Clinical Review of Amendment to Product License Application

(STN# 103905 10031)

General Information

Product Names:	Prevnar™ Pneumococcal 7-valent Conjugate Vaccine Diphtheria CRM_{197} Protein
Manufacturer:	Wyeth-Lederle Vaccines
Proposed Indication:	Prevention of otitis media caused by *Streptococccus pneumonia* serotypes included in the vaccine
Dosage Form:	Liquid, single use vials, preservative-free
Adjuvant:	Aluminum phosphate
Route of Administration:	Intramuscular (im)
Review committee:	
Marion Gruber	Chairperson/Regulatory Review
Douglas Pratt	Clinical review
Jingyee Kou	Biostatistics

List of Abbreviations

7VPnC	7-valent pneumococcal conjugate vaccine, manufactured by Wyeth-Lederle; Pre-licensure notation for Prevnar, used in the Northern California Kaiser Permanente study report.
AOM	Acute otitis media
BLA	Biologics license application
CI	Confidence interval
DTP	Diphtheria, tetanus, pertussis vaccine
GMC	Geometric mean concentration
HBV	Hepatitis B vaccine
Hib	Hemophilus influenza type b vaccine
ITT	Intent-to-treat
MEF	Middle ear fluid
MnCC	Meningococcal conjugate type C vaccine, investigational vaccine, manufactured by Wyeth-Lederle; control vaccine in Northern California Kaiser Permanente study
NCKP	Northern California Kaiser Permanente
PCR	Polymerase chain reaction
PncCRM	7-valent pneumococcal conjugate vaccine, manufactured by Wyeth-Lederle; Pre-licensure notation for Prevnar, used in the Finnish otitis media study report.
PncOMPC	7-valent pneumococcal conjugate vaccine, investigational vaccine manufactured by Merck & Co., used in the Finnish otitis media study
PP	Per protocol
VRBPAC	Vaccines and Related Biologic Products Advisory Committee

1.0 Scope of Discussion

Prevnar™, pneumococcal 7-valent conjugate vaccine, was licensed in the U.S. on February 17, 2000, for active immunization of infants and toddlers against invasive disease caused by the 7 pneumococcal serotypes represented in the vaccine (serotypes 4, 6B, 9V, 14, 18C, 19F, 23F). With the present supplement to the product license application, Wyeth-Lederle now seeks to extend the approved indication to include prevention of acute otitis media. Specifically, regulatory approval has been requested to market Prevnar:

> "**For active immunization of infants and toddlers against invasive disease and otitis media caused by *Streptococcus pneumoniae* due to capsular serotypes included in the vaccine (4, 6B, 9V, 14, 18C, 19F, 23F)."**

Data intended to support this additional indication have been provided from two well-controlled clinical trials: 1) Northern California Kaiser Permanente Efficacy Trial, and 2) Finnish Acute Otitis Media trial.

This FDA review will focus largely on the additional efficacy data from these 2 clinical trials and the specific indication these data may support. Discussion of safety data will be limited to clinical trial data not provided or addressed in the original Prevnar™ license application. No issues related to vaccine production or product characterization of this licensed vaccine are discussed in this document.

Prevnar is currently the only licensed pneumococcal conjugate vaccine. Prevnar is recommended by the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP) for all children under 2 years of age, and for older children in some groups at high-risk for invasive pneumococcal disease. Extending the licensed indication to prevention of acute otitis media may not impact use of the vaccine in the U.S. in the near future.

The application was brought to the VRPAC for consideration of the additional indication and to address the following concerns:

1) The efficacy estimates for otitis media outcomes are comparatively low for preventive vaccines.
2) Data from the Finnish study suggest that there may be increased risk of AOM (negative efficacy) due to pneumococcal serotypes not included in Prevnar. Consequently, the reduction in overall AOM may be less due to serotype replacement in the population.
3) Concern has been expressed in the medical community about the potential for unrealistic public expectations regarding the benefit of the vaccine in preventing otitis media.

Following publication of the Finnish otitis media study, (Eskola J et al., 2001), a number of letters to the editor regarding that article were submitted

to the New England Journal of Medicine (N Engl J Med 2001;344:1719-20). Correspondents questioned the overall clinical significance of the treatment effect (Lavin A; Damoiseaux R; Cantekin E; Sauder K). Concerns that the limited benefit of Prevnar in preventing otitis media may be misunderstood by the public (Sauder K) or would lessen the credibility of the existing recommendations for its use, were also expressed. One letter (Cantekin, E) incorrectly stated that FDA rejected the use of Prevnar for prevention of otitis media due to a clinically and statistically insignificant difference.

2.0 Regulatory Background

Licensure of Prevnar in the U.S. followed a priority review by FDA. Priority status had been granted to the application and an expedited review was conducted, based on: 1) the severity of disease for which the vaccine would be indicated, i.e., invasive pneumococcal disease (meningitis and bacteremia), 2) lack of alternative licensed vaccines for use among infants and small children, and 3) preliminary results indicating substantial evidence of efficacy. Specifically, estimates of vaccine efficacy for prevention of invasive disease due to vaccine serotypes in the large efficacy trial conducted at NCKP were high [100% in the per protocol analysis (95%CI: 75.4, 100), and 90% in the intent-to-treat analysis (95%CI: 81.7, 100)].

Efficacy of Prevnar in preventing acute otitis media was examined among the secondary endpoints in the NCKP efficacy study, and analyses of endpoints relating to AOM were included in the initial license application. However, prevention of AOM was not the focus of the initial license application review, in part because the disease severity did not satisfy requirements of a priority review. Moreover, it was recognized by Wyeth-Lederle and FDA that results from the Finnish otitis media study, which were only preliminary at the time the original license application was submitted, would be critical to the regulatory assessment of the specific indication of prevention of AOM. Thus, AOM efficacy results from the NCKP trial were only briefly discussed in the sponsor's presentation at the November 1999 VRBPAC, and the committee was not asked to consider or discuss data relating to AOM.

Regulatory approval to market Prevenar (Prevnar^{TM}) in Europe for prevention of invasive disease was granted by the European Agency for the Evaluation of Medicinal Products (EMEA) in October 2000. An indication for prevention of otitis media was also considered in that review, but not granted. Results of both the Finnish otitis media study and the Kaiser efficacy study were available and evaluated by European regulators. As stated in the scientific discussion of the review committee, "…the overall impact of the vaccine on total number of otitis media episodes was small, approximately 6%. Even if otitis media is a very common disease in children, this extent of vaccine efficacy does not support an indication" (European Public Assessment Report (EPAR) for the Marketing Authorization for Prevenar, 2000, Scientific Discussion, page 28).

No FDA regulations or published guidance specifically address the minimum level of efficacy required for licensure of a preventive vaccine. Approvals of most drugs and other therapeutic biological products are based on substantial evidence of efficacy from at least 2 well-controlled clinical studies. Substantial evidence for therapeutic products is commonly determined by hypothesis testing using an acceptable level of statistical significance (e.g., $p< 0.05$). For preventive vaccines, more emphasis is placed on efficacy estimates with 95% confidence limits.

Approval of an otitis media indication for Prevnar could set a level of evidence adequate for licensure of other pneumococcal conjugate vaccines for the same indication, independent of whether or not license applications for these other vaccines include evidence of efficacy for prevention of invasive disease.

3.0 Pathogenesis, Epidemiology, and Treatment of Acute Otitis Media

Acute otitis media occurs when pathogenic bacteria within the nasopharynx traverse the Eustachian tube into the middle ear space, multiply to some threshold number, and provoke an inflammatory response. Bacteria consistently documented to be associated with AOM include *S. pneumoniae, H. influenzae, Moraxella catarrhalis*, and *Group A Streptococcus* (Bluestone CD, et al., 1992). A preceding upper respiratory viral infection appears to be a precipitating factor in much of AOM of early childhood (Heikkinen T, 2001). Viral infections could predispose to AOM by increasing bacterial adherence to epithelial cells in the nasopharynx (Tuomanen EI, 2001). Viral infections may also result in impaired Eustachian tube dysfunction by destroying ciliated epithelium leading to increased mucous and cellular debris within the tubal lumen, which can result in development of negative middle ear pressure. Fluid may remain in the middle ear for weeks to months after an episode of AOM (Klein JO, 2001). Recurrent AOM has been associated with an earlier age at first episode of AOM (Kvaerner KJ, et al., 1997). Among children with onset of AOM before age 9 months, approximately 25% went on to develop recurrent AOM by age 2 years.

Bacteria ascending into the middle ear may be newly acquired, but most are probably carried asymptomatically in the nasopharynx. Pneumococcal serotypes are carried in the nasopharynx of approximately 1/2 of healthy preschool age children in developed countries (Lopez B et al., 1999), and in nearly 100% of young children in some developing countries (Montgomery JM et al.,1990).

Otitis media caused by pneumococci may be more severe than AOM caused by other common bacteria such as nontypeable *Hemophilus influenza* and *Moraxalla catarrhalis*, as evidenced by higher rates of fever and less frequent spontaneous resolution of episodes (Klein JO, 1994). Acute otitis media due to pneumococcus is characterized by profound inflammation. Pneumococcal cell

wall fragments (peptidoglycan-teichoic acid) activate the alternative pathway of the complement cascade, leading to migration of neutrophils into the middle ear.

In the U.S., AOM is diagnosed in more than 60% of children during the first year of life, and in more than 90% of children by age 5 years. The peak incidence falls between 6 and 18 months of age. A 1990 surveillance report by the Center for Disease Control and Prevention (CDC) comparing reports in the years 1975 and 1990 identified otitis media as the most frequently reported morbidity-related diagnosis among visits made by children under age 10 years, for both years. The 7 serotypes included in Prevnar were shown to account for 60% of AOM due to *S. pneumoniae* (12-24% of all AOM) among pre-school children in the U.S.

The bacteriology of AOM among a cohort of 329 Finnish children age 2 to 24 months was investigated prior to the Finnish AOM vaccine efficacy study (Kilpi T 2001). *S. pneumoniae, Moraxella catarrhalis,* and *Hemophilus influenzae* were isolated from 26%, 23% and 23%, respectively, of middle ear fluid isolates from 772 AOM events. Vaccine serotypes accounted for 68% of all pneumococcal AOM events. The most common pneumococcal serotypes isolated were types 19F (25%), 23F (20%), 6A (11%), 6B (9%), and 14 (7%).

The prevalence of pneumococci resistant to penicillin has been increasing worldwide over the past 30 years. In the U.S., surveys conducted in 1980 and 1987 showed that 96% of pneumococcal isolates in a multi-laboratory survey were penicillin susceptible. Similar surveys in 1996-97 showed that 17% of isolates were resistant to penicillin, and another 14% were of intermediate penicillin susceptibility (Barry AL, 1999). Penicillin-resistant strains are often resistant to multiple antimicrobial agents, including trimethoprim-sulfmethoxazole, erythromycin, tetracycline, and chloramphenicol (McDougal LK et al., 1992).

Pneumococcal serotypes included in Prevnar are responsible for much of the antibiotic resistance among circulating pneumococcal strains. In a cross-sectional study of over 500 pneumococcal isolates from middle ear fluids collected from children with AOM throughout the U.S. from 1996-1999, 57% showed decreased susceptibility to penicillin, and 32% showed multiple-drug (penicillin, azithromycin, trimethoprim-sulfa) resistance (Joloba ML et al., 2001). Serotypes included in Prevnar accounted for 78% of the penicillin-nonsusceptible strains and nearly all of the multiply-resistant pneumococci.

Injudicious use of antibiotics for the treatment of common upper respiratory symptoms in children, including otitis media, likely contributes to the increasing prevalence of antibiotic resistance. Rates of antimicrobial drug use are highest in children. Children treated with antimicrobial medications have a greater risk of becoming carriers of nonsusceptible pneumococci as a result of that treatment. Current treatment guidelines (Dowell SF, 1998) are intended to avoid unnecessary prescriptions for antibiotics by 1) distinguishing acute otitis media from otitis media with effusion (OME); 2) discouraging early antibiotic treatment of OME; 3) prescribing short courses (5-7 days) of antimicrobials in children over

age 2 years; 4) reserving prophylactic use of antimicrobials for recurrent AOM, as defined by 3 episodes/6 months, or 4 episodes/12 months.

Surgical placement of tympanostomy tubes has also been proposed as a rational alternative to long-term prophylactic antibiotics for recurrent AOM, and for children with chronic otitis media with effusion (Bluestone CD, 1998).

4.0 Clinical Studies Reviewed[1]

The clinical section of this application contains study reports for 2 studies:

1) Finnish Acute Otitis Media study;
2) Northern California Kaiser Permanente large efficacy and safety study.

Key characteristics of these trials are compared in the tables below:

Characteristics of clinical studies in the Product License Application (PLA) Supplement

Study	Number of children enrolled	Schedule (Months)	Control Vaccine	New Episode Interval	Case Definition	Regulatory Objective/ Other Information
Finnish	1,662†	2, 4, 6, 12-15	HBV	30 days	Bacterial cultures (myringotomy)	Demonstrate efficacy for prevention of AOM;
Kaiser (NCKP)	34,146‡	2, 4, 6, 12-15	MnCC	21 days	Automated database search for AOM visits	Demonstrate efficacy for prevention of invasive disease, AOM, and pneumonia; Large safety data base for assessing rates of adverse events;

† Subjects distributed equally to PncCRM and HBV control vaccine; entire study was randomized 1:1:1, PncCRM:PncOMP:HBV.
‡ Subjects randomized 1:1, 7VPnC:MnCC control vaccine

The Finnish otitis media study used a specific case definition based on culture of bacterial pathogens and serotyping of pneumococcal isolates collected from middle ear fluid by means of myringotomy in the context of a clinical episode of AOM.

[1] In the tables and summaries of studies conducted pre-licensure, Prevnar, 7-valent pneumococcal conjugate vaccine, is referred to as 7VPnC in the NCKP study, and as PncCRM in the Finnish study; meningococcal group C conjugate vaccine was abbreviated as MnCC; Hepatitis B vaccine is abbreviated HBV.

The NCKP study identified cases of AOM from searches of automated databases. No prospectively defined case definition was used. Rather, cases of AOM were diagnosed and recorded in the NCKP database in the course of routine practice of medicine at Kaiser clinics. Tympanocentesis with cultures of middle ear fluid was not routinely performed in the Kaiser study, and, thus, the presence of pneumococcus in middle ear fluid was not confirmed for most cases. Also, follow-up visits for AOM could not be clearly differentiated from initial encounters for new episodes.

The clinical study designs, analysis plans, and results are described in greater detail in the sections that follow.

4.1 Finnish otitis media study

4.1.1 Finnish otitis media study description

Title: Efficacy Trial in Finnish Children of Pneumococcal Conjugate Vaccine (PncCRM) for Prevention of Acute Otitis Media Due to Pneumococcal Serotypes in the Vaccine

The study was randomized, double-blind, multi-center cohort study conducted in Finland. Children were enrolled and received the first doses of study vaccines at age 2 months, and were followed for efficacy and safety until 24 months of age.

The study was conducted by the National Public Health Institute of Finland (Kansanterveyslaitos FIkhalsoinstitutet, KTL).

