HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PREVNAR 13 safely and effectively. See full prescribing information for PREVNAR 13.

PREVNAR 13 (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein])

Suspension for intramuscular injection

Initial US Approval: 2010

---------- RECENT MAJOR CHANGES----------

Indications and Usage (1) 01/2012

Dosage and Administration, Vaccination Schedule for Adults 50 Years of Age and Older (2.6) 01/2012

---------- INDICATIONS AND USAGE----------

In children 6 weeks through 5 years of age (prior to the 6th birthday), Prevnar 13 is a vaccine indicated for:

- active immunization for the prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.
- active immunization for the prevention of otitis media caused by *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. No otitis media efficacy data are available for serotypes 1, 3, 5, 6A, 7F, and 19A. (1.1)

In adults 50 years of age and older, Prevnar 13 is a vaccine indicated for:

- active immunization for the prevention of pneumonia and invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. This indication is based on immune responses elicited by Prevnar 13. There have been no controlled trials in adults demonstrating a decrease in pneumococcal pneumonia or invasive disease after vaccination with Prevnar 13. (1.2)

Limitations of Use

- Prevnar 13 will not protect against disease caused by *Streptococcus pneumoniae* serotypes that are not in the vaccine. (1.3)
- The effectiveness of Prevnar 13 administered less than 5 years after pneumococcal polysaccharide vaccine is not known. (1.3)

---------- DOSAGE AND ADMINISTRATION ----------

Children 6 weeks through 5 years: The four-dose immunization series consists of a 0.5 mL intramuscular injection administered at 2, 4, 6, and 12-15 months of age. (2.3)

Adults 50 years and older: a single dose. (2.6)

----------DOSAGE FORMS AND STRENGTHS ----------

0.5 mL suspension for intramuscular injection, supplied in a single-dose prefilled syringe. (3)

----------CONTRAINDICATIONS----------

Severe allergic reaction (e.g., anaphylaxis) to any component of Prevnar 13 or any diphtheria toxoid-containing vaccine. (4)

---------- WARNINGS AND PRECAUTIONS----------

Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including Prevnar 13, to infants born prematurely should be based on consideration of the individual infant's medical status, and the potential benefits and possible risks of vaccination. (5.3)

---------- ADVERSE REACTIONS ----------

In infants and toddlers vaccinated at 2, 4, 6, and 12-15 months of age in US clinical trials, the most commonly reported solicited adverse reactions were irritability (>70%), injection site tenderness (>50%), decreased appetite (>40%), decreased sleep (>40%), increased sleep (>40%), fever (>20%), injection site redness (>20%), and injection site swelling (>20%). (6.1)

In adults aged 50 years and older the commonly reported solicited adverse reactions were pain at the injection site (>50%), fatigue (>30%), headache (>20%), muscle pain (>20%), joint pain (>10%), decreased appetite (>10%), injection site redness (>10%), injection site swelling (>10%), limitation of arm movement (>10%), chills (>5%) or rash (>5%). (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Wyeth Pharmaceuticals Inc. at 1-800-438-1985 or VAERS at 1-800-822-7967 or http://vaers.hhs.gov.

---------- DRUG INTERACTIONS----------

In adults, antibody responses to Prevnar 13 were diminished when given with inactivated Influenza Virus Vaccine. (14.3)

---------- USE IN SPECIFIC POPULATIONS ----------

Pregnancy: Safety and effectiveness of Prevnar 13 in pregnant women have not been established. (8.1)
Pediatric Use: Safety and effectiveness of Prevnar 13 in children below the age of 6 weeks or on or after the 6th birthday have not been established. (8.4)
Geriatric Use: Antibody responses to Prevnar 13 were lower in persons >65 years of age compared to antibody responses in persons 50 through 59 years of age. (8.5)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 01/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*** Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Children 6 Weeks Through 5 Years of Age

In children 6 weeks through 5 years of age (prior to the 6th birthday), Prevnar 13 is indicated for:

- active immunization for the prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.
- active immunization for the prevention of otitis media caused by *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. No otitis media efficacy data are available for serotypes 1, 3, 5, 6A, 7F, and 19A.

1.2 Adults 50 Years of Age and Older

In adults 50 years of age and older, Prevnar 13 is indicated for:

- active immunization for the prevention of pneumonia and invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. This indication is based on immune responses elicited by Prevnar 13. There have been no controlled trials in adults demonstrating a decrease in invasive pneumococcal disease or pneumococcal pneumonia after vaccination with Prevnar 13.

1.3 Limitations of Prevnar 13 Use and Effectiveness

- Prevnar 13 will not protect against disease caused by *Streptococcus pneumoniae* serotypes that are not in the vaccine.

- The effectiveness of Prevnar 13 administered less than 5 years after Pneumovax 23® (pneumococcal vaccine polyvalent, PPSV23) is not known *[see Clinical Studies 14.3]*.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

Since this product is a suspension containing an adjuvant, shake vigorously immediately prior to use to obtain a homogenous, white suspension in the vaccine container. Do not use the vaccine, if it cannot be resuspended. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration *[see Description (11)]*. This product should not be used if particulate matter or discoloration is found.

Do not mix Prevnar 13 with other vaccines/products in the same syringe.

2.2 Administration Information

For intramuscular injection only. Do not inject intravenously, intradermally, or subcutaneously.

Each 0.5 mL dose is to be injected intramuscularly using a sterile needle attached to the supplied

prefilled syringe. The preferred sites for injection are the anterolateral aspect of the thigh in infants and the deltoid muscle of the upper arm in toddlers, young children and adults. The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk and/or blood vessel.

2.3 Vaccination Schedule for Infants and Toddlers

Prevnar 13 is to be administered as a four-dose series at 2, 4, 6, and 12-15 months of age.

Table 1: Vaccination Schedule for Infants and Toddlers

Dose	Dose 1*†	Dose 2†	Dose 3†	Dose 4‡
Age at Dose	2 months	4 months	6 months	12-15 months

* Dose 1 may be given as early as 6 weeks of age.
† The recommended dosing interval is 4 to 8 weeks.
‡ The fourth dose should be administered at approximately 12-15 months of age, and at least 2 months after the third dose.

2.4 Vaccination Schedule for Unvaccinated Children ≥ 7 Months of Age

For children who are beyond the age of the routine infant schedule and have not received Prevnar® or Prevnar 13, the following catch-up schedule applies:

Table 2: Vaccination Schedule for Unvaccinated Children ≥ 7 Months of Age

Age at First Dose	Total Number of 0.5 mL Doses
7-11 months of age	3*
12-23 months of age	2†
24 months through 5 years of age (prior to the 6th birthday)	1

* The first 2 doses at least 4 weeks apart; third dose after the one-year birthday, separated from the second dose by at least 2 months.
† Two doses at least 2 months apart.

The immune responses induced by this catch-up schedule may result in lower antibody concentrations for some serotypes, compared to antibody concentrations following 4 doses of Prevnar 13 (given at 2, 4, 6, and 12 to 15 months). In children 24 months through 5 years of age, the catch-up schedule may result in lower antibody concentrations for some serotypes, compared to antibody concentrations following 3 doses of Prevnar 13 (given at 2, 4, and 6 months).

2.5 Vaccination Schedule for Children Previously Vaccinated With Prevnar Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein)

Children who have received one or more doses of Prevnar may complete the immunization series with Prevnar 13. Children 15 months through 5 years of age who are considered completely immunized with Prevnar may receive one dose of Prevnar 13 to elicit immune responses to the six additional serotypes. This catch-up (supplemental) dose of Prevnar 13 should be administered with an interval of at least 8 weeks after the final dose of Prevnar. The immune responses induced by this Prevnar 13 schedule may result in lower antibody concentrations for the 6

additional serotypes (types 1, 3, 5, 6A, 7F, and 19A), compared to antibody concentrations following 4 doses of Prevnar 13 (given at 2, 4, 6, and 12 to 15 months).

2.6 Vaccination Schedule for Adults 50 years of Age and Older

Prevnar 13 is administered as a single dose.

3 DOSAGE FORMS AND STRENGTHS

Prevnar 13 is a suspension for intramuscular injection available in 0.5 mL single-dose prefilled syringes.

4 CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) to any component of Prevnar 13 or any diphtheria toxoid-containing vaccine.

5 WARNINGS AND PRECAUTIONS

5.1 Management of Allergic Reactions

Epinephrine and other appropriate agents used to manage immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur following administration of Prevnar 13.

5.2 Altered Immunocompetence

Data on the safety and effectiveness of Prevnar 13 when administered to immunocompromised individuals including those at higher risk for invasive pneumococcal disease (e.g., individuals with congenital or acquired splenic dysfunction, HIV infection, malignancy, hematopoietic stem cell transplant, nephrotic syndrome) are not available. Individuals in these groups may have reduced antibody response to active immunization due to impaired immune responsiveness.

5.3 Apnea in Premature Infants

Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including Prevnar 13, to infants born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse-reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. As with any vaccine, there is the possibility that broad use of Prevnar 13 could reveal adverse reactions not observed in clinical trials.

6.1 Clinical Trials Experience With Prevnar 13 in Infants and Toddlers

The safety of Prevnar 13 was evaluated in 13 clinical trials in which 4,729 infants and toddlers received at least one dose of Prevnar 13 and 2,760 infants and toddlers received at least one dose of Prevnar active control. Safety data for the first three doses are available for all 13 infant studies; dose 4 data are available for 10 studies; and data for the 6-month follow-up are available

for 7 studies. The vaccination schedule and concomitant vaccinations used in these infant trials were consistent with country-specific recommendations and local clinical practice. There were no substantive differences in demographic characteristics between the vaccine groups. By race, 84.0% of subjects were White, 6.0% were Black or African-American, 5.8% were Asian and 3.8% were of 'Other' race (most of these being biracial). Overall, 52.3% of subjects were male infants.

Three studies in the US evaluated the safety of Prevnar 13 when administered concomitantly with routine US pediatric vaccinations at 2, 4, 6, and 12-15 months of age. Solicited local and systemic adverse events were recorded daily by parents/guardians using an electronic diary for 7 consecutive days following each vaccination. For unsolicited adverse events, study subjects were monitored from administration of the first dose until one month after the infant series, and for one month after the administration of the toddler dose. Information regarding unsolicited and serious adverse events, newly diagnosed chronic medical conditions, and hospitalizations since the last visit were collected during the clinic visit for the fourth-study dose and during a scripted telephone interview 6 months after the fourth-study dose. Serious adverse events were also collected throughout the study period. Overall, the safety data show a similar proportion of Prevnar 13 and Prevnar subjects reporting serious adverse events. Among US study subjects, a similar proportion of Prevnar 13 and Prevnar recipients reported solicited local and systemic adverse reactions as well as unsolicited adverse events.

