0.1, 0.4)
23F	Pre	0.5 (0.2, 1.0)	0.5 (0.2, 1.3)	0.4 (0.1, 0.9)	0.0 (0.0, 0.1)
	Post	7.0 (3.7, 13.2)	8.1 (3.5, 18.7)	4.2 (1.7, 10.4)	0.2 (0.1, 0.7)

Adapted from Table 6, page 51, Volume 1 of Clinical Section of PLA.
Conjugate oligosaccharide formulations data not shown for simplicity of presentation.

118-02: A randomized, double-blind, controlled trial of the acute safety of heptavalent (4, 6B, 9V, 14, 18C, 19F, 23F) pneumococcal conjugate vaccine as a single injection in healthy adults

This study was intended to demonstrate safety of 7VPnC in adults before initiation of studies in children and infants. Initiated in December 1994 and completed February 1995, this was the first clinical study conducted under U.S. IND using the 7-valent pneumococcal conjugate vaccine (7VPnC).

Thirty adult subjects, 18 to 60 years of age, were enrolled at a single center, and randomized to receive a single dose of either 7VPnC or 23-valent pneumococcal polysaccharide vaccine (PNU-IMUNE®23). Local and systemic reactions were assessed over the first 72 hours post inoculation through use of diary cards; data entry was solicited for specific local and systemic reactions. Blood samples were obtained before, and one month after inoculations, for assessment and comparison of antibody responses to polysaccharide antigens common to 7VPnC and the licensed pneumococcal polysaccharide vaccine.

Local reactions (erythema, induration, or tenderness) were reported for 93% of 7VPnC recipients, and 73% of PNU-IMUNE®23 recipients; more severe local reactions occurred with similar frequency (33%) in both groups. Any systemic reaction (decreased appetite, vomiting, headache, rash, muscle pain, joint pain, fever) was reported for 60% of 7VPnC recipients and 27% of PNU-IMUNE®23 recipients. Fever ($\geq$ 38.0 °C) was reported for 1 subject in the 7VPnC group, and 2 subjects who received PNU-IMUNE®23. No adverse events were reported during the 1-month post-immunization observation period.

Antibody responses to the 7 pneumococcal serotypes included in 7VPnC, as determined by IgG ELISA assays, did not differ significantly between groups in this small study, with the exception of serotype 23F, which was significantly greater in the conjugate vaccine group.

Supporting Study 118-02: Geometric Mean Concentrations (95% CI) Pre- and Post-Inoculation of 7VPnC and PNU-IMUNE23 in Adults

		7VPnC N=14		PNU-IMUNE23 N=15		p-value[1]
Serotype	Visit	GMC (µg/mL)	95% CI	GMC (µg/mL)	95% CI	
4	Pre	1.1	0.4, 3.3	0.6	0.3, 1.4	0.37
	Post	5.6	3.1, 10.3	2.9	1.2, 6.7	0.32
6B	Pre	3.7	1.8, 7.8	2.2	1.0, 4.5	0.26
	Post	22.7	12.1, 42.4	11.9	5.6, 25.1	0.37
9V	Pre	1.5	0.7, 3.3	1.5	0.8, 2.8	0.97
	Post	7.6	3.2, 18.1	8.5	4.4, 16.3	0.79
14	Pre	1.9	0.5, 7.0	1.1	0.3, 4.5	0.53
	Post	38.1	12.1, 119.6	14.1	3.4, 58.4	0.35
18C	Pre	1.9	1.0, 3.8	1.1	0.5, 2.7	0.33
	Post	20.3	8.7, 47.2	7.7	3.3, 18.0	0.18
19F	Pre	6.7	4.0, 11.3	4.8	2.2, 10.4	0.46
	Post	28.4	16.3, 49.4	16.0	9.2, 27.8	0.19
23F	Pre	1.1	0.5, 3.1	1.0	0.3, 2.9	0.82
	Post	34.1	14.1, 82.4	5.1	1.9, 13.2	**<0.01**

Reproduced from Table 3 o[redacted] clinical study report

[1] GMTs compared suing analysis of covariance model; group comparisons adjusted for pre-immunization log-titers (Sponsor's analysis)

Study 118-03: A Randomized Double-Blind, Trial of the Safety and Immunogenicity of Heptavalent (4, 6B, 9V, 18C, 19F, 23F) Pneumococcal Conjugate Vaccine and Meningococcal Group C Conjugate Vaccine in Healthy Infants at 2, 4, and 6 Months of Age, followed by a Booster Dose at 12-15 months of Age of the Same Vaccines.

