Name of Sponsor/Company: Wyeth-Lederle Vaccines and Pediatrics	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: 7-valent pneumococcal conjugate vaccine, meningococcal group C conjugate vaccine	**Volume:**	
Name of Active Ingredient: saccharide-CRM_{197} conjugates of pneumococcal serotypes 4,6B,9V,14,18C,19F,23F, saccharide - CRM_{197} conjugate of mening C	**Page:**	

Criteria for evaluation:

Efficacy:

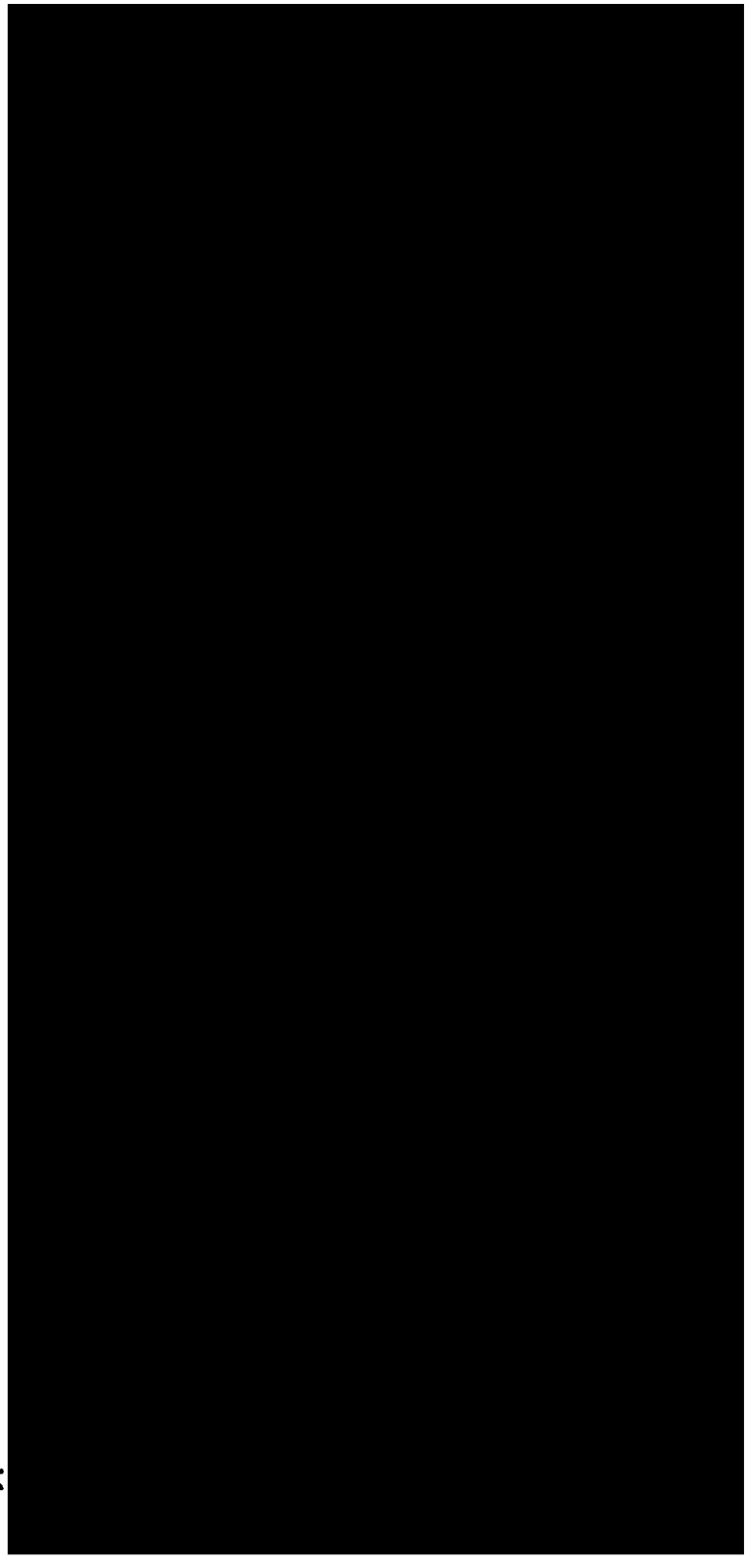
Invasive Disease: A case of invasive pneumococcal disease was defined as a positive culture of *S. pneumoniae* from a normally sterile body fluid obtained from a child presenting with an acute illness consistent with pneumococcal disease. A subject was considered vaccinated per protocol if the following criteria were met: first dose ≥42 days of age, minimum 35 days between primary series doses, third dose given by 365 days of age, booster dose administered between 365 days (12 months) and 480 days (16 months), and ≥60 days between primary series and booster dose. Per-protocol follow-up started 14 days after dose 3 and continued until the earliest of the following: onset of invasive pneumococcal disease, 480 days (16 months) without receipt of booster dose, termination of trial. Intent-to-treat follow-up occurred in all subjects who were randomized into the study and began immediately following randomization. The primary efficacy variable was cases of invasive disease due to a serotype contained in the vaccine during the per-protocol follow-up period in children immunized per-protocol. Secondary efficacy variables were 1)cases of invasive pneumococcal disease due to a vaccine serotype in the intent-to-treat population, 2)cases of any invasive pneumococcal disease, regardless of serotype, during the per-protocol follow-up period in children immunized per-protocol, and 3)cases of any invasive pneumococcal disease, regardless of serotype, in the intent-to-treat population.

Otitis Media (OM): A subject was immunized per-protocol if the following criteria were met: first dose ≥42 days of age, interval of 35-120 days between primary series doses, third dose given by 365 days of age, booster dose administered between 365 days (12 months) and 480 days (16 months), and ≥60 days between primary series and booster dose. Per-protocol follow-up began 14 days after dose 3 and continued until either dropout from the health plan, age 16 months without receipt of booster dose, or April 30, 1998. Intent-to-treat follow-up occurred in all subjects who were randomized into the study and began immediately following randomization. The primary outcome was the overall incidence of OM episodes ("new visits") in the per-protocol follow-up. A child experienced a "new visit" if they had not had a visit for OM in the preceding 21 days. Secondary outcome variables included overall incidence of OM episodes in intent-to-treat population, and the risk of first OM episode, frequent OM episodes, tympanostomy tube placement, and all OM clinic visits in per-protocol and intent-to-treat follow-up. Cases of spontaneously-ruptured ear drums were also assessed.

Immunogenicity: Antibodies (IgG) to the 7 pneumococcal serotypes included in the 7VPnC vaccine were determined by ELISA on samples drawn at 2, 7 12-15, and 13-16 months of age. GMCs and % of subjects achieving defined values (i.e.≥0.15µg/mL and ≥0.50µg/mL for pneumococcal assays) were determined.

Safety: In a subset of subjects, prompted local reactions (erythema, induration, tenderness) were assessed for 2 days following each dose and prompted systemic events (irritability, change in sleep patterns, loss of appetite, vomiting, diarrhea, hives, change in skin tone, fever) and other systemic events (wheezing, convulsions, lethargic/limp, loss of consciousness, twitching) were assessed for 14 days after each dose. Emergency room visits within 3, 14 and 30 days of each dose, hospitalizations within 3, 14, 30 and 60 days of each dose, and outpatient clinic visits for seizures within 3 and 30 days and allergic reactions including hives as well as wheezing, asthma, breath holding and shortness of breath within 3 days were also assessed. All subjects who received a dose of study vaccine were included in the assessment of hospitalizations, ER visits, and outpatient clinic visits.

Attachment 5



Efficacy Estimates With 95% Confidence Limits For All Possible Case Splits That Would Permit Rejection of the Null Hypothesis.

Attachment 6

Primary Analysis

Per Protocol Subjects With Invasive Disease

Case definition: any case of invasive disease due to vaccine serotypes occurring in an immune competent per protocol subject during the per protocol specified follow-up intervals - both for the primary and booster series. All cases must have at least one isolate of pneumococcus of one of the seven vaccine serotypes isolated from a normally sterile site. More than one isolate from a single sample will count as a single event.

The analysis is described in the submitted protocol. The analysis takes the total number of cases and evaluates whether the split between the vaccine and control group is different from that expected if occurring at random (i.e. the vaccine has 0% efficacy). It has been agreed that an interim analysis may be done with 17 cases and the trial stopped if the vaccine/control split is better than or equal to 2/15.

It should be noted that the test depends on the ratio of follow-up times in the groups, but not on the specific follow-up time in the groups. In a completely randomized design with dropouts completely at random a ratio of 0.5 is expected. The planned interim analysis assumed a follow-up ratio of exactly 0.5.