Serious Adverse Events in All Infant and Toddler Clinical Studies

Serious adverse events were collected throughout the study period for all 13 clinical trials. This reporting period is longer than the 30-day post-vaccination period used in some vaccine trials. The longer reporting may have resulted in serious adverse events being reported in a higher percentage of subjects than for other vaccines. Serious adverse events reported following vaccination in infants and toddlers occurred in 8.2% among Prevnar 13 recipients and 7.2% among Prevnar recipients. Serious adverse events observed during different study periods for Prevnar 13 and Prevnar respectively were: 1) 3.7% and 3.5% from dose 1 to the bleed approximately 1 month after the infant series; 2) 3.6% and 2.7% from the bleed after the infant series to the toddler dose; 3) 0.9% and 0.8% from the toddler dose to the bleed approximately 1 month after the toddler dose and 4) 2.5% and 2.8% during the 6 month follow up period after the last dose.

The most commonly reported serious adverse events were in the 'Infections and infestations' system organ class including bronchiolitis (0.9%, 1.1%), gastroenteritis, (0.9%, 0.9%), and pneumonia (0.9%, 0.5%) for Prevnar 13 and Prevnar respectively.

There were 3 (0.063%) deaths among Prevnar 13 recipients, and 1 (0.036%) death in Prevnar recipients, all as a result of sudden infant death syndrome (SIDS). These SIDS rates are consistent with published age specific background rates of SIDS from the year 2000.

Among 6,839 subjects who received at least 1 dose of Prevnar 13 in clinical trials conducted globally, there was 1 hypotonic-hyporesponsive episode adverse reaction reported (0.015%). Among 4,204 subjects who received at least 1 dose of Prevnar in clinical trials conducted globally, there were 3 hypotonic-hyporesponsive episode adverse reactions reported (0.071%).

All 4 events occurred in a single clinical trial in Brazil in which subjects received whole cell pertussis vaccine at the same time as Prevnar 13 or Prevnar.

Solicited Adverse Reactions in the Three US Infant and Toddler Studies

A total of 1,907 subjects received at least 1 dose of Prevnar 13 and 701 subjects received at least 1 dose of Prevnar in the three US studies. Most subjects were White (77.3%), 14.2% were Black or African-American, and 1.7% were Asian; 79.1% of subjects were non-Hispanic and non-Latino and 14.6% were Hispanic or Latino. Overall, 53.6% of subjects were male infants.

The incidence and severity of solicited adverse reactions that occurred within 7 days following each dose of Prevnar 13 or Prevnar administered to US infants and toddlers are shown in Tables 3 and 4.

Table 3: Percentage of US Infant and Toddler Subjects Reporting Solicited Local Reactions at the Prevnar 13 or Prevnar Injection Sites Within 7 Days After Each Vaccination at 2, 4, 6, and 12-15 Months of Age[a]

	Dose 1		Dose 2		Dose 3		Dose 4	
Graded Local Reaction	**Prevnar 13** (N^b=1375-1612) %	**Prevnar** (N^b=516-606) %	**Prevnar 13** (N^b=1069-1331) %	**Prevnar** (N^b=405-510) %	**Prevnar 13** (N^b=998-1206) %	**Prevnar** (N^b=348-446) %	**Prevnar 13** (N^b=874-1060) %	**Prevnar** (N^b=283-379) %
Redness[c]								
Any	24.3	26.0	33.3	29.7	37.1	36.6	42.3	45.5
Mild	23.1	25.2	31.9	28.7	35.3	35.3	39.5	42.7
Moderate	2.2	1.5	2.7	2.2	4.6	5.1	9.6	13.4*
Severe	0	0	0	0	0	0	0	0
Swelling[c]								
Any	20.1	20.7	25.2	22.5	26.8	28.4	31.6	36.0*
Mild	17.2	18.7	23.8	20.5	25.2	27.5	29.4	33.8
Moderate	4.9	3.9	3.7	4.9	3.8	5.8	8.3	11.2*
Severe	0	0	0.1	0	0	0	0	0
Tenderness								
Any	62.5	64.5	64.7	62.9	59.2	60.8	57.8	62.5
Interferes with limb movement	10.4	9.6	9.0	10.5	8.4	9.0	6.9	5.7

***** Statistically significant difference $p < 0.05$. No adjustments for multiplicity.

[a] Data are from three primary US safety studies (the US phase II infant study [National Clinical Trial (NCT) number NCT00205803], the US noninferiority study [NCT00373958], and the US consistency study [NCT00444457]). All infants received concomitant routine infant immunizations. Concomitant vaccines and pneumococcal conjugate vaccines were administered in different limbs.

[b] Number of subjects reporting Yes for at least 1 day or No for all days.

[c] Diameters were measured in caliper units of whole numbers from 1 to 14 or 14+. One caliper unit = 0.5 cm. Measurements were rounded up to the nearest whole number. Intensity of induration and erythema were then characterized as Mild (0.5-2.0 cm), Moderate (2.5-7.0 cm), or Severe (> 7.0 cm).

Table 4: Percentage of US Infant and Toddler Subjects Reporting Solicited Systemic Adverse Reactions Within 7 Days After Each Vaccination at 2, 4, 6, and 12-15 Months of Age[a,b]

	Dose 1		Dose 2		Dose 3		Dose 4	
Graded Systemic Events	**Prevnar 13** (N[a]=1360 - 1707) %	**Prevnar** (N[a]=497-640) %	**Prevnar 13** (N[a]=1084-1469) %	**Prevnar** (N[a]=409-555) %	**Prevnar 13** (N[a]=997-1361) %	**Prevnar** (N[a]=354-521) %	**Prevnar 13** (N[a]=850-1227) %	**Prevnar** (N[a]=278-436) %
Fever[c]								
Any	24.3	22.1	36.5	32.8	30.3	31.6	31.9	30.6
Mild	23.6	21.7	34.9	31.6	29.1	30.2	30.3	30.0
Moderate	1.1	0.6	3.4	2.8	4.2	3.3	4.4	4.6
Severe	0.1	0.2	0.1	0.3	0.1	0.7	1.0	0
Decreased appetite	48.3	43.6	47.8	43.6	47.6	47.6	51.0	49.4
Irritability	85.6	83.6	84.8	80.4	79.8	80.8	80.4	77.8
Increased sleep	71.5	71.5	66.6	63.4	57.7	55.2	48.7	55.1
Decreased sleep	42.5	40.6	45.6	43.7	46.5	47.7	45.3	40.3

[a] Number of subjects reporting Yes for at least 1 day or No for all days.
[b] Data are from three primary US safety studies (the US phase II infant study [NCT00205803], the US noninferiority study [NCT00373958], and the US consistency study [NCT00444457]). All infants received concomitant routine infant immunizations. Concomitant vaccines and pneumococcal conjugate vaccines were administered in different limbs.
[c] Fever gradings: Mild (≥ 38°C but ≤ 39°C), Moderate (> 39°C but ≤ 40°C), and Severe (> 40°C). No other systemic event other than fever was graded. Parents reported the use of antipyretic medication to treat or prevent symptoms in 62 to 75% of subjects after any of the 4 doses. There were no statistical differences between the Prevnar 13 and Prevnar groups.

Unsolicited Adverse Reactions in the Three US Infant and Toddler Safety Studies

The following were determined to be adverse drug reactions based on experience with Prevnar 13 in clinical trials.

Reactions occurring in greater than 1% of infants and toddlers: diarrhea, vomiting, and rash.

Reactions occurring in less than 1% of infants and toddlers: crying, hypersensitivity reaction (including face edema, dyspnea, and bronchospasm), seizures (including febrile seizures), and urticaria or urticaria-like rash.

Safety Assessments in the Catch-Up Studies in Infants and Children

In a catch-up study conducted in Poland, 354 children (7 months through 5 years of age) receiving at least one dose of Prevnar 13 were also monitored for safety. All subjects in this

study were White and non-Hispanic. Overall, 49.6% of subjects were male infants. The incidence and severity of solicited adverse reactions that occurred within 4 days following each dose of Prevnar 13 administered to pneumococcal-vaccine naïve children 7 months through 5 years of age are shown in Tables 5 and 6.

Table 5: Percentage of Subjects 7 Months Through 5 Years of Age Reporting Solicited Local Reactions Within 4 Days After Each Catch-Up Prevnar 13 Vaccination[a]

	7 through 11 months			**12 through 23 months**		**24 months through 5 years**
Graded Local Reaction	**Dose 1** N[b]=86 %	**Dose 2** N[b]=86-87 %	**Dose 3** N[b]=78-82 %	**Dose 1** N[b]=108-110 %	**Dose 2** N[b]=98-106 %	**Dose 1** N[b]=147-149 %
Redness[c]						
Any	48.8	46.0	37.8	70.0	54.7	50.0
Mild	41.9	40.2	31.3	55.5	44.7	37.4
Moderate	16.3	9.3	12.5	38.2	25.5	25.7
Severe	0.0	0.0	0.0	0.0	0.0	0.0
Swelling[c]						
Any	36.0	32.2	25.0	44.5	41.0	36.9
Mild	32.6	28.7	20.5	36.7	36.2	28.2
Moderate	11.6	14.0	11.3	24.8	12.1	20.3
Severe	0.0	0.0	0.0	0.0	0.0	0.0
Tenderness						
Any	15.1	15.1	15.2	33.3	43.7	42.3
Interferes with limb movement	1.2	3.5	6.4	0.0	4.1	4.1

[a] Study conducted in Poland (NCT00452452).
[b] Number of subjects reporting Yes for at least 1 day or No for all days.
[c] Diameters were measured in caliper units of whole numbers from 1 to 14 or 14+. One caliper unit = 0.5 cm. Measurements were rounded up to the nearest whole number. Intensity of redness and swelling were then characterized as Mild (0.5-2.0 cm), Moderate (2.5-7.0 cm), or Severe (> 7.0 cm).

Table 6: Percentage of Subjects 7 Months Through 5 Years of Age Reporting Solicited Systemic Adverse Reactions Within 4 Days After Each Catch-Up Prevnar 13 Vaccination[a]

	7 through 11 months			12 through 23 months		24 months through 5 years
Systemic Reaction	**Dose 1** N[b]=86-87 %	**Dose 2** N[b]=86-87 %	**Dose 3** N[b]=78-81 %	**Dose 1** N[b]=108 %	**Dose 2** N[b]=98-100 %	**Dose 1** N[b]=147-148 %
Fever[c]						
Mild	3.4	8.1	5.1	3.7	5.1	0.7
Moderate	1.2	2.3	1.3	0.9	0.0	0.7
Severe	0.0	0.0	0.0	0.0	0.0	0.0
Decreased appetite	19.5	17.2	17.5	22.2	25.5	16.3
Irritability	24.1	34.5	24.7	30.6	34.0	14.3
Increased sleep	9.2	9.3	2.6	13.0	10.1	11.6
Decreased sleep	24.1	18.4	15.0	19.4	20.4	6.8

[a] Study conducted in Poland (NCT00452452).
[b] Number of subjects reporting Yes for at least 1 day or No for all days.
[c] Fever gradings: Mild (≥ 38°C but ≤ 39°C), Moderate (> 39°C but ≤ 40°C), and Severe (> 40°C). No other systemic event other than fever was graded.

A US study evaluated the use of Prevnar 13 in children previously immunized with Prevnar. In this open label trial, 284 healthy children 15 through 59 months of age previously vaccinated with at least 3 doses of Prevnar, received 1 or 2 doses of Prevnar 13. Children 15 months through 23 months of age (group 1) received 2 doses, and children 24 months through 59 months of age (group 2) received one dose. Most subjects were White (75.0%), 15.8% were Black or African-American, and 1.6% were Asian; 86.6% of subjects were non-Hispanic and non-Latino and 13.4% were Hispanic or Latino. Overall, 54.0% of subjects were male infants.