As originally designed, the 3-arm study was to evaluate the efficacy of two 7-valent pneumococcal conjugate vaccines (PncCRM, Wyeth-Lederle and PncOMPC, Merck & Co.) compared to the same control vaccine (Hepatitis B vaccine, HBV, Merck & Co.). The submitted study report described results of the study only for the PncCRM and HBV groups.

The study was initiated in December 1995; enrollment ceased April, 1997. The clinical phase of the study ended March 16, 1999.

Objectives

The primary objective was to determine the protective efficacy of the pneumococcal conjugate vaccine against culture-confirmed pneumococcal acute otitis media due to vaccine serotypes, compared to a control vaccine.

Secondary objectives included assessments of the vaccine effect on:

- efficacy using different levels of etiologic diagnosis,
- efficacy in preventing nasopharyngeal carriage of pneumococci compared to control vaccine,
- magnitude and persistence of antibody response, and to correlate serological data with clinical protection,
- safety and tolerability of pneumococcal conjugate vaccine when administered concurrently with other vaccines relevant for age.

Schedule of Study Vaccines and Concurrently Administered Vaccines

Subjects received 0.5 mL intramuscular injections of either PncCRM or HBV vaccine at 2, 4, 6 and 12-15 months of age.

Half the children received DTP-HbOC (Tetramune) and half received DTP-PRP-T concurrently at 2, 4, 6, and 24 months.

Inactivated polio vaccine (IPV, IMOVAX) and MMR were also administered to children as per the schedule below:

Vaccination schedule--Finnish study

Vaccines Administered	Age of child (months)						
	2	4	6	7	12	18	24
Study vaccine	+	+	+		+		
DTP-Hib	+	+	+				+
IPV				+	+		
MMR						+	

Adapted from Table 9.1.1, page 39 of study report.

Allowable time frames for study vaccine administration—Finnish study

Scheduled visit (Months)	Time window, Age of Child	Time window, Interval after Preceding Study Vaccination
2	6-13 weeks	
4	14-21 weeks	6-11 weeks
6	22-29 weeks	6-11 weeks
12	11-14.9 months	

Adapted from Table 10.2.2 of the study report.

Randomization and Blinding

Subjects were equally randomized in blocks of twelve into one of six treatment groups (groups A-G), and two letter codes were assigned to each vaccine (PncCRM, PncOMP, HBV). Clinics received treatment codes in blocks of 12 to assure balanced allocation; treatment codes were assigned sequentially within each block to subjects at enrollment.

Blinding was maintained through the study period for parents, investigators, or to study personnel, except for those administering the vaccines.

Vaccinators, who were not blinded, were public health nurses, not involved in the diagnosis or treatment of AOM.

Study population

Children born between August 26, 1995 through March 19, 1997 in 3 municipalities in southern Finland (Tampere, Nokia, and Kangasala) could participate. The total birth cohort in the area was approximately 3000 per year. Well baby clinics administer all routine childhood vaccination with coverage approaching 100%.

Eligible subjects were in good health as determined by medical history, physical examination and clinical judgment. Children were excluded from study participation for known or suspected impairment of immunologic function, history of invasive pneumococcal disease, prior receipt of vaccine for hepatitis B, or any pneumococcal vaccine.

> **Note:** Premature infants could be enrolled according to chronologic age if they were judged to be in good health.

Case surveillance and ascertainment

Parents were encouraged to bring their children to the study clinics if the child had respiratory infections or symptoms suggesting AOM. Children had free access to the study clinics, which provided both well-child care as well as follow-up for AOM. Clinics were open every day of the week. Myringotomy with aspiration of middle ear fluid for culture was done if AOM was diagnosed at the visit. If pneumococcus was found, the serotype was determined.

> **Note:** Guidelines for antibiotic treatment in use in Finland during the study were provided upon FDA request. Recommendations for prophylactic antibiotics were said to be similar in Finland and in the US, as outlined in the 2000 Red Book: Report of the Committee on Infectious Diseases American Academy of Pediatrics (Pickering LK, ed. 2000 Red Book:*Report of the Committee on Infectious Disease*).

Definitions of efficacy outcome variables

Acute Otitis Media

Acute otitis media was defined as a visually abnormal tympanic membrane (in regard to color, position, and/or mobility) suggesting effusion in the middle ear cavity, concomitantly with at least one of the following: fever, ear pain, irritability, diarrhea, vomiting, acute otorrhea not caused by external otitis, or other symptoms of respiratory infection.

AOM episode

An episode begins on the day of the clinic visit when the clinical diagnosis of AOM is made. A new episode was considered to start if at least 30 days had elapsed since the beginning of the previous episode.

AOM episode due to vaccine serotypes

AOM due to vaccine serotypes was defined as culture-confirmed pneumococcal AOM due to any of the serotypes included in the pneumococcal conjugate vaccine (serotypes 4, 6B, 9V, 14, 18C, 19F, 24F). A new episode was considered to start if at least 30 days had elapsed since the beginning of the previous AOM due to the same serotype, or any interval for different vaccine serotypes.

> **Note:** If two or more vaccine serotypes were present at the beginning of an episode, this was considered to be a single episode for this outcome.

Culture-confirmed pneumococcal AOM episode

Culture-confirmed pneumococcal AOM episode was an AOM episode in which any pneumococcal serotype was isolated. A new episode began if at least 30 days had elapsed since the beginning of the previous pneumococcal AOM, irrespective of serotype.

AOM episode with MEF regardless of etiology

AOM with MEF was AOM in which at least one MEF sample had been obtained. A new episode began if at least 30 days had elapsed since the beginning of the previous AOM with MEF, irrespective of findings in culture or PCR.

AOM episode regardless of etiology

A new episode was considered to start if at least 30 days had elapsed since the beginning of the previous AOM, irrespective of existence or non-existence of MEF sample.

Child with recurrent AOM

A child was considered to have recurrent AOM if he/she was diagnosed with 3 or more episodes of AOM in 6 months, or 4 or more episodes in 12 months at any time during the follow-up.

> **Note:** The definition of recurrent AOM is based on clinical AOM; the AOM episodes need not be associated with a middle ear fluid isolate

of pneumococcus or any bacterial pathogen, but clinical episodes must be separated by at least 30 days to contribute to a recurrent AOM diagnosis.

Pneumococcal carriage

Pneumococcal carriage was assessed for all subjects at 12 and 18 months based on bacterial culture results from nasopharyngeal swabs, and recorded as either present or absent for vaccine serotypes.

Definition of follow-up periods

Per protocol follow-up started 14 days after the 3rd injection of the study vaccine and ended on the day of discontinuation as per protocol, or on the day of the close-out visit or the 2nd birthday.

Intention-to-treat (sponsor defined) follow-up began on the day that the first dose of study vaccine was administered, and ended on the day of permanent discontinuation or the 2nd birthday.

Efficacy outcomes assessed

Primary endpoint: All episodes of AOM due to vaccine serotypes

AOM episodes due to vaccine serotypes was the prospectively defined primary endpoint.

Secondary endpoints: First and subsequent episodes

Secondary efficacy endpoints specified in the protocol included first and subsequent episodes of AOM.

Other prospectively defined otitis media endpoints

- All episodes AOM by vaccine dose
- All pneumococcal AOM, regardless of pneumococcal serotype (culture and/or PCR confirmed)
- All AOM episodes with MEF, regardless of etiology
- All AOM episodes regardless of etiology
- Children with recurrent AOM
- Efficacy for all specified AOM endpoints under intent-to-treat
- Pneumococcal carriage
- Antibody response to pneumococcal conjugate vaccine; Geometric mean concentration (GMC) of serum antibodies as determined by ELISA, and percent of subjects exceeding antibody concentration cut-off levels of 0.3 mcg/mL, 0.5 mcg/mL, and 1.0 mcg/mL were provided.

Analysis plan

Intent-to-treat analyses were provided in the study report only for the primary analysis (episodes due to vaccine serotypes), and for the analysis of efficacy by dose. It was expected that per protocol and intent-to-treat analyses would yield similar results because it was anticipated that few subjects would be lost to follow-up. Intent-to-treat analyses for other endpoints were provided upon FDA request during the review period.

No interim analyses were planned or conducted.

Primary endpoint: AOM episodes due to vaccine serotypes

Vaccine efficacy for the primary endpoint was estimated by a generalized Cox regression model (Anderson and Gill,1982), as was specified prospectively in the analysis plan . As it was applied here, this model provides an average vaccine effect on all AOM episodes (first and subsequent) where treatment (vaccinated, unvaccinated) is the only covariate. An underlying assumption of this model is that relative hazard of episodes be proportional over time for two treatment groups. Vaccine efficacy was calculated as 1- R, where R is the hazards ratio estimated from the Cox model.

That repeated episodes of AOM within the same individual would not be independent events was recognized in the analysis plan. The risk of AOM was therefore estimated “piecewise”, i.e., from event to event. The analysis plan also states that dependence due to recurrences was taken into account by estimating robust standard errors for the hazard regression parameters. The proportionality of hazards over time was checked by graphing cumulative hazard over time for each treatment group.

Secondary endpoints: First and subsequent episodes

If the vaccine effect on all episodes is significant, the time to first AOM episode due to vaccine serotype is also expected to be significant. To distinguish between the effect of vaccination on first and subsequent episodes, a recurrent event proportional hazards model (Eerola M,1989) was used. The increasing or decreasing effect of vaccination on subsequent episodes compared to the first episodes is given by an interaction parameter between an indicator of the time of the first AOM episode and the treatment covariate.

Other prospectively defined AOM outcomes

The Anderson-Gill model was also used for other endpoints where the hazard of all episodes is considered regardless of the episodes being first or subsequent.

Recurrent otitis media

The number of children with recurrent AOM was compared between treatment groups by chi-square test.

Dose timing and follow-up

The vaccine effect for the period after each dose until the next dose in the series was estimated using a person-time nonparametric relative risk estimator.

Immunogenicity

A special serology cohort comprised all children enrolled at one (Kangasala) clinic. Follow-up started on the day of enrollment.

Geometric mean concentrations (GMC) of serum antibody were presented with 95% confidence intervals. Reverse cumulative distributions of antibody concentrations at each time point were also presented.

No adjustments for covariates were made. The immunogenicity evaluations were considered exploratory.

Carriage of pneumococci in the nasopharynx

The difference in relative frequencies of carriers of vaccine serotypes between treatment groups as measured at 12 and 18 months were tested by the chi square test.

4.1.2 Finnish otitis media study efficacy results

Efficacy results from the Finnish study as presented in the initial BLA amendment submission, some of which were published (Eskola et al., 2001), are shown in the tables that follow immediately below. Supplementary analyses performed in response to issues raised during the FDA review are presented and discussed subsequently.

Population characteristics

Information was collected for demographic variables and some characteristics associated with increased risk of AOM.

Small imbalances between treatment groups at study entry are apparent for premature gestational age (< 37 weeks), low birth weight (<2500 grams), and history of AOM episodes prior to first vaccine dose. Each of these characteristics are risk factors for AOM that, due to the observed imbalance, would be expected to increase the risk for AOM in the control group, and thus could be a source of potential bias toward a PncCRM treatment effect.

Information about breastfeeding and cigarette smoking in the households was collected during the course of the study. Little difference between rates of breastfeeding and household smoking between treatment groups was observed.

Population characteristics—Finnish study

		HBV	(%)	PncCRM	(%)
Gender	Female	403	(48.5)	396	(47.7)
	Male	428	(51.5)	435	(52.3)
Gestational Age	< 37 weeks	53	(6.4)	41	(4.9)
	≥ 37 weeks	778	(93.6)	790	(95.1)
Birth weight	< 2.5 kg	42	(5.1)	25	(3.0)
	≥ 2.5 kg	789	(94.9)	806	(97.0)
No. of siblings	Mean	0.7		0.7	
Subjects with prior episodes of AOM		39	(4.7)	27	(3.2)
Middle ear effusion at enrollment	None	804	(96.8)	804	(96.8)
	Unilateral	16	(1.9)	22	(2.6)
	Bilateral	10	(1.2)	3	(0.4)
	No visibility	1	(0.1)	2	(0.2)
	Total	831	(100)	831	(100)
Breast Feeding at least 6 months		441	(53.1)	444	(53.4)
Smoking within Family reported at least once		16	(1.9)	18	(2.2)

Adapted from Tables 11.1.1 and 11.1.3, Volume 2 of BLA.

Primary analysis: AOM episodes caused by vaccine serotypes

In the protocol defined primary analysis, AOM episodes due to vaccine serotypes observed during per protocol follow-up, the vaccine efficacy estimate was 57% (95%CI: 44%-67%). Results of the intent-to-treat analysis were consistent with results of the per protocol analysis.

Primary analysis, AOM episodes due to vaccine serotypes—Finnish study

	Follow-up Period	Number of Episodes		Rate/person year		Vaccine Efficacy	
		HBV	PncCRM	HBV	PncCRM	Estimate	(95% CI)
AOM due to vaccine serotypes	Per Protocol	250	107	0.21	0.09	0.57	(0.44, 0.67)
	Intent-to-treat	292	135	0.20	0.09	0.54	(0.41, 0.64)

Adapted from Table 11.1.5, p 83, Volume 2 of BLA.

Secondary analyses

The table below summarizes results of analyses of secondary and other prospectively defined study endpoints.

Secondary analyses—Finnish study

	Follow-up Period	Number of Episodes		Rate/person year		Vaccine Efficacy	
		HBV	PncCRM	HBV	PncCRM	Estimate	(95% CI)
First AOM Episode due to Vaccine Serotype	PP	177	89	0.171	0.081	0.52	(0.39, 0.63)
	ITT	196	109	0.152	0.079	0.48	(0.34, 0.59)
Subsequent AOM Episode due to Vaccine Serotype	PP	73	18	0.467	0.249	0.45	(0.05, 0.69)
	ITT	96	26	0.491	0.250	0.49	(0.20, 0.67)

Adpated from Table 11.1.6, page 85, Volume 2 of BLA, and Table Q1.1 of January 10, 2002 submission to BLA.

In the primary analysis of efficacy for vaccine serotypes, most of the vaccine serotype AOM episodes were observed as first episodes. First AOM episode due to vaccine serotypes accounted for 83% (89/107) of AOM episodes in the PncCRM group, and 71% (177/250) of all vaccine type AOM episodes in the HBV group.

Efficacy estimates for prevention of both first (52%) and subsequent (45%) AOM episodes were statistical significance in the per protocol analysis.

Results of the intent-to-treat analyses, provided upon FDA request during the review period, were consistent with the per protocol analysis.

Other prospectively specified analyses

The efficacy estimate for culture-confirmed pneumococcal AOM, regardless of serotype, was 34% in the per protocol analysis; this was statistically significant. Efficacy estimates for prevention of AOM with middle ear effusion, and all cause AOM episodes did not attain statistical significance (95% confidence interval includes 0).

Intent-to-treat analyses were large consistent with the per protocol analyses for these outcomes.

