PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Prevnar® / Prevenar® / 7-Valent pneumococcal conjugate vaccine (7vPnC)

PROTOCOL NO.: 6106A1-500

PROTOCOL TITLE: A Randomized Controlled Open-Label Phase IV Multi Center Study to Assess the Effect of Antipyretic Prophylactic Treatment on the Rate of Febrile Reactions Following Concomitant Contralateral Administration of a 7-Valent Pneumococcal Conjugate Vaccine (Prevenar®) and DTPa-HBV-IPV+Hib Vaccine (Infanrix Hexa®) in Children at 2, 3, 4, and 11-14 Months of Age

Study Centers: Twenty-two (22) centers in Germany took part in the study and randomized subjects.

Study Initiation and Final Completion Dates: 24 May 2005 to 11 December 2006

Phase of Development: Phase 4

Study Objective:

Primary Objective: To determine the percent reduction in the rate of febrile reactions when prophylactic antipyretic treatment was administered relative to no prophylactic antipyretic treatment after vaccination with a 7-valent pneumococcal conjugate vaccine (7vPnC) and routine diphtheria, tetanus, and acellular pertussis vaccine (DTPa)-hepatitis B virus vaccine (HBV)-inactivated poliovirus vaccine (IPV) solution combined with the lyophilyzed *Haemophilus influenzae* type b (Hib) oligosaccharide conjugate vaccine component (DTPa-HBV-IPV+Hib) vaccination at 2, 3, 4 (primary series), and 11-14 (booster dose) months of age.

Secondary Objective: To determine additional safety and tolerability of a single injection of 7vPnC and DTPa-HBV-IPV+Hib when concomitantly administered, with or without prophylactic antipyretic treatment at 2, 3, 4 and 11-14 months of age.

METHODS

Study Design:

This was an open-label, Phase 4, randomized, controlled, multicenter study to determine the effect of antipyretic prophylaxis on febrile reactions when given in 3 single doses to children after vaccination with 7vPnC and DTPa-HBV-IPV+Hib, compared with febrile reactions in children who receive the same vaccinations without antipyretic medication at the age of 2, 3, and 4 months and again at 11 to 14 months.

This study could not be conducted in a blinded manner because 1 group of subjects was to receive additional medication, and a placebo control was not possible. The control group received the same study vaccines as the antipyretic prophylaxis group, but no other prophylactic medications thus permitting a direct evaluation of the effect of prophylactic paracetamol.

Informed consent and medical history were obtained and a physical examination was performed before administration of study vaccines. Demographic data, including sex, race, birth date, weight at enrollment and age at time of vaccination were collected. Allocation of eligible subjects to study groups was performed at Visit 1.

Each subject was randomly assigned to receive antipyretic prophylaxis or no antipyretic prophylaxis at a 1:1 ratio; all subjects were to receive 7vPnC and DTPa-HBV-IPV+Hib. For each vaccination, subjects were administered their study vaccines and their first dose of prophylactic antipyretic (paracetamol), if randomly assigned to that group. Parent(s)/legal guardian(s) of subjects in the prophylaxis group administered the second and third dose of paracetamol at 8 hour intervals. The dosage of paracetamol was determined based on the subject's weight.

After each vaccination, parents completed a diary each day for 4 days beginning on the day of each vaccination (Days 1 to 4) detailing core (rectal) temperature, use of antipyretics, local reactions, and systemic events. Rectal temperature was recorded twice each day (morning and evening), except for Day 1 (evening only). Local reactions (tenderness, redness, and swelling) were recorded for each injection site separately; 7vPnC was injected into the anterolateral muscle of the left thigh and DTPa-HBV-IPV+Hib was injected into the same muscle of the right thigh. If redness or swelling was noted, parents recorded the diameter of the affected area using calipers provided by the Sponsor. Systemic events monitored included rash, irritability, drowsiness, decreased appetite, persistent inconsolable crying, and decreased activity. Concomitant medications, including nonprescription medications and antipyretics, were recorded for 15 days (Days 1 to 15) after each vaccination.