The incidence and severity of solicited adverse reactions that occurred within 7 days following one dose of Prevnar 13 administered to children 15 months through 59 months of age are shown in Tables 7 and 8.

Table 7: Percentage of Subjects 15 Months Through 59 Months of Age, Previously Vaccinated With 3 or 4 Prior Infant Doses of Prevnar, Reporting Solicited Local Reactions Within 7 Days After One Supplemental Prevnar 13 Vaccination

	15 months through 23 months[a]		24 months through 59 months[b]
Graded Local Reaction	**1 dose Prevnar 13 3 prior Prevnar doses** N[c]=28-32 %	**1 dose Prevnar 13 4 prior Prevnar doses** N[c]=62-76 %	**1 dose Prevnar 13 3 or 4 prior Prevnar doses** N[c]=138-155 %
Redness[d]			
Any	46.9	36.6	34.9
Mild	31.0	31.4	31.5
Moderate	22.6	7.9	9.9
Severe	0.0	0.0	0.0
Swelling[d]			
Any	35.5	21.2	22.2
Mild	26.7	18.8	20.3
Moderate	13.8	7.7	5.7
Severe	0.0	0.0	0.0
Tenderness			
Any	53.1	50.0	61.9
Interferes with limb movement	10.3	6.3	10.6

[a] Dose 2 data not shown.
[b] The data for this age group are only represented as a single result as 95% of children received 4 doses of Prevnar prior to enrollment.
[c] Number of subjects reporting Yes for at least 1 day or No for all days.
[d] Diameters were measured in caliper units of whole numbers from 1 to 14 or 14+. One caliper unit = 0.5 cm. Measurements were rounded up to the nearest whole number. Intensity of redness and swelling were then characterized as Mild (0.5-2.0 cm), Moderate (2.5-7.0 cm), or Severe (> 7.0 cm).
Note – Clinical trial.gov NCT number is as follows: NCT00761631.

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Table 8: Percentage of US Subjects 15 Months Through 59 Months of Age, Previously Vaccinated With 3 or 4 Prior Infant Prevnar Doses, Reporting Solicited Systemic Adverse Reactions Within 7 Days After One Supplemental Prevnar 13 Vaccination

	15 through 23 months[a]		24 months through 59 months[b]
Systemic Reaction	**1 dose Prevnar 13 3 prior Prevnar doses** N[c]=28-33 %	**1 dose Prevnar 13 4 prior Prevnar doses** N[c]=62-75 %	**1 dose Prevnar 13 3 or 4 prior Prevnar doses** N[c]=138-151 %
Fever[d]			
Mild	10.7	18.8	5.1
Moderate	7.1	3.2	0.7
Severe	0.0	0.0	0.7
Decreased appetite	56.7	36.2	24.8
Irritability	66.7	57.3	39.7
Increased sleep	30.0	33.8	15.9
Decreased sleep	22.6	22.7	14.0

[a] Dose 2 data not shown.
[b] The data for this age group are only represented as a single result as 95% of children received 4 doses of Prevnar prior to enrollment.
[c] Number of subjects reporting Yes for at least 1 day or No for all days.
[d] Fever gradings: Mild (≥ 38°C but ≤ 39°C), Moderate (> 39°C but ≤ 40°C), and Severe (> 40°C). No other systemic event other than fever was graded.
Note – Clinical trial.gov NCT number is as follows: NCT00761631.

6.2 Clinical Trials Experience With Prevnar 13 in Adults Aged ≥ 50 years

The safety of Prevnar 13 was assessed in 6 clinical studies conducted in the US and Europe which included 6,198 adults (5,667 received Prevnar 13) ranging in age from 50 through 95 years.

The 5,667 Prevnar 13 recipients included 2,616 adults who were aged 50 through 64 years and 3,051 adults aged 65 years and older. Of the 5,667 Prevnar 13 recipients, 3,751 adults had not previously received PPSV23 ("PPSV23 unvaccinated") and 1,916 adults were previously vaccinated ("PPSV23 previously vaccinated") with PPSV23 at least 3 years prior to enrollment.

Two of the 6 clinical studies supporting safety were randomized comparing the safety and immunogenicity of Prevnar 13 with PPSV23 as a single dose in PPSV23 unvaccinated adults aged 50 through 64 years (Study 1) and in adults ≥ 70 years PPSV23 previously vaccinated (≥ 5 years prior to enrollment) (Study 2). One study was randomized comparing the safety and immunogenicity of a single dose of Prevnar 13 compared to a single dose of PPSV23 in PPSV23 unvaccinated adults aged 60 through 64 years (Study 3). One clinical safety study (Study 4) of Prevnar 13, conducted in PPSV23 previously vaccinated (≥ 3 years prior to enrollment) adults

aged ≥ 68 years was a single arm study. Two studies, one in the US (Study 5) in adults age 50 through 59 years and the other in Europe (Study 6) in adults aged ≥ 65 years, evaluated the concomitant administration of Prevnar 13 with trivalent inactivated influenza vaccine (Fluarix®, A/H1N1, A/H3N2, and B, Fall 2007/Spring 2008: TIV) in these two age groups in PPSV23 unvaccinated adults.

The total safety population in the 6 studies was 6,198. In 5 of the 6 studies, more females than males were enrolled (50.2% - 61.8%) . Across the 6 studies the racial distribution included : > 91% White; 0.2%-7.5% Black or African American; 0%-1.7% Asian ;< 1%, Native Hawaiian or other Pacific Islander; < 1%, American Indian; and < 1%, Alaskan Native. Ethnicity data were not collected in study 6; in the 5 other studies 0.6%-4.8% were Hispanic or Latino.

In five studies, persons with pre-existing underlying diseases were enrolled if the medical condition was stable (did not require a change in therapy or hospitalization for worsening disease for 12 weeks before receipt of study vaccine) except in study 4 where subjects were enrolled if the medical condition was stable for 6 or more weeks before receipt of study vaccine.

Persons were excluded from study participation due to prior receipt of diphtheria toxoid containing vaccines within 6 months of study vaccine. However, the time of prior receipt of a diphtheria toxoid containing vaccine was not recorded.

Solicited adverse reactions for Prevnar 13 were monitored by subjects recording local adverse reactions and systemic reactions daily using an electronic diary for 14 consecutive days following vaccination. Unsolicited serious and non-serious adverse events were collected for one month after each vaccination. In addition, serious adverse events were collected for an additional 5 months after each vaccination (at the 6-month follow-up phone contact) in all studies except Study 6.

Serious Adverse Events in Adult Clinical Studies

Across the 6 studies, serious adverse events within 1 month of vaccination were reported after an initial study dose in 0.2%-1.4% of 5055 persons vaccinated with Prevnar 13 and in 0.4%-1.7% of 1124 persons vaccinated after an initial study dose of PPSV23. From 1 month to 6 months after an initial study dose , serious adverse events were reported in 1.2%-5.8% of persons vaccinated during the studies with Prevnar 13 and in 2.4%-5.5% of persons vaccinated with PPSV23. One case of erythema multiforme occurred 34 days after receipt of a second dose of Prevnar 13.

Twelve of 5,667 (0.21%) Prevnar 13 recipients and 4 of 1,391 (0.28%) PPSV23 recipients died. Deaths occurred between day 3 and day 309 after study vaccination with Prevnar 13 or PPSV23. Two of 12 deaths occurred within 30 days of vaccination with Prevnar 13 and both deaths were in subjects > 65 years of age. One death due to cardiac failure occurred 3 days after receiving Prevnar 13 administered with TIV and the other death was due to peritonitis 20 days after receiving Prevnar 13. The reported causes of the 10 remaining deaths occurring greater than 30 days after receiving Prevnar 13 were cardiac disorders (4), neoplasms (4), *Mycobacterium avium* complex pulmonary infection (1) and septic shock (1).

Solicited Adverse Reactions in Adult Clinical Studies

The incidence and severity of solicited adverse reactions that occurred within 14 days following each dose of Prevnar 13 or PPSV23 administered to adults in 4 studies are shown in Tables 9, 10, 11, and 12.

The commonly reported local adverse reactions after Prevnar 13 vaccination in PPSV23 unvaccinated and PPSV23 previously vaccinated adults were redness, swelling and pain at the injection site, or limitation of arm movement (Tables 9 and 10). The commonly reported systemic adverse reactions in PPSV23 unvaccinated and PPSV23 previously vaccinated adults were fatigue, headache, chills, rash, decreased appetite, or muscle pain and joint pain (Tables 11 and 12).

Table 9 - Percentage of Subjects With Solicited Local Reactions Within 14 Days After Vaccination with Prevnar 13 or PPSV23 in PPSV23 Unvaccinated Adults

	Study 1			Study 3	
Age in Years	**50-59**	**60-64**		**60-64**	
Local Reaction	**Prevnar 13**[a] N[b]=152-322 %	**Prevnar 13** N[b]=193-331 %	**PPSV23** N[b]=190-301 %	**Prevnar 13** N[b]=270-370 %	**PPSV23** N[b]=134-175 %
Redness[c]					
Any	15.8	20.2	14.2	12.2	11.2
Mild	15.2	15.9	11.2	8.3	9.7
Moderate	5.0	8.6	4.9	6.4	3.9
Severe	0.7	1.7	0.0	1.2	0.8
Swelling[d]					
Any	21.7	19.3	13.1	10.0	10.4
Mild	20.6	15.6	10.1	8.2	6.1
Moderate	4.3	8.2	4.4	3.8	7.6
Severe	0.0	0.6	1.1	0.0	0.0
Pain[e]					
Any	88.8	80.1	73.4	69.2*	58.3
Mild	85.9	78.6*	68.6	66.1*	52.9
Moderate	39.5	23.3	30.0	20.1	21.7
Severe	3.6	1.7	8.6*	2.3	0.8
Limitation of arm movement[e]					
Any	40.7	28.5	30.8	23.5	28.2
Mild	38.6	26.9	29.3	22.7	26.1
Moderate	2.9	2.2	3.8	1.2	3.1
Severe	2.9	1.7	4.3	1.1	2.3

*Statistically significant difference $p < 0.05$. No adjustments for multiplicity.

[a] Open label administration of Prevnar 13.

[b] Number of subjects with known values.

[c] Diameters were measured in caliper units of whole numbers from 1 to 21 or 21+. One caliper unit = 0.5 cm. Measurements were rounded up to the nearest whole number. Intensity of redness and swelling were then characterized as Mild = 2.5 to 5.0 cm, Moderate = 5.1 to 10.0 cm, and severe is >10.0 cm.

[d] Mild = awareness of symptom but easily tolerated, moderate = discomfort enough to cause interference with usual activity, severe = incapacitating with inability to do usual activity.

[e] Mild = some limitation of arm movement, Moderate = unable to move arm above head but able to move arm above shoulder, and Severe = unable to move arm above shoulder.

Note – Clinical trial.gov NCT numbers are as follows: Study 1 NCT00427895, Study 3 NCT00574548.