The raw, actual per protocol follow-up (pers-mnths) as of March 31 has been calculated as follows:

Vaccine 1 - 141,118 ratio = 0.5007 [redacted]
Vaccine 2 - 141,516

The databases necessary for the calculation of the follow-up time ratio will be closed by April 30, 1998. The next databases will be available September 30, 1998 and then December 31, 1998. Efficacy calculations done prior to September 30 will use the April 30 database and calculations done between September 30 and December 31 will use the September 30 database. As noted previously, these follow-up time differences will have a minimal effect on the expected binomial p of 0.5.

In addition to the per protocol analysis, the robustness of the conclusion will be tested using an intent to treat analysis (all subjects randomized to treatment and all cases regardless of when they occurred).

9.7.1.1.1 Statistical Methods for Invasive Pneumococcal Disease

Protective efficacy against invasive pneumococcal disease was estimated as

[redacted]

Exact Binomial Test

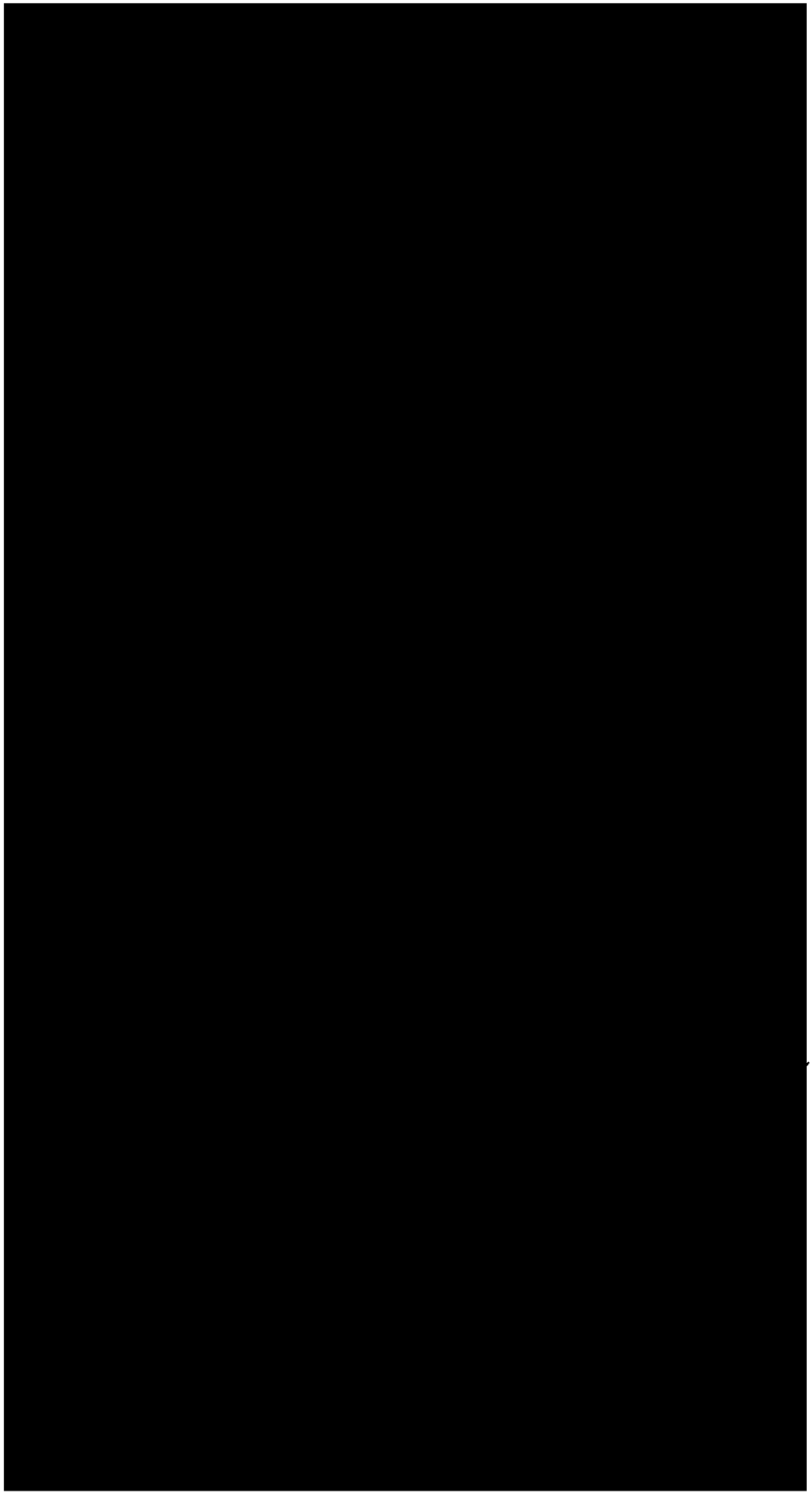
[redacted]

[redacted]

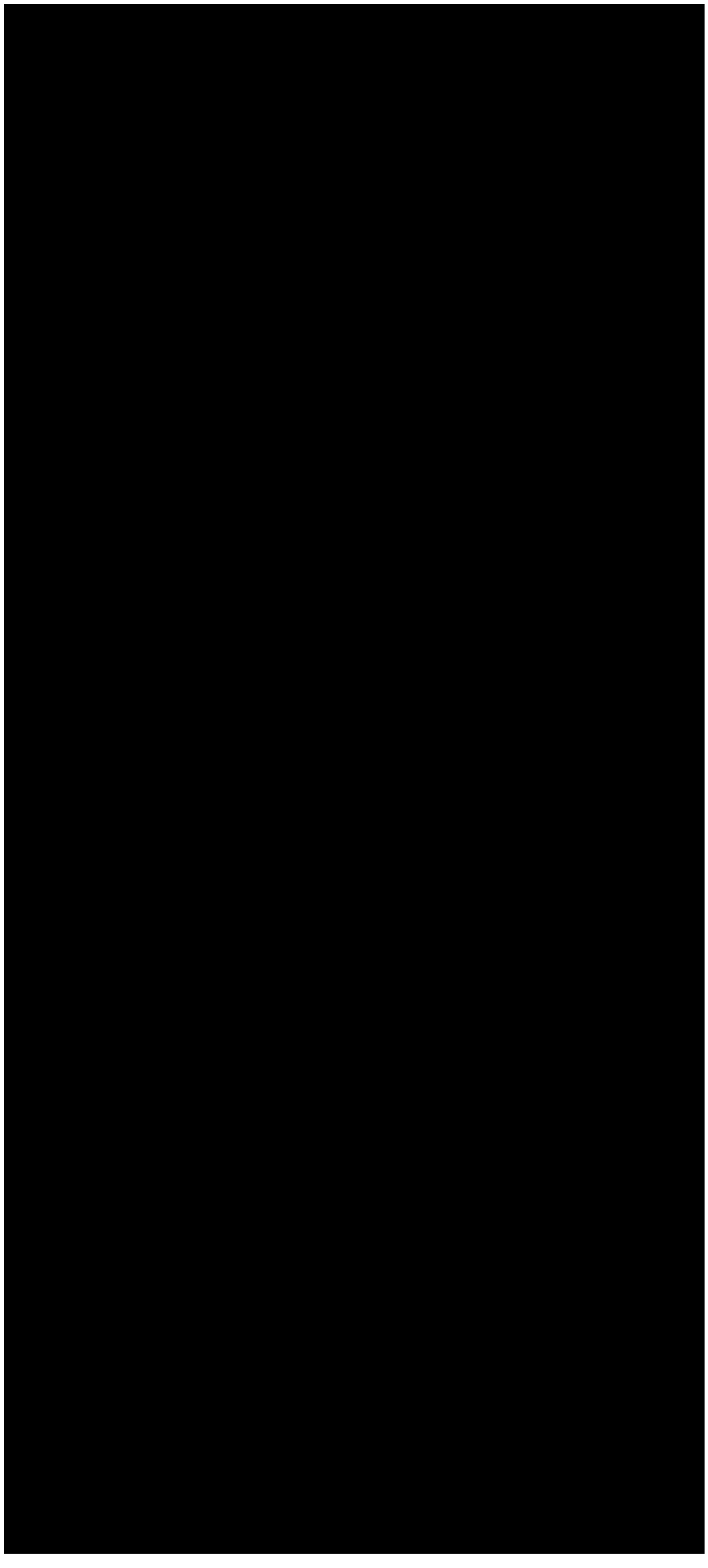
[redacted]