The objectives of the study were to determine the safety and immunogenicity of 7VPnC among infants, and to assess the safety of meningococcal polysaccharide C vaccine (MnCC) as a control for 7VPnC. Safety data from the MnCC served to support continued use of MnCC as a control in subsequent phase II and III studies. The 4-study conducted from February 1995 through June 1997, at 4 study sites. The original protocol was amended to allow for open-label study of the "booster dose". Potential interference with concurrent DTP, HbOC, and MMR was also assessed.

A total of 212 healthy infants were randomized 1:1 to receive 7VPnC or MnCC at 2, 4, and 6 months of age in the left thigh. Each infant also received DTP-HbOC in the right thigh, and OPV with the primary series.

As a 4th dose, 7VPnC subjects were again randomized 1:1 to receive either HbOC, or MMR.

Subjects were actively monitored for local and systemic reactions and antipyretic use for 3 days after each dose. Adverse events included clinic visits within 7 days of

a dose, hospitalizations during the 24-month study period, or any event resulting in study termination.

Blood samples were obtained for IgG antibody concentration (ELISA) assessments pre dose 1, pre and post doses 3 and 4, and at 24 months of age. Opsonophagocytic antibody for the 7 pneumococcal serotypes was also assessed.

Immunogenicity

After the 3rd dose, GMCs ranged from 0.98 μg/mL for serotype 9V, to 3.48 μg/mL for serotype 14. Antibody levels declined substantially after the primary series for some serotypes; pre dose 4 GMCs were lowest for serotypes 4 (0.20 μg/mL) and 18C (0.22 μg/mL). After the 4th dose, GMCs for each serotype exceeded 2.0 μg/mL.

Duration of antibody levels assessed at 24 months of age were not included in the PLA.

Supporting Study 118-03: GMC (μg/mL) of Pneumococcal Antibodies Prior to and Following the Primary Series and 4th Dose

Serotype	4	6B	9V	14	18C	19F	23F
Pre dose 1 (N=90)	0.05	0.31	0.12	0.18	0.09	0.28	0.11
Post dose 3 (N=90)	1.36	1.37	0.98	3.48	1.24	3.45	1.80
Pre dose 4 (N=55)	**0.20**	0.68	0.37	1.77	**0.22**	0.76	0.35
Post dose 4 (N=55)	2.32	8.13	3.75	9.33	3.01	4.50	5.11

Adapted from Tables, 6, 7, and 9, pages 50, 51, 57 Volume 7, Part IV of PLA

Safety

No deaths occurred during the study period. Five 7VPnC recipients were hospitalized, none for events within 1 week of vaccinations or for events considered related to vaccine by investigators. One subject in the 7VPnC group had onset of a seizure disorder 8 months after the 4th dose.

Seven subjects were withdrawn from the study due significant adverse events: 4 7VPnC recipients and 3 MnCC recipients. In the 7VPnC group, 3 infants were discontinued for persistent or unusual cry, and one for an apparent hypotonic-hyporesponsive episode accompanied by urticaria.

The sponsor concluded that there were no trends in adverse events that were clinically significant for either study vaccine.

Study 118-07: A Randomized, Double-Blind Trial of the Safety and Immunogenicity of Heptavalent Pneumococcal Conjugate Vaccine and Meningococcal Group C Conjugate Vaccine in Healthy Infants at 2, 4 and 6 Months of Age with a Booster Dose Administered at 12-15 Months of Age

This was a phase II study conducted within the Northern California Kaiser Permanente health care system, a population similar to that of the subsequent efficacy study. The study, initiated in June 1995, and completed July 1997, served as a pilot study for the large-scale safety and efficacy trial of 7VPnC. The stated primary objective was to gain experience with respect to the safety and immunogenicity of MnCC and 7VPnC.

The main contributions of this study to the PLA are: 1) reactogenicity data for 7VPnC given against a background of DTP-HbOC in the primary series, and DTaP as a 4th dose; 2) compatibility of 7VPnC with concurrent immunizations.

Protocol amendment 1 provided for a 4th dose to be administered at 12-15 months of age with or without DTaP and HbOC. Amendment 2 allowed for assessing duration of post dose 4 antibody levels at 24 months of age; however, data addressing duration of antibody were not included in the PLA.

A total of 302 healthy 2 month old infants were randomized (2:1) to receive 7VPnC or MnCC at 2, 4, and 6 months of age, which was injected into the left thigh muscle. All subjects received DTP and HbOC vaccines at 2, 4 and 6 months of age into the anterior thigh muscle of the right leg, and a dose of OPV at 2, 4 and 6 months of age. One-half of the subjects in each cohort were also randomized to receive Hepatitis B vaccine in the right thigh at 2, 4, and 6 months of age.