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Table 10 - Percentage of Subjects With Solicited Local Reactions Within 14 Days After Vaccination With Prevnar 13 or PPSV23 in PPSV23 Previously Vaccinated Adults

	Study 2		Study4
Age in Years	**≥ 70**		**≥ 68**
Local Reaction	**Prevnar 13** N[b]=306-362 %	**PPSV23** N[b]=324-383 %	**Prevnar 13** N[b]=664-777 %
Redness[c]			
Any	10.8	22.2*	14.3
Mild	9.5	13.5	12.6
Moderate	4.7	11.5*	6.5
Severe	1.7	4.8*	1.1
Swelling[d]			
Any	10.4	23.1*	12.8
Mild	8.9	14.0*	10.9
Moderate	4.0	13.6*	5.5
Severe	0.0	4.8*	0.6
Pain[e]			
Any	51.7	58.5	51.0
Mild	50.1	54.1	49.4
Moderate	7.5	23.6*	9.0
Severe	1.3	2.3	0.2
Limitation of arm movement[e]			
Any	10.5	27.6*	16.2
Mild	10.3	25.2*	14.8
Moderate	0.3	2.6*	1.6
Severe	0.7	3.0*	1.6

*Statistically significant difference $p < 0.05$. No adjustments for multiplicity .

[a] Open label administration of Prevnar 13.

[b] Num.ber of subjects with known values.

[c] Diameters were measured in caliper units of whole numbers from 1 to 21 or 21+. One caliper unit = 0.5 cm. Measurements were rounded up to the nearest whole number. Intensity of redness and swelling were then characterized as Mild = 2.5 to 5.0 cm, Moderate = 5.1 to 10.0 cm, and severe is >10.0 cm.

[d] Mild = awareness of symptom but easily tolerated, moderate = discomfort enough to cause interference with usual activity, severe = incapacitating with inability to do usual activity.

[e] Mild = some limitation of arm movement, Moderate = unable to move arm above head but able to move arm above shoulder, and Severe = unable to move arm above shoulder

Note – Clinical trial.gov NCT numbers are as follows: Study 2 NCT00546572, Study 4 NCT00500266.

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Table 11 - Percentage of Subjects With Solicited Systemic Events Within 14 Days After Vaccination With Prevnar 13 or PPSV23 in PPSV23 Unvaccinated Adults

	Study 1			Study 3	
Age in Years	**50-59**	**60-64**		**60-64**	
	Prevnar 13 N[b]=137-248 %	**Prevnar 13** N[b]=180-277 %	**PPSV23** N[b]=185-273 %	**Prevnar 13** N[b]=263-324 %	**PPSV23** N[b]=127-173 %
Systemic Event					
Fever					
≥ 100.4°F	1.5	4.0	1.1	4.2	1.6
100.4°F to 101.1°F	1.5	4.0	1.1	3.8	0.8
101.2°F to 102.0°F	0.0	0.6	0.0	0.8	0.0
102.1°F to 104.0°F	0.0	0.0	0.0	0.4	0.8
> 104.0°F	0.0	0.0	0.0	0.0	0.0
Fatigue	63.3	63.2	61.5	50.5	49.1
Headache	65.9	54.0	54.4	49.7	46.1
Chills	19.6	23.5	24.1	19.9	26.9
Rash	14.2	16.5	13.0	8.6	13.4
Vomiting	6.9	3.9	5.4	3.1	3.1
Decreased appetite	25.3	21.3	21.7	14.7	23.0*
Generalized new muscle pain	61.8	56.2	57.8	46.9	51.5
Generalized aggravated muscle pain	39.9	32.6	37.3	22.0	32.5*
Generalized new joint pain	31.5	24.4	30.1	15.5	23.8*
Generalized aggravated joint pain	25.6	24.9	21.4	14.0	21.1

***** Statistically significant difference $p < 0.05$. No adjustments for multiplicity.

[a] Open label administration of Prevnar 13.

[b] Number of subjects with known values.

Note – Clinical trial.gov NCT numbers are as follows: Study 1 NCT00427892, Study 3 NCT00574548

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Table 12 - Percentage of Subjects With Systemic Events Within 14 Days After Vaccination With Prevnar 13 or PPSV23 in PPSV23 Previously Vaccinated Adults

	Study2		Study 4
Age in Years	**≥ 70**		**≥ 68**
	Prevnar 13 N[b]=299-350 %	**PPSV23** N[b]=304-367 %	**Prevnar 13**[a] N[b]=638-733 %
Systemic Event			
Fever			
≥ 100.4°F	1.0	2.3	1.1
100.4°F to 101.1°F	1.0	2.0	0.8
101.2°F to 102.0°F	0.0	0.0	0.0
102.1°F to 104.0°F	0.0	0.3	0.3
> 104.0°F	0.0	0.0	0.0
Fatigue	34.0	43.3*	34.4
Headache	23.7	26.0	26.1
Chills	7.9	11.2	7.5
Rash	7.3	16.4*	8.4
Vomiting	1.7	1.3	0.9
Decreased appetite	10.4	11.5	11.2
Generalized new muscle pain	36.8	44.7*	25.3
Generalized aggravated muscle pain	20.6	27.5*	12.3
Generalized new joint pain	12.6	14.9	12.8
Generalized aggravated joint pain	11.6	16.5	9.7

*Statistically significant difference $p < 0.05$. No adjustments for multiplicity.
[a] Open label administration of Prevnar 13.
[b] Number of subjects with known values.
Note – Clinical trial.gov NCT numbers are as follows: Study 2 NCT00546572, Study 4 NCT00500266

Solicited Adverse Reactions in Adult Clinical Studies of Concomitant Administration of Prevnar 13 and TIV (Fluarix)

The safety of concomitant administration of Prevnar 13 with TIV was assessed in 2 studies in PPSV23 unvaccinated adults aged 50 through 59 years (Study 5) and aged ≥ 65 years (Study 6).

Frequencies of local reactions within 14 days postvaccination in adults aged 50 through 59 years and in adults aged ≥ 65 years were similar after Prevnar 13 was administered with TIV compared to Prevnar 13 administered alone, with the exception of mild redness at the injection site, which was increased when Prevnar 13 was administered concomitantly with TIV.

An increase in some solicited systemic reactions within 14 days postvaccination was noted when Prevnar 13 was administered concomitantly with TIV compared with TIV given alone (headache, chills, rash, decreased appetite, muscle and joint pain) or with Prevnar 13 given alone (fatigue, headache, chills, decreased appetite, and joint pain).

6.3 Clinical Trials Experience With Prevnar in Infants and Toddlers

The safety experience with Prevnar is relevant to Prevnar 13 because the two vaccines share common components.

Generally, the adverse reactions reported in clinical trials with Prevnar 13 were also reported in clinical trials with Prevnar.

Overall, the safety of Prevnar was evaluated in a total of five clinical studies in the U.S. in which 18,168 infants and children received a total of 58,699 doses of vaccine at 2, 4, 6, and 12-15 months of age.

Adverse events reported in clinical trials with Prevnar that occurred within 3 days of vaccination in infants and toddlers and resulted in emergency room visits or hospitalizations, but were not presented in Section 6.1 as adverse reactions for Prevnar 13 are listed below.
Bronchiolitis, UTI, acute gastroenteritis, asthma, aspiration, breath holding, influenza, inguinal hernia repair, viral syndrome, URI, croup, thrush, wheezing, choking, conjunctivitis, pharyngitis, colic, colitis, congestive heart failure, roseola, sepsis.

6.4 Post-marketing Experience With Prevnar in Infants and Toddlers

The following adverse events have been reported through passive surveillance since market introduction of Prevnar and therefore, are considered adverse events for Prevnar 13 as well. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

Administration site conditions: Injection-site dermatitis, injection-site pruritus, injection-site urticaria

Blood and lymphatic system disorders: Lymphadenopathy localized to the region of the injection site

Immune system disorders: Anaphylactic/anaphylactoid reaction including shock

Skin and subcutaneous tissue disorders: Angioneurotic edema, erythema multiforme

Respiratory: Apnea

Post-marketing Safety Study

The safety of Prevnar given concomitantly with other vaccines as part of routine care was assessed in a three-year observational study performed at Northern California Kaiser Permanente (NCKP) in which 65,927 children received three doses of Prevnar in the first year of life. Primary safety outcomes analyses included an evaluation of pre-defined adverse events occurring in temporal relationship to immunization. Rates of adverse events occurring within various time periods post-vaccination (e.g., 0-2, 0-7, 0-14, and 0-30 days) were compared to the rates of those events occurring within a control time window (i.e., 31-60 days). Secondary safety outcomes analyses included comparisons to a historical control population of infants (1995-1996, N=40,223) prior to the introduction of Prevnar. In addition, the study included extended follow-up of subjects originally enrolled in the NCKP efficacy trial (N=37,866).

The primary safety outcomes analyses did not demonstrate a consistently elevated risk of healthcare utilization for croup, gastroenteritis, allergic reactions, seizures, wheezing diagnoses, or breath-holding across doses, healthcare settings, or multiple time windows. As in prelicensure

trials, fever was associated with Prevnar administration. In analyses of secondary safety outcomes, the adjusted relative risk of hospitalization for reactive airways disease was 1.23 (95% CI: 1.11, 1.35). Potential confounders, such as differences in concomitantly administered vaccines, yearly variation in respiratory infections, or secular trends in reactive airways disease incidence, could not be controlled. Extended follow-up of subjects originally enrolled in the NCKP efficacy trial revealed no increased risk of reactive airways disease among Prevnar recipients. In general, the study results support the previously described safety profile of Prevnar.

7 DRUG INTERACTIONS

7.1 Concomitant Immunizations

In clinical trials with infants and toddlers, Prevnar 13 was administered concomitantly with the following US licensed vaccines: Pediarix [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined] (DTaP-HBV-IPV) and ActHIB [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)] (PRP-T) for the first three doses and with PedvaxHIB [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] (PRP-OMP), M-M-R II [Measles, Mumps, Rubella Virus Vaccine Live] (MMR) and Varivax [Varicella Virus Vaccine Live], or ProQuad [Measles, Mumps, Rubella and Varicella Virus Vaccine Live] (MMRV) and VAQTA [Hepatitis A vaccine, Inactivated] (HepA) for dose 4 *[see Clinical Studies (14.2)]*.

In adults, Prevnar 13 was administered concomitantly with US licensed Fluarix (TIV) for the 2007/2008 influenza season *[see Clinical Studies (14.3)]*. There are no data on the concomitant administration of Prevnar 13 with diphtheria toxoid containing vaccines and other vaccines licensed for use in adults 50 years of age and older.

When Prevnar 13 is administered at the same time as another injectable vaccine(s), the vaccines should always be administered with different syringes and given at different injection sites.

Do not mix Prevnar 13 with other vaccines/products in the same syringe.

7.2 Immunosuppressive Therapies

Individuals with impaired immune responsiveness due to the use of immunosuppressive therapy (including irradiation, corticosteroids, antimetabolites, alkylating agents, and cytotoxic agents) may not respond optimally to active immunization.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

A developmental and reproductive toxicity study has been performed in female rabbits at a dose approximately 20 times the human dose (on mg/kg basis) and revealed no evidence of impaired female fertility or harm to the fetus due to Prevnar 13. There are, however, no adequate and wellcontrolled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this vaccine should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether this vaccine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Prevnar 13 is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of Prevnar 13 in children below the age of 6 weeks or on or after the 6th birthday have not been established.