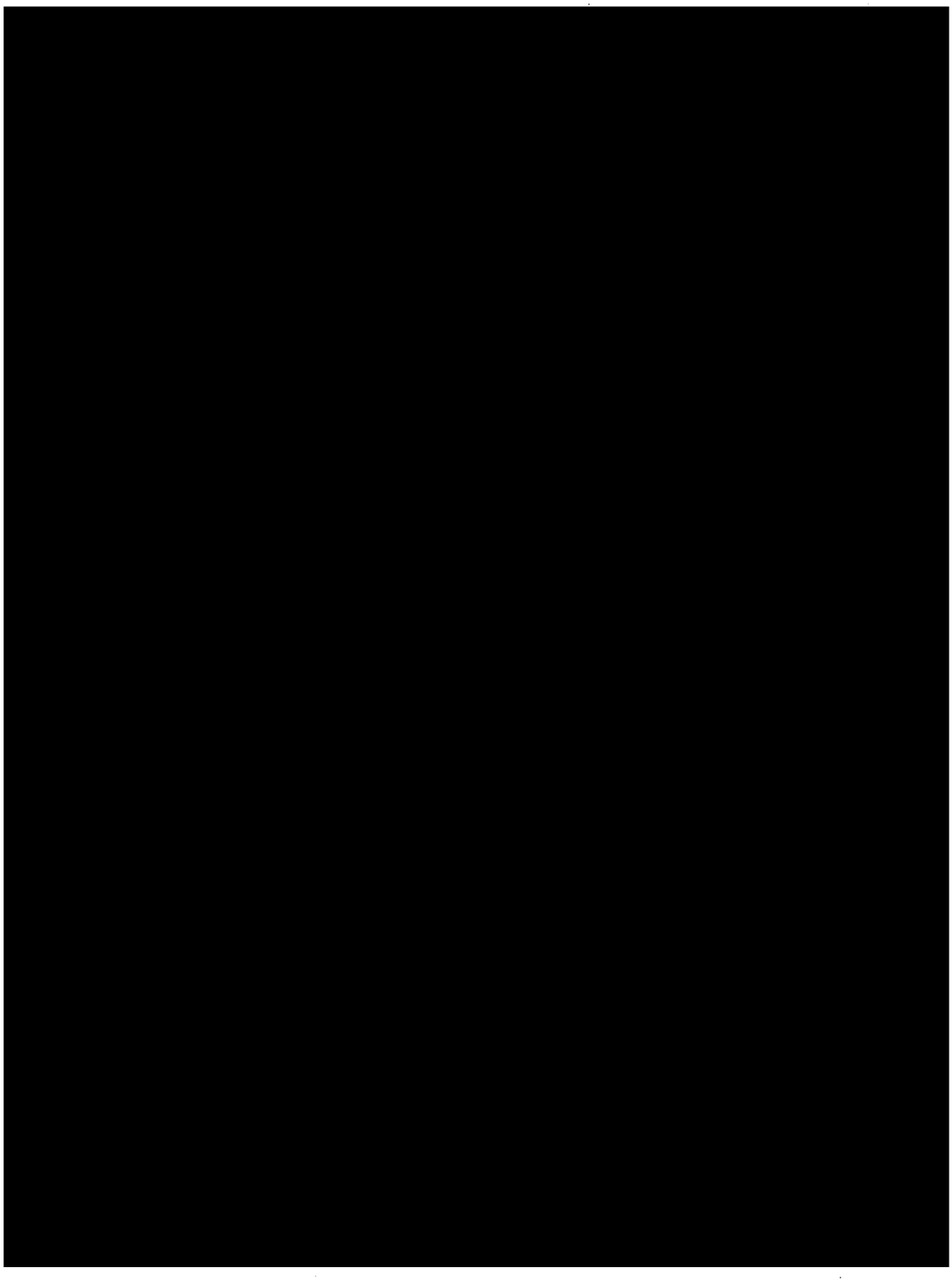
Exact Confidence Interval

[redacted]



9.7.1.1.2





[redacted]

[redacted]

[redacted]

9.7.2 Determination of Sample Size

[redacted]

[redacted]

Attachment 7

a. Exclusions from per protocol analysis

Table 6 summarizes the number of subjects excluded from the per-protocol analysis for invasive disease by the reason for their exclusion. Table 7 summarizes the number of subjects who were included in the per-protocol analysis of invasive disease but with shortened per-protocol follow-up period for protocol violation, death, or invasive disease (as of April 30, 1999).

No disparity in the percentage of subjects excluded from per-protocol analysis of invasive disease was seen between the two study vaccine groups: 21.6% and 21.8% of children enrolled as of April 30, 1998 in the 7VPnC and MnCC group respectively (Table 6). Similarly, no disparity was seen between the two study vaccine groups in the percentage of subjects whose invasive disease per-protocol follow-up period ended early due to protocol violations, death or invasive disease: 7.6% and 7.5% of children enrolled as of April 30, 1998 in the 7VPnC and MnCC group respectively (Table 7). The per-protocol follow-up time, therefore, was nearly identical between the two vaccine groups as of April 30, 1998: 12889.15 and 12886.11 child years in the 7VPnC and MnCC group respectively[1]. The ratio of the per-protocol follow-up time in 7VPnC subjects versus the total PP follow-up time was 0.500059. The intent-to-treat follow-up time as of April 30, 1998 was 21265.94 and 21254.42 child years in the 7VPnC and MnCC group respectively. The ratio of the ITT follow-up time in 7VPnC subjects versus the total ITT follow-up time was 0.500135.

b. Effect of <u>not</u> excluding subjects who failed to get the 4th dose on time

In the primary analysis for invasive disease, subjects were dropped from the PP analysis if they did not receive their 4th dose by 16 months of age. In a telephone conversation with Dr. Lydia Falk, we were asked to determine what effect including these subjects would have on follow-up time and efficacy. If the PP follow-up period of those subjects who did not receive dose 4 by 16 months of age is allowed to continue to April 30, 1998, the PP follow-up time would be13635.36 and 13593.93 child years in the 7VPnC and MnCC group, respectively. The ratio of the follow-up time in 7VPnC subjects versus the total PP follow-up time would then be 0.500761. Since none of the invasive disease cases (PP or ITT) that occurred prior to interim analysis were in children who either had dose 4 out-of-schedule or missed dose 4, the vaccine efficacy estimate will be the same as the vaccine efficacy estimate from per-protocol analysis and

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[1] Please note that in the submission dated August 30, 1999, Table 1 showed that the PP follow-up (days at risk) as of April 30, 1998 was 10047 and 10098 child years in the 7VPnC and MnCC group respectively. Those were PP follow-up time for otitis media endpoints. The [redacted] dataset FDAREQ2 submitted on September 13, 1999 contains the complete follow-up time data for invasive disease. These numbers: 12889.15 and 12886.11 child years quoted here are directly derived from the dataset FDAREQ2.

Table 6: Number (Percentage) of Subjects Excluded from Per-Protocol Analysis for Invasive Disease as of April 30, 1998

	7VPnC Group	MnCC Group	Total
Total number of subject randomized	17070	17076	34146
Total number (%) of subjects excluded from per-protocol analysis of invasive disease	3696 (21.6%)	3723 (21.8%)	7419 (21.7%)
Reasons for Exclusion			
Dose 3 was not given prior to 4/16/98 (the last day a subject could receive dose 3 and still contribute per-protocol follow-up prior to 4/30/98)	2859 (16.7%)	2877 (16.8%)	5736 (16.8%)
Reached 365 days of age without receiving three doses	629 (3.7%)	607 (3.6%)	1236 (3.6%)
Age at dose 1 < 42 days or > 120 days	35 (0.2%)	35 (0.2%)	70 (0.2%)
Interval between dose 1 and dose 2 < 35 days	15 (0.1%)	19 (0.1%)	34 (0.1%)
Interval between dose 2 and dose 3 < 35 days	32 (0.2%)	36 (0.2%)	68 (0.2%)
Dose 4 given within 14 days of dose 3	1 (<0.1%)	0	1 (<0.1%)
Required other vaccines not given at dose 1, or 2, or 3	7 (<0.1%)	1 (<0.1%)	8 (<0.1%)
Other vaccine given prior to the dose 1	41 (0.2%)	55 (0.3%)	96 (0.3%)
More than one vaccine with Hib or pertussis components given at dose 1, or 2, or 3	1 (<0.1%)	1 (<0.1%)	2 (<0.1%)
Not eligible at enrollment (did not meet all protocol subject enrollment criteria)	12 (0.1%)	13 (0.1%)	25 (0.1%)
Received incorrect study vaccine given at dose 1 (departure from randomized assignment)	14 (0.1%)	10 (0.1%)	24 (0.1%)
Received incorrect vaccine at dose 2 or dose 3	29 (0.2%)	48 (0.3%)	77 (0.2%)
Received gamma globulin	14 (0.1%)	8 (<0.1%)	22 (0.1%)
Died prior to the start of per-protocol follow-up	6 (<0.1%)	7 (<0.1%)	13 (<0.1%)
Invasive pneumococcal disease prior to the start of per-protocol follow-up	1 (<0.1%)	6 (<0.1%)	7 (<0.1%)