For this study, diary information was to be collected using an electronic diary (e-diary). Any adverse events (AEs), including visits to hospital and to Physicians from the first vaccination at Visit 1 through Visit 4 and from the fourth vaccination at Visit 5 through Visit 6 were collected. Serious adverse events (SAEs) were monitored and collected from the first vaccination at Visit 1 through Visit 4 and from the fourth vaccination at Visit 5 through Visit 6.

The schedule of activities is presented in Table 1.

Table 1. Schedule of Activities

Procedure	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Visit Window	**56-112 Days of Age**	**28-42 Days After Visit 1**	**28-42 Days After Visit 2**	**28-42 Days After Visit 3**	**335-455 Days of Age**	**28-42 Days After Visit 5**
Obtain informed consent	X					
Check eligibility criteria	X					
Core (rectal) temperature (°C)	X	X	X		X	
Medical history	X	X (interim)	X (interim)	X (interim)	X (interim)	X (interim)
Physical examination	X	X	X		X	
Randomization	X					
Vaccination with 7vPnC (left thigh) and DTPa-HBV-IPV+Hib (right thigh)	X	X	X		X	
Administer paracetamol suppositories (test group)[a]	X	X	X		X	
Post vaccination observation to assess acute reactions (at least 30 minutes)	X	X	X		X	
Diary presented	X	X	X		X	
Diary collected		X	X	X		X
Document antipyretics	X	X	X	X	X	X
Document concomitant medication[b]	X	X	X	X	X	X
Assess acute reactions	X	X	X		X	
Document adverse events[c]	X	X	X	X	X	X
Report serious adverse events[c]	X	X	X	X	X	X

7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine (DTPa)-hepatitis B virus vaccine (HBV)-inactivated poliovirus vaccine (IPV) solution combined with the lyophilyzed *Haemophilus influenzae* type b (Hib) oligosaccharide conjugate vaccine component.

a. Dosage: First dose administered by site staff directly after the vaccination at the study site. Second and third dose administered at home: for body weight 4 kg to <7 kg, paracetamol total dose given was 3 × 125 mg; for body weight 7 kg to <10 kg, paracetamol total dose given was 1 × 250 mg/2 × 125 mg; and for body weight ≥10.0 kg, paracetamol total dose given was 3 × 250 mg.
b. Concomitant medication within 15 days of a study immunization visit (Days 1 to 15).
c. Serious adverse events and adverse events were monitored and collected from the first vaccination at Visit 1 through to Visit 4 and from the fourth vaccination at Visit 5 through to Visit 6.

Number of Subjects (Planned and Analyzed): Approximately 150 children were planned to be enrolled into each treatment group (with or without antipyretic prophylaxis), for a total of 300 subjects. The actual number of vaccinated subjects was 148 in the prophylaxis group and 152 in the no prophylaxis group.

Diagnosis and Main Criteria for Inclusion: Subjects eligible to participate in the study were healthy infants 56 to 112 days of age, for whom both parent(s)/guardian(s) provided written informed consent.

The key exclusion criteria were:

- Vaccination with any licensed or investigational vaccine (other than study vaccines allowed) before enrollment (Visit 1) up to Visit 4, or 2 weeks before the toddler vaccination (Visit 5) up to Visit 6;
- Receipt of blood products within 12 weeks before study entry;
- A previous anaphylactic reaction or serious vaccine-associated adverse reaction;
- Contraindication to immunization with DTPa-HBV-IPV+Hib, or 7vPnC;
- Participation in another investigational study;
- Any serious chronic disease;
- Known or suspected impairment or abnormality of immune function.

Study Vaccine:

The study vaccines (7vPnC and DTPa-HBV-IPV+Hib) were provided by the Sponsor to cover the infant series (Visits 1 to 3) and toddler (Visit 5) vaccinations for each subject.

7vPnC: This was a commercially available liquid preparation that was supplied in single-dose (0.5 mL) vials. The vaccine wass formulated to contain 2 μg of Serotypes 4, 9V, 14, 18C, 19F, and 23F, respectively, and 4 μg of Serotype 6B. One (1) dose contains 0.125 mg aluminum as aluminum phosphate and approximately 20 μg cross-reacting material 197. The entire contents of the vial were drawn into a syringe and administered into the anterolateral muscle of the left thigh.