Immune responses elicited by Prevnar 13 among infants born prematurely have not been specifically studied.

8.5 Geriatric Use

Of the total number of Prevnar 13 recipients (N=5,667), 3,051/5,667 or 53.8% were 65 years and older and 1,266/5,667 or 22.3% were 75 years and older.

Antibody responses to Prevnar 13 were lower in persons > 65 years of age compared to antibody responses in persons 50 through 59 years of age.

No overall differences in safety outcomes were observed in persons aged ≥ 65 years as compared to persons 50 through 59 years of age.

11 DESCRIPTION

Prevnar 13, Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) is a sterile suspension of saccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, individually linked to non-toxic diphtheria CRM_{197} protein. Each serotype is grown in soy peptone broth. The individual polysaccharides are purified through centrifugation, precipitation, ultrafiltration, and column chromatography. The polysaccharides are chemically activated to make saccharides, which are directly conjugated by reductive amination to the protein carrier CRM_{197}, to form the glycoconjugate. CRM_{197} is a nontoxic variant of diphtheria toxin isolated from cultures of *Corynebacterium diphtheriae* strain C7 (β197) grown in a casamino acids and yeast extract-based medium. CRM_{197} is purified through ultrafiltration, ammonium sulfate precipitation, and ion-exchange chromatography. The individual glycoconjugates are purified by ultrafiltration and column chromatography and analyzed for saccharide to protein ratios, molecular size, free saccharide, and free protein.

The individual glycoconjugates are compounded to formulate Prevnar 13. Potency of the formulated vaccine is determined by quantification of each of the saccharide antigens and by the saccharide to protein ratios in the individual glycoconjugates. Each 0.5 mL dose of the vaccine is formulated to contain approximately 2.2 µg of each of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F saccharides, 4.4 µg of 6B saccharides, 34 µg CRM_{197} carrier protein, 100 µg polysorbate 80, 295 µg succinate buffer and 125 µg aluminum as aluminum phosphate adjuvant.

The tip cap and rubber plunger of the prefilled syringe do not contain latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Prevnar 13, comprised of pneumococcal polysaccharides conjugated to a carrier protein (CRM_{197}), elicits a T-cell dependent immune response. Protein carrier-specific T-cells provide the signals needed for maturation of the B-cell response.

Nonclinical and clinical data support opsonophagocytic activity, as measured by opsonophagocytic antibody (OPA) assay, as a contributor to protection against pneumococcal disease. OPA provides an in vitro measurement of the ability of serum antibodies to eliminate pneumococci by promoting complement-mediated phagocytosis and is believed to reflect relevant in vivo mechanisms of protection against pneumococcal disease. OPA titers are expressed as the reciprocal of the highest serum dilution that reduces survival of the pneumococci by at least 50%.

In infants that have received Prevnar 13, opsonophagocytic activity correlates well with serotype specific anti-capsular polysaccharide IgG levels as measured by ELISA.A serum anti-capsular polysaccharide antibody concentration of 0.35 µg/mL as measured by ELISA one month after the third dose as a single antibody reference concentration was used to estimate the effectiveness of Prevnar 13 against invasive pneumococcal disease (IPD) in infants and children. The assay used for this determination is a standardized ELISA involving pre-absorption of the test sera with pneumococcal C-polysaccharide and serotype 22F polysaccharide to reduce non-specific background reactivity. The single antibody reference value was based on pooled efficacy estimates from three placebo-controlled IPD efficacy trials with either Prevnar or the investigational 9-valent CRM_{197} conjugate pneumococcal polysaccharide vaccine. This reference concentration is only applicable on a population basis and cannot be used to predict protection against IPD on an individual basis. Functional antibodies elicited by the vaccine (as measured by a drip opsonophagocytic assay [dOPA]) were also evaluated in infants.

In adults, an antipolysaccharide binding antibody IgG level to predict protection against invasive pneumococcal disease or non-bacteremic pneumonia has not been defined. Noninferiority trials for Prevnar 13 were designed to show that functional OPA antibody responses (as measured by a microcolony OPA [mcOPA]) for the Prevnar 13 serotypes are non-inferior and for some serotypes superior to the common serotypes in the currently licensed pneumococcal polysaccharide vaccine (PPSV23). OPA titers measured in the mcOPA cannot be compared directly to titers measured in the dOPA assay.

14 CLINICAL STUDIES

14.1 Prevnar Efficacy Data

Invasive Pneumococcal Disease (IPD)

Prevnar was licensed in the US for infants and children in 2000, following a randomized, double-blind clinical trial in a multiethnic population at Northern California Kaiser Permanente (NCKP) from October 1995 through August 20, 1998, in which 37,816 infants were randomized to receive either Prevnar or a control vaccine (an investigational meningococcal group C conjugate vaccine [MnCC]) at 2, 4, 6, and 12-15 months of age. In this study, the efficacy of Prevnar

against invasive disease due to *S. pneumoniae* in cases accrued during this period was 100% in both the per-protocol and intent-to-treat analyses (95% CI: 75.4%-100% and 81.7%-100%, respectively). Data accumulated through an extended follow-up period to April 20, 1999, resulted in similar efficacy estimates of 97.4% in the per-protocol analysis and 93.9% in the intent-to-treat analysis (95% CI: 82.7% - 99.9% and 79.6% - 98.5%, respectively).

Acute Otitis Media (AOM)

The efficacy of Prevnar against otitis media was assessed in two clinical trials: a trial in Finnish infants at the National Public Health Institute and the efficacy trial in US infants at Northern California Kaiser Permanente (NCKP).

The Finnish Otitis Media (FinOM) trial was a randomized, double-blind trial in which 1,662 infants were equally randomized to receive either Prevnar or a control vaccine Recombivax HB (Hepatitis B vaccine (Recombinant) [Hep B]) at 2, 4, 6, and 12-15 months of age. In this study, conducted between December 1995 and March 1999, parents of study participants were asked to bring their children to the study clinics if the child had respiratory infections or symptoms suggesting acute otitis media (AOM). If AOM was diagnosed, tympanocentesis was performed, and the middle-ear fluid was cultured. If *S. pneumoniae* was isolated, serotyping was performed; the primary endpoint was efficacy against AOM episodes caused by vaccine serotypes in the per-protocol population. In the NCKP trial, the efficacy of Prevnar against otitis media was assessed from the beginning of the trial in October 1995 through April 1998. The otitis media analysis included 34,146 infants randomized to receive either Prevnar (N=17,070), or the control vaccine (N=17,076), at 2, 4, 6, and 12-15 months of age. In this trial, no routine tympanocentesis was performed, and no standard definition of otitis media was used by study physicians. The primary otitis media endpoint was efficacy against all otitis media episodes in the per-protocol population.

The vaccine efficacy against AOM episodes due to vaccine serotypes assessed in the Finnish trial, was 57% (95% CI: 44%-67%) in the per-protocol population and 54% (95% CI: 41%-64%) in the intent-to-treat population. The vaccine efficacy against AOM episodes due to vaccine-related serotypes (6A, 9N, 18B, 19A, 23A), also assessed in the Finnish trial, was 51% (95% CI: 27, 67) in the per-protocol population and 44% (95% CI: 20, 62) in the intent-to-treat population. There was a nonsignificant increase in AOM episodes caused by serotypes unrelated to the vaccine in the per-protocol population, compared to children who received the control vaccine, suggesting that children who received Prevnar appeared to be at increased risk of otitis media due to pneumococcal serotypes not represented in the vaccine. However, vaccination with Prevnar reduced pneumococcal otitis media episodes overall. In the NCKP trial, in which the endpoint was all otitis media episodes regardless of etiology, vaccine efficacy was 7% (95% CI: 4%-10%) and 6% (95% CI: 4%-9%), respectively, in the per-protocol and intent-to-treat analyses. Several other otitis media endpoints were also assessed in the two trials.

Recurrent AOM, defined as 3 episodes in 6 months or 4 episodes in 12 months, was reduced by 9% in both the per-protocol and intent-to-treat populations (95% CI: 3%-15% in per-protocol and 95% CI: 4%-14% in intent-to-treat) in the NCKP trial; a similar trend was observed in the Finnish trial. The NCKP trial also demonstrated a 20% reduction (95% CI: 2, 35) in the placement of tympanostomy tubes in the per-protocol population and a 21% reduction (95% CI: 4, 34) in the intent-to-treat population. Data from the NCKP trial accumulated through an

extended follow-up period to April 20, 1999, in which a total of 37,866 children were included (18,925 in Prevnar group and 18,941 in MnCC control group), resulted in similar otitis media efficacy estimates for all endpoints.

14.2 Evaluation of Prevnar 13 Effectiveness in Infants and Toddlers

Prevnar 13 effectiveness against invasive pneumococcal disease was inferred from comparative studies to a US licensed 7-valent pneumococcal conjugate vaccine, Prevnar, in which Prevnar 13 elicited immune responses as measured by antipolysaccharide binding and functional OPA antibodies. These studies were designed to evaluate immunologic noninferiority of Prevnar 13 to Prevnar.

Clinical trials have been conducted in the US using a 2, 4, 6, and 12 to 15 month schedule.

The US noninferiority study was a randomized, double-blind, active-controlled trial in which 2 month-old infants were randomly assigned to receive either Prevnar 13 or Prevnar in a 1:1 ratio. The 2 vaccine groups were well balanced with respect to race, ethnicity, and age and weight at enrollment. Most subjects were White (69.1%), 19.6% were Black or African-American, and 2.4% were Asian; 82.1% of subjects were non-Hispanic and non-Latino and 17.3% were Hispanic or Latino. Overall, 54.0% of subjects were male infants.

In the US noninferiority study, immune responses were compared in subjects receiving either Prevnar 13 or Prevnar using a set of noninferiority criteria. Co-primary endpoints included the percentage of subjects with serum pneumococcal anti-capsular polysaccharide IgG $\geq$ 0.35 μg/mL measured one month after the third dose and serum pneumococcal anti-capsular polysaccharide IgG geometric mean concentrations (GMCs) one month after the fourth dose. The assay used for this determination was a standardized ELISA involving pre-absorption of the test sera with pneumococcal C-polysaccharide and serotype 22F polysaccharide to reduce non-specific background reactivity. Responses to the 7 common serotypes in Prevnar 13 and Prevnar recipients were compared directly. Responses to the 6 additional serotypes in Prevnar 13 recipients were each compared to the lowest response observed among the Prevnar serotypes in Prevnar recipients.

Pneumococcal Immune Responses Following Three Doses

In the US noninferiority study, the noninferiority criterion for the proportion of subjects with pneumococcal anti-capsular polysaccharide IgG antibody concentrations $\geq$ 0.35 μg/mL one month after the third dose was met for 10 of the 13 serotypes. The exceptions were serotypes 6B, 9V, and 3. Although the response to serotypes 6B and 9V did not meet the pre-specified noninferiority criterion, the differences were marginal.