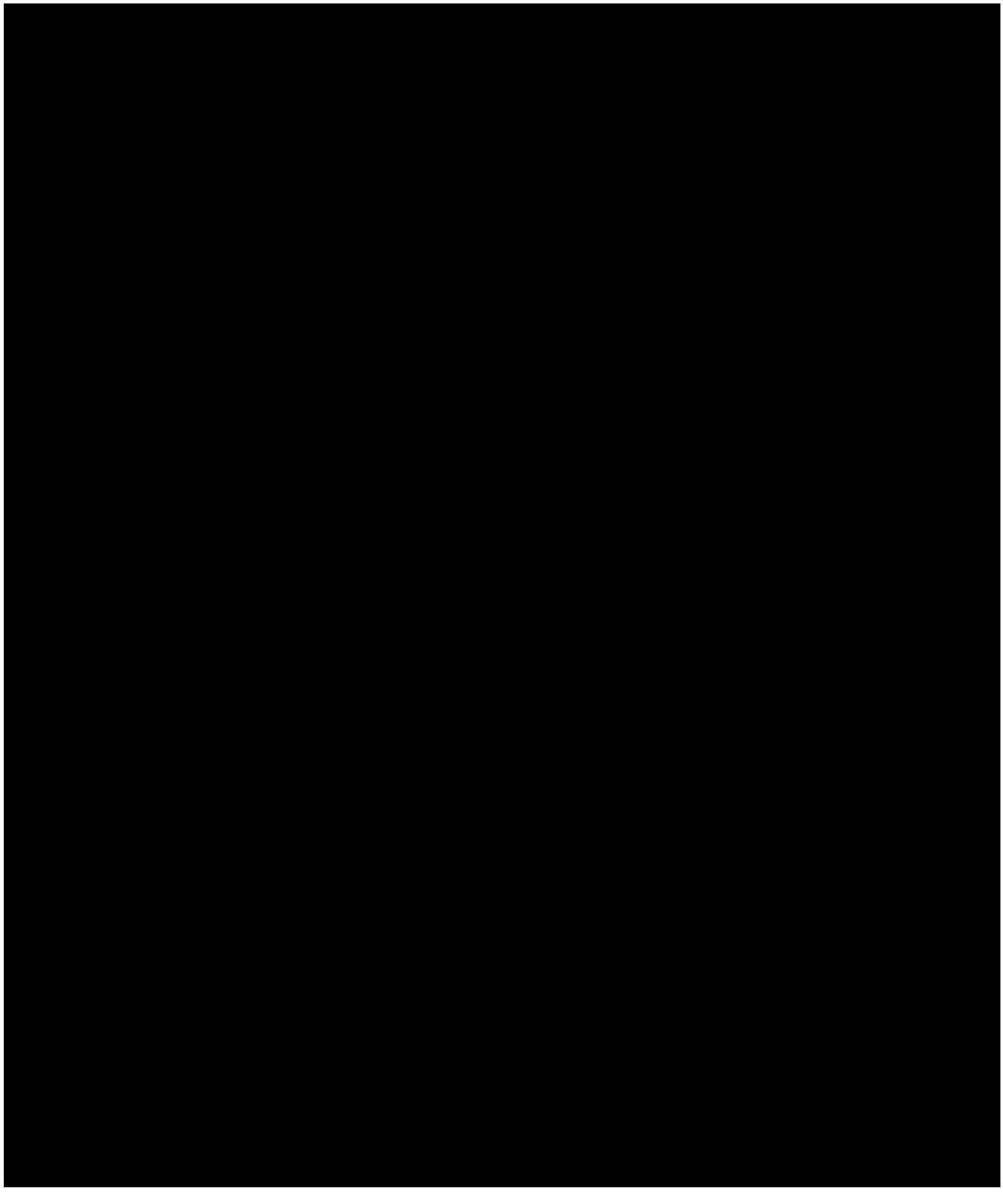
Table 7: Number of Subjects Whose Per-Protocol Follow-up Period for Invasive Disease Ended Due to Protocol Violations, Death, or Invasive Disease as of April 30, 1998

	7VPnC Group	MnCC Group	Total
Total number of subject randomized	17070	17076	34146
Total number (%) of subjects included in per-protocol analysis of invasive disease	13375 (78.4%)	13353 (78.2%)	26728 (78.3%)
Total number (%) of subjects included in per-protocol analysis of invasive disease but with shortened per-protocol follow-up period due to protocol violations, death, or invasive disease	1300 (7.6%)	1289 (7.5%)	2589 (7.6%)
Reasons for Ending Per-Protocol Follow-up Period			
Reached 16 months of age without receiving dose 4	1213 (7.1%)	1171 (6.9%)	2384 (7.0%)
Age at dose 4 < 12 months	41 (0.2%)	69 (0.4%)	110 (0.3%)
Interval between dose 3 and dose 4 < 60 days	9 (0.1%)	10 (0.1%)	19 (0.1%)
More than one vaccine with Hib or pertussis components given at dose 4	2 (<0.1%)	0	2 (<0.1%)
Received incorrect vaccine at dose 4	11 (0.1%)	8 (<0.1%)	19 (0.1%)
Received a 5th dose of study vaccine	19 (0.1%)	13 (0.1%)	32 (0.1%)
Died after the start of per-protocol follow-up period†	2 (<0.1%)	2 (<0.1%)	4 (<0.1%)
Invasive pneumococcal disease after the start of per-protocol follow-up period*	2 (<0.1%)	16 (0.1%)	18 (0.1%)

† These are deaths occurred prior to May 1, 1998

* These are the cases of invsive pneumococcal disease of any serotype that occurred prior to May 1, 1998.