DTPa-HBV-IPV+Hib: This was a combination vaccine commercially available as DTPa-HBV-IPV+Hib. The DTPa-HBV-IPV (diphtheria, tetanus, acellular pertussis; hepatitis B; and inactivated poliovirus) solution (0.5 mL) was packaged in a prefilled syringe. The lyophilized Hib vaccine was supplied as a powder in a single-dose vial and had to be reconstituted with the liquid DTPa-HBV-IPV. Directly after mixing, 0.5 mL of the solution was drawn into a syringe and administered into the anterolateral muscle of the right thigh.

Paracetamol: This commercially available analgesic and antipyretic drug was supplied as 125 mg and 250 mg suppositories. Paracetamol suppositories registered for antipyretic use

were provided from commercial stock as 125 mg and 250 mg suppositories packed in foil strips. Children assigned to the prophylaxis group received 3 doses at intervals of 6 to 8 hours after each vaccination.

Duration of Treatment: At the first visit, each subject was randomly assigned to receive a single-dose of each vaccine with or without prophylactic antipyretic medication: 7vPnC and DTPa-HBV-IPV+Hib and paracetamol; or 7vPnC and DTPa-HBV-IPV+Hib. Infants were enrolled into the study at their first scheduled routine vaccination (Visit 1) when they were 2 months (56 to 112 days) old. They received their second vaccination (Visit 2) 28 to 42 days after Visit 1 and a third vaccination (Visit 3) 28 to 42 days after Visit 2. A follow-up visit (Visit 4) was performed 28 to 42 days after Visit 3. At 11 to 14 months of age (335 to 455 days) the subjects received their routine toddler vaccination (Visit 5). A final follow-up visit (Visit 6) was performed 28 to 42 days after Visit 5.

Efficacy and Safety Endpoints:

Primary Endpoints:

- Core (rectal) fever ≥38°C within Days 1 to 4 post-vaccination after any of the Doses 1-3;
- Core (rectal) fever ≥38°C within Days 1 to 4 post-vaccination after the fourth dose.

Secondary Endpoints:

- Core (rectal) fever >39°C, occurring within 4 days (Days 1 to 4) of vaccine administration after each dose of the primary series;
- Core (rectal) fever >39°C, occurring within 4 days (Days 1 to 4) of booster dose.

Safety Endpoints:

- Reactogenicity events reported in the diary within 4 days (Days 1 to 4) of study vaccination;
- AEs from the first vaccination at Visit 1 through to Visit 4 and from the fourth vaccination at Visit 5 through to Visit 6;
- SAEs from the first vaccination at Visit 1 through to Visit 4 and from the fourth vaccination at Visit 5 through to Visit 6.

Immunogenicity was not evaluated in this study.

Safety Evaluations:

Local reactions on both legs, recorded separately for 7vPnC and DTPa-HBV-IPV+Hib sites, were tenderness, redness, and swelling at the injection sites. Redness and swelling at the injection site were measured, on a numeric scale from 1 to 14, or 14+, using a caliper, each caliper unit representing one half of a centimeter. Tenderness was assessed as: no discernible

tenderness, or tenderness present (cried briefly when leg was touched), or tenderness interfered with leg movement.

Systemic events that were recorded were rash, irritability, drowsiness, decreased appetite, persistent inconsolable crying, and decreased activity. Core temperature was also evaluated as a safety measure.

AEs occurring from the first vaccination at Visit 1 through Visit 4 and from the fourth vaccination at Visit 5 through Visit 6, including visits to hospital and Physicians, were recorded by the parent(s)/legal guardians on an e-diary and were transcribed to the corresponding AE section in the study related documents. SAEs were monitored and collected from the first vaccination at Visit 1 through Visit 4 and from the fourth vaccination at Visit 5 through Visit 6.