The percentage of infants achieving pneumococcal anti-capsular polysaccharide IgG antibody concentrations $\geq$ 0.35 μg/mL one month after the third dose is shown below (Table 13).

Table 13: Percentage of Subjects With Anti-capsular Antibody Concentration ≥ 0.35 µg/mL One Month After a Three Dose Series Administered at 2, 4 and 6 Months of Age, US Noninferiority Study*[†a]

Serotype	Prevnar 13 N=249-252 (95% CI)	Prevnar N=250-252 (95% CI)	Difference in % responders (95% CI)
Prevnar Serotypes			
4	94.4 (90.9, 96.9)	98.0 (95.4, 99.4)	-3.6 (-7.3, -0.1)
6B	87.3 (82.5, 91.1)	92.8 (88.9, 95.7)	-5.5 (-10.9, -0.1)
9V	90.5 (86.2, 93.8)	98.4 (96.0, 99.6)	-7.9 (-12.4, -4.0)
14	97.6 (94.9, 99.1)	97.2 (94.4, 98.9)	0.4 (-2.7, 3.5)
18C	96.8 (93.8, 98.6)	98.4 (96.0, 99.6)	-1.6 (-4.7, 1.2)
19F	98.0 (95.4, 99.4)	97.6 (99.4, 99.1)	0.4 (-2.4, 3.4)
23F	90.5 (86.2, 93.8)	94.0 (90.4, 96.6)	-3.6 (-8.5, 1.2)
Additional Serotypes[††]			
1	95.6 (92.3, 97.8)	††	2.8 (-1.3, 7.2)
3	63.5 (57.1, 69.4)	††	-29.3 (-36.2, -22.4)
5	89.7 (85.2, 93.1)	††	-3.1 (-8.3, 1.9)
6A	96.0 (92.8, 98.1)	††	3.2 (-0.8, 7.6)
7F	98.4 (96.0, 99.6)	††	5.6 (1.9, 9.7)
19A	98.4 (96.0, 99.6)	††	5.6 (1.9, 9.7)

* Noninferiority was met when the lower limit of the 95% CI for the difference between groups (Prevnar 13 minus Prevnar) was greater than -10%.

[†] Antibody measured by a standardized ELISA involving pre-absorption of the test sera with pneumococcal C-polysaccharide and serotype 22F polysaccharide to reduce non-specific background reactivity.

[††] Comparison for the 6 additional serotypes was to the lowest responder of the 7 common serotypes in Prevnar recipients, which for this analysis was serotype 6B (92.8%; 95% CI: 88.9, 95.7).

[a] Evaluable Immunogenicity Population.

Note – Clinical trial.gov NCT number is as follows: NCT00373958.

498 Functional OPA antibody responses were elicited for all 13 serotypes, as shown in Table 14.

Table 14: Pneumococcal OPA Geometric Mean Titers One Month After a Three Dose Series Administered at 2, 4 and 6 Months of Age, US Noninferiority Study*†

Serotype	Prevnar 13 N=91-94 (95% CI)	Prevnar N=89-94 (95% CI)
Prevnar Serotypes		
4	359 (276, 468)	536 (421, 681)
6B	1055 (817, 1361)	1514 (1207, 1899)
9V	4035 (2933, 5553)	3259 (2288, 4641)
14	1240 (935, 1646)	1481 (1133, 1934)
18C	276 (210, 361)	376 (292, 484)
19F	54 (40, 74)	45 (34, 60)
23F	791 (605, 1034)	924 (709, 1204)
Additional Serotypes		
1	52 (39, 69)	4 (4, 5)
3	121 (92, 158)	7 (5, 9)
5	91 (67, 123)	4 (4, 4)
6A	980 (783, 1226)	100 (66, 152)
7F	9494 (7339, 12281)	128 (80, 206)
19A	152 (105, 220)	7 (5, 9)

***** The OPA (opsonophagocytic activity) assay measures the ability of immune sera, in conjunction with complement, to mediate the uptake and killing of *S. pneumoniae* by phagocytic cells.
† Evaluable Immunogenicity Population.
Note – Clinical trial.gov NCT number is as follows: NCT00373958.

Pneumococcal Immune Responses Following Four Doses

In the US noninferiority study, post-dose 4 antibody concentrations were higher for all 13 serotypes than those achieved after the third dose. The noninferiority criterion for pneumococcal anti-capsular polysaccharide GMCs after 4 doses was met for 12 of the 13 pneumococcal serotypes. The noninferiority criterion was not met for the response to serotype 3 (Table 15).

Table 15: Pneumococcal IgG GMCs (µg/mL) One Month After a Four Dose Series Administered at 2, 4, 6 and 12-15 Months, US Noninferiority Study*†a

Serotype	Prevnar 13 N=232-236 (95% CI)	Prevnar N=222-223 (95% CI)	GMC Ratio (95% CI)
Prevnar Serotypes			
4	3.73 (3.28, 4.24)	5.49 (4.91, 6.13)	0.68 (0.57, 0.80)
6B	11.53 (9.99, 13.30)	15.63 (13.80, 17.69)	0.74 (0.61, 0.89)
9V	2.62 (2.34, 2.94)	3.63 (3.25, 4.05)	0.72 (0.62, 0.85)
14	9.11 (7.95, 10.45)	12.72 (11.22, 14.41)	0.72 (0.60, 0.86)
18C	3.20 (2.82, 3.64)	4.70 (4.18, 5.28)	0.68 (0.57, 0.81)
19F	6.60 (5.85, 7.44)	5.60 (4.87, 6.43)	1.18 (0.98, 1.41)
23F	5.07 (4.41, 5.83)	7.84 (6.91, 8.90)	0.65 (0.54, 0.78)
Additional Serotypes††			
1	5.06 (4.43, 5.80)	††	1.40 (1.17, 1.66)
3	0.94 (0.83, 1.05)	††	0.26 (0.22, 0.30)
5	3.72 (3.31, 4.18)	††	1.03 (0.87, 1.20)
6A	8.20 (7.30, 9.20)	††	2.26 (1.93, 2.65)
7F	5.67 (5.01, 6.42)	††	1.56 (1.32, 1.85)
19A	8.55 (7.64, 9.56)	††	2.36 (2.01, 2.76)

* Noninferiority was declared if the lower limit of the 2-sided 95% CI for Geometric Mean Ratio (Prevnar 13:Prevnar) was greater than 0.5.

† Antibody measured by a standardized ELISA involving pre-absorption of the test sera with pneumococcal C-polysaccharide and serotype 22F polysaccharide to reduce non-specific background reactivity.

†† Comparison for the 6 additional serotypes was to the lowest responder of the 7 common serotypes in Prevnar recipients, which for this analysis was serotype 9V (3.63; 95% CI 3.25, 4.05).

[a] Evaluable Immunogenicity Population.

Note – Clinical trial.gov NCT number is as follows: NCT00373958.

Following the 4th dose, the functional OPA response for each serotype was quantitatively greater than the response following the 3rd dose (see Table 16).

Table 16: Pneumococcal OPA Geometric Mean Titers One Month After the Fourth Dose-Evaluable Toddler Immunogenicity Population, US Noninferiority Study*

Serotype	Prevnar 13 N=88-92 (95% CI)	Prevnar N=92-96 (95% CI)
Prevnar Serotypes		
4	1180 (847, 1643)	1492 (1114, 1999)
6B	3100 (2337, 4111)	4066 (3243, 5098)
9V	11856 (8810, 15955)	18032 (14125, 23021)
14	2002 (1453, 2760)	2366 (1871, 2992)
18C	993 (754, 1308)	1722 (1327, 2236)
19F	200 (144, 276)	167 (121, 230)
23F	2723 (1961, 3782)	4982 (3886, 6387)
Additional Serotypes		
1	164 (114, 237)	5 (4, 6)
3	380 (300, 482)	12 (9, 16)
5	300 (229, 393)	5 (4, 6)
6A	2242 (1707, 2945)	539 (375, 774)
7F	11629 (9054, 14938)	268 (165, 436)
19A	1024 (774, 1355)	29 (19, 44)

* The OPA (opsonophagocytic activity) assay measures the ability of immune sera, in conjunction with complement, to mediate the uptake and killing of *S. pneumoniae* by phagocytic cells.
Note – Clinical trial.gov NCT number is as follows: NCT00373958.

Simultaneous Administration With Other Vaccines

The concomitant administration of routine US infant vaccines *[see Drug Interactions (7.1)]* with Prevnar 13 was evaluated in two studies: the US noninferiority study *[see Clinical Studies (14.2), Pneumococcal Immune Responses Following Three Doses]* and the US lot consistency study. In the lot consistency study, subjects were randomly assigned to receive one of 3 lots of Prevnar 13 or Prevnar in a 2:2:2:1 ratio. The total number of infants vaccinated was 663 (US noninferiority study) and 1699 (US lot consistency study). Immune responses to concomitant vaccine antigens were compared in infants receiving Prevnar and Prevnar 13. Responses to diphtheria toxoid, tetanus toxoid, pertussis, polio types 1, 2, and 3, hepatitis B, PRP-T, PRP-OMP, measles, and varicella antigens in Prevnar 13 recipients were similar to those in Prevnar recipients. Based on limited data, responses to mumps and rubella antigens in Prevnar 13 recipients were similar to those in Prevnar recipients.

Previously Unvaccinated Older Infants and Children

In an open-label descriptive study of Prevnar 13 in Poland, children 7 through 11 months of age, 12 through 23 months of age and 24 months through 5 years of age (prior to the 6th birthday) who were naïve to pneumococcal conjugate vaccine, were given 3, 2 or 1 dose of Prevnar 13 respectively, according to the age-appropriate schedules in Table 1. Serum IgG concentrations were measured one month after the final dose in each age group and the data are shown in Table 17.

Table 17: Pneumococcal Anti-capsular Polysaccharide IgG Antibody Geometric Mean Concentrations (µg/mL) One Month After the Final Prevnar 13 Catch-Up Dose in Pneumococcal Vaccine Naïve Children 7 Months Through 5 Years of Age by Age Group, Poland Catch-Up Study[*]

Serotype	3 doses Prevnar 13 7 through 11 months N=83-84 (95% CI)	2 doses Prevnar 13 12 through 23 months N=104-110 (95% CI)	1 dose Prevnar 13 24 months through 5 years N=135-152 (95% CI)
1	2.88 (2.44, 3.39)	2.74 (2.37, 3.16)	1.78 (1.52, 2.08)
3	1.94 (1.68, 2.24)	1.86 (1.60, 2.15)	1.42 (1.23, 1.64)
4	3.63 (3.11, 4.23)	4.28 (3.78, 4.86)	3.37 (2.95, 3.85)
5	2.85 (2.34, 3.46)	2.16 (1.89, 2.47)	2.33 (2.05, 2.64)
6A	3.72 (3.12, 4.45)	2.62 (2.25, 3.06)	2.96 (2.52, 3.47)
6B	4.77 (3.90, 5.84)	3.38 (2.81, 4.06)	3.41 (2.80, 4.16)
7F	5.30 (4.54, 6.18)	5.99 (5.40, 6.65)	4.92 (4.26, 5.68)
9V	2.56 (2.21, 2.96)	3.08 (2.69, 3.53)	2.67 (2.32, 3.07)
14	8.04 (6.95, 9.30)	6.45 (5.48, 7.59)	2.24 (1.71, 2.93)
18C	2.77 (2.39, 3.23)	3.71 (3.29, 7.19)	2.56 (2.17, 3.03)
19A	4.77 (4.28, 5.33)	4.94 (4.31, 5.65)	6.03 (5.22, 6.97)
19F	2.88 (2.35, 3.54)	3.07 (2.68, 3.51)	2.53 (2.14, 2.99)
23F	2.16 (1.82, 2.55)	1.98 (1.64, 2.39)	1.55 (1.31, 1.85)

[*] Open label administration of Prevnar 13.
Note – Clinical trial.gov NCT number is as follows: NCT00452452 (Poland).