Attachment 8



October 1999 communication

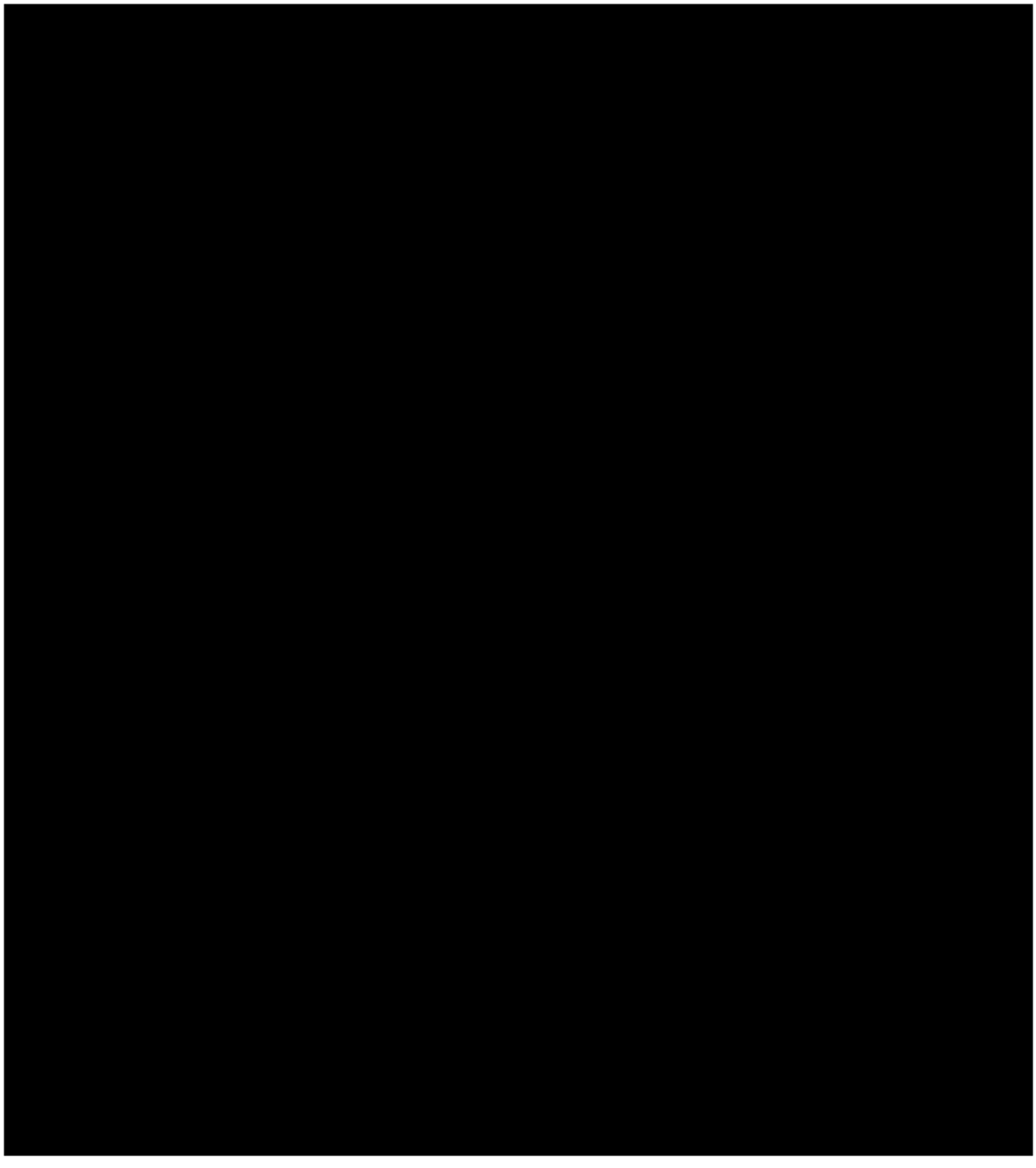


Table 1: Follow-Up Time for Invasive Disease

	Through April 30, 1998		Through August 20, 1998†	
	7VPnC	MnCC	7VPnC	MnCC
Per-Protocol (PP) Analysis				
Number of Children Included	13374	13353	15161	15115
Total Follow-up (child years)	12889.2	12886.1	16834.5	16828.5
Proportion of Follow-up Time in 7VPnC Group	0.50006		0.50009	
Intent-to-Treat (ITT) Analysis				
Number of Children Included*	17070	17076	18906	18910
Total Follow-up (child years)	21265.9	21254.4	26773.3	26757.3
Proportion of Follow-up Time in 7VPnC Group	0.50014		0.50015	

* All randomized children.

† Preliminary database for the period May 1, 1998 through August 20, 1998.

December 1999 communication

Attachment 9

Initial Catch-up Protocols

The results from the following clinical studies were analyzed to determine the appropriate catch up schedules. In most instances these results are only a part of a more encompassing protocol. Details on each study are presented in the sections on the individual catch up studies.

Dl 18-P9: Eligible subjects, 15-24 months of age, were recruited and randomized to receive a single dose of one of two pilot plant lots of 7VPnC vaccine. For this report the immunogenicity of a single dose of 7VPnC vaccine (regardless of lot) in toddlers with the age at 1st vaccination of 15-17 months and 18-23 months was evaluated. The safety at > 12-24+ months was also tabulated.

D118-P12: For Amendments 2 and 4 to protocol D118-P12, control subjects who had not received the primary series (2, 4, 6 month) of 7VPnC vaccine were reenrolled in order to evaluate the immunogenicity and safety of 7VPnC vaccine administered at 7 and 9 months (catch up series) and 15-18 months (booster dose).

D118-P15: The primary objective of this protocol was to demonstrate that 7VPnC vaccine is effective in preventing invasive vaccine-type pneumococcal disease in Native American infants and toddlers after a primary 3 dose series or a primary series and booster dose. For this report the immunogenicity of one or two doses of 7VPnC vaccine in children who received the lst dose of 7VPnC vaccine at 12-17 months and 18-23 months of age is described. This is an ongoing, blindedstudy, and only subjects with immunogenicity results from the described catch up schedules have been unblinded.

D 118-P8: The primary objective of this study was to determine the efficacy of 7VPnC vaccine in infants enrolled at Northern California Kaiser Permanente. The 7VPnC vaccine has been shown to be 100% efficacious against vaccine type invasive pneumococcal disease in this study. Therefore, the immune response in two subsets of infants who received the primary series of 7VPnC vaccine concomitant with either DTP/HbOC or DTaP + HbOC vaccines are used as a reference of acceptability for the various catch up schedules. Please refer to the individual clinical study reports of the D118-P8 study for additional information on the immune responses to 7VPnC vaccine in these infant subjects.

Study 118-16

Objectives:

To compare the safety and immunogenicity of a pilot plant lot of heptavalent pneumococcal conjugate (formulated with Adjuphos aluminum phosphate and filled in blow-molded vials, referred to as pilot)) to the first full-scale manufacturing lot of this vaccine, formulated with commercial Lederle aluminum phosphate in place of Adjuphos and filled in single dose tubing vials instead of blow-molded vials (referred to as Manufacturing New)

To compare the safety and immunogenicity of a pilot plant lot of heptavalent pneumococcal conjugate to the first full-scale manufacturing lot of this vaccine using the same formulation (Adjuphos aluminum phosphate and filled in blow-molded vials and referred to as Manufacturing Pilot).

To assess the compatibility of heptavalent pneumococcal conjugate with simultaneously administered inactivated poliovirus vaccine (IPV) and hepatitis B vaccine, a control group received only routine vaccinations at 2,4, and 6 months of age. This Control group received 7VPnC vaccine at 7 and 9 months of age.

Amendment #1 implemented a 7VPnC booster dose to all children at 12-15 months of age.

The results for the subjects who received primary immunization with 7VPnC at 2, 4, and 6 months of age have been submitted as a separate report with the PLA.

In this synopsis, the immunogenicity and safety of the 7VPnC vaccine administered at 7, 9 and 12-15 months of age was evaluated.

Study 118-18

This study was an open-label, non-controlled outpatient study. Subjects were enrolled in one of five study treatment groups dependent on age of subject as follows:
(1) Group A: Subjects >12 and <18 months old received two IM injections of 0.5 ml of 7VPnC in the left thigh, one injection was given at enrollment and the second given two months later.

(2) Group B: Subjects >_18 and <24 months old received two IM injections of 0.5 ml of 7VPnC in the left thigh, one injection was given at enrollment and the second given two months later.

(3) Group C: Subjects >24 months and < 36 months of age received one IM injection of 0.5m1 7VPnC in the left deltoid.

(4) Group D: Subjects > 36 months and < 60 months of age received one IM injection of 0.5m17VPnC in the left deltoid.

(5) Group E: Subjects >5 and <10 years of age received one IM injection of 0.5ml 7VPnC in the left deltoid.

[redacted]

The acceptable interval between the two doses in Groups A and B was 42-72 days. No concomitant vaccinations were given.

Parents were instructed to contact the investigator immediately in the case of any severe adverse event or hospitalization for any reason.

Blood was drawn from each subject on two occasions during the course of the subject's participation in the study: preimmunization (at time of enrollment) and at 1 month (21 - 42 days) following the second immunization in Groups A and B, or the single immunization for Groups C, D and E. For the analysis 21-42 days was widened to 21-63 days to be consistent with the other catch up analyses.

Attachment 10

In all studies in which the immune responses to Prevnar™ were contrasted to control, a significant antibody response was seen to all vaccine serotypes following three or four doses, although geometric mean concentrations of antibody varied among serotypes.[18,19,20,21,22,23,24,25]

The minimum serum antibody concentration necessary for protection against invasive pneumococcal disease has not been determined for any serotype. Prevnar™ induces functional antibodies to all vaccine serotypes, as measured by opsonophagocytosis following three doses.[25]

Previously Unvaccinated Older Infants and Children

To determine an appropriate schedule for children 7 months of age or older at the time of the first immunization with Prevnar™, 764 children in [redacted] ancillary studies received Prevnar™ at various schedules. GMCs attained using the various schedules among older infants and children were comparable to immune responses of children in the NCKP efficacy study (118-8) after 3 doses for most serotypes, as shown in Table 4. These data support the schedule for previously unvaccinated older infants and children who are beyond the age of the infant schedule. For usage in older infants and children see DOSAGE AND ADMINISTRATION.