Other prospectively specified analyses—Finnish study

	Follow-up Period	Number of Episodes		Rate/person year		Vaccine Efficacy	
		HBV	PncCRM	HBV	PncCRM	Estimate	(95% CI)
Culture-confirmed pneumococcal AOM	PP	414	271	0.36	0.23	0.34	(0.21, 0.45)
	ITT	467	322	0.32	0.22	0.32	(0.19, 0.42)
AOM with MEF	PP	1267	1177	1.16	1.09	0.07	(-0.05, 0.17)
	ITT	1445	1390	1.06	1.01	0.04	(-0.07, 0.14)
AOM regardless of etiology	PP	1345	1251	1.24	1.16	0.06	(-0.04, 0.16)
	ITT	1532	1474	1.13	1.08	0.04	(-0.07, 0.14)

Adapted from Table 11.1.5, page 83, Volume 2 of BLA, and Table Q1.1 of January 10, 2002 submission to BLA.

Note: Analysis of all pneumococcal AOM as determined by culture or PCR analyses of middle ear fluids was also prospectively specified in the analysis plan. However, the PCR data were not available at the time of the initial amendment submission. These supplemental analyses were provided upon FDA request during the review period (see below).

Efficacy by dose

Vaccine efficacy by dose was also analyzed for AOM episodes due to vaccine serotypes under a modified intent-to-treat analysis. Efficacy estimates after dose 3 (57%) and after dose 4 (55%) were of similar magnitude, and both were statistically significant.

Vaccine efficacy by dose against AOM episodes due to vaccine serotypes (ITT)—Finnish study

	Number of Episodes		Rate/person year		Vaccine Efficacy	
	HBV	PncCRM	HBV	PncCRM	Estimate	95% CI
Dose 1 (2 to 4 months)	14	11	0.09	0.11	0.22	-0.74, 0.65
Dose 2 (4 to 6 months)	24	13	0.19	0.10	0.46	-0.04, 0.72
Dose 3 (6 to 12 months)	93	40	0.24	0.10	0.57	0.36, 0.71
Dose 4 (12 to 24 months)	159	71	0.20	0.09	0.55	0.39, 0.67

Reproduced from Table 11.1.7, Volume 2 of BLA.

Vaccine efficacy by serotype

The contribution of each vaccine serotype to efficacy as measured by the primary endpoint is shown in the table below. Results of the intent-to-treat analyses were provided upon FDA request during the review period.

Efficacy Results of Individual Vaccine Serotypes—Finnish study

AOM Episode due to Serotype	Follow-up Period	Number of Episodes		Rate/100 person year		Vaccine Efficacy	
		HBV	PncCRM	HBV	PncCRM	Estimate	95%CI
4	PP	4	2	0.34	0.17	0.49	(-1.76, 0.91)
	ITT	4	2	0.27	0.13	0.50	(-1.72, 0.91)
6B	PP	56	9	4.71	0.76	0.84	(0.62, 0.93)
	ITT	61	12	4.12	0.81	0.80	(0.60, 0.90)
9V	PP	11	5	0.92	0.42	0.54	(-0.48, 0.86)
	ITT	11	6	0.74	0.40	0.45	(-0.66, 0.82)
14	PP	26	8	2.18	0.68	0.69	(0.20, 0.88)
	ITT	31	8	2.09	0.54	0.74	(0.34, 0.90)
18C	PP	17	7	1.43	0.59	0.58	(-0.04, 0.83)
	ITT	18	7	1.21	0.47	0.61	(0.02, 0.85)
19F	PP	58	43	4.88	3.66	0.25	(-0.14, 0.51)
	ITT	67	60	4.53	4.06	0.10	(-0.32, 0.39)
23F	PP	82	33	6.91	2.81	0.59	(0.35, 0.75)
	ITT	104	40	7.04	2.70	0.62	(0.41, 0.75)

Adapted from Table 11.1.10, page 90, Volume 2 of BLA, and Table Q1.2 of January 10, 2002 submission to BLA.

The 3 most common vaccine serotypes associated with AOM were serotypes 23F, 19F, 6B, and 14. Vaccine efficacy estimates under the per protocol analysis ranged from 84% for serotype 6B, to 25% for serotype 19F. Statistical significance for vaccine efficacy was demonstrated for individual serotypes 6B, 14, and 23F. Efficacy estimates under intent-to-treat and per protocol analyses were largely consistent, with higher estimates for some of the serotypes under intent-to-treat. The greatest difference between PP and ITT analyses was for type 19F (25% vs. 10%).

Efficacy of PncCRM in preventing episodes of pneumococcal serotypes belonging to the same serogroups as vaccine serotypes was also analyzed. Results of analyses of efficacy for these vaccine related serotypes are shown below.

Efficacy for serotypes related to vaccine serotypes—Finnish study

AOM Episode due to Serotype	Follow-up Period	Number of Episodes		Rate/100 person year		Vaccine Efficacy	
		HBV	PncCRM	HBV	PncCRM	Estimate	95%CI
6A	PP	45	19	3.78	1.61	0.57	(0.24, 0.76)
	ITT	48	23	3.24	1.55	0.52	(0.17, 0.72)
9N	PP	8	2	0.67	0.17	0.75	(-0.24, 0.95)
	ITT	9	2	0.61	0.13	0.78	(-0.06, 0.95)
18B	PP	1	2	0.08	0.17	-1.03	(-21.30, 0.82)
	ITT	1	2	0.07	0.13	-1.01	(-21.08, 0.82)
19A	PP	26	17	2.18	1.44	0.34	(-0.26, 0.65)
	ITT	28	22	1.89	1.48	0.21	(-0.40, 0.56)
23A	PP	4	1	0.34	0.08	0.75	(-1.51, 0.97)
	ITT	4	1	0.27	0.07	0.75	(-1.49, 0.97)

Adapted from Table 11.1.10 of BLA and Table Q1.2 of January 10, 2002 submission to BLA.

Serotype 6A, although not a vaccine serotype, was associated with a substantial number of cases, and the efficacy estimate for type 6A was statistically significant. Statistically significant demonstration of efficacy was not observed for any of the other individual vaccine-related serotypes, but few episodes of AOM due to the vaccine associated serotypes 9N, 18B, and 23A were observed.

Interestingly, the efficacy estimates for the related serotype 19A, although not statistically significant, exceeded that of the vaccine serotype 19F.

Taken together, the vaccine-related serotypes contributed to a significant treatment effect, as shown in the table below.

AOM caused by non-vaccine, but vaccine-related serotypes—Finnish study

	Follow-up Period	Number of Episodes		Rate/person year		Vaccine Efficacy	
		HBV	PncCRM	HBV	PncCRM	Estimate	(95% CI)
AOM due to vaccine-related serotypes	PP	84	41	0.070	0.035	0.51	(0.27, 0.67)
	ITT	90	50	0.061	0.034	0.44	(0.20, 0.62)

Adapted from Table Q1.1 of January 10, 2002 submission to BLA.

As was shown above, the efficacy estimate for all pneumococcal AOM episodes regardless of serotype was 34% (95%CI 21, 45) in the per protocol analysis. As would be expected, this estimate is lower than the efficacy estimates for vaccine serotypes, and vaccine-related serotypes; one would not anticipate comparable or added efficacy by inclusion of the unrelated pneumococcal serotypes in the analysis. When analyzed together, the pneumococcal serotypes unrelated to vaccine serotypes actually contributed to statistically significant negative vaccine efficacy estimates in both the per protocol [-0.34, (95%CI –0.81, 0.0) and ITT [-0.39 (95%CI: -0.86, -0.03)] analyses.

AOM caused by pneumococcal serotypes other than vaccine or vaccine-related serotypes—Finnish study

	Follow-up Period	Number of Episodes		Rate/person year		Vaccine Efficacy	
		HBV	PncCRM	HBV	PncCRM	Estimate	(95% CI)
AOM due to other than vaccine related serotypes	PP	95	126	0.080	0.107	-0.34	(-0.81, 0.00)
	ITT	101	140	0.068	0.094	-0.39	(-0.86, -0.03)

Adapted from Table Q1.1 of January 10, 2002 submission to BLA.

The most common vaccine-unrelated pneumococcal serotypes isolated from middle ear fluids were from serogroups 3, 11, 15, and 35. All 7 isolates of serogroup 33 were from the PncCRM group. Efficacy estimates for the individual vaccine-unrelated serotypes are summarized below:

AOM due to vaccine-unrelated serotypes—Finnish study

Serotype/Serogroup	Number of Episodes		Rate/100 person year	
	HBV	PncCRM	HBV	PncCRM
3	15	17	1.01	1.15
7*	3	4	0.20	0.27
10*	6	3	0.40	0.20
11*	25	34	1.68	2.29
12*	0	1	0.00	0.07
15*	25	28	1.68	1.89
16*	3	5	0.20	0.34
22*	7	8	0.47	0.54
28*	0	1	0.00	0.07
33*	0	7	0.00	0.47
34	2	0	0.13	0.00
35*	10	15	0.67	1.01
38	3	7	0.20	0.47
Pool G**	1	2	0.07	0.13
Rough	2	7	0.13	0.47

Adapted from table 14.2.2, page 124, Volume 2 of BLA.

* Typing to serogroup level only;

** Pool G consists of serogroups/types 29, 34, 35, 42, 47

Children with recurrent AOM

The efficacy estimate for percent reduction in the number of children who met a definition of recurrent AOM (3 episodes/6 months or 4 episodes/12 months) was 16% in the per protocol analysis, and 9% in the intent-to-treat analysis. Neither estimate was statistically significant.

Children with Recurrent Acute Otitis Media (all causes)— Finnish study

	Follow-up Period	Number of Episodes		Rate/person year		Vaccine Efficacy	
		HBV	PncCRM	HBV	PncCRM	Estimate	(95% CI)
Children with Recurrent AOM	PP	149	123	0.125	0.104	0.16	(-0.06, 0.35)
	ITT	174	158	0.117	0.106	0.09	(-0.12, 0.27)

Adapted from Table Q3.1 of January 10, 2002 submission to BLA.

Nasopharyngeal carriage

At 12 months of age, the carriage rate of vaccine serotype pneumococci was 10% in the PncCRM group vs. 12% in the HBV group. This difference was not statistically significant.

At 18 months, the carriage rate for vaccine serotypes was 10% in the PncCRM group vs. 16% in the HBV group. This difference was statistically significant.

Analyses of carriage by individual serotypes, and for carriage of non-vaccine pneumococcal serotypes, were not provided with the application.

Nasopharyngeal carriage of vaccine serotypes, per protocol —Finnish study

	No. Children		No. Carriers		% Carriage		Difference of %		p-value
	HBV	7VPnC	HBV	7VPnC	HBV	7VPnC	Estimate	95% CI	
12 mos	809	801	99	81	12.2	10.1	2.1	-1.1, 5.3	0.2
18 mos	797	787	129	75	16.2	9.5	6.7	3.3, 10.1	<0.01

Adapted from Table 11.1.9, page 89, Volume 2 of PLA.

Serological responses

A special serology cohort was comprised of children enrolled at one of the 3 centers, the Kangasala clinic, and consisted of 115 children, 58 in the HBV group and 57 in the 7VPnC group. Of these children, 111 (96.5%) completed the study, and 94 (81.7%) had a full series of blood samples drawn. All children in the immunogenicity study received DTP-HbOC as their DTP-Hib vaccine.

The serology cohorts for the two treatment groups were well-balanced for gender, gestational age, birth weight, number of siblings, and maternal education.

The geometric mean concentration (GMC) of serum antibody to type-specific pneumococcal polysaccharides as determined in ELISA assays are summarized below.

Geometric mean concentration (mcg/mL) of pneumococcal antibodies following the 3rd dose—Finnish study

Serotype	HBV N=52		PncCRM N=54	
	GMC	95% CI	GMC	95% CI
4	0.05	0.04, 0.07	1.70	1.32, 2.20
6B	2.00	0.07, 0.13	2.00	1.35, 2.96
9V	2.48	0.07, 0.13	2.48	1.97, 3.11
14	6.28	0.16, 0.27	6.28	4.78, 8.23
18C	3.55	0.06, 0.11	3.55	2.80, 4.49
19F	3.28	0.16, 0.29	3.28	2.57, 4.18
23F	2.51	0.07, 0.12	2.51	1.84, 3.43

Adapted from Tables 11.2.1 page 95, Volume 2 of BLA.

Geometric mean concentration (mcg/mL) of pneumococcal antibodies following the 4th dose—Finnish study

Serotype	HBV N=54		PncCRM N=55	
	GMC	95% CI	GMC	95% CI
4	0.11	0.08, 0.14	2.56	2.00, 3.28
6B	0.16	0.12, 0.20	9.05	6.50, 12.59
9V	0.21	0.16, 0.27	3.97	3.20, 4.91
14	0.21	0.17, 0.27	10.82	8.30, 14.09
18C	0.10	0.08, 0.13	6.51	5.04, 8.41
19F	0.41	0.31, 0.53	4.96	3.86, 6.37
23F	0.15	0.12, 0.20	6.25	4.54, 8.61

Adapted from Tables 11.2.3, page 97 Volume 2 of BLA.

Pre-dose 1 GMC's were said to be similar between HBV and 7VPnC groups; those data were not provided to CBER.

Tables were also provided in the application showing percentages of subjects with antibody concentrations above defined levels (0.3 mcg/mL, 0.5 mcg/mL, and 1.0 mcg/mL).

Percentages of subjects achieving given antibody concentration after the 3rd dose—Finnish Study

Serotype	% >0.30 mcg/mL		% >0.50 mcg/mL		% > 1.0 mcg/mL	
	HBV	PncCRM	HBV	PncCRM	HBV	PncCRM
4	7.7	94.4	5.8	92.6	0	75.9
6B	9.6	85.2	7.7	83.3	3.8	66.7
9V	13.5	98.1	7.7	94.4	3.8	88.9
14	34.6	100	19.2	96.3	7.7	94.4
18C	15.4	100	7.7	100	1.9	94.4
19F	38.5	100	25	100	5.8	90.7
23F	9.6	94.4	3.8	92.6	1.9	77.8

Adapted from Tables 11.2.2a, b, and c, page 96, Volume 2 of BLA.

Percentages of subjects achieving given antibody concentration after the 4th dose—Finnish Study

Serotype	% >0.30 mcg/mL		% >0.50 mcg/mL		% > 1.0 mcg/mL	
	HBV	PncCRM	HBV	PncCRM	HBV	PncCRM
4	18.5	98.2	3.7	94.5	0	90.9
6B	24.1	98.2	14.8	96.4	0	92.7
9V	37	100	27.8	100	5.6	96.4
14	38.9	100	20.4	100	5.6	100
18C	11.1	100	5.6	100	0	96.4
19F	63	100	40.7	100	13	94.5
23F	25.9	100	9.3	100	1.9	94.5

Adapted from Tables 11.2.4a, b, and c, page 98, Volume 2 of BLA.

Invasive disease

Four cases of confirmed invasive pneumococcal disease were reported in the Finnish study, 2 of which were due to vaccine serotypes (see table below).

Invasive Disease due to Pneumococcus—Finnish study

Study group	Serotype	Clinical syndrome	Age
PncCRM	7**	Bacteremia	19 months
HBV	15**	Meningitis	8 months
	23F*	Meningitis	14 months
	19F*	Bacteremia	9 months

Table compiled by FDA.
* Vaccine serotypes
** Non-vaccine serotype

4.2.3 Review issues and supplementary analyses for the Finnish trial

Early in FDA's review of the application, specific issues were identified, and additional analyses were requested in order to better understand the treatment effect of Prevnar on otitis media outcomes. Some of these supplementary analyses are discussed below.