Statistical Methods:

Analysis Populations: Six (6) analysis populations were defined for the study: 2 for the efficacy analyses (intent-to-treat [ITT] and per-protocol [PP]) and 4 for the safety analyses (1 for each vaccine dose). The definitions of these populations are given below:

- ITT Efficacy Population: Any randomly assigned subject who had at least 1 recorded post-vaccination temperature was included in the ITT efficacy population.
- PP Efficacy Population: Subjects included in the PP efficacy population were those who:
  - Were eligible for the study;
  - Were randomly assigned;
  - Were 56 to 112 days of age, inclusive, on the day of first vaccination;
  - Were 335 to 455 days of age, inclusive, at the toddler dose;
  - Received the vaccine to which they were randomly assigned at all 4 doses (when vaccinated);
  - Received all 4 study vaccinations;
  - Received all doses of paracetamol during all 4 doses;
  - Received all expected study concomitant vaccinations at all 4 doses (when vaccinated);
  - Had at least 75% of Days 1 to 4 (at least 3 out of 4 days) after each vaccination with a temperature measurement to permit evaluation of fever incidence;
  - Received no prohibited vaccines (eg, pneumococcal vaccine, Hib conjugate, DTPa, or IPV vaccines);

- Had no other protocol violations as determined by the clinical team leader (CTL) or medical monitor (MM).

- Safety Populations: All participants who received any study vaccine and concomitant medication were included in the analyses of safety data. For the safety analyses, participants were analyzed according to the vaccine received: 7vPnC with paracetamol and 7vPnC without paracetamol. Subjects who lacked any safety data (AE, reactogenicity, or temperature) for a particular vaccination were excluded from that analysis. Separate safety populations were defined for each vaccination.

Efficacy: The coprimary efficacy endpoints were the incidence rates of fever ≥ 38ºC after any of the first 3 doses in the infant series and after the toddler dose. The secondary efficacy endpoints were the incidence rates of fever >39ºC after each dose. For each of these 6 efficacy endpoints, efficacy (E) of 7vPnC with paracetamol relative to 7vPnC without paracetamol was estimated by 1 minus the relative risk. For each efficacy estimate 95% confidence intervals (CIs) were constructed using exact methods conditional on the total number of fevers (ie, conditional binomial distribution).

The ITT efficacy population was the primary analysis population. The PP efficacy population was used to confirm the results of the primary analyses.

Safety: The local reactions, systemic events, and AEs were summarized for each dose using descriptive statistics, and comparisons between the prophylaxis group and control group were performed using a 2-sided, Fisher's exact test.

RESULTS

Subject Disposition and Demography:

A total of 301 subjects were enrolled and randomly assigned in a 1:1 ratio to either the antipyretic prophylaxis group (148 subjects) or to the control group (153 subjects). One (1) subject was randomly assigned to control group but informed consent was not signed by both parents; therefore a total of 300 subjects received vaccination in the 2 groups. The study completion rate was comparable between the 2 groups: 93.9% (139/148) and 96.1% (147/153) of subjects completed the 4-dose series in the group with and the group without concomitant paracetamol, respectively. More subjects dropped out after the third dose of vaccines in the prophylaxis group (6 subjects) than in the control group (4 subjects). Details of the subject numbers vaccinated at each dose and reasons for withdrawal are shown in Table 2.

Table 2. Disposition of All Subjects

	Vaccine Group (as Randomized)[a]					
	7vPnC With Paracetamol		7vPnC Without Paracetamol		Total	
	n	%	n	%	n	%
Consented	148	100.0	152	99.3	300	99.7
Randomized[b]	148	100.0	153	100.0	301	100.0
Vaccinated						
Dose 1	148	100.0	152	99.3	300	99.7
Dose 2	145	98.0	151	98.7	296	98.3
Dose 3	145	98.0	151	98.7	296	98.3
Dose 4	139	93.9	147	96.1	286	95.0
Completed	139	93.9	147	96.1	286	95.0
Withdrawn	9	6.1	6	3.9	15	5.0
Reasons for withdrawal						
Lost to follow-up	7	4.7	2	1.3	9	3.0
Parent/legal guardian request	1	0.7	2	1.3	3	1.0
Investigator request	1	0.7	0	0.0	1	0.3
Protocol violation	0	0.0	2	1.3	2	0.7

Informed consent form for 1 subject was not signed by both parents.
7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine (DTPa)-hepatitis B virus vaccine (HBV)-inactivated poliovirus vaccine (IPV) solution combined with the lyophilyzed *Haemophilus influenzae* type b (Hib) oligosaccharide conjugate vaccine component; n = number of subjects.
a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.
b. These values are used as the denominators for the percentages.