TABLE 4

Geometric Mean Concentrations (µg/mL) of Pneumococcal Antibodies Following Immunization of Children From 7 Months Through 9 Years of Age With Prevnar™[26]

Age group, Vaccinations	Study	Sample Size(s)	4	6B	9V	14	18C	19F	23F
7-11 mo. 3 doses	118-12	22	**2.34**	**3.66**	**2.11**	**9.33**	**2.31**	**1.60**	**2.50**
	118-16	39	**3.60**	**4.63**	**2.04**	**5.48**	**1.98**	**2.15**	**1.93**
12-17 mo. 2 doses	118-15*	82-84†	**3.91**	**4.67**	**1.94**	**6.92**	**2.25**	**3.78**	**3.29**
	118-18	33	**7.02**	**4.25**	**3.26**	**6.31**	**3.60**	**3.29**	**2.92**
18-23 mo. 2 doses	118-15*	52-54†	**3.36**	**4.92**	**1.80**	**6.69**	**2.65**	**3.17**	**2.71**
	118-18	45	**6.85**	**3.71**	**3.86**	**6.48**	**3.42**	**3.86**	**2.75**
24-35 mo. 1 dose	118-18	53	**5.34**	**2.90**	**3.43**	1.88	**3.03**	**4.07**	**1.56**
36-59 mo. 1 dose	118-18	52	**6.27**	**6.40**	**4.62**	**5.95**	**4.08**	**6.37**	**2.95**
5-9 years, 1 dose	118-18	101	**6.92**	**20.84**	**7.49**	**19.32**	**6.72**	**12.51**	**11.57**
118-8, DTaP	Post dose 3	31-32†	1.47	2.18	1.52	5.05	2.24	1.54	1.48

Bold = GMC not inferior to 118-8, DTaP post dose 3 (one-sided lower limit of the 95% CI of GMC ratio ≥ 0.50).

* Study in Navajo and Apache populations.

† Numbers vary with serotype.

Name of Sponsor/Company: Wyeth-Lederle Vaccines and Pediatrics	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Produ pneumococcal conjugate	**Attachment 11**	
Name of Active Ingredie Saccharide CRM_{197} conjugate of serotypes 4, 6B, 9V, 14, 18C, 19F, 23F,		

Methodology: This was a multicenter, randomized, double-blind study in healthy 2 month old (defined as 50 - 100 days of age) infants. Subjects in three of the groups received heptavalent (4, 6B, 9V, 14, 18C, 19F, 23F) pneumococcal conjugate vaccine (one of three different lots) administered concurrently with HbOC from separate syringes in the left leg, with DTaP in the right leg. The fourth group received HbOC only in the left leg and DTaP in the right leg and served as a control group for evaluating compatibility of pneumococcal conjugate administered concurrently with these vaccines. As the immunization schedule coincided with that of polio vaccine, OPV (2, 4, 6 months) or IPV (2, 4 months) were also concurrently administered.

Subjects were monitored for reactogenicity for three days post immunization and for any significant adverse events defined as those requiring prescription medications or a physician visit within 7 days of immunization, a hospitalization at any time during the 5 month study period or any event resulting in study termination.

Blood samples were obtained prior to the first vaccination (at approximately 2 months of age), prior to the third vaccination (at 6 months of age) and one month following the third vaccination (at approximately 7 months of age).

Number of subjects (planned and analyzed): Planned total=300;75 per treatment group.
Included for safety: Total 342; 84 lot A, 86 lot B, 86 lot C, 86 Control.
Included for immunogenicity: Total 283; 74 lot A, 67 lot B, 74 lot C, 68 Control.

Diagnosis and main criteria for inclusion: Healthy infants 2 months of age (defined as 50 - 100 days of age).

Test product, dose and mode of administration, lot number: Each 0.5 ml dose of 7-valent pneumococcal conjugate vaccine contained 2 µg per serotype of 4, 9V, 14, 18C, 19F, 23F and 4 µg of serotype 6B (16 µg total saccharide); approximately 20 µg of CRM_{197} carrier protein and approximately 0.5 mg aluminum phosphate.

Mode of administration: Intramuscular in the lower left thigh.
Lot numbers: [redacted]

Duration of treatment:
Each subject received pneumococcal conjugate vaccine at 2, 4, and 6 months, followed by a final bleed at 7 months.

Reference therapy, dose and mode of administration, batch number: None

Criteria for evaluation:

Immunogenicity: Geometric mean concentrations (anti-PnC IgG, µg/mL) to each of the 7 serotypes were obtained by ELISA from samples drawn at 2, 6, and 7 months. The results were also expressed as % subjects with defined IgG concentrations (≥ 0.15 µg/mL, ≥ 0.5 µg/mL) to each of the 7 pneumococcal serotypes. Sera was also analyzed for antibody responses to the components of DTaP and HbOC vaccines. The results were expressed as geometric mean concentrations (GMC - µg/mL) and % subjects that achieved defined IgG concentrations to the Hib-PRP (% ≥ 0.15 µg/mL, % ≥ 1.0 µg/mL), Diphtheria (% ≥ 0.01 IU/mL, % ≥ 0.10 IU/mL), Tetanus (% ≥0.01 IU/mL, % ≥ 0.10 IU/mL), or seroconverted to Pertussis toxin (% ≥ 2 fold rise, ≥ 4 fold rise), Pertussis fimbriae (% ≥ 2 fold rise, ≥ 4 fold rise), Pertussis pertactin (69 kDa) (% ≥ 2 fold rise, ≥ 4 fold rise), Pertussis FHA (% ≥ 2 fold rise, ≥ 4 fold rise) antigens of the DTaP and HbOC vaccines. Reverse cumulative distribution curves of the antibody responses to the seven serotypes of the 7VPnC vaccine and to the DTaP and HbOC vaccine antigens were also generated.

Name of Sponsor/Company: Wyeth-Lederle Vaccines and Pediatrics	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: 7-valent pneumococcal conjugate vaccine **Name of Active Ingredient:** Saccharide CRM_{197} conjugate of serotypes 4, 6B, 9V, 14, 18C, 19F, 23F,	**Volume:** **Page:**	

Safety: Local reactions (induration, erythema, and tenderness), systemic events (fussiness, drowsiness, decreased appetite, and temperature), and use of antipyretics were assessed by the parent or guardian on the day of each immunization and for three days following each immunization. Any serious adverse events were reported at any time during the study period.

Statistical Methods:

Immunogenicity:

ELISA IgG Antibody Response by 7 VPnC Lot: The geometric mean concentration (GMC) of antibody titers along with confidence intervals were determined for the seven vaccine serotypes in each vaccine lot. Analysis of covariance was performed on logarithmic transformed titers for each serotype to compare the responses of the three vaccine lots. Vaccine lot and study center were used as classification variables in the analysis of covariance and the pre-vaccination titer (on a logarithmic scale) was used as a covariate. Differences in the proportion of subjects in the two vaccine groups reaching a given level of antibody concentration (≥ 0.15 μg/mL, ≥ 0.5 μg/mL) were determined by Pearson chi-square test. In addition, the shape and spread of the entire antibody titer distribution was evaluated using reverse cumulative distribution plots.

Effect of 7VPnC on Antibody Response to DTaP and HbOC: To determine whether simultaneous administration of pneumococcal conjugate vaccine and routine immunization was compatible, antibody responses to diphtheria, tetanus, pertussis, and HbOC antigens were compared between the subjects receiving the DTaP/HbOC vaccines concurrently with or without 7VPnC vaccine. Comparisons were made on the antibody response to the DTaP and HbOC antigens based on (1) GMC, (2) sero-conversion rate [proportion of subjects achieving ≥ 0.15 μg/mL and ≥ 1 μg/mL anti-PRP antibody for *Haemophilus influenzae* type b (Hib-PRP); ≥ 0.01 IU/mLand ≥ 0.1 IU/mL antitoxin for diphtheria; ≥ 0.01 IU/mL and ≥ 0.1 IU/mL antitoxin for tetanus; and $\geq$ 2-fold and $\geq$ 4-fold rise for pertussis toxin, fimbriae, pertactin, and FHA] (3) the overall antibody titer distribution by reverse cumulative distribution curves.

Kinetics of the 7VPnC Antibody Response: The anti-pneumococcal antibody responses following the second and third doses were analyzed to determine the kinetics of immune response. GMCs and sero-conversion rates at 0.15 μg/mL and 0.5 μg/mL and their confidence intervals were determined.

Safety: Rates of local reactions and systemic events among the three 7VPnC groups were compared using the Pearson chi-square test; comparisons between the pooled 7VPnC and Control groups were made using the Fisher's Exact Test or McNemar's Test. The rate of adverse events reported post-vaccination was tabulated.