Analysis of covariates in the Finnish study

Despite randomization, some imbalances between treatment groups for certain risk factors for otitis media were observed after unblinding. To determine whether the vaccine efficacy estimates were robust against imperfect distribution of risk factors between the two groups, covariate adjusted analyses were performed by the sponsor upon FDA request. This supplementary analysis was not part of the pre-unblinding analysis plan.

Andersen-Gill analyses that incorporated AOM history prior to enrollment and other potential risk factors (gender, gestational age, birth weight, daycare attendance, breast-feeding, and household smoking) as covariates were conducted. The effect of gender, AOM history prior to enrollment, and daycare attendance on the number of AOM episodes were highly significant. However, the interaction between these variables and vaccine effect was not significant at the 0.05 level in the sponsor's analysis. Thus, in spite of a significant impact of these risk factors on the overall incidence of episodes, no significant vaccine effect in the populations defined by these factors was evident. Similarly, no significant interactions were seen at the 0.05 level between vaccine effect and gestational age, birth weight, breast-feeding or household smoking.

Vaccine efficacy estimates adjusted for these covariates were derived with these factors incorporated as main effects, since none of the interactions were significant. All adjusted vaccine efficacy estimates were similar to the un-adjusted estimates previously reported.

Vaccine Efficacy Estimates Adjusted for Gender, AOM Prior to Enrollment, Gestational Age, Birth Weight, Daycare Attendance, Breast-feeding, and Household Smoking—Finnish study

	Vaccine Efficacy (95% CI)			
	Un-adjusted for Covariates		Adjusted for Covariates (Covariates Included as Main Effects in Andersen-Gill Analysis)	
AOM due to Vaccine Serotypes				
Per Protocol	0.57	(0.44, 0.67)	0.57	(0.45, 0.67)
Intent-to-treat	0.54	(0.41, 0.64)	0.54	(0.41, 0.64)
Culture-confirmed Pneumococcal AOM				
Per Protocol	0.34	(0.21, 0.45)	0.36	(0.23, 0.46)
Intent-to-treat	0.32	(0.19, 0.42)	0.32	(0.20, 0.43)
AOM with MEF				
Per Protocol	0.07	(-0.05, 0.17)	0.08	(-0.02, 0.18)
Intent-to-treat	0.04	(-0.07, 0.14)	0.05	(-0.06, 0.14)
AOM Regardless of Etiology				
Per Protocol	0.06	(-0.04, 0.16)	0.08	(-0.02, 0.18)
Intent-to-treat	0.04	(-0.07, 0.14)	0.05	(-0.06, 0.14)

Adapted from Table Q13.3 of January 10, 2002 submission to BLA.

Efficacy by serotype, subsequent episodes of the same serotype excluded

According to the case definition used in the analysis of the primary endpoint, if the same pneumococcal serotype were isolated from the same child on multiple occasions, separated by at least 30 days, each episode would be counted as a separate event and contribute to the efficacy analysis.

In FDA's review it was noted that the same pneumococcal serotypes were cultured repeatedly from middle ear fluid samples over extended periods of time for some subjects. Repeated AOM episodes due to the same serotype in the control group would tend to increase the efficacy estimate. Repeated episodes due to the same vaccine serotype in the PncCRM vaccine group would diminish the efficacy etimates.

FDA requested supplemental analyses, in which each pneumococcal serotype is counted only once, at the first AOM episode due to that serotype. The requested analyses for vaccine serotypes, by individual vaccine serotypes, and by all pneumococcal serotypes, were provided during the review period, and are shown in the tables below.

Serotype Efficacy, Subsequent AOM Episodes due to Same Serotypes Included or Excluded—Finnish study

Type of Episode	Follow-up Period	Inclusion/Exclusion of Multiple Episodes of Same Serotype	Number of Episodes		Rate/ person year		Vaccine Efficacy	
			HBV	PncCRM	HBV	PncCRM	Estim.	95% CI
AOM due to vaccine serotypes	PP	Per Analysis Plan	250	107	0.21	0.09	0.57	0.44, 0.67
		Exclude all subseq. episodes of same serotype	216	95	0.18	0.08	0.55	0.43, 0.65
	ITT	Per Analysis Plan	292	135	0.20	0.09	0.54	0.41, 0.64
		Exclude all subseq. episodes of same serotype	239	118	0.16	0.08	0.51	0.38, 0.61
All culture-confirmed pneumo-coccal AOM	PP	Per Analysis Plan	414	271	0.36	0.23	0.34	0.21, 0.45
		Exclude all subseq. episodes of same serotype	374	245	0.31	0.21	0.34	0.21, 0.44
	ITT	Per Analysis Plan	467	322	0.32	0.22	0.32	0.19, 0.42
		Exclude all subseq. episodes of same serotype	405	288	0.27	0.19	0.29	0.16, 0.40

Adapted from Table Q2.1 of January 10, 2002 submission to BLA.

Individual Serotype Efficacy Results with Subsequent AOM Episodes due to Same Serotypes Included or Excluded, Per Protocol Follow-up—Finnish study

AOM due to serotypes	Inclusion/Exclusion of Multiple Episodes of Same Serotype	Number of Episodes		Rate/100 person year		Vaccine Efficacy	
		HBV	PncCRM	HBV	PncCRM	Estimate	95%CI
4	Per Analysis Plan	4	2	0.34	0.17	0.49	(-1.76, 0.91)
	Exclude all subsequent episodes of same serotype	4	2	0.34	0.17	0.49	(-1.76, 0.91)
6B	Per Analysis Plan	56	9	4.71	0.76	0.84	(0.62, 0.93)
	Exclude all subsequent episodes of same serotype	46	7	3.98	0.60	0.85	(0.67, 0.93)
9V	Per Analysis Plan	11	5	0.92	0.42	0.54	(-0.48, 0.86)
	Exclude all subsequent episodes of same serotype	8	5	0.67	0.43	0.37	(-0.93, 0.79)
14	Per Analysis Plan	26	8	2.18	0.68	0.69	(0.20, 0.88)
	Exclude all subsequent episodes of same serotype	24	6	2.04	0.51	0.75	(0.39, 0.90)
18C	Per Analysis Plan	17	7	1.43	0.59	0.58	(-0.04, 0.83)
	Exclude all subsequent episodes of same serotype	14	7	1.18	0.60	0.50	(-0.25, 0.80)
19F	Per Analysis Plan	58	43	4.88	3.66	0.25	(-0.14, 0.51)
	Exclude all subsequent episodes of same serotype	51	41	4.45	3.58	0.20	(-0.21, 0.47)
23F	Per Analysis Plan	82	33	6.91	2.81	0.59	(0.35, 0.75)
	Exclude all subsequent episodes of same serotype	73	27	6.43	2.34	0.63	(0.43, 0.77)

Adapted from Table Q2.2 of January 10, 2002 submission to BLA.

Individual Serotype Efficacy Results with Subsequent AOM Episodes due to Same Serotypes Included or Excluded, Intent-to-treat Follow-up—Finnish study

AOM due to serotypes	Inclusion/Exclusion of Multiple Episodes of Same Serotype	Number of Episodes		Rate/100 person year		Vaccine Efficacy	
		HBV	PncCRM	HBV	PncCRM	Estimate	95%CI
4	Per Analysis Plan	4	2	0.27	0.13	0.50	(-1.72, 0.91)
	Exclude all subsequent episodes of same serotype	4	2	0.27	0.13	0.50	(-1.73, 0.91)
6B	Per Analysis Plan	61	12	4.12	0.81	0.80	(0.60, 0.90)
	Exclude all subsequent episodes of same serotype	48	10	3.33	0.68	0.80	(0.60, 0.90)
9V	Per Analysis Plan	11	6	0.74	0.40	0.45	(-0.66, 0.82)
	Exclude all subsequent episodes of same serotype	8	6	0.54	0.41	0.25	(-1.16, 0.74)
14	Per Analysis Plan	31	8	2.09	0.54	0.74	(0.34, 0.90)
	Exclude all subsequent episodes of same serotype	26	6	1.78	0.41	0.77	(0.45, 0.91)
18C	Per Analysis Plan	18	7	1.21	0.47	0.61	(0.02, 0.85)
	Exclude all subsequent episodes of same serotype	14	7	0.95	0.47	0.50	(-0.23, 0.80)
19F	Per Analysis Plan	67	60	4.53	4.06	0.10	(-0.32, 0.39)
	Exclude all subsequent episodes of same serotype	56	55	3.92	3.84	0.02	(-0.42, 0.32)
23F	Per Analysis Plan	104	40	7.04	2.70	0.62	(0.41, 0.75)
	Exclude all subsequent episodes of same serotype	87	32	6.21	2.20	0.64	(0.47, 0.76)

Adapted from Table Q2.2 of January 10, 2002 submission to BLA.

In general, these supplemental analyses in which episodes subsequent to the first episode of AOM due to the same serotype are excluded, yielded efficacy estimates similar to those calculated in accordance with the original analysis plan. Exceptions include serotypes 9V and 19F for which the efficacy estimates were substantially reduced in the supplementary analysis. However, in neither analysis were the efficacy estimates statistically significant for these two serotypes.

PCR confirmed pneumococcal AOM episodes

Analyses of AOM episodes using a case definition that included identification of pneumococci in middle ear fluid by PCR were specified in the study protocol, but were not available at the time of the study report was written, and were not provided with the initial BLA submission. The PCR assay detects pneumolysin gene, a gene common to all *S. pneumoniae*, but does not distinguish among serotypes. Potential advantages of using PCR to detect pneumococci in middle ear fluids were cited in the study protocol, and have been described in the literature (Virolainen A, 1994). Results of the analyses of pneumococcal AOM episodes based on PCR were provided during the review period upon FDA request.

A moderate concordance between pneumococcal AOM episodes based on PCR and culture results was observed (kappa < 0.6). A substantial number of samples were positive for *S. pneumoniae* by PCR, but culture negative (532 and 486 in the PncCRM and HBV groups, respectively).

Comparison of Culture and PCR Results—Finnish study

		PCR		Kappa (95% CI)
	Culture	Pnc-	Pnc+	
HBV	Pnc-	1353	532	0.56 (0.53, 0.59)
	Pnc+	24	684	
PncCRM	Pnc-	1563	486	0.52 (0.48, 0.55)
	Pnc+	13	432	

Reproduced from Table Q6.2, of January 10, 2002 submission to BLA.

In the per protocol analysis, the vaccine efficacy estimate for AOM episodes due to pneumococci regardless of serotype was lower (20%) if based on PCR or culture confirmed episodes, than efficacy estimate based solely on culture methods (34%).

In the intent-to-treat analysis for the same outcomes, the efficacy estimate was 18% for pneumococcal AOM episodes confirmed by PCR or culture, versus 32% for episodes confirmed by culture alone.

Efficacy for all pneumococcal AOM episodes, by culture and PCR—Finnish Study

Follow-up Period	Method of Diagnosis	Number of Episodes		Rate/person year		Vaccine Efficacy	
		HBV	PncCRM	HBV	PncCRM	Estimate	95%CI
PP	Determined by culture	414	271	0.36	0.23	0.34	(0.21, 0.45)
	Determined by PCR	678	541	0.60	0.48	0.20	(0.07, 0.31)
	Determined by culture or PCR	687	548	0.60	0.48	0.20	(0.07, 0.31)
	Determined by PCR/ excluding Culture Confirmed *H. flu, M.cat, and S. pyo*	459	321	0.40	0.28	0.30	(0.17, 0.41)
	Determined by PCR or Culture / excluding Culture Confirmed *H. flu, M.cat, and S. pyo*	466	325	0.40	0.28	0.30	(0.17, 0.41)
ITT	Determined by culture	467	322	0.32	0.22	0.32	(0.19, 0.42)
	Determined by PCR	764	635	0.54	0.44	0.18	(0.05, 0.29)
	Determined by culture or PCR	775	642	0.54	0.45	0.18	(0.05, 0.29)
	Determined by PCR/ excluding Culture Confirmed *H. flu, M.cat, and S. pyo*	527	396	0.37	0.27	0.25	(0.13, 0.36)
	Determined by PCR or Culture / excluding Culture Confirmed *H. flu, M.cat, and S.pyo*	536	400	0.37	0.28	0.26	(0.13, 0.37)

Reproduced from Table Q6.1 of January 10, 2002 submission to BLA.

Other bacteria (*H. influenzae, M. catarrhalis, S. pyogenes)* were detected by culture in 42.6% of the MEF samples for which the PCR was positive and culture was negative for pneumococcus. The sponsor also calculated efficacy estimates for pneumococcal AOM episodes confirmed by either culture or PCR, but excluding episodes for which other bacteria (*H. influenzae, M. catarrhalis and S. pyogenes*) were cultured; that efficacy estimate was 30% in the per protocol analysis.

The clinical significance of an AOM episode with MEF that is PCR positive and culture negative for *S. pneumoniae*, but culture positive for other known otitis pathogens, is unknown. Some authors have suggested that pneumolysin PCR is a sensitive and more accurate diagnostic tool than culture, and that a positive PCR suggests pneumococcal involvement, even if cultures are negative for pneumococcus (Virolainen A, et al., 1994). The sponsor suggests that while PCR could be a sensitive probe for actual pneumococcal otitis media, it may also be detecting pneumococcal organisms present in small numbers but not contributing to the pathogenesis of the acute event.

Use of antibiotics in the Finnish study

As noted earlier, guidelines for antibiotic usage in the Finnish population do not differ appreciably from practices in the U.S. Data about antibiotic usage during the Finnish study were recorded onto case report forms during the course of the study. However, antibiotic usage was not included among the prospectively defined study outcomes, and no analyses were provided with the initial BLA submission.

Clearly, patterns of antibiotic use could impact AOM outcomes. If use of antibiotics were significantly greater in the PncCRM group than in the control group, some of the apparent vaccine treatment effect might be attributed to the differential use of antibiotics. Thus, FDA requested that additional data and analyses relating to antibiotic usage be provided.

As shown in the table below, the number of subjects receiving antibiotics for the treatment of AOM was less in the vaccine group; this difference approached statistical significance. The number of subjects receiving antibiotics for prophylaxis, and for any purpose, was also nominally smaller in the PncCRM group.

Number of Subjects with Antimicrobial Prescriptions During ITT Follow-up—Finnish Study

	Number (%) of Subjects Who Had Antibiotics Prescriptions during ITT Follow-up				
	PncCRM (N=831)		HBV (N=831)		P-Value*
AOM Treatment**	551	(66.3%)	589	(70.9%)	0.051
AOM Prevention**	132	(15.9%)	143	(17.2%)	0.509
Other Purposes	157	(18.9%)	147	(17.7%)	0.568
Regardless of Purpose	578	(69.6%)	605	(72.8%)	0.159

Adapted from Table Q5.1 of January 10, 2002 submission to BLA.
P-value based on Fisher's exact test.
** All etiologies of AOM

Similarly, when antibiotic usage was examined by the number of courses prescribed for the treatment of AOM, usage in the PncCRM group was nominally lower than in the control group.