Of 301 randomly assigned subjects vaccinated with 7vPnC and DTPa-HBV-IPV+Hib, 148 were randomly assigned to the prophylaxis group at Dose 1. Of these 148 subjects, 147 (99.3%) were included in the ITT population and of 153 subjects randomly assigned to the control group, 152 (99.3%) were included in the ITT population. Of 301 randomized subjects, 245 (81.4%) were protocol compliant and were included in the PP population. Of 148 subjects randomly assigned to the prophylaxis group, 116 (78.4%) were included in the PP population, and of 153 subjects randomly assigned to the control group, 129 (84.3%) were included in the PP population. The number of subjects included in the ITT and PP efficacy populations are presented in Table 3.

Table 3. ITT and PP Efficacy Populations

	Vaccine Group (as Randomized)[a]					
	7vPnC With Paracetamol		7vPnC Without Paracetamol		Total	
	n	%	n	%	n	%
Randomized	148	100.0	153	100.0	301	100.0
ITT efficacy population	147	99.3	152	99.3	299	99.3
Subjects excluded from the ITT efficacy population[b]	1	0.7	1	0.7	2	0.7
Not eligible – only 1 parent consented but both are required	0	0.0	1	0.7	1	0.3
Had no post-vaccination temperature recorded for any dose	1	0.7	1	0.7	2	0.7
PP efficacy population	116	78.4	129	84.3	245	81.4
Subjects excluded from the PP efficacy population[b]	32	21.6	24	15.7	56	18.6
Had <75% of required temperature measurements at Dose 4	18	12.2	14	9.2	32	10.6
Had <75% of required temperature measurements at Dose 3	10	6.8	8	5.2	18	6.0
Had <75% of required temperature measurements at Dose 2	9	6.1	6	3.9	15	5.0
Did not receive study vaccination at Dose 4	9	6.1	6	3.9	15	5.0
Had <75% of required temperature measurements at Dose 1	4	2.7	4	2.6	8	2.7
Not 335-455 days old at Dose 4	2	1.4	3	2.0	5	1.7
Did not receive study vaccination at Dose 2	3	2.0	2	1.3	5	1.7
Did not receive study vaccination at Dose 3	3	2.0	2	1.3	5	1.7
Not eligible	0	0.0	3	2.0	3	1.0
Did not receive all required paracetamol at Dose 1	2	1.4	0	0.0	2	0.7
Did not receive all required paracetamol at Dose 2	2	1.4	0	0.0	2	0.7
Did not receive all required paracetamol at Dose 4	2	1.4	0	0.0	2	0.7
Prohibited vaccine - received MMR prior to post-toddler dose follow-up	1	0.7	1	0.7	2	0.7
Was not in the ITT efficacy population	1	0.7	1	0.7	2	0.7
Protocol violation - enrolled in another clinical trial between Visits 4 and 5	1	0.7	1	0.7	2	0.7
Did not receive all required paracetamol at Dose 3	1	0.7	0	0.0	1	0.3
Protocol violation - birth weight <2,500 g	0	0.0	1	0.7	1	0.3
Protocol violation - received paracetamol prior to vaccination	1	0.7	0	0.0	1	0.3
Protocol violation - had febrile seizure between infant series and toddler vaccination	0	0.0	1	0.7	1	0.3
Protocol violation - forced randomization assignment	1	0.7	0	0.0	1	0.3
>112 days old at enrollment	0	0.0	1	0.7	1	0.3

Table 3. ITT and PP Efficacy Populations

	Vaccine Group (as Randomized)[a]					
	7vPnC With Paracetamol		7vPnC Without Paracetamol		Total	
	n	%	n	%	n	%
Did not receive study vaccination at Dose 1	0	0.0	1	0.7	1	0.3

7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine (DTPa)-hepatitis B virus vaccine (HBV)-inactivated poliovirus vaccine (IPV) solution combined with the lyophilyzed *Haemophilus influenzae* type b (Hib) oligosaccharide conjugate vaccine component; ITT = intent-to-treat; MMR = measles, mumps, and rubella (vaccine); n = number of subjects; PP = per-protocol.

a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.

b. Subjects may have been excluded for >1 reason.