Table 17: GMC of Antibody to Antigens in DTaP and HbOC in Each 7VPnC Lot Group

Antigen	Antibody GMC (95% Confidence Interval) of 7VPnC Lot Groups							
	Pre Dose 1				Post Dose 3			
	Lot A*	Lot B*	Lot C*	P-Value‡	Lot A	Lot B	Lot C	P-Value†
	N¶ = 74	N¶ = 67	N¶ = 72		N¶ = 74	N¶ = 67	N¶ = 72	
PRP	0.08 (0.07, 0.10)	0.11 (0.08, 0.14)	0.10 (0.08, 0.13)	0.208	5.98 (4.30, 8.31)	5.44 (3.92, 7.56)	7.24 (5.43, 9.65)	0.428
Diphtheria	0.03 (0.03, 0.04)	0.03 (0.02, 0.05)	0.05 (0.03, 0.06)	0.223	0.85 (0.71, 1.02)	0.91 (0.74, 1.10)	0.87 (0.72, 1.05)	0.641
Tetanus	0.54 (0.42, 0.70)	0.73 (0.50, 1.07)	0.72 (0.54, 0.97)	0.290	3.53 (2.95, 4.22)	3.21 (2.63, 3.93)	3.61 (3.06, 4.24)	0.604
Pertussis Toxin	1.81 (1.40, 2.34)	1.93 (1.44, 2.58)	2.02 (1.58, 2.59)	0.817	21.41 (18.10, 25.32)	17.72 (14.61, 21.50)	18.08 (15.05, 21.73)	0.386
Fimbriae	1.04 (0.84, 1.28)	1.00 (0.80, 1.25)	1.20 (0.93, 1.55)	0.482	3.29 (2.50, 4.32)	3.33 (2.50, 4.44)	3.24 (2.44, 4.31)	0.998
69K	4.30 (3.35, 5.53)	5.93 (4.65, 7.58)	7.92 (6.06, 10.35)	0.004	41.69 (33.87, 51.33)	39.69 (32.17, 48.98)	38.90 (31.36, 48.25)	0.990
FHA	5.40 (4.25, 6.86)	5.55 (4.45, 6.91)	7.58 (5.76, 9.98)	0.107	49.55 (40.88, 60.05)	40.18 (34.01, 47.47)	41.78 (35.29, 49.46)	0.294

* [redacted]

† P-values of Post Dose 3 comparison of the three lots were based on an ANCOVA model with vaccine lot, study site as classification variables, and pre dose 1 level (centered around the overall pre dose 1 mean in log scale) as a covariate for all antigens.

‡ P-values of Pre Dose 1 comparison of the three lots were based on an ANOVA model with vaccine lot, study site as classification variables.

¶ The maximum number of available samples for each group. The actual number of samples sample for which each assay was done may be smaller (see Appendix A.I, Table A.I.3).

Attachment 12

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Table 20: Comparisons of GMCs of Antibody to Antigens in DTaP and HbOC Between 7VPnC Recipients and Control

Antigen	GMC (95% Confidence Interval) of Post Dose 3 Antibody with Concurrent 7VPnC*	GMC (95% Confidence Interval) of Post Dose 3 Antibody without Concurrent 7VPnC	P-Value†	Ratio of GMC of Concurrent 7VPnC to Control (with 90% CI)
	N¶ = 214	N¶ = 67		
PRP	6.21 (5.17, 7.44)	4.36 (3.07, 6.19)	0.067 •	1.43 (1.04, 1.96)
Diphtheria	0.88 (0.79, 0.97)	0.80 (0.63, 1.01)	0.741	1.04 (0.87, 1.23)
Tetanus	3.45 (3.11, 3.83)	4.14 (3.39, 5.07)	0.037	0.80 (0.67, 0.95)
Pertussis Toxin	19.05 (17.15, 21.15)	17.83 (14.93, 21.28)	0.404	1.09 (0.92, 1.29)
Fimbriae	3.29 (2.79, 3.86)	4.17 (3.24, 5.37)	0.316	0.81 (0.58, 1.14)
69K	40.11 (35.52, 45.29)	50.93 (41.65, 62.27)	0.067 •	0.80 (0.65, 0.98)
FHA	43.77 (39.50, 48.49)	46.70 (39.85, 54.74)	0.595	0.95 (0.81, 1.12)

* Three 7VPnC lot groups combined.

† P-values of Post Dose 3 comparison of the two treatment groups were based on an ANCOVA model with vaccine lot, study site as classification variables, and pre dose 1 level (centered around the overall pre dose 1 mean in log scale) as a covariate for all antigens except antigens except diphtheria and fimbriae. For diphtheria, the model also included the interaction term between treatment (with or without 7VPnC) and pre dose 1 level, as the P-value for the interaction term was 0.015 (details in Appendix II). For fimbriae, the model also included the interaction term between treatment (with or without 7VPnC) and study site, as the P-value for the interaction term was 0.027 (details in Appendix II).

¶ The maximum number of available samples for each group. The actual number of samples sample for which each assay was done may be smaller (see Appendix A.I, Table A.I.3).

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Appendix II

Table 19: GMC of Antibody to Antigens in DTaP and HbOC – Three 7VPnC Lot Groups Combined

Antigen	Geometric Mean Concentration (95% Confidence Interval) of Antibody							
	Pre Dose 1				Post Dose 3			
	with Concurrent 7VPnC*		without Concurrent 7VPnC	P-Value†	with Concurrent 7VPnC*		without Concurrent 7VPnC	P-Value†
	N¶ = 214		N¶ = 67		N¶ = 214		N¶ = 67	
PRP	0.10	(0.08, 0.11)	0.12 (0.10, 0.16)	0.087	6.21	(5.17, 7.44)	4.36 (3.07, 6.19)	0.067
Diphtheria	0.04	(0.03, 0.04)	0.05 (0.04, 0.07)	0.067	0.88	(0.79, 0.97)	0.80 (0.63, 1.01)	0.741
Tetanus	0.66	(0.55, 0.79)	0.84 (0.66, 1.06)	0.190	3.45	(3.11, 3.83)	4.14 (3.39, 5.07)	0.037
Pertussis Toxin	1.92	(1.65, 2.23)	1.79 (1.37, 2.33)	0.653	19.05	(17.15, 21.15)	17.83 (14.93, 21.28)	0.404
Fimbriae	1.08	(0.94, 1.23)	0.82 (0.67, 1.00)	0.047	3.29	(2.79, 3.86)	4.17 (3.24, 5.37)	0.316
69K	5.83	(5.02, 6.78)	5.34 (4.22, 6.74)	0.550	40.11	(35.52, 45.29)	50.93 (41.65, 62.27)	0.067
FHA	6.09	(5.28, 7.03)	5.87 (4.63, 7.43)	0.803	43.77	(39.50, 48.49)	46.70 (39.85, 54.74)	0.595

* Three 7VPnC lot groups combined.

† P-values of Post Dose 3 comparison of the two treatment groups were based on an ANCOVA model with vaccine lot, study site as classification variables, and pre dose 1 level (centered around the overall pre dose 1 mean in log scale) as a covariate for all antigens except fimbriae. For fimbriae, the model also included the interaction term between treatment (with or without 7VPnC) and study site, as the P-value for the interaction term was 0.027 (details in Appendix II).

¶ The maximum number of available samples for each group. The actual number of samples sample for which each assay was done may be smaller (see Appendix A.I, Table A.I.3).

Attachment 13

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Table 20: Comparisons of GMCs of Antibody to Antigens in DTaP and HbOC Between 7VPnC Recipients and Control

Antigen	GMC (95% Confidence Interval) of Post Dose 3 Antibody		P-Value†	Ratio of GMC of Concurrent 7VPnC to Control (with 90% CI)
	with Concurrent 7VPnC*	without Concurrent 7VPnC		
	N¶ = 214	N¶ = 67		
PRP	6.21 (5.17, 7.44)	4.36 (3.07, 6.19)	0.067 •	1.43 (1.04, 1.96)
Diphtheria	0.88 (0.79, 0.97)	0.80 (0.63, 1.01)	0.741	1.04 (0.87, 1.23)
Tetanus	3.45 (3.11, 3.83)	4.14 (3.39, 5.07)	0.037	0.80 (0.67, 0.95)
Pertussis Toxin	19.05 (17.15, 21.15)	17.83 (14.93, 21.28)	0.404	1.09 (0.92, 1.29)
Fimbriae	3.29 (2.79, 3.86)	4.17 (3.24, 5.37)	0.316	0.81 (0.58, 1.14)
69K	40.11 (35.52, 45.29)	50.93 (41.65, 62.27)	0.067 •	0.80 (0.65, 0.98)
FHA	43.77 (39.50, 48.49)	46.70 (39.85, 54.74)	0.595	0.95 (0.81, 1.12)

* Three 7VPnC lot groups combined.

† P-values of Post Dose 3 comparison of the two treatment groups were based on an ANCOVA model with vaccine lot, study site as classification variables, and pre dose 1 level (centered around the overall pre dose 1 mean in log scale) as a covariate for all antigens except antigens except diphtheria and fimbriae. For diphtheria, the model also included the interaction term between treatment (with or without 7VPnC) and pre dose 1 level, as the P-value for the interaction term was 0.015 (details in Appendix II). For fimbriae, the model also included the interaction term between treatment (with or without 7VPnC) and study site, as the P-value for the interaction term was 0.027 (details in Appendix II).