Number of Courses of Antibiotics Prescribed during ITT Follow-up—Finnish Study

	Total Number of Courses during ITT Follow-up		Mean† ± SD Number of Courses Per Subject during ITT Follow-up		P-Value*
	PncCRM (N= 831)	HBV (N= 831)	PncCRM (N= 831)	HBV (N= 831)	
AOM Treatment**	1940	2018	2.33 ± 2.65	2.43 ± 2.60	0.164
AOM Prevention**	299	300	0.36 ± 0.98	0.36 ± 0.94	0.531
Other Purposes	195	177	0.23 ± 0.54	0.21 ± 0.51	0.471
Regardless of Purpose	2277	2342	2.74 ± 3.14	2.82 ± 3.10	0.275

Adapted from Table Q5.2 of January 10, 2002 submission to the BLA.
* P-value based on Wilcoxon rank sum test.
** All etiologies of AOM.
† Mean and SD of the whole treatment group including children who did not have any prescriptions.

Taken together, these data relating to antibiotic use during the Finnish study are consistent with, and largely supportive of, a vaccine treatment effect in the prevention of AOM in the study population.

Tympanostomy tube placement in Finnish study

Information about tympanostomy tube placement during the Finnish study was recorded onto case report forms during the course of the study. However, the study report did not provide group data summaries or statistical analyses of these data. During the review period, FDA requested that recommendations regarding ear tube placement in Finland be provided and that available data relating to ear tube placement be analyzed and submitted to the BLA.

Recommendations regarding ear tube placement during the Finnish study were provided upon FDA request. Children who experience ≥ 3 to 5 AOM episodes within 6 months or ≥ 4 to 6 AOM episodes within a year, or who have asymptomatic bilateral otitis media with effusion (OME) persisting for ≥ 3 months, or unilateral OME persisting for ≥ 6 months are referred for consideration of adenoidectomy and/or insertion of tympanostomy tubes.

The incidence of first ear tube placement in the Finnish study was substantially higher than was consistent with standard practice in Finland. The incidence of tympanostomy tube placement in children under 2 years of age in Finland was estimated to be 0.03 per child year in a study of daycare attendees (Niemela et al., 1999), compared to an incidence of 0.12 per child year observed in the Finnish AOM trial. The ear tube placement incidence in the Finnish study was also substantially higher than the rate observed in the NCKP trial (see below) and in a region served by a large New England health insurer (Thompson et al., 1999). The sponsor suggests that because of the close follow-up within the trial framework, parents may have sought treatment at an earlier phase of disease.

Little difference was observed between the treatment groups with respect to patient characteristics or rate of tympanostomy tube placement, as shown in the table below.

Characteristics of Children Who Underwent Tympanostomy Procedure, Intent-to-treat Follow-Up—Finnish study

	PncCRM	HBV Control
FinOM Trial		
No. of Randomized Subjects	831	831
No. of Subjects Who Had ≥ 1 AOM Visit	548	587
No of Subjects Undergoing Tympanostomy	153	161
Incidence of Tympanostomy (per person yr)	0.11	0.12
≤ 12 mo. of age	0.05	0.05
> 12 mo. of age	0.15	0.16
Mean Age (mo.) of Procedure (interquartile range)	15.9 (4, 24)	15.7 (4, 24)
Mean Number of Prior AOM Episodes (interquartile range)	3.21 (2, 4)	3.13 (2, 4)
Mean Number of Prior AOM Visits (interquartile range)	4.57 (4, 5)	4.48 (3, 5)
Mean Number of Visits / Episode Prior to Tympanostomy Procedure	1.42	1.43

Adapted from Tables Q5.4 and Q5.5 of January 10, 2002 submission to BLA.

If the relatively frequent tympanostomy tube placement in the Finnish AOM trial had prevented AOM episodes that would have been otherwise observed, such undercounting would likely affect the two treatment groups similarly, since the rate of tube placement was similar in the tube groups. Thus, the direction of the treatment effect would not be expected to change; the likely effect on the magnitude and confidence limits of the efficacy estimates is less clear.

In discussing how the tympanostomy tube placement results from the Finnish AOM trial may apply to a U.S. population, the sponsor suggests that lower vaccine efficacy than what was observed in the Finnish OM trial would be unlikely in a population with less frequent tympanostomy tube placement, as more observable AOM episodes in unimmunized children may be preventable by vaccine.

The sponsor also suggested (January 10, 2002 BLA submission) that because of the increased rates of this procedure in the Finnish trial, tympanostomy tube placement would not be an informative efficacy endpoint for providing inferences that could be generalized to the U.S. population.

Subsequently, a long-term follow-up study of the Finnish AOM cohort was completed. In a February 12, 2002 submission, the sponsor proposed an analysis plan of these data for submission to the BLA. All eligible children were 4 to 5 years of age at the planned follow-up visit, which took place between March and June 2001. The vaccination status of all children was made known to parents and investigators following

the unblinding in August 1999. Nasopharyngeal sampling, serum for antibody determinations, parental interview for otitis media history, and pneumatic otoscopy were performed. Records of procedures were verified through hospital or private physicians' records.

The primary analysis compared the risk of first ear tube placement between treatment groups among children enrolled in the follow-up study, counting events since enrollment at 2 months of age in the Finnish AOM trial until 4 to 5 years of age. Relative risk was estimated based on a generalized Cox regression model with vaccine group as a covariate. Results are reported as vaccine efficacy (1- relative risk) with 95% confidence intervals.

Results of the Finnish follow-up study relating to tympanostomy tube placement were submitted to the license application late in the review period (March 29, 2002). A total of 756 of the original 1662 randomized children enrolled and completed assessments in the follow-up study. Of the participants, 353 received HBV and 403 received PncCRM. Demographic characteristics of children who participated did not differ markedly by vaccine group. Likewise, characteristics for non-participants were similar between the vaccine groups.

The efficacy estimate for tube placement during the efficacy trial among the cohort participating in the long-term follow-up was 12%; however, this was not as statistically significant result.

During the long-term follow-up in this cohort, ear tube placement was reduced 39%; this was a statistically significant result.

Tympanostomy tube placement among children enrolled in Finnish AOM follow-up study

	HBV	PncCRM	Efficacy estimate	95% CI
Number enrolled	353	403		
ITT follow-up, Finnish AOM trial (age 2 months to 2 years)				
Number of subjects with events	84	82		
Number of events	95	95		
Rate of events (/100 child years)	14.8	12.9	0.12	-0.17, 0.34
Long-term follow-up (age 2 years to 4-5 years)				
Number of subjects with events	46[†]	33[‡]		
Number of events	57	40		
Rate of events (/100 child years)	5.7	3.5	0.39	0.04, 0.61

Adapted from Table 4 of March 29, 2002 submission to the BLA.
[†] 23 subjects had tube placed during the efficacy trial
[‡] 17 subjects had tube placed during the efficacy trial

A secondary analysis was performed in which data on ear tube placement was collected for the entire Finnish AOM study population using only available hospital medical records. Children known to have discontinued study participation in the AOM study or who moved from the area were excluded from this analysis.

Tympanostomy tube placement among all children enrolled in Finnish AOM study who were known to be at risk[§]— Finnish Follow-up study

	HBV	PncCRM	Efficacy estimate	95% CI
Number enrolled	831	831		
ITT follow-up, Finnish AOM trial (age 2 months to 2 years)				
Number of subjects with events	161	153		
Number of events	189	178		
Rate of events (/100 child years)	12.7	12.0	0.04	-0.19, 0.23
Long-term follow-up (age 2 years to 4-5 years)				
Number included[§]	744	746		
Number of subjects with events	71[†]	46[‡]		
Number of events	92	53		
Rate of events (/100 child years)	4.1	2.4	0.44	0.19, 0.62

Adapted from Table 5 of March 29, 2002 submission to the BLA.
[§] Subjects discontinued from Finnish AOM study or moved from study area were excluded.
[†] 38 subjects had tube placed during the efficacy trial.
[‡] 19 subjects had tube placed during the efficacy trial.

The efficacy estimate for tympanostomy tube placement during the Finnish AOM study was 4%; this was not statistically significant.

During the long-term follow-up of the original Finnish AOM study cohort, excluding subjects known to have left the area, ear tube placement was reduced 44%, based on available hospital records; this was a statistically significant result.

4.2 Northern California Kaiser Permanente (NCKP) study

4.2.1 NCKP study description

Title: Evaluation of the Safety, Immunogenicity and Efficacy of Heptavalent Pneumococcal Conjugate Vaccine and Safety of Meningococcal Group C Conjugate Vaccine in Infants at 2, 4, 6 and 12-15 Months of Age in Northern California Kaiser Permanente (NCKP) Medical Care Program

This was a randomized, double-blind study conducted at multiple clinics within the Northern California Kaiser Permanente health care system.

The study was initiated in October 1995; enrollment ceased August 24, 1998, after results of the planned interim analysis demonstrated substantial evidence of efficacy for the primary study outcome- prevention of invasive disease. The otitis media database had been locked on April 30, 1998. Follow-up of infants for invasive pneumococcal disease and serious adverse events continued through April 20, 1999.

The study design of the NCKP study was discussed at the November 1999 VRBPAC, and will not be presented again here in detail. Only efficacy data relating to otitis media were submitted with the application.

Additional information about concurrent immunizations, vaccine schedules, eligibility criteria, randomization and blinding are provided in Attachment B of this document.

Objectives of the NCKP study

The primary objective of this study was to determine the protective efficacy of 7VPnC against invasive pneumococcal disease caused by serotypes represented in the vaccine.

One of the multiple secondary objectives of the NCKP study was to assess the effectiveness of 7VPnC on rates of acute otitis media.

Case surveillance and ascertainment in the NCKP study

No special provisions were made for surveillance and ascertainment of otitis media cases. AOM cases were diagnosed by the child's health care provider within the Kaiser Health Care system and identified by a check in a box for "acute otitis media" or "otitis media" on a patient encounter form for data capture and entry into the Kaiser automated databases for emergency room and clinic visits.

Tympanocentesis and bacterial culture of middle ear fluid from cases of AOM were not routinely performed. Fluid from spontaneous drainage of ears was cultured for

pneumococcus in some cases. However, the presence of pneumococcus or other pathogens was not confirmed for most AOM cases.

Note: Follow-up visits could not be clearly differentiated from initial encounters for new episodes using the automated databases.

Definitions of outcome variables

AOM diagnoses were based on the clinical practices of the participating clinicians. No definition of AOM based on a set of clinical characteristics was uniformly applied across centers.

AOM episode is a clinic visit at which AOM was diagnosed and at least 21 days had elapsed since any previous visit for AOM.

Note: The period defining a new AOM episode in the NCKP and Finnish studies differs. The Finnish study uses a period of at least 30 days.

Recurrent otitis media was defined prospectively by 3 otitis media episodes within 6 months, or 4 episodes within 12 months.

Definition of follow-up periods

Per protocol (PP) follow-up started 14 days after the 3rd injection of the study vaccine and continued until the earliest of: 1) dropout from the NCKP health plan, 2) attainment of age 16 months without receipt of a 4th dose, or 3) April 30, 1998.

Intention-to-treat (ITT) follow-up began the day after randomization and continued until April 30, 1998, and included all subjects who were randomized into the study. For ITT follow-up, children were not censored when they disenrolled from the Kaiser health plan.

Efficacy outcomes assessed

Primary otitis media endpoint was the overall reduction in the incidence of all otitis media episodes.

Secondary endpoints prospectively identified included:

- Risk of at least 1 episode of otitis media
- Risk of frequent otitis media
- Risk of tympanostomy tube placement
- Overall incidence of clinic visits for otitis media

Exploratory endpoints included:

- Incidence of spontaneously ruptured tympanic membranes that yielded a positive culture for vaccine-serotype pneumococcus.
- Risk of frequent otitis media using other definitions

Analysis plan

The Anderson-Gill model was used to analyze recurrent event data, including the primary outcome, all otitis media episodes, and the secondary outcome, all clinic visits. Relative risk was assumed to be fixed over time. This assumption was checked graphically by plotting the relative risk over time. Robust estimates of variance were used.

The Cox proportional hazard model was used for single event data, including first AOM episode, frequent otitis media, and tympanostomy tube placement.

The exact binomial test was used to analyze cases of ruptured ear drums.

A Poisson regression model was used to examine the effects of gender, age, and season on overall incidence of otitis media.

4.2.2 NCKP study AOM efficacy results

Disposition of subjects

Enrollment into the study continued until the planned interim analysis of efficacy for invasive disease demonstrated substantial evidence of efficacy. At the time enrollment stopped, 37,868 infants had been randomized. However, the AOM data base was closed for the purpose of analysis and preparation of a study report on April 30, 1998, after 34,146 children had been enrolled. The table below provides the number of children included in the AOM analysis by study group and the number of children who had received each dose.

Number of subjects included in the AOM analysis who received each dose—NCKP Study

Dose (age in months)	7VPnC	MnCC	Total
1 (2 months)	17,066	17,080	34,146
2 (4 months)	15,427	15,410	30,837
3 (6 months)	13,812	13,775	27,587
4 (12-15 months)	9,047	9,122	18,169

Adapted from Table 2, page 42, Volume 5 of BLA.

Demographic characteristics

Information about gender and age at start of AOM follow-up was available for all subjects in the AOM analysis.

Characteristics of subjects included in the Otitis Media Analysis—NCKP Study

	7VPnC	MnCC
Per-Protocol Analysis Population		
Number of Children	11849	11897
Male (%)	51.9	51.5
Mean (±SD) Age at Start of Follow-up (days)	207.8 ± 19.1	207.7 ± 19.0
Intent-to-Treat Analysis Population		
Number of Children*	17070	17076
Male (%)	51.6	51.1
Mean (±SD) Age at Start of Follow-up (days)	64.5 ± 11.1	64.3 ± 10.9

Adapted from Table 10, page 49, Volume 5 of BLA.
* The number of children randomized to each treatment group and included in the ITT analysis, as shown in this table, differs from the number of children receiving the first dose, as shown in the previous table, due to errors in administration of treatments as per assignments.

A substantial proportion of AOM episodes among the randomized population were excluded from the per protocol analysis. The proportions excluded in each treatment group were similar, 37% (7VPnC) vs. 36% (MnCC). The most common reason for excluding children from the per protocol analysis was that subjects had not received 3 doses of vaccine at data cut-off.

Additional information about demographics of the study population was collected on a subset of approximately 7500 randomly selected subjects by means of parental telephone interview.

The proportion of the population subset identifying with specific race/ethnicity groups is shown below.

Race/Ethnicity As Reported at 48 Hour Interview After Dose 1-- NCKP study

	Asian %	Black %	Hispanic %	White %	Multi-ethnic %	Other/ Unknown %	p-value*
7VPnC (N=3708)	13.4	7.7	19.6	39.3	19.4	0.6	0.123
MnCC (N=3693)	13.0	8.4	17.9	40.5	19.3	1.0	

Reproduced from Table 7, page 46, Volume 5 of BLA
*Chi-Square Test (sponsor's analysis)

The study groups appear to be well-balanced with respect to gender, race/ethnicity, and age at onset of follow-up for AOM outcomes.

Information about day-care attendance, household income, and mother's education was also collected by parental interview of the randomized subset. No important

differences between study groups for these demographic characteristics were identified.

Primary endpoint analysis: All AOM episodes

A total of 16,124 AOM episodes were identified in the 11,849 children in the 7VPnC group as compared to 17,405 episodes in 11,897 children in the MnCC group, a reduction of 7% (95% CI 4.1%, 9.7%).