Demographic characteristics of all subjects in the study are presented in Table 4, Table 5, Table 6 and Table 7 and were similar to those of the ITT population. Demographic characteristics of subjects in the PP population were similar to those of the ITT population.

Table 4. Demographic Characteristics – Dose 1 Safety Population

	Vaccine Group (as Randomized)[a]					
	7vPnC With Paracetamol N=148		7vPnC Without Paracetamol N=152		Total N=300	
	n	%	n	%	n	%
Gender						
Male	74	50.0	81	53.3	155	51.7
Female	74	50.0	71	46.7	145	48.3
Race						
White	146	98.6	149	98.0	295	98.3
Asian	1	0.7	1	0.7	2	0.7
Black	1	0.7	1	0.7	2	0.7
Other	0	0.0	1	0.7	1	0.3
Age at vaccination (months)						
n	148		152		300	
Mean (SD)	2.6 (0.6)		2.6 (0.5)		2.6 (0.5)	
Median	2.4		2.4		2.4	
Min, Max	1.9, 3.7		1.9, 3.8		1.9, 3.8	
Weight at vaccination (kg)						
Mean (SD)	5.9 (0.8)		6.0 (0.8)		5.9 (0.8)	
Median	5.9		5.9		5.9	
Min, Max	4.0, 7.6		4.4, 8.2		4.0, 8.2	

7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine (DTPa)-hepatitis B virus vaccine (HBV)-inactivated poliovirus vaccine (IPV) solution combined with the lyophilyzed *Haemophilus influenzae* type b (Hib) oligosaccharide conjugate vaccine component; max = maximum; min = minimum; N = number of subjects; n = number of subjects with the specified characteristic in a vaccine group; SD = standard deviation.

a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.

Table 5. Demographic Characteristics – Dose 2 Safety Population

	Vaccine Group (as Randomized)[a]					
	7vPnC With Paracetamol N=145		7vPnC Without Paracetamol N=141		Total N=296	
	n	%	n	%	n	%
Gender						
Male	72	49.7	80	53.0	152	51.4
Female	73	50.3	71	47.0	144	48.6
Race						
White	143	98.6	148	98.0	291	98.3
Asian	1	0.7	1	0.7	2	0.7
Black	1	0.7	1	0.7	2	0.7
Other	0	0.0	1	0.7	1	0.3
Age at vaccination (months)						
n	145		151		296	
Mean (SD)	3.7 (0.6)		3.7 (0.6)		3.7 (0.6)	
Median	3.6		3.7		3.6	
Min, Max	2.8, 5.0		2.7, 5.2		2.7, 5.2	
Weight at vaccination (kg)						
Mean (SD)	6.7 (0.8)		6.8 (0.9)		6.7 (0.9)	
Median	6.7		6.7		6.7	
Min, Max	4.5, 9.2		4.8, 9.7		4.5, 9.7	

7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine (DTPa)-hepatitis B virus vaccine (HBV)-inactivated poliovirus vaccine (IPV) solution combined with the lyophilyzed *Haemophilus influenzae* type b (Hib) oligosaccharide conjugate vaccine component; max = maximum; min = minimum; N = number of subjects; n = number of subjects with the specified characteristic in a vaccine group; SD = standard deviation.

a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.

Table 6. Demographic Characteristics – Dose 3 Safety Population

	Vaccine Group (as Randomized)[a]					
	7vPnC With Paracetamol N=145		7vPnC Without Paracetamol N=151		Total N=296	
	n	%	n	%	n	%
Gender						
Male	72	49.7	80	53.0	152	51.4
Female	73	50.3	71	47.0	144	48.6
Race						
White	143	98.6	148	98.0	291	98.3
Asian	1	0.7	1	0.7	2	0.7
Black	1	0.7	1	0.7	2	0.7
Other	0	0.0	1	0.7	1	0.3
Age at vaccination (months)						
n	145		151		296	
Mean (SD)	4.8 (0.6)		4.9 (0.6)		4.8 (0.6)	
Median	4.7		4.8		4.7	
Min, Max	3.8, 6.4		3.8, 6.3		3.8, 6.4	
Weight at vaccination (kg)						
Mean (SD)	7.3 (0.9)		7.4 (1.0)		7.4 (0.9)	
Median	7.3		7.4		7.3	
Min, Max	5.0, 10.3		5.3, 10.0		5.0, 10.3	