¶ The maximum number of available samples for each group. The actual number of samples sample for which each assay was done may be smaller (see Appendix A.I, Table A.I.3).

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Table 21: Comparisons of GMCs of Antibody to Antigens in DTaP and HbOC Between 7VPnC Recipients and Control – All subjects with Pre Dose 1 and Post Dose 3 Samples Included

Antigen	GMC (95% Confidence Interval) of Post Dose 3 Antibody		P-Value†	Ratio of GMC of Concurrent 7VPnC to Control (with 90% CI)
	with Concurrent 7VPnC*	without Concurrent 7VPnC		
	N¶ = 229	N¶ = 73		
PRP	5.89 (4.93, 7.04)	4.16 (2.90, 5.97)	0.073	1.42 (1.03, 1.94)
Diphtheria	0.86 (0.77, 0.96)	0.77 (0.61, 0.97)	0.836	1.02 (0.85, 1.23)
Tetanus	3.30 (2.98, 3.66)	3.92 (3.23, 4.75)	0.043	0.81 (0.68, 0.96)
Pertussis Toxin	18.60 (16.74, 20.67)	16.97 (14.19, 20.30)	0.357	1.10 (0.93, 1.31)
Fimbriae	3.15 (2.70, 3.69)	3.87 (3.03, 4.94)	0.379	0.84 (0.61, 1.16)
69K	39.65 (35.24, 44.62)	46.95 (38.28, 57.58)	0.181	0.85 (0.70, 1.04)
FHA	43.05 (38.98, 47.54)	45.71 (39.42, 53.00)	0.434	0.93 (0.79, 1.09)

[redacted]

* Three 7VPnC lot groups combined.

† P-values of Post Dose 3 comparison of the two treatment groups were based on an ANCOVA model with vaccine lot, study site as classification variables, and pre dose 1 level (centered around the overall pre dose 1 mean in log scale) as a covariate for all antigens except antigens except diphtheria and fimbriae. For diphtheria, the model also included the interaction term between treatment (with or without 7VPnC) and pre dose 1 level For fimbriae, the model also included the interaction term between treatment (with or without 7VPnC) and study site (details see Appendix II).

¶ The maximum number of available samples for each group. The actual number of samples sample for which each assay was done may be smaller (see Appendix A.I, Table A.I.3).

[redacted]

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Table 22: Comparisons of Seroconversion Rates to Antibody to Antigens in DTaP and HbOC Between 7VPnC Recipients and Control– Three 7VPnC Lot Groups Combined

Antigen	% Children Achieving Antibody Level (95% CI†) With Concurrent 7VPnC*	Without Concurrent 7VPnC	P-Value†	Difference in Proportion (Concurrent - Control) and 90% Confidence Limits*
	N¶ = 214	N¶ = 67		
PRP				
≥ 0.15 µg/mL	99.5 (97.4, 100.0)	97.0 (89.6, 99.7)	0.142	2.5 (-1.8, 10.4)
≥ 1 µg/mL	88.3 (83.2, 92.3)	88.1 (77.8, 94.8)	1.000	0.2 (-8.0, 10.9)
Diphtheria				
≥ 0.01 IU /mL	100 (98.2, 100.0)	100 (94.5, 100.0)	1.000	0 (-3.5, 6.1)
≥ 0. 1 IU /mL	100 (98.2, 100.0)	97.0 (89.4, 99.7)	0.056	3.0 (-1.1, 10.7)
Tetanus				
≥ 0.01 IU /mL	100 (98.2, 100.0)	100 (94.5, 100.0)	1.000	0 (-3.5, 6.1)
≥ 0. 1 IU /mL	100 (98.2, 100.0)	100 (94.5, 100.0)	1.000	0 (-3.5, 6.1)
Pertussis Toxin				
≥ 2 fold rise	82.2 (76.3, 87.2)	83.3 (72.1, 91.4)	1.000	-1.1 (-11.9, 9.8)
≥ 4 fold rise	74.0 (67.5, 79.9)	69.7 (57.1, 80.5)	0.526	4.3 (-6.6, 16.4)
Fimbriae				
≥ 2 fold rise	62.6 (55.6, 69.3)	75.0 (62.6, 85.0)	0.073	-12.4 (-24.7, -0.6)
≥ 4 fold rise	44.7 (37.7, 51.8)	62.5 (49.5, 74.3)	0.015	-17.8 (-30.8, -6.0)
69K				
≥ 2 fold rise	79.9 (73.8, 85.2)	87.9 (77.5, 94.7)	0.199	-8.0 (-18.1, 2.6)
≥ 4 fold rise	65.6 (58.6, 72.0)	77.3 (65.3, 86.7)	0.095	-11.7 (-23.6, -0.2)
FHA				
≥ 2 fold rise	78.4 (72.1, 83.8)	78.8 (66.9, 87.9)	1.000	-0.4 (-11.9, 10.8)
≥ 4 fold rise	66.4 (59.4, 72.8)	69.7 (57.1, 80.5)	0.654	-3.3 (-15.9, 8.3)

* Three 7VPnC lot groups combined

¶ The maximum number of available samples for each group. The actual number of samples sample for which each assay was done may be smaller (see Appendix A.I, Table A.I.3).

† Exact P-values and exact confidence intervals computed using StatXact.

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Table 67: Comparisons of Post Dose 3 GMCs (118-16)

	GMC (µg/mL)			Ratio of GMC and 90% Lower Confidence Limit			
				Manuf. N Lot versus Pilot Lot		Manuf. P Lot versus Pilot Lot	
	Pilot Lot	Manuf. N	Manuf. P	Ratio	90% Lower Limit*	Ratio	90% Lower Limit*
Serotype	N=152	N=159	N=154				
4	1.53	2.03	2.02	1.33	1.10	1.32	1.09
6B	3.62	2.97	2.39	0.82	0.64	0.66	0.51
9V	1.45	1.18	1.14	0.82	0.68	0.79	0.66
14	5.83	4.64	4.33	0.80	0.63	0.74	0.59
18C	2.09	1.96	1.77	0.93	0.78	0.84	0.70
19F	1.91	1.91	1.68	1.00	0.83	0.88	0.73
23F	2.21	1.71	1.40	0.78	0.62	0.64	0.51

* The lower limit of the 90% confidence interval. The 90% confidence interval was derived based on t-distribution of the difference between the two lot groups in the mean of log concentrations.

Table 68: Comparisons of Proportions of Children Achieving Given Antibody Concentrations (118-16)

		% Children Achieving Given Antibody Level			Difference in Percentage and 90% Lower Confidence Limit			
					Manuf. N versus Pilot Lot		Manuf. P versus Pilot Lot	
	Level (µg/mL)	Pilot Lot	Manuf. N	Manuf. P	Difference	90% Lower Limit*	Difference	90% Lower Limit*
Serotype		N=152	N=159	N=154				
4	0.15	99.34	99.37	98.70	0.03	-3.81	-0.64	-5.50
6B	0.25	96.71	97.48	92.86	0.77	-4.21	-3.85	-10.59
9V	0.28	100	95.60	92.21	-4.40	-9.91	-7.79	-14.20
14	0.38	98.03	94.34	95.42	-3.69	-9.76	-2.60	-8.72
18C	0.21	100	97.48	96.10	-2.52	-7.52	-3.90	-9.49
19F	0.26	97.37	96.23	94.81	-1.14	-6.91	-2.56	-8.86
23F	0.18	96.71	98.11	94.16	1.40	-3.40	-2.56	-9.07

* Exact confidence limit using StatXact.

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Table 69: Comparisons of Proportions of Children Achieving Antibody Concentrations ≥ 0.15 µg/mL (118-16)

	% Children Achieving Antibody ≥ 0.15 µg/mL			Difference in Percentage and 90% Lower Confidence Limit			
				Manuf. N versus Pilot Lot		Manuf. P versus Pilot Lot	
	Pilot Lot	Manuf. N	Manuf. P	Difference	90% Lower Limit*	Difference	90% Lower* Limit
Serotype	N=152	N=159	N=154				
4	99.34	99.37	98.70	0.03	-3.81	-0.64	-5.50
6B	98.03	98.11	96.10	0.09	-4.51	-1.92	-7.83
9V	100	98.11	96.75	-1.89	-6.67	-3.25	-8.67
14	99.34	97.48	97.39	-1.86	-6.98	-1.96	-7.34
18C	100	97.48	97.40	-2.52	-7.52	-2.60	-7.82
19F	100	96.86	97.40	-3.15	-8.33	-2.60	-7.82
23F	96.71	98.11	94.16	1.40	-3.40	-2.56	-9.07

* Exact confidence limit using StatXact.

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