Local and systemic reactions during the first 48 hours post dose were assessed by parents or caretakers and recorded on diary cards. Systemic events and body temperature were recorded daily on days 0, 1, and 2 post-immunization, and at any time within 14 days post-immunization. Data was collected by telephone interviews at 48-72 hours and again at 10-14 days.

Adverse events included hospitalizations within 60 days and emergency room visit within 30 days of vaccination, and any event resulting in study termination.

Blood samples were obtained immediately prior to the first dose of vaccine and the 4th dose, and one month following the 3rd (7 months) and 4th (13 months) doses. IgG antibody concentration (GMC) and response rates at 0.15 and 0.5 μg/mL serum levels to 7VPnC vaccine serotypes were assessed.

A substantial decline in % of subjects achieving 0.50 μg/mL was observed between dose 3 and dose 4 for some serotypes; only 15% of subjects were able to maintain 0.50 μg/mL of serum antibody for serotype 4 until the 4th dose. Although the serum antibody concentration associated with protection from disease is unknown, these

data indicate that protection against disease afforded by 3 doses of 7VPnC may vary considerably with serotype.

Fever ≥38°C was reported in up to over one third of subjects after the 2nd dose. Fever > 39°C was reported with increasing frequency with subsequent doses in the primary series; after the 3rd dose, fever > 39°C was reported by over 6% of children receiving 7VPnC, compared to 3.7% in the MnCC group (p=0.053, Chi square). Irritability was the most common systemic event, occurring in 58%-69% of 7VPnC recipients with the primary series, although irritability was also common in the MnCC arm.

Late onset of hives following doses 1, 2, or 3 (3-14 days) were more common in the 7VPnC group compared to the MnCC group (8 vs 0). Similar findings were not observed within the first 48 hours, nor following the 4th dose during the 3-14 day window.

One infant experienced a hyporesponsive episode on the day of the 1st dose of 7VPnC; the event was considered probably related to 7VPnC and no additional doses were administered. Two additional events, both in the 7VPnC group, resulted in study termination: inconsolable crying 1 day after 1st dose, and fever, fussiness, vomiting 2 days after dose 2. This latter event resulted in hospitalization, but investigators did not consider the event related to vaccine.

No deaths or seizures were reported during the study period.

Study 118-09: A Randomized, Double-Blind Trial Comparing the Safety and Immunogenicity of Two Lots of Heptavalent (4, 6B, 9V, 14, 18C, 19F, 23F) Pneumococcal Conjugate Vaccine in Toddlers 15-24 Months of Age

This was a single-center, randomized and double-blind study, initiated in May 1995, and completed November, 1995. The original objectives of the study were to assess safety and immunogenicity among toddlers following a single dose of 7VPnC from two pilot lots. The role of the study in the PLA is to support a catch-up schedule.

Sixty healthy toddlers, age 12-24 months were randomized to receive a single dose of 7VPnC from one of two pilot lots. Subjects were actively monitored for local and systemic reactions.

Immunogenicity results were categorized by age at enrollment: 12-17 months and 18-23 months. Immunogenicity results for the two lots were similar, so they were combined for inclusion in the tables of data supporting vaccinations of older children.

Safety and immunogenicity data were presented by age at vaccinations: 12-17 months and 18-23 months. Local reactions occurred with similar frequency in the two age groups. More severe, clinically significant, local reactions were uncommon.

Systemic reactions occurred more commonly in the younger age group. Fever ≥38.0°C was reported by 52% (13 of 25) subjects in the 12-17 month age group, vs. 24% (8 of 33) in the 18-23 age group. No subject in either group reported fever >39°. Fussiness, drowsiness, decreased appetite and antipyretic use were all reported more frequently in the younger age group.

No serious or unusual adverse events were reported.

Study 118-15: A Double-Blinded, Controlled Study of the Efficacy, Immunogenicity, Safety and Tolerability, and Effectiveness of a Pneumococcal Conjugate Vaccine Containing Seven Serotypes (6B, 14, 19F, 23F, 18C, 4 and 9V) Compared to a Control Meningococcal C Vaccine in Navajo and Apache Indian Infants

The primary objective of the study is to demonstrate effectiveness of 7VPnC in preventing invasive pneumococcal disease occurring in infants and toddlers. Subjects received either 7VPnC or meningococcal C conjugate (MnCC). Randomization was 1:1 for 40 allocation units based on geographical criteria. All subjects in a unit receive the same vaccine. Infants 6 weeks to < 7 months of age receive 3 doses at least 1 month apart and a 4th dose at 12-15 months. Infants 7 to 12 months of age receive 2 doses at least 1 month apart and a 3rd dose at 12-15 months. Infants 12 to 24 months of age receive 2 doses, approximately 2 months apart. Total planned enrollment is 18,000 children. The study is ongoing.