Children Previously Vaccinated with Prevnar

In an open-label descriptive study in the US, children previously vaccinated with 3 or 4 doses of Prevnar, received 2 doses of Prevnar 13 (children 15 through 23 months of age) or 1 dose of Prevnar 13 (children 24 months through 59 months of age). The data following one dose of Prevnar 13 in children 24 months through 59 months of age are shown in Table 18.

Table 18: Pneumococcal Anti-capsular Polysaccharide IgG Antibody Geometric Mean Concentrations (µg/mL) One Month After One Prevnar 13 Catch-Up Dose in Children 24 Through 59 Months of Age With 3 or 4 Prior Doses of Prevnar, US Catch-Up Study*	
Serotype	**1 dose Prevnar 13** **24 months through 59 months** N=173-175 (95% CI)
1	2.43 (2.15, 2.75)
3	1.38 (1.17, 1.61)
5	2.13 (1.89, 2.41)
6A	12.96 (11.04, 15.21)
7F	4.22 (3.74, 4.77)
19A	14.18 (12.37, 16.25)
*Open label administration of Prevnar 13. Note – Clinical trial.gov NCT number is as follows: NCT00761631.	

14.3 Prevnar 13 Immunogenicity Clinical Trials in Adults

Five phase 3 clinical trials were conducted in the US and Europe evaluating the immunogenicity of Prevnar 13 in different adult age groups, in individuals who were either not previously vaccinated with PPSV23 (PPSV23 unvaccinated) or who had received one dose of PPSV23 (PPSV23 previously vaccinated).

Each study included healthy adults and immunocompetent adults with stable underlying conditions including chronic cardiovascular disease, chronic pulmonary disease, renal disorders, diabetes mellitus, chronic liver disease, and medical risk conditions and behaviors (e.g. alcoholism and smoking) that are known to increase the risk of serious pneumococcal pneumonia and invasive pneumococcal disease. A stable medical condition was defined as a medical condition not requiring significant change in therapy (i.e., change to new therapy category due to worsening disease) or hospitalization for worsening disease 12 weeks before receipt of the study vaccine.

Immune responses elicited by Prevnar 13 and PPSV23 were measured by a mcOPA assay for the thirteen pneumococcal serotypes contained in Prevnar 13. Serotype-specific OPA geometric mean titers (GMTs) measured 1 month after each vaccination were calculated. For the 12 serotypes in common to both vaccines, noninferiority between vaccines was met if the lower limit of the 2-sided 95% confidence interval (CI) of the GMT ratio (Prevnar 13/PPSV23) was greater than 0.5.

The response to the additional serotype 6A, which is contained in Prevnar 13 but not in PPSV23, was assessed by demonstration of a 4-fold increase in the anti-6A OPA titer above preimmunization levels. A statistically significantly greater response for Prevnar 13 was defined, for the difference in percentages (Prevnar 13 minus PPSV23) of adults achieving a 4-fold increase in anti-6A OPA titer, as the lower limit of the 2-sided 95% CI greater than zero. For comparison of OPA GMTs, a statistically greater response for serotype 6A was defined as the lower limit of the 2-sided 95% CI of the GMT ratio (Prevnar 13/PPSV23) greater than 2.

Of the five phase 3 clinical trials, 2 noninferiority trials were conducted in which the immune responses to Prevnar 13 were compared with the immune responses to PPSV23; one in PPSV23 unvaccinated adults aged 50 through 64 years (Study 1), and one in PPSV23 prevaccinated adults aged ≥ 70 years (Study 2). A third study compared immune responses of Prevnar 13 as a single dose compared to the response to Prevnar 13 administered one year after a dose of PPSV23 in adults aged 60 through 64 years who were PPSV23 unvaccinated at enrollment (Study 3). The study also compared immune responses of PPSV23 as a single dose compared to the responses to PPSV23 administered one year after a dose of Prevnar 13. Two studies assessed the concomitant administration of Prevnar 13 with seasonal inactivated Fluarix (TIV) in the US (Study 5) and Europe (Study 6).

Clinical Trials Conducted in PPSV23 Unvaccinated Adults

In an active-controlled modified[a] double-blind clinical trial (Study 1) of Prevnar 13 in the US, PPSV23 unvaccinated adults aged 60 through 64 years were randomly assigned (1:1) to receive Prevnar 13 or PPSV23. In addition, adults aged 50 through 59 years were enrolled and received one dose of Prevnar 13 (open-label).

In adults aged 60 through 64 years, the OPA antibody GMTs elicited by Prevnar 13 were noninferior to those elicited by PPSV23 for the 12 serotypes in common to both vaccines (see Table 19). In addition, the lower limit of the 95% confidence interval for the OPA GMT ratio (Prevnar 13/PPSV23) was greater than 1 for 8 of the serotypes in common.

For serotype 6A, which is unique to Prevnar 13, the proportions of subjects with a 4-fold increase after Prevnar 13 (88.5%) was statistically significantly greater than after PPSV23 (39.2%) in PPSV23-unvaccinated adults aged 60 through 64 years. OPA GMTs for serotype 6A were statistically significantly greater after Prevnar 13 compared with after PPSV23 (see Table 19).

The OPA antibody GMTs elicited by Prevnar 13 in adults aged 50 through 59 years were noninferior to the corresponding OPA antibody GMTs elicited by Prevnar 13 in adults aged 60 through 64 years for all 13 serotypes (see Table 19).

[a] Modified double-blind means that the site staff dispensing and administering the vaccine were unblinded, but all other study personnel including the principal investigator and subject were blinded.

Table 19: OPA GMTs in PPSV23-Unvaccinated Adults Aged 50 through 59 Years Given Prevnar 13; and in Adults Aged 60 through 64 Years Given Prevnar 13 or PPSV23 (Study 1)[a,b,c,d,e]

	Prevnar 13	Prevnar 13	PPSV23	Prevnar 13 50-59 Relative to 60-64 Years		Prevnar 13 Relative to PPSV23, 60-64 Years	
	50-59 Years* N=350-384	60-64 Years N=359-404	60-64 Years N=367-402				
Serotype	GMT	GMT	GMT	GMT Ratio	(95% CI)	GMT Ratio	(95% CI)
1	200	146	104	1.4	(1.08, 1.73)	1.4	(1.10, 1.78)
3	91	93	85	1.0	(0.81, 1.19)	1.1	(0.90, 1.32)
4	2833	2062	1295	1.4	(1.07, 1.77)	1.6	(1.19, 2.13)
5	269	199	162	1.4	(1.01, 1.80)	1.2	(0.93, 1.62)
6A†	4328	2593	213	1.7	(1.30, 2.15)	12.1	(8.63, 17.08)
6B	3212	1984	788	1.6	(1.24, 2.12)	2.5	(1.82, 3.48)
7F	1520	1120	405	1.4	(1.03, 1.79)	2.8	(1.98, 3.87)
9V	1726	1164	407	1.5	(1.11, 1.98)	2.9	(2.00, 4.08)
14	957	612	692	1.6	(1.16, 2.12)	0.9	(0.64, 1.21)
18C	1939	1726	925	1.1	(0.86, 1.47)	1.9	(1.39, 2.51)
19A	956	682	352	1.4	(1.16, 1.69)	1.9	(1.56, 2.41)
19F	599	517	539	1.2	(0.87, 1.54)	1.0	(0.72, 1.28)
23F	494	375	72	1.3	(0.94, 1.84)	5.2	(3.67, 7.33)

GMT, Geometric Mean Titer.

† 6A is a serotype unique to Prevnar 13 but not contained in PPSV23.

[a] Noninferiority was defined for the 12 common serotypes in cohort 1 and for the 13 serotypes in cohort 2 as the lower limit of the 2-sided 95% CI for GMT ratio (Prevnar 13/PPSV23) greater than 0.5

[b] For serotype 6A, which is unique to Prevnar 13, a statistically significantly greater response was defined for analysis in cohort 1 as the lower limit of the 2-sided 95% CI for the GMT ratio (Prevnar 13/PPSV23) greater than 2.

[c] OPA for the 11serotypes unique to PPSV23 but not contained in Prevnar 13 were not measured.

[d] Individual OPA assay values below the assay LLOQ (lower limit of quantitation) were set at a titer of 1:4 (1/2 the assay limit of detection) for the purpose of calculating the OPA GMT.

[e] Evaluable Immunogenicity Population.

* Open label administration of Prevnar 13.

Note – Clinical trial.gov NCT number is as follows: NCT00427895.

Clinical Trials Conducted in PPSV23 Previously Vaccinated Adults

In a phase 3 active-controlled, modified double-blind clinical trial (Study 2) of Prevnar 13 in the US and Sweden, PPSV23 prevaccinated adults aged ≥ 70 years who had received one dose of PPSV23 ≥ 5 years prior were randomly assigned (1:1) to receive either Prevnar 13 or PPSV23.

The OPA antibody GMTs elicited by Prevnar 13 were noninferior to those elicited by PPSV23 for the 12 serotypes in common, when Prevnar 13 or PPSV23 were administered at a minimum of 5 years after a prior dose of PPSV23. In addition, the lower limit of the 95% confidence interval for the OPA GMT ratio (Prevnar 13/PPSV23) was greater than 1 for 10 of the serotypes in common.

For serotype 6A, which is unique to Prevnar 13, the proportion of subjects with a 4-fold increase in OPA titers after Prevnar 13 (71.1%) was statistically significantly greater than after PPSV23 (27.3%) in PPSV23-prevaccinated adults aged ≥ 70 years. OPA GMTs for serotype 6A were statistically significantly greater after Prevnar 13 compared with after PPSV23.

This clinical trial demonstrated that in adults aged ≥ 70 years and prevaccinated with PPSV23 ≥ 5 years prior, vaccination with Prevnar 13 elicited noninferior immune responses as compared with re-vaccination with PPSV23 (see Table 20).