Results of the intent-to-treat analysis were similar.

Primary endpoint analysis, all AOM episodes—NCKP study

Outcome	Episodes		Rate/child year		Vaccine efficacy[1]	
	7VPnC	MnCC	7VPnC	MnCC	% Reduction	(95% CI)
All AOM Episodes, Per protocol	16,124	17,405	1.60	1.72	7.0%	(4.1, 9.7)
All AOM Episodes, Intent-to-treat	25,590	27,199	1.29	1.37	6.4%	(3.9, 8.7)

[1] Estimates of relative risk based on Andersen-Gill counting process over time with treatment as the only covariate.

Secondary endpoints analyses

First AOM episode

The risk of at least one AOM episode (or risk of first episode) counts no more than one AOM episode per subject. Vaccine efficacy estimates for the risk of at least one episode (or risk of first episode) were statistically significant in both per protocol and intent-to-treat analyses, 5.4% and 4.9%, respectively.

In the per protocol analysis, first episodes of AOM accounted for approximately 44% and 43% of all AOM episodes in the 7VPnC and MnCC groups, respectively. In the intent-to-treat analysis, first episodes of AOM accounted for approximately 40% and 38% of all AOM episodes in the 7VPnC and MnCC groups, respectively.

Risk of at least one episode—NCKP study

Outcome	Number of Children with ≥ 1 Episode		Rate/child year		Vaccine efficacy	
	7VPnC	MnCC	7VPnC	MnCC	% Reduction	(95% CI)
Risk of ≥ 1 Episode AOM Per protocol	7,126	7,411	0.651	0.669	5.4	(2.3, 8.4)
Risk of ≥ 1 Episode AOM Intent-to-treat	10,112	10,394	0.474	0.488	4.9	(2.3, 7.5)

Adapted from Table 12, page 58, Volume 5 of BLA.
Estimates of relative risk and confidence intervals were based on Cox-regression model of hazard over time, with gender as covariate.

Frequent otitis media

The definition of frequent otitis media was specified as 3 episodes (new visits) within a 6-month period, or 4 episodes within a 1-year period of follow-up. A total of 1,647 (13.9%) children in the 7VPnC group met the definition of frequent AOM, compared to 1,809 (15.2%) children in the MnCC group. The risk reduction for frequent AOM was 9.5% (95% CI: 3.2% to 15.3%). Results of the intent-to-treat analysis were similar.

Children with frequent otitis media—NCKP study

Outcome	Number of Children with Frequent AOM		Rate/100 child years		Vaccine efficacy	
	7VPnC	MnCC	7VPnC	MnCC	% Reduction	95% CI
Frequent AOM Per protocol	1,647	1,809	16.4	17.9	9.5%	(3.2, 15.3)
Frequent AOM Intent-to-treat	2,612	2,839	12.3	13.3	9.2%	(4.3, 13.9)

Adapted from Table 13, page 62, Volume 5 of BLA.
Estimates of relative risk and confidence intervals were based on Cox regression model over time with gender as a covariate.

Tympanostomy tube placement

A total of 157 children in the 7VPnC group had tympanostomy tubes placed during the per-protocol follow-up, compared to 198 children in the MnCC group. The reduction in tube placement was 20.3%, which was statistically significant, although the confidence interval was relatively wide (95%CI: 1.8%, 35.4%). Results of the intent-to-treat analysis were consistent with the per protocol analysis.

Tympanostomy tube placement—NCKP study

Outcome	Number of Children with Tube Placement		Rate/100 child years		Vaccine efficacy	
	7VPnC	MnCC	7VPnC	MnCC	% Reduction	(95% CI)
Tube Placement Per protocol	157	198	1.43	1.79	20.3%	(1.8, 35.4)
Tube Placement Intent-to-treat	192	240	0.90	1.13	20.6%	(4.0, 34.3)

Adapted from Table 14, page 66, Volume 5 of BLA.
Estimates of relative risk and confidence intervals were based on Cox regression model of hazard over time.

Clinic visits for otitis media

A total of 22,478 clinic visits for AOM were recorded in the 7VPnC group during the per protocol follow-up period, compared to 24,914 visits in the MnCC group. The overall incidence of AOM visits was reduced from 2.25 visits per child-year in the MnCC group, to 2.05 visits per child-year in the 7VPnC group, an 8.9% (95% CI: 5.8% to 11.8%) reduction. Results of the intent-to-treat analysis were consistent with per protocol.

Overall incidence of all otitis media visits—NCKP study

Outcome	Number of Children with Tube Placement		Rate/100 child years		Vaccine efficacy	
	7VPnC	MnCC	7VPnC	MnCC	% Reduction	(95% CI)
All AOM visits Per protocol	22,478	24,914	2.05	2.25	8.9%	(5.8, 11.8)
All AOM visits Intent-to-treat	35, 031	38,010	1.64	1.78	7.8%	(5.2, 10.5)

Adapted from Table 15, page 69, Volume 5 of BLA.
Estimates of relative riskwere based on Andersen-Gill counting process over time with treatment as the only covariate.

Exploratory analysis—Ruptured eardrums due to pneumococcal infection

Although the otitis media database was “locked” April 30, 1998, cases of ruptured tympanic membranes were analyzed by the sponsor for data accumulated through November 6, 1998. The number of ruptured eardrums in the dataset locked in April 1998 was too small for meaningful analysis. The later data cut-off for this endpoint was chosen so that the additional cases accrued could be included in the analysis. This analysis took place prior to unblinding of the otitis media dataset, however, the timing of this analysis was not pre-specified in the analysis plan.

Of the 13 cases of ruptured eardrums with a bacterial culture positive for vaccine serotype pneumococcus during per protocol follow-up, 4 were in the 7VPnC group and 9 were in the control group. The vaccine efficacy estimate, 55.6%, was not statistically significant . Likewise, the efficacy estimate of vaccine serotypes during intent-to-treat follow-up was 57%; this result was not statistically significant.

The efficacy estimate for ruptured eardrums with a positive culture for any pneumococci, regardless of serotype, was 61% in the intent-to-treat analysis; this result was statistically significant.

Ruptured eardrums with pneumococcus isolated—NCKP study

Ruptured Eardrum (Cases through November 6, 1998)	Number of Cases		Vaccine Efficacy	
	7VPnC	MnCC	% Reduction	(95% CI)
Vaccine Serotypes				
Per Protocol	4	9	55.6%	(-59.3, 90)
Intent-to-treat	6	14	57.1%	(-18.7, 86.5)
All pneumococcal serotypes				
Per Protocol	5	13	61.5%	(-15.0, 89.3)
Intent-to-treat	7	18	61.1%	(2.4, 86.3)

Adapted from Table 19, Volume 1 of PLA.
Confidence limits were determined based on exact binomial distributions.

Vaccine sertoype 19F and related serotype 19A accounted for all isolates from ruptured tympanic membranes in the 7VPnC group. Serotype 19F accounted for 39% of all isolates from the MnCC group. Vaccine serotypes accounted for 78% (14/18) of all isolates from the control group, and 80% (20/35) of all isolates in both groups.

Serotype distribution of isolates from ruptured ear drums due to pneumococcus, intent-to-treat analysis--NCKP study

	Number of cases (%) due to each serotype	
Serotype	7VPnC	MnCC
19F	6	7 (38.9%)
14	0	4 (22.2%)
9V	0	1 (5.6%)
23F	0	2 (11.1%)
Total of vaccine serotypes	6	14 (77.8%)
19A	1	1 (5.6%)
6A	0	1 (5.6%)
3	0	1 (5.6%)
29 & 35	0	1 (5.6%)
Total of non-vaccine serotypes	1	4 (22.2%)
Total of all serotypes	7	18

Adapted from Table 17, page 73, Volume 5 of BLA.

Follow-up analyses

The data cut-off for the AOM efficacy analysis was April 30, 1998. However, children continued to enroll in the study until August 24, 1998, when the data were unblinded for the efficacy analysis for invasive disease. All enrolled children were followed within NCKP using the computerized patient data for AOM outcomes until April 20, 1999, at which time parents and participating clinicians were made aware of treatment assignments. AOM efficacy data through the extended follow-up are shown below.

Efficacy Analysis for AOM During Intent-to-treat Follow-up, All Data of NCKP Trial through April 20, 1999—NCKP study

	ITT Follow-up					
	Number of Subjects		Number of Events		Risk Reduction Estimate	
	April 30, 1998	April 20, 1999	April 30, 1998	April 20, 1999	April 30, 1998	April 20, 1999
All AOM Episodes	34146*	37866†	52789	84978	6.4% (3.9%, 8.7%)	5.9% (3.8%, 7.9%)
First AOM Episode	34146	37866	20506	27343	4.9% (2.3%, 7.5%)	4.4% (2.1%, 6.7%)
First Tube Placement	34146	37866	432	751	20.6% (4.0%, 34.3%)	23.2% (11.3%, 33.5%)
All AOM Clinic Visit	34146	37866	73041	116636	7.8% (5.2%, 10.5%)	7.0% (4.8%, 9.2%)
Frequent AOM	34146	37866	5451	12252	9.2% (4.3%, 13.9%)	10.2% (7.7%, 14.0%)
Ruptured Ear Drum due to Vaccine Serotype	34146	37866	20	24	57.1% (-18.7%, 86.5%)	66.7% (12.3%, 89.2%)

Adapted from Table Q17.1 of BLA submission of April 15, 2002.
* 7VPnC: 17070; MnCC: 17076
† 7VPnC: 18925; MnCC: 18941

Efficacy results for all outcomes in the extended follow-up period are consistent with results of the planned AOM analyses. Efficacy estimates are similar and confidence intervals are generally narrower with the additional follow-up data.

5.0 FDA discussion of review issues related to acute otitis media

The safety of Prevnar had been carefully examined in several studies at the time of licensure for prevention of invasive disease, including the large safety and efficacy study conducted at NCKP. Safety data from the Finnish AOM study were reviewed with this submission, and are discussed in Attachment A of this document. Discussion of the proposed indication for prevention of AOM that follows will focus on describing additional benefits of Prevnar, i.e., prevention of AOM.

Finnish AOM study

The Finnish study provided serotype specific, direct causal evidence of prevention of AOM due to *S. pneumoniae*, as the bacteria were isolated from the middle ears of subjects presenting with AOM. This type of trial would be quite difficult to conduct in the U.S. since tympanocentesis and culture of middle ear fluid are not the standard of care for the management of AOM in most communities.

An important anomalous finding from the Finnish study was the increased risk of AOM due to pneumococci from serogroups not represented in Prevnar. This "negative efficacy" for non vaccine serotypes has been referred to as "serotype replacement". These AOM episodes due to non-vaccine serotypes are clearly of clinical significance, as affected subjects suffered symptoms sufficient to bring them to medical attention and subsequent myringotomy. Thus, consideration of this finding is essential to the evaluation and description of the overall benefit afforded by Prevnar. However, to the extent that the replacing pneumococcal serotypes are more susceptible to commonly used antimicrobials, which is likely based on the known association of antibiotic resistance with vaccine serotypes, the replacement of antibiotic-resistant pneumococci by antibiotic-susceptible organisms might be interpreted as a favorable outcome.

Although the overall vaccine effect on all cause AOM was not statistically significant in the Finnish study, the trial was not designed or powered to detect an effect on this outcome. The efficacy point estimate (6%) was nevertheless comparable to what was observed in the NCKP study for a similar endpoint.

The repeated isolation of the same serotype from middle ear fluids over extended periods (several months) of some subjects observed in the Finnish study may simply reflect nasopharyngeal carriage of those serotypes. However, as was pointed out in a letter to the editor following publication of study results (Cantekin, 2001), an implication for the analysis of counting multiple AOM episodes per subject is that the true treatment effect can be inflated. In the sponsor's planned secondary analysis of first AOM episodes due to vaccine serotypes, (i.e., one AOM episode per subject), the efficacy estimates were similar to those of the primary analysis and were statistically significant (52% per protocol, 48% intent-to-treat). Supplemental analyses requested by FDA to examine alternative estimates of the treatment effect, in which only one episode per serotype per subject contributes to the analysis, showed that the efficacy estimates for vaccine serotypes and for all pneumococcal serotypes were statistically significant and

not markedly changed from those of the planned analyses, which included multiple episodes per subject.

Examination of characteristics of the subject population revealed some differences between the study groups for AOM risk factors. The supplemental covariate analyses conducted by the sponsor provided some assurance that results for the primary endpoints would not be significantly affected by these differences.

Other supplementary analyses requested by FDA, such as analyses of the use of antibiotics and the placement of ear tubes, provided results largely consistent with a positive treatment effect of Prevnar on AOM. Analysis of AOM episodes based on the identification of pneumococcus using PCR did yield efficacy estimates slightly lower than efficacy estimates based on bacterial culture. Some authors have suggested that PCR provides a sensitive indicator of pneumococcal involvement in AOM (Virolainen A, et al., 1994). Culture will identify viable organisms, while PCR can detect non-viable organisms or fragments of residual DNA in middle ear fluid. The most appropriate interpretation of efficacy results based on PCR is not readily apparent.

NCKP study

The NCKP study was limited by the lack of common uniform diagnostic criteria for AOM, and the lack of culture confirmation for most cases of AOM. Strengths of the NCKP study for AOM outcomes included the great power to detect small differences in overall benefit, and the "real world" approximation of the diagnosis and management of AOM, which may be generalizable to a wider US population. Also, the randomization of such a large study population practically assures good balance between the study groups at baseline of subjects with AOM risk factors.

The efficacy estimate for the primary endpoint, all AOM episodes, of 7.0% (95%CI: 4.1%, 9.7%) in the per protocol analysis, is comparable to the efficacy estimate from the Finnish trial for the similar endpoint. It is worth emphasizing that the outcome of "all AOM episodes" included AOM episodes due to viral pathogens, *M. catarrhalis, H. influenzae, S. pyogenes*, and non-vaccine serotype pneumococci. Nevertheless, the NCKP study had sufficient power to demonstrate statistical significance for this outcome.

The 21-day period between "AOM episodes" used in the NCKP AOM definitions, differs from the 30-day period used to define new episodes in the Finnish study. The most appropriate period for defining a new AOM episode is uncertain. However, it is likely that shorter period defining new episodes will lead to inclusion of more new episodes in the analysis, some of which may be the same slowly resolving AOM episodes, or simply follow-up visits encoded as clinic visits for AOM on the patient encounter forms.

One check on the possibility that the definition used in the NCKP study for "all AOM episodes" may overcount cases or otherwise inflate the treatment effect is the secondary outcome of "at least one AOM episode". This outcome counts no more than

one AOM episode per subject. The efficacy estimate for "at least one AOM episode" in the per protocol analysis was 5.4% (95%CI: 2.3, 8.4), slightly lower than the efficacy estimate for the primary analysis, but nevertheless a statistically significant result.

The highest statistically significant efficacy estimate among the secondary AOM endpoints in the NCKP study was for prevention of ear tube placement, 20.6% in the intent-to-treat analysis; however, the 95% confidence intervals for this estimate were wide (95% CI: 4.0, 34.3). After an additional year of extended follow-up, the efficacy estimate for prevention of ear tube placement was 23.2%, and the confidence intervals had narrowed with the additional follow-up data (11.3%, 33.5%).