7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine (DTPa)-hepatitis B virus vaccine (HBV)-inactivated poliovirus vaccine (IPV) solution combined with the lyophilyzed *Haemophilus influenzae* type b (Hib) oligosaccharide conjugate vaccine component; max = maximum; min = minimum; N = number of subjects; n = number of subjects with the specified characteristic in a vaccine group; SD = standard deviation.

a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.

Table 7. Demographic Characteristics – Dose 4 Safety Population

	Vaccine Group (as Randomized)[a]					
	7vPnC With Paracetamol N=139		7vPnC Without Paracetamol N=147		Total N=286	
	n	%	n	%	n	%
Gender						
Male	70	50.4	78	53.1	148	51.7
Female	69	49.6	69	46.9	138	48.3
Race						
White	137	98.6	144	98.0	281	98.3
Asian	1	0.7	1	0.7	2	0.7
Black	1	0.7	1	0.7	2	0.7
Other	0	0.0	1	0.7	1	0.3
Age at vaccination (months)						
n	139		147		286	
Mean (SD)	12.0 (0.9)		11.9 (1.0)		12.0 (0.9)	
Median	11.7		11.6		11.7	
Min, Max	10.2, 15.8		11.0, 16.8		10.2, 16.8	
Weight at vaccination (kg)						
Mean (SD)	9.7 (1.0)		9.8 (1.1)		9.8 (1.1)	
Median	9.7		9.7		9.7	
Min, Max	7.1, 13.1		7.5, 12.5		7.1, 13.1	

7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine (DTPa)-hepatitis B virus vaccine (HBV)-inactivated poliovirus vaccine (IPV) solution combined with the lyophilyzed *Haemophilus influenzae* type b (Hib) oligosaccharide conjugate vaccine component; max = maximum; min = minimum; N = number of subjects; n = number of subjects with the specified characteristic in a vaccine group; SD = standard deviation.
a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.

Efficacy Results:

The number and percentage of subjects with fever ≥38°C are presented in Table 8. In the efficacy analyses, when fewer than 5 subjects had a febrile reaction in the control group the CIs were not computed and only the estimate of efficacy was presented.

Of 100 subjects included in the infant series who received paracetamol, 43 (43%) had fever ≥38°C, compared with 95 of 126 subjects (75.4%) receiving no post-vaccination paracetamol with this same degree of fever. These results demonstrate that paracetamol given prophylactically after vaccination with 7vPnC and concomitant DTPa-HBV-IPV+Hib was 43% efficacious in preventing fever in children 2 to 4 months of age relative to the control group (95% CI: 17.4, 61.2). After the toddler dose, fever ≥38°C was reported in 58 of 108 subjects (53.7%) in the prophylaxis group and in 76 of 119 subjects (63.9%) in the control group. Prophylactic paracetamol reduced fever by 15.9%, and statistical significance was not shown (95% CI: -19.9, 41.3).

Too few subjects in the control group reported fever >39°C to make a definitive assessment of efficacy after any vaccination. After Dose 1, 0 of 115 subjects in the prophylaxis group

compared with 5 of 124 (4%) control subjects reported fever >39°C. The estimate of efficacy was 100%, although not statistically significant (95% CI: -17.7, 100.0). After Dose 2 and Dose 3, too few subjects in the control group had fever >39°C and thus CIs were not computed. After the toddler dose, 4 of 87 subjects (4.6%) in the prophylaxis group had fever >39°C compared with 13 of 99 (13.1%) subjects in the control group. The estimate of efficacy was 65.0% (95% CI: -13.3, 91.7).