Table 20: OPA GMTs in PPSV23-Previously Vaccinated Adults Aged ≥ 70 Years Given Prevnar 13 or PPSV23 (Study 2) [a,b,c,d,e]

Serotype	Prevnar 13 N=400-426 GMT	PPSV23 N=395-445 GMT	Prevnar 13 Relative to PPSV23	
			GMT Ratio	(95% CI)
1	81	55	1.5	(1.17, 1.88)
3	55	49	1.1	(0.91, 1.35)
4	545	203	2.7	(1.93, 3.74)
5	72	36	2.0	(1.55, 2.63)
6A[†]	903	94	9.6	(7.00, 13.26)
6B	1261	417	3.0	(2.21, 4.13)
7F	245	160[f]	1.5	(1.07, 2.18)
9V	181[f]	90[f]	2.0	(1.36, 2.97)
14	280	285	1.0	(0.73, 1.33)
18C	907	481	1.9	(1.42, 2.50)
19A	354	200	1.8	(1.43, 2.20)
19F	333	214	1.6	(1.17, 2.06)
23F	158	43	3.7	(2.69, 5.09)

GMT, Geometric Mean Titer.
[†] 6A is a serotype unique to Prevnar 13 but not contained in PPSV23.
[a] For the 12 common serotypes, noninferiority was defined as the lower limit of the 2-sided 95% CI for GMT ratio (Prevnar 13/PPSV23) greater than 0.5.
[b] For serotype 6A, which is unique to Prevnar 13, a statistically significantly greater response was defined as the lower limit of the 2-sided 95% CI for the GMT ratio (Prevnar 13/PPSV23) greater than 2.
[c] OPA for the 11 serotypes unique to PPSV23 but not contained in Prevnar 13 were not measured.
[d] Individual OPA assay values below the assay LLOQ (lower limit of quantitation) were set at a titer of 1:4 (1/2 the assay limit of detection) for the purpose of calculating the OPA GMT.
[e] Evaluable Immunogenicity Population.
[f] These GMT values for serotypes 7F and 9V are below the respective assay's LLOQ.
Note – Clinical trial.gov NCT number is as follows: NCT00546572.

Clinical Trial of Sequential Vaccination of Prevnar 13 and PPSV23 in PPSV23 Unvaccinated Adults

In a randomized clinical trial conducted in PPSV23-unvaccinated adults 60 through 64 years of age (Study 3), 223 persons received PPSV23 followed by Prevnar 13 one year later (PPSV23/Prevnar 13), and 478 received only Prevnar 13. OPA antibody titers were measured 1 month after vaccination with Prevnar 13 and are shown in Table 21. OPA GMTs in those that received Prevnar 13 one year after PPSV23 were diminished when compared to those who received Prevnar 13 alone. Similarly, in exploratory analyses in PPSV23-pre-vaccinated adults ≥ 70 years of age in Study 2, diminished OPA GMTs were observed in those that received Prevnar 13 one year after PPSV23 when compared to those who received Prevnar 13 alone.

Table 21: OPA GMTs for the Prevnar 13 Serotypes in PPSV23 Unvaccinated Adults Aged 60 through 64 Years Given Prevnar 13 Alone or Prevnar 13 One Year After PPSV23 (Study 3) (PPSV23/Prevnar 13)[*†a]

	Prevnar 13 N=410-457		PPSV23/Prevnar 13 N=180-196	
Serotype	**GMT**	**(95% CI)**	**GMT**	**(95% CI)**
1	207	(178, 241)	77	(61, 98)
3	75	(66, 85)	50	(41, 62)
4	2536	(2192, 2933)	935	(740, 1182)
5	215	(176, 262)	85	(64, 112)
6A**	2766	(2333, 3278)	1133	(876, 1465)
6B	1948	(1614, 2352)	710	(529, 953)
7F	1063	(869, 1302)	126[††]	(86, 185)
9V	767	(620, 949)	114[††]	(77, 169)
14	650	(525, 806)	435	(323, 586)
18C	1576	(1321, 1881)	564	(418, 762)
19A	709	(619, 811)	289	(236, 354)
19F	711	(596, 849)	286	(217, 377)
23F	354	(284, 441)	124	(88, 173)

[*] OPA for the 11serotypes unique to PPSV23 but not contained in Prevnar 13 were not measured.
[†] Individual OPA assay values below the assay LLOQ (lower limit of quantitation) were set at a titer of 1:4 (1/2 the assay limit of detection) for the purpose of calculating the OPA GMT.
[a] Evaluable Immunogenicity Population.
[††] These GMT values for serotypes 7F and 9V are below the respective assay's LLOQ.
**6A is a serotype unique to Prevnar 13 but not contained in PPSV23.
GMT =Geometric Mean Titer.
Note – Clinical trial.gov NCT number is as follows: NCT00574548.

No data are available on a dosing interval greater than 1 year. No data are available in response to Prevnar 13 given one year after PPSV23 in previously unvaccinated persons.

Also in Study 3, 266 persons received Prevnar 13 followed by PPSV23 one year later (Prevnar 13/PPSV23). OPA antibody GMTs following PPSV23 administered one year after Prevnar 13 (Prevnar 13/PPSV23) were noninferior to those following a single dose of PPSV23 (N=237) for the 12 common serotypes [the lower limit of the 95% CI for the GMT ratio [Prevnar 13/PPSV23 relative to PPSV23] was > 0.5] (see Table 22). In Study 1, which was conducted in PPSV23-unvaccinated adults 60 through 64 years of age day 1, 108 persons received PPSV23 3.5 to 4 years after PCV13 (Prevnar 13/PPSV23) and 414 received a single dose of PPSV23. Higher serotype-specific OPA GMT ratios [(Prevnar 13/PPSV23) / PPSV23] were generally observed compared to the one year dosing interval in Study 3.

Table 22: OPA GMTs for the Prevnar 13 Serotypes in PPSV23 Unvaccinated Adults Aged 60 through 64 Years Given PPSV23 One Year After Prevnar 13 Relative to PPSV23 Alone (Study 3)[*] [†] [a]

	Prevnar 13/PPSV23 N=216-233		PPSV23 N=214-229		GMT Ratio (Prevnar 13/PPSV23 to PPSV23) and 95% CI	
Serotype	**GMT**	**95% CI**	**GMT**	**95% CI**	**Ratio**	**95% CI**
1	148	(124, 177)	148	(1178, 186)	1.0	0.75, 1.33
3	125	(109, 143)	80	(68, 96)	1.6	1.24, 1.94
4	1385	(1171, 1639)	1357	(1023, 1799)	1.0	0.74, 1.41
5	199	(161, 246)	140	(107, 184)	1.4	1.01, 2.00
6A**	1268	(1010, 1592)	275	(194, 388)	4.6	3.05, 6.98
6B	1215	(965, 1528)	706	(522, 954)	1.7	1.18, 2.51
7F	537	(422, 683)	331	(234, 469)	1.6	1.07, 2.47
9V	373	(268, 518)	288[††]	(198, 419)	1.3	0.79, 2.12
14	622	(486, 796)	734	(544, 990)	0.8	0.58, 1.25
18C	1062	(863, 1308)	789	(586, 1062)	1.3	0.94, 1.93
19A	467	(404, 541)	376	(303, 466)	1.2	0.96, 1.61
19F	774	(642, 934)	509	(386, 673)	1.5	1.09, 2.12
23F	198	(965, 1528)	70	(522, 954)	2.8	1.86, 4.35

[*]OPA for the 11 serotypes unique to PPSV23 but not contained in Prevnar 13 were not measured.
[†] Individual OPA assay values below the assay LLOQ (lower limit of quantitation) were set at a titer of 1:4 (1/2 the assay limit of detection) for the purpose of calculating the OPA GMT.
[a] Evaluable Immunogenicity Population.
[††] This GMT value for serotype 9V is below the assay LLOQ.
**6A is a serotype unique to Prevnar 13 but not contained in PPSV23. Anti-6A OPA GMTs were descriptive in nature.
GMT =Geometric Mean Titer.
Note – Clinical trial.gov NCT number is as follows: NCT00574548.

Clinical Trials to Assess Prevnar 13 Given With Seasonal Trivalent Inactivated Influenza Vaccine (TIV) in PPSV23 Unvaccinated Adults

Two randomized, double-blind clinical trials evaluated the immunogenicity of Prevnar 13 given with inactivated TIV (Fall 2007/ Spring 2008 Fluarix, A/H1N1, A/H3N2, and B strains) in PPSV23 unvaccinated adults aged 50 through 59 years (Study 5, conducted in the U.S.) and in adults ≥ 65 years (Study 6, conducted in Europe).

In each clinical trial one group received Prevnar 13 and TIV concurrently, followed approximately one month later by placebo. The other group received TIV and placebo concurrently, followed approximately one month later by Prevnar 13.

Antibody responses elicited by TIV were measured by hemagglutination inhibition assay (HAI) one month after TIV vaccination. The proportion of subjects achieving a ≥ 4-fold increase in HAI titer (responder) for each TIV strain was evaluated 1 month after vaccination. Noninferiority was demonstrated for each TIV vaccine antigen if the lower limit of the 95% CI for the difference in proportions of responders between the two groups (concomitant minus (TIV+Placebo)) was greater than -10%.

In subjects 50 through 59 years of age, noninferiority was demonstrated for each of the 3 TIV strains after Prevnar 13 given concomitantly with TIV compared with TIV given alone.

In subjects ≥ 65 years of age, noninferiority was demonstrated for A/H1N1 and B-strains, but not for A/H3N2, which had a lower limit of the 95% CI of -10.4%.

The studies also assessed the antibody responses of Prevnar 13 when Prevnar 13 was given concomitantly with TIV compared with Prevnar 13 given alone. The antipolysaccharide binding antibody responses (IgG) were measured by ELISA IgG one month after Prevnar 13 vaccination in a subset of subjects. Noninferiority was demonstrated if the lower limit of the 2-sided, 95% CI for the IgG GMC ratios (Prevnar 13+ TIV relative to Prevnar 13 alone) was > 0.5. In a post hoc analysis, OPA antibody response was evaluated using the same criterion.

In subjects 50 through 59 years of age, Prevnar 13 IgG antibody responses, as measured by ELISA, met noninferiority for all 13 serotypes after Prevnar 13 was given concomitantly with TIV compared to Prevnar 13 given alone, and noninferiority of the OPA GMT ratios was observed for 8 of 13 serotypes.

In subjects ≥ 65 year of age, Prevnar 13 IgG antibody responses, as measured by ELISA, met noninferiority for 12 of 13 serotypes after Prevnar 13 was given concomitantly with TIV compared with Prevnar 13 given alone, and noninferiority of the OPA GMT ratios was observed for 10 of 13 serotypes.

16 HOW SUPPLIED/STORAGE AND HANDLING

Prefilled Syringe, 1 Dose (10 per package) – NDC 0005-1971-02.

Store refrigerated at +2ºC to +8ºC (36ºF to 46ºF).

The tip cap and rubber plunger of the prefilled syringe do not contain latex.

Do not freeze. Discard if the vaccine has been frozen.

17 PATIENT COUNSELING INFORMATION

17.1 Potential Benefits and Risks

Prior to administration of this vaccine, the healthcare professional should inform the individual, parent, guardian, or other responsible adult of the potential benefits and risks to the patient *[see Warnings and Precautions (5) and Adverse Reactions (6)]*. Parents, guardians, or other responsible adults should be informed of the importance of completing the immunization series for their child(ren) unless contraindicated.

Vaccine Information Statements are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

17.2 Adverse Reactions

Instruct the individuals, parents, guardians, or other responsible adults to report any suspected adverse reactions to their healthcare professional.

US Govt. License No. 3

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