Analysis issues

The efficacy estimates for the primary endpoints in both the Finnish and NCKP studies use analytic methods for repeated measures over time. This type of analysis is not typical for most vaccine studies, in which each study participant contributes no more than one case to the analysis.

The Anderson-Gill model of proportional hazards that was chosen for the analysis of repeated episodes of AOM is said to analyze risk periods "piecewise" with "robust standard errors". These statistical methods may be the best available for the analysis of repeated episodes of AOM following vaccination as a means to measure efficacy using all available outcome data. Nevertheless, the methods are likely not intuitive to most clinicians, and applicability of these methods in a vaccine trial may not be readily apparent.

Sequential episodes of AOM within subjects will be dependent to some extent based on inherent risk or resistance factors. Episodes of AOM may not be entirely resolved by the end of 21 days (NCKP) or 30 days (Finnish study), in which case a new episode may be counted that is in fact an extension of the same episode. Based on what is known about the pathogenesis of AOM, persistence of edema around the Eustachian tube and persistence of middle ear fluid after an episode of AOM resolves may contribute to conditions favorable to a repeated episodes. Carriage of a serotype in the nasopharynx likely impacts on repeated isolation of that serotype on repeated samplings of middle ear fluid during AOM episodes. The risks of AOM episodes might also be expected to increase disproportionately between groups over time if early episodes predispose to later episodes.

One check on the repeated measures data that was included among secondary endpoints in both trials, was the analysis of "risk of first episode". If only first episodes are considered, much of the AOM outcome data would be discarded, but uncertainty related to carry over effects of previous episodes beyond the 21-day or 30-day periods would be avoided. FDA also requested additional analyses to check the robustness of the original analysis and to elucidate the effects of baseline imbalances for risk factors, which may also carry forward. Other analyses from the Finnish study based "one episode per pneumococcal serotype per subject" were requested in order to better

understand whether counting multiple episodes of the same serotype in individuals inflates efficacy estimates. While the efficacy estimates from these supplementary and secondary analyses vary, they remain statistically significant, and, therefore, provide confirmatory evidence of a positive treatment effect of Prevnar on prevention of AOM.

Level of evidence sufficient for an approved indication

Approvals of most drugs and other therapeutic biological products are based on substantial evidence of efficacy from at least 2 well-controlled clinical studies. This follows from the Code of Federal Regulations (CFR), Section 505 [21 CFR 355] (d), defining substantial evidence as "consisting of adequate and well controlled investigations". As modified under the Food and Drug Modernization Act (FADMA) of 1997, a single well-controlled clinical investigation may be deemed sufficient to meet a level of substantial evidence if confirmatory data from other studies are also available. For many vaccines, a single study has been deemed sufficient for providing evidence of efficacy; however, vaccine efficacy studies are typically quite large, multi-center, and demonstrate a high level of efficacy.

The Finnish study and the NCKP study provide efficacy data using complementary study designs. The Finnish study was designed to provide direct causal evidence of efficacy, by isolation and identification of pneumococci from the middle ears fluids of subjects. The Kaiser study was a large trial that provided empirical evidence of a small treatment effect in preventing all cause AOM in infants and small children. In each study, statistical significance was demonstrated for the primary endpoints. Evidence from secondary endpoints was supportive and consistent with the expected treatment effects.

Arguably, the sponsor has provided efficacy data from two adequate and well-controlled studies demonstrating a level of evidence that is sufficient by FDA regulations for an approved indication.

The lowest level of efficacy acceptable for approval of a vaccine indication has not been set by FDA regulation or CBER policy. For most preventive vaccines, vaccine efficacy estimates are high (>80%) and are associated with a high level of statistical significance. Examples of licensed vaccines associated with relatively low efficacy estimates for the primary outcome measures in studies include cholera (~50%) (MMWR, 1988), typhoid (50-79%) (MMWR, 1994), and influenza (20-80%) (Patriarca P et al., 1987).

Description of the treatment effect

If one accepts that substantial evidence of efficacy in preventing AOM has been demonstrated, then a new indication that describes the treatment effect of Prevnar regarding AOM will be included in the label indication. The sponsor proposes an indication for prevention of AOM limited to serotypes represented in Prevnar. Such an indication would reflect the primary endpoint of the Finnish AOM study, but not the

primary AOM endpoint in the NCKP study. Focusing on vaccine serotype-specific efficacy would not capture the treatment effect for vaccine-related serotypes, nor the increased risk of AOM due to other, non-vaccine- related pneumococcal serotypes observed in the Finnish study.

Preventing as much otitis media as possible is clearly the goal of a vaccine to prevent otitis media. While it may not be realistic to expect a large preventive effect on otitis media caused by pneumococcal serotypes not covered by Prevnar, the potential for serotype replacement appears to be a real possibility. An indication for prevention of all pneumococcal AOM, regardless of serotypes would be based on a lower efficacy estimate (34%) from the Finnish study, but it appears to capture the effect on vaccine-related serotypes, serotype replacement, and would provide a standard of efficacy that could be reasonably applied to other pneumococcal vaccines that may be active against additional serotypes. If serotype specific efficacy serves as the basis for the AOM indication, then information about overall efficacy for pneumococcal AOM disease (vaccine and non-vaccine combined) as well as unrelated serotypes should also be included in the label.

Approval of Prevnar for prevention of invasive disease was for an indication limited to vaccine serotypes. However, vaccine serotypes accounted for over 80% of all invasive disease isolates. Moreover, replacement of vaccine serotypes by non-vaccine serotypes was not observed during the large efficacy study, and has not been observed, even after prolonged follow-up at NCKP (Black SB, et al., 2001).

Implications for licensure of other pneumococcal vaccines

At the March 2001 VRBPAC, the committee was asked to consider pathways to licensure of future pneumococcal vaccines. Specifically, the committee was asked to comment on whether efficacy data demonstrating a significant treatment effect in preventing AOM would provide a basis for licensure of a pneumococcal vaccine for an indication of invasive disease. The predominant opinion expressed by committee members was that demonstration of efficacy for AOM alone would not provide sufficient support for an invasive disease indication. It was noted that while prevention of otitis media may be a stringent test of vaccine efficacy, other variables such as the level of preventive efficacy for AOM, and the relative distribution of important serotypes for the two disease conditions, complicate the translation of efficacy for AOM to efficacy against invasive disease.

To date, Prevnar is the only licensed pneumococcal conjugate vaccine for any indication. No correlation between a serological parameter and efficacy for any indication has been clearly demonstrated or generally accepted. With the availability of Prevnar, efficacy trials using invasive disease endpoints could be difficult to conduct in any setting.

In the future, FDA may be asked to consider license applications for other pneumococcal vaccines for prevention of acute otitis media. The approval of an

indication for Prevnar for prevention of AOM, would likely set a precedent for the type of data and level of efficacy sufficient for approval of future pneumococcal vaccines for this indication, independent of whether or not the license applications for these new vaccines include evidence of efficacy for prevention of invasive disease. The description of the treatment effect could influence the type of data used as a basis for approval of other pneumococcal vaccines for prevention of AOM. One can envision a scenario where a vaccine might have a lower efficacy estimate than Prevnar for serotypes included in the vaccine, yet prevent more cases of AOM as a result of greater coverage of pneumococcal serotypes, either due to increased number of serotypes represented in the vaccine, or by some other mechanism.

Clinical benefit vs. economic benefit as basis of regulatory approval

In the risk/benefit assessment of product approvals by FDA, substantial evidence of clinical benefit must be provided from well-controlled studies. A decrease in office visits for AOM and potential cost savings of medical care related to AOM have been cited by the sponsor and in the literature among the benefits of Prevnar. To the extent that office visits reflect patient disease, they may be considered in the assessment of clinical benefit for the basis of a regulatory decision. However, economic benefit to individuals or society cannot provide the basis of efficacy for a product approval.

Antibody responses in Finnish study

Serum antibody concentrations (GMC) from the Finnish study based on standardized ELISA assays, appear to be consistent with antibody levels observed among 7VPnC recipients in other pre-licensure studies. However, the antibody levels do not provide any insight regarding observed differences in efficacy by serotype. For example, the estimate of vaccine efficacy against type 6B was greatest among the serotypes, yet the GMC after the first 3 doses was 2nd lowest. Little efficacy was observed for serotype 19F, yet GMCs after the 3rd and 4th doses were similar to those of other serotypes. Likewise, using percent of subjects responding above defined antibody cutoff levels, 100% of subjects in the serology cohort had antibody levels to serotype 19F above 0.3 mcg/mL and 0.5 mcg/mL, and 91% had antibody levels above 1.0 mcg/mL after 3 doses. For serotype 6B, 85%, 83% and 67% of subjects had antibody levels above 0.3 mcg/mL, 0.5 mcg/mL, and 1.0 mcg/mL, respectively.

It may be informative to determine the presence of opsonophagocytic antibody (OPA) by serotype and to examine its predictive value for protection against AOM. It would also be of interest to examine ELISA and GMCs for related vaccine serotypes. These data were not provided in the application. However, the sponsor does not propose any specific claims regarding the relationship of immune response parameters with efficacy for otitis media.

Results from the Finnish and NCKP studies regarding serotype 19F deserve additional comment. In the Finnish study, statistical significance for serotype specific efficacy for 19F was not observed, despite a substantial number of AOM episodes due to serotype

19F. In the supplemental analysis in which each serotype contributes no more than one episode of AOM to the analysis, the efficacy estimate for 19F was only 2% in the ITT analysis. Moreover, in the NCKP study, 6 of the 7 isolates from ruptured tympanic membranes in the 7VPnC group were due to serotype 19F (and the remaining isolate was the related type 19A). Taken together, these data suggest that the pathogenesis of AOM due to serotype 19F, or the immune response to serotype 19F induced by Prevnar, may be fundamentally different for this serotype.

Marketing implications of an AOM indication

Approval of an indication for prevention of otitis media would normally allow the manufacturer to distribute marketing materials promoting use of the product based on information included in the approved labeling. The potential for misleading public expectations in marketing materials would exist for Prevnar, as for any product and approved indication. However, FDA is empowered to restrict unrealistic marketing claims. Regulations for post-marketing reporting requires applicants to submit advertisements and promotional labeling to CBER for review. Advertisements that are judged false, lacking in fair balance, or are otherwise misleading (defined in CFR 202.1) can result in a product being misbranded. If a company fails to correct such violations, CBER is empowered to suspend or revoke an approved license (21 CFR 601.6 and 601.5).

Summary remarks

Results from two, randomized, well-controlled clinical studies demonstrated statistically significant reduction in acute otitis media outcomes. In each study, the primary analysis demonstrated a statistically significant effect on the prospectively chosen outcome of interest. Results of secondary and ancillary outcome measures in both trials, as well as supplementary analyses requested by FDA, were largely consistent with a positive treatment effect afforded by Prevnar. The magnitude of the efficacy estimates for the primary outcomes were relatively low compared to efficacy results of most preventive vaccines. Whether the impact of Prevnar on acute otitis media represents substantial evidence of efficacy for this new indication, and if so, the most appropriate description of the treatment effect, merit discussion in a public forum by a panel of experts.

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Attachment A: Review of safety from Finnish study

No questions regarding safety data were asked of VRBPAC at the May 2002 meeting. Safety data from the Kaiser efficacy study were reviewed at the November 1999 VRBPAC, in the context of consideration of the invasive disease indication. Safety data from the Finnish study were reviewed with the BLA for prevention of AOM. A discussion of these data follows.

Description of Finnish safety data

Safety follow-up for each participant began at the time of enrollment (2 months of age), and ended at 24 months of age.

Local and systemic reactions were monitored in all children for 3 days after each vaccine dose using a 3-day diary card completed by parents. Presence or absence and severity of local tenderness, redness, swelling, fever, and crying were recorded. Rectal temperatures were to be measured and recorded at 24, 48, and 72 hours after inoculations. The diameter of redness and swelling was to be measured and recorded by parents.

Parent compliance with reporting of vaccine reactions was nearly complete. Data on vaccine reactions were available for 6523 cards (98.9%) after 6597 inoculations.

Local and systemic reaction rates are summarized in the following tables:

Vaccine Reactions Reported within 72 Hours of HBV and PncCRM vaccines, First 3 doses—Finnish study

Systemic Reaction	Dose 1			Dose 2			Dose 3		
	PncCRM N=825[a] %	HBV N=825[a] %	p-value[1]	PncCRM N=818[a] %	HBV N=826[a] %	p-value[1]	PncCRM N=817[a] %	HBV N=816[a] %	p-value[1]
Fever ≥38°C	14.3	9.3	0.01	18.4	12.7	<0.01	23.5	13.3	<0.01
Fever >39°C	0.4	0.2	1	1.0	0.5	0.38	2.0	0.5	0.01
Crying increased	41.6	36.4	0.03	42.0	32.9	<0.01	39.6	30.6	<0.01
Crying > 4 hrs	0.6	0.4	0.72	0.5	0.1	0.37	0.4	0.1	0.62
Pain	3.4	1.9	0.09	3.7	0.7	0.02	5.1	2.8	0.02
Redness (Any)	14.2	9.3	<0.01	16.0	12.6	0.06	20.0	15.9	0.02
≥ 2.5 cm	0	0.1	1	0.2	0.2	0.62	0.4	0.0	0.25
Swelling (Any)	4.7	1.7	<0.01	4.0	3.0	0.16	4.8	3.6	0.19
≥ 2.5 cm	1.0	0.1	1	0.9	0.4	0.33	0.5	0.2	0.68

Adapted from Tables 13 and 14, pages 21and 22, Volume 1 of PLA (Sponsor's analysis).

Vaccine Reactions Reported within 72 Hours of HBV and PncCRM vaccines, 4th dose—Finnish study

Systemic Reaction	Dose 4 (12 months)		
	PncCRM N=798[a] %	HBV N=798 [a] %	p-value[1]
Fever ≥38°C	11.5	6.9	<0.01
Fever >39°C	1.6	1.7	0.97
Crying increased	28.2	19.3	<0.01
Crying > 4 hours	0	0	NA
Pain	7.5	2.3	<0.01
Redness (Any)	14.7	14.4	0.60
≥ 2.5 cm	0.8	0.0	0.04
Swelling (Any)	4.9	5.4	0.83
≥ 2.5 cm	1.3	0.4	0.09

[a] Total number monitored varied from 771-798, depending on number of completed reports received.
[1] p-valus derived from Ch-square tests; for comparisons of mild or any, each variable dichotomized by combining severity classes mild and moderate/severe. For comparisons of more severe reactions, each variable dichotomized by combining classes none and mild (Sponsor's analysis).

Systemic reactions

Rectal temperatures were to be measured at 24, 48, and 72 hours after inoculations. Other than fever and increased crying, no other common vaccine reactions were actively monitored in this study.

Fever (≥38°C) was reported more commonly in the PncCRM group than in the HBV group after each of the 4 doses. Fever rates in the PncCrm7 group were 14.7%, 19.3%, 25.5% and 13.1% following doses 1-4 respectively. Higher grade fever (>39°C) was reported by no more than 2% after any dose. The difference in rates of higher grade fever was statistically significant after the 3rd dose.

Note: Whole cell pertussis vaccine (DTP-Hib) was administered concurrently with doses 1-3, and IPV was co-administered with dose 4. These concurrently administered vaccines likely contributed to the observed systemic vaccine reactions.