Only subjects who received the first vaccination after 12 months of age and who consented to participate in a serology subset were included in the data submitted to the PLA to support catch-up schedules. There were 204 subjects available at the time of the analysis. Results are shown in the summary table for catch-up immunizations.

No safety data were provided with the PLA.

Study 118-18: A Phase II Open-Label Study to Determine the Safety, Tolerability, and Immunogenicity of a Heptavalent Pneumococcal Capsular Polysaccharide-CRM$_{197}$ Conjugate Vaccine in Children Between 1 and 9 Years of Age

The purpose of this study was to provide additional safety and immunogenicity data for 7VPnC among children over 1 year of age who received 1 or 2 doses of vaccine. The study was open-label and uncontrolled. It was initiated in May 1999 and completed in October 1999. Children who had received MnCC control vaccine in the completed efficacy study 118-8 were eligible to participate, but were analyzed separately (group M, below).

Study 118-18: Ages, Doses and Planned Enrollment

	Age	Number of Doses	Number of Subjects
Group A	≥ 12 and < 18 mos	2	50
Group B	≥ 18 and < 24 mos	2	50
Group C	≥ 24 and < 36 mos	1	50
Group D	≥ 36 mos and < 60 mos	1	50
Group E	≥ 5 yrs and < 10 yrs	1	100
Group M	≥ 12 mos and < 24 mos	2	100
	≥ 24 mos and < 36 mos	1	

The allowable interval between vaccine doses was 42-72 days.
Vaccine reactions were recorded on diary cards for 7 days and data collected from parents by telephone on days 3 and 7. Physician visits within one week, and prescription medications within one week were collected. In addition, hospitalizations, ER and outpatient visits were collected for the entire study period.

Blood for antibody assessments was collected pre-immunization and 1 month following the last immunization.

Vaccine reaction data and ELISA GMCs data were included among the tables in the vaccine label to support use of Prevnar in previously unvaccinated older children.

Study 124-2: Safety and Immunogenicity of a Booster Dose of Nine Valent (1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F) Pneumococcal Conjugate Vaccine Administered Concurrently with MMR in Toddlers 12-15 Months of Age.

The original study compared safety and immunogenicity of 7VPnC and 9VPnC vaccines. A total of 184 subjects were randomized 1:1 to receive 7VPnC or 9VPnC at 2, 4, and 6 months of age. An amendment to the study provided for a 4th dose of 9VPnC to be given to children of both groups at 12-15 months of age, administered concurrently with MMWR. No other vaccines were administered concurrently with the 4th dose. A total of 75 subjects were analyzed for immunogenicity to MMR.

Antibody responses to measles, mumps and rubella were determined by ELISA methods. Seroconversion was defined as a change from seronegative to seropositive or a 4-fold rise in antibody titer.

A full study report was not provided in the PLA. Data were included in the PLA intended to support concurrent immunizations of MMR with a 4th dose of Prevnar. No comparative immunogenicity data (7VPnC vs. 9VPnC) were provided in the PLA. Only data intended to support concurrent immunization of 7VPNC with MMR were provided. Because the MMR concurrent immunization data was obtained using 9VPnC at the 4th dose, these data were not viewed as adequate to support concurrent immunization of MMR with Prevnar.

Study 124-501: A Randomized, Blinded, Controlled Trial Evaluating the Effect of Immunization with 9-valent Pneumococcal Conjugate Vaccine on Nasopharyngeal Carriage of S. pneumoniae in Israeli Toddlers Enrolled in Day Care Centers

A full study report was not included in the PLA. Immunogenicity data from this study were intended to support vaccination schedules for older children. Subjects age 12-17 months were randomized 1:1 to receive two injections 2-3 months apart of either 9VPnC or MnCC. Subjects age 18-35 months were randomized 1:1 to receive a single injection of 9VPnC or MnCC.

The 9-valent formulation used in this study contains pneumococcal conjugates for all serotypes represented in the 7-valent formulation, plus serotypes 1 and 5. The 9-valent vaccine is reconstituted from a lyophylized preparation, while Prevnar is a liquid formulation. No comparative immunogenicity data (7VPnC vs. 9VPnC) were provided to "bridge" to Prevnar.

The safety and immunogenicity data from this trial for the 9-valent formulation were not viewed to be of sufficient weight or relevance to support vaccine schedules for Prevnar among older children.

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