Results in the PP efficacy population are not presented, but were similar to those observed in the ITT population for the prevention of fever ≥38ºC. In the infant series, prophylactic paracetamol prevented fever by 52.3% (95% CI: 26.3, 69.9). However, after the toddler dose, the estimate of efficacy was 16.1%, which could not be demonstrated with statistical significance (95% CI: -23.1, 43.2). Prevention of fever >39ºC due to paracetamol prophylaxis again could not be demonstrated for any Dose (1, 2 or 3) in the infant series. However, a statistically significant rate of fever reduction (79.0%, 95% CI: 3.9, 97.7) was observed in the prophylaxis group after the toddler dose.

Table 8. Efficacy of Paracetamol in Preventing Fever – ITT Efficacy Population

	Vaccine Group (as Randomized)[a]							
	7vPnC With Paracetamol			7vPnC Without Paracetamol			Efficacy[b]	
Study Endpoint	N[c]	n[d]	%	N[c]	n[d]	%	%	(95% CI)
Core (rectal) fever ≥38°C[e]								
Infant series	100	43	43.0	126	95	75.4	43.0	(17.4, 61.2)
Toddler dose	108	58	53.7	119	76	63.9	15.9	(-19.9, 41.3)
Core (rectal) fever >39°C[f]								
Dose 1	115	0	0.0	124	5	4.0	100.0	(-17.7, 100.0)
Dose 2	117	0	0.0	112	2	1.8	100.0	N/A
Dose 3	102	1	1.0	103	2	1.9	49.5	N/A
Dose 4	87	4	4.6	99	13	13.1	65.0	(-13.3, 91.7)

7vPnC = 7-valent pneumococcal conjugate vaccine; CI = confidence interval; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine (DTPa)-hepatitis B virus vaccine (HBV)-inactivated poliovirus vaccine (IPV) solution combined with the lyophilyzed *Haemophilus influenzae* type b (Hib) oligosaccharide conjugate vaccine component; N = number of subjects in the analysis; n = number of subjects with the specified fever; N/A = not assessed.

a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.
b. Efficacy relative to 7vPnC without paracetamol. CI computed using exact methods conditional upon the number of subjects having reported the specific fever. If there were <5 subjects who had a febrile reaction in the 7vPnC without paracetamol group, only the estimate of efficacy computed; no CIs presented.
c. N = number of subjects in the analysis.
d. n = Number of subjects with the specified fever.
e. Coprimary efficacy endpoints.
f. Secondary efficacy endpoints.

Safety Results:

Local Reactions:

7vPnC:

Analyses of local reactions after each vaccine dose with or without prophylactic paracetamol are presented in Table 9, Table 10, Table 11 and Table 12. In general, in each study group the percentages of subjects experiencing local tenderness, induration (ie, swelling), or erythema were lowest after Dose 1 and highest after the toddler dose.

Table 9. Subjects Reporting Local Reactions for 7vPnC – Dose 1 Infant Series

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol			7vPnC Without Paracetamol			
Local Reactions	N[b]	n[c]	%	N[b]	n[c]	%	p-Value[d]
Tenderness							
Any	114	6	5.3	132	17	12.9	0.049
Significant[e]	114	0	0.0	127	1	0.8	>0.99
Induration							
Any	116	11	9.5	134	23	17.2	0.096
Mild[f]	115	9	7.8	133	19	14.3	0.158
Moderate[f]	115	3	2.6	128	7	5.5	0.341
Severe[f]	114	0	0.0	126	0	0.0	>0.99
Erythema							
Any	120	27	22.5	136	37	27.2	0.470
Mild[f]	117	20	17.1	134	34	25.4	0.125
Moderate[f]	117	7	6.0	129	6	4.7	0.778
Severe[f]	114	1	0.9	126	0	0.0	0.475
Any of the above	120	34	28.3	140	54	38.6	0.089

7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine (DTPa)-hepatitis B virus vaccine (HBV)-inactivated poliovirus vaccine (IPV) solution combined with the lyophilyzed *Haemophilus influenzae* type b (Hib) oligosaccharide conjugate vaccine component.

a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.
b. N = number of subjects reporting "yes" for at least 1 day or "no" for all days.
c. n = number of subjects reporting the specific characteristic.
d. Fisher's exact test, 2-sided.
e. Significant = present and interfered with limb movement.
f. Mild = 0.5-2 cm, moderate = 2.5-7 cm, and severe >7 cm.