Increased crying was also reported significantly more often by recipients of PncCRM after all 4 doses (41.6%, 42%, 39.6% and 28.2% after doses 1-4, respectively). Prolonged crying (>4 hours) was reported by no more than 1% of PncCRM7 recipients after any dose, and no significant differences between groups were observed for any dose.

Local reactions

In general, rates of induration (swelling), erythema (redness), and tenderness (pain) were greater at PncCRM injections sites than at HBV inoculation sites. Compared to local reactions at DTP-Hib injection sites within the same individuals, local reactions

at PncCRM sites were significantly less frequent for all comparisons (data not shown above). Local reactions were more common at the PncCRM injection sites than at IPV injection sites with the 4th dose.

Adverse events

Deaths

One death occurred during follow-up, in an 8-month old child, 85 days after the 3rd dose of PncCRM. The cause of death was a congenitally anomalous mesentery leading to obstruction and necrosis of the bowel.

Serious and unexpected adverse events

Serious adverse reactions (hospitalizations, fatal or life-threatening event, disabling event) and unexpected events were tabulated and analyzed together. A total of 354 SAEs cases were reported—348 were serious adverse events and 6 were cases of unexpected events deemed possibly related to study vaccines.

Of the 354 SAEs cases, 160 serious adverse events were reported in the PncCRM7 group, and 194 in the HBV group. These are summarized in the following table:

Cases of serious or unexpected adverse events by primary diagnosis, intent-to-treat follow-up

SAE Diagnosis	Number of Cases		Hazard Ratio	
	HBV	PncCRM7	Estimate	95% CI
HHE	1	0	0	NA
Invasive bacterial infection	4	1	0.25	(0.03, 2.21)
Wheezy bronchiolitis	43	39	0.91	(0.50, 1.66)
Upper respiratory infection	9	7	0.78	(0.29, 2.05)
Laryngitis	7	7	1.00	(0.34, 2.93)
Pneumonia	8	4	0.50	(0.15, 1.64)
Gastroenteritis	15	19	1.27	(0.63, 2.55)
Urinary Tract Infection	13	6	0.46	(0.17, 1.24)
Exanthema subitum	1	1	1.00	(0.06, 15.97)
Indefinite viral infection	4	2	0.50	(0.09, 2.70)
Suspected infection	13	4	0.31	(0.10, 0.95)
Skin infection	2	4	2.00	(0.33, 12.17)
Other infections with etiology	2	1	0.50	(0.05, 5.46)
Febrile seizure	14	12	0.86	(0.37, 1.99)
Indefinite neurologic symptoms	0	3	Inf.	NA
Urticaria	3	4	1.33	(0.09, 20.53)
Rash/other skin reactions	1	3	3.00	(0.32, 28.15)
Elective procedure	13	8	0.62	(0.24, 1.60)
Social reasons	1	1	1.00	(0.06, 15.64)
Other reasons	40	34	0.85	(0.49, 1.48)
Total	194	160		

Adapted from Table 12.3.1, Volume 2, Page 107 of PLA.

Most primary hospitalization diagnoses were more common in the HBV group, although statistical significance was reached only for “suspected infection”. Hospitalizations for gastroenteritis were notably increased in the PncCRM group. However, only 2 of the 19 cases of gastroenteritis occurred within 30 days of a vaccine dose.

Line listings of “other reasons” for serious adverse event reports were included in an appendix to the study report.

One case of diabetes mellitus with ketoacidosis occurred in PncCRM recipient, onset 43 days after the 4th vaccine dose.

Also in the PncCRM group were: 1 case of neutropenia (subject 1650, see below), and 1 case of transient erythrocytic aplasia, with onset of uncertain date, but likely greater than 1 year after the 4th dose.

In the HBV group were: 1 case of transient erythroblasopenia (subject 1031), onset 131 days after the 4th dose, 1 case of transient anemia (subject 3193), onset 105 days after the 4th dose, and one case of Kawasaki’s disease (subject 3549), onset 77 days after the 3rd vaccine dose.

Also noted were 10 hospitalizations for afebrile convulsions/seizures/attacks (see discussion below).

Two hospitalizations were considered at least possibly related to receipt of PncCRM7. Narratives of each case were provided:

> Subject 1343 was hospitalized for excessive crying at age 3 months, 1 day after the first dose of PncCRM7. He had fever and local reaction at the DTP-Hib site. Additional doses of pertussis vaccine were omitted. No reactions were observed with subsequent doses of PncCRM7.
>
> Subject 1650 was hospitalized 62 days after the 2nd dose of PncCRM7 at age 6 months for fever, acute otitis media, viral respiratory infection. Granulocytopenia was noted on hospitalization. No obvious reason for granulocytopenia was found. He was hospitalized again 5 days after the 3rd vaccine dose for fever and restlessness. Granulocytopenia was still marked. The condition remitted spontaneously over 11 months. The second hospitalization was considered possibly related to vaccine because of fever.

Adverse events leading to discontinuation from study

Two subjects in the PncCRM7 group discontinued study participation due to urticarial reactions (see below), thought by investigators to be at least possibly related to study vaccines.

Two subjects in the HBV control group also discontinued study participation due to adverse events thought by investigators to be possibly related to study vaccines, one for a hypotonic episode, and another for an urticarial reaction.

Adverse events with special surveillance diagnoses

Some diagnoses were designated for special surveillance in the Finnish study. These included:

- Sudden infant death (SIDS)
- Invasive bacterial infection
- Aseptic meningitis
- Acute encephalopathy
- Shock or shock-like state
- Anaphylaxis

Nine cases with a diagnosis under special surveillance were noted—8 in the HBV control group and 1 in the PncCRM7 group.

Seizure events

Febrile seizures

Febrile seizures accounted for 12 hospitalizations in the PncCRM7 group vs. 14 in the HBV control group. In the PncCRM7 group, the shortest interval between a vaccine dose and a febrile seizure was 28 days. One subject in the HBV control group experienced a febrile seizure 4 days after a vaccine dose. All other febrile seizures in the control group occurred at least 34 days after a dose of HBV.

Afebrile convulsions/seizures/attacks

A total of 6 children accounted for 10 hospitalizations for afebrile seizures in the PncCRM7 group vs. 2 hospitalizations for 1 child in the HBV group. Case narratives were provided for each child.

Despite the increased number of subjects with reports of afebrile seizures in the PncCRM7 group, the case narratives provide no reason to suspect a relationship of afebrile seizures with pneumococcal conjugate vaccine. Onset of symptoms showed no clear temporal relationship to vaccinations. Questionable or alternative diagnoses (e.g. GE reflux, cervical spasms) accounted for most cases. Among the 6 PncCRM recipients with reported afebrile seizures, work-up for neurological abnormalities (electroencephalograms and MRIs) were normal in 5, and not reported for one. Long-term outcomes appear to be favorable in all cases.

Urticarial reactions

In the Finnish study, urticarial reactions were reported as a reason for hospitalization, as an unexpected adverse event, and as a reason for discontinuation from the study.

Number of subjects with reports of urticarial reactions—Finnish study

Data Source	PncCRM	HBV
Reason for discontinuation	2236, 1 day post 2nd dose, 2705, 0 days after 3rd dose	1256, 1 day post 2nd dose
Hospitalization diagnosis	1295, 1 day post 4th dose 1670, 29 days post 2nd dose 2705 (as above)	1256 (as above) 3445, 2 days post 4th dose
Among "other" adverse events	2360, 30 days post 3rd dose, 1 day post 4th dose	1562, 80 days post 4th dose, 3560, 389 days post 4th dose

Table compiled by FDA review of all data sources for urticarial reactions.

Considering only urticarial reactions occurring within 14 days after a vaccine dose as a criterion for plausible relationship to study vaccines, there were 4 cases in the PncCRM group vs. 2 in the control group.

Sponsor's conclusions regarding safety data from the Finnish study

The sponsor acknowledges that PncCRM was more reactogenic than HBV, but less reactogenic than DTP-Hib. For systemic events, PncCRM resulted in increased rate of fever (≥38°C) within 3 days than did HBV administered with the same concurrent vaccines.

The overall rate of serious or unexpected adverse events tended to be less in the PncCRM group compared to the HBV group.

The sponsor concluded that based on safety data from the Finnish study, PncCRM7 was safe when administered in a 3 doses schedule in infancy followed by a 4th dose at 12 months of age.

FDA comments regarding safety data in the application

Relevance of vaccine reaction data from the Finnish AOM study to the US population is limited, given that current practice in the U.S. makes use of less reactogenic co-administered acellular pertussis vaccines, and possibly due to differences in populations. Also, the safety database in the Finnish study is substantially smaller and thus, of more limited power to detect less common adverse reactions than was the NCKP study. However, parent compliance with reporting of vaccine reactions appears to have been nearly complete in the Finnish study, thus likely enhancing the reliability of the reported data. These data do confirm an incremental increased rate of fever attributable to Prevnar, as was also observed in the NCKP study and other pre-licensure studies.

Complications of fever can include febrile seizures. In the Finnish study, occurrences of febrile seizures occurred with greater frequency in the control group. Furthermore, no temporal association with PncCRM was evident for any of the 12 reports of febrile seizures.

No hospitalizations for fever, or fever with irritability within 3 days of a vaccine dose were reported. A diagnosis of suspected infection accounted for 13 hospitalizations in the HBV control group, vs. 4 in the PncCRM7 group during the course of the study. This difference was statistically significant, and may indicate that some occult pneumococcal infections were prevented in the PncCRM group. Regardless, an increased risk of hospitalizations as a complication of fever related to PncCRM was not observed.

Urticarial reactions were a cause for study discontinuation in 2 PncCRM recipients, and when all datasources were combined a slight imbalance in a small number urticarial episodes within 14 days of a vaccine dose was observed in the PncCRM group.

In the NCKP study urticaria-like rash was reported in 0.4%-1.4% of children within 48 hours following immunization with Prevnar administered concurrently with other routine childhood vaccines. Urticaria-like rash was reported in 1.3-6% of children in the period from 3 to 14 days following immunization. Interpretation of the rates rates of urticaria in the different periods post-vaccination must take into account the length of the observation period. The 3-14 day window is 4-5 times as long as the 48 hour post-vaccination period; higher rates would be expected between 3-14 days if the background rate were constant over the 14 days post-inoculation period. Little reassurance can be taken from the lack of statistical differences in rates of urticarial reactions between 7VPnC and MnCC in the NCKP study, since both vaccines use the same protein carrier (CRM_{197}).

Reports of urticarial reactions following use of Prevnar, both alone and with concurrent vaccines, have been received by the sponsor through their world-wide post-marketing safety reports, and also through the Vaccine Adverse Event Reporting System (VAERS). The vaccine label has been amended since initial licensure to include this safety information from post-marketing reports.

An important question regarding post-vaccination urticaria is whether one occurrence predicts future occurrences on re-exposure, and whether repeat occurrences are of increasing severity. Supplementary analyses from the NCKP study, provided on FDA request during the AOM review period, appear to show that urticaria is most often reported following the fourth dose when it was administered concurrently with MMR vaccine. Also, based on limited data, it appears that children with urticaria-like rash after a dose of Prevnar may be more likely to report urticaria-like rash following a subsequent dose of Prevnar. However, there have been no reports from clinical studies or available post marketing reports of possible serious complications of allergic reactions, such as

anaphylaxis or Stevens-Johnson syndrome, following rechallenge with Prevnar after a previous episode of urticaria after a dose of Prevnar.

Overall, safety data from the Finnish otitis media study are consistent with earlier observations regarding the safety of Prevnar. No new safety concerns were identified in the Finnish study. As had been previously observed, Prevnar was associated with an increased rate of low-grade fever, but complications of post-vaccination fever were uncommon.

Attachment B: Additional Details Regarding NCKP Trial Design and Description

Timetable of Study Events

The study was initiated in October 1995; enrollment ceased August 24, 1998, and data regarding invasive disease outcomes was unblinded by the DSMB to conduct the planned interim analysis, which demonstrated substantial evidence of efficacy. The AOM database had been locked on April 30, 1998. Follow-up of infants for invasive pneumococcal disease and serious adverse events continued through April 20, 1999, at which time vaccine assignments were unblinded to all study personnel and families of subjects. The 7VPnC vaccine was then offered to subjects in the control group.

Schedule of study vaccines and concurrently administered vaccines

Subjects received 0.5 mL intramuscular injections of either PncCRM7 or MnCC vaccine at 2, 4, 6 and 12-15 months of age.

Licensed vaccines used in the study were: DTP-HbOC (Tetramune), OPV (Orimune), DTaP (Acel-imune), HbOC (HibTITER), MMR, Varicella, Hepatitis B (Recombivax HB), and IPV (IPOL).

In the original protocol, DTP-HbOC (Tetramune) and OPV (Orimune) were given concurrently with study vaccine at 2, 4, and 6 months of age. Subjects could also receive one or more doses of hepatitis B vaccine concurrently. An amendment implemented in August 1996 allowed for the substitution of DTaP and HbOC for DTP-HbOC, and for the substitution of inactivated poliovirus vaccine (IPV) for OPV for immunization of infants at 2, 4, and 6 months of age.

Allowable time frames for study vaccine administration were:

- Dose 1: 42-120 days after birth,
- Dose 2: 35-120 days after the first dose
- Dose 3: 35-120 days after the second dose
- Dose 4: 12 to 15 months of age, and at least 60 days after dose 3.

At 12-15 months of age, DTP-HbOC or DTaP and HbOC (HibTITER), MMR, and varicella vaccine could be given concurrently.

Study vaccines were given in the left thigh. Other concurrently administered injectable vaccines were to be inoculated into the right thigh or deltoid, as appropriate.

Study Design and Conduct

This was a randomized, double-blind, controlled, multi-center trial.

Randomization and Blinding

Healthy infants were randomly assigned to receive PncCRM7 or MnCC, identified by A, B, C, or D; block sizes were randomly chosen among 4, 6, 8, and 10, with treatment groups equally allocated. Treatment assignments (A, B, C, or D) were randomly permuted within each block.

Group assignments were not to be disclosed to parents of children in the study, others involved with the child's care or involved in the trial, including pediatricians, study investigators, and telephone interviewers.

Study population

Healthy male and female infants age 2 months (range 42-120 days) enrolled in the NCKP health care system were eligible to participate.

Exclusion criteria included:

- Known or suspected disease of the immune system including HIV infection, or those receiving immunosuppressive therapy
- Progressive neurological disease
- Uncontrolled epilepsy/infantile spasms or history of seizures
- Any serious chronic disease (such as signs of cardiac or renal failure, or failure to thrive
- Sickle cell disease, functional or anatomic asplenia, Down syndrome, or nephrotic syndrome
- Known hypersensitivity to any of the components of the vaccines used in the study
- History of invasive pneumococcal disease
- History of idiopathic thrombocytopenic purpura
- Prior receipt of any vaccine other than vaccine for hepatitis B
- History of meningococcal disease (defined as a positive culture of *N. meningitidis* from a normally sterile body site).

Note: Infants born prematurely could be enrolled if they were judged to be in good health.

Demographic information

A randomly selected subset of about 7500 subjects provided demographic information collected via telephone interview with the subjects' parents. The subset was selected based on the last digit of the subject's medical record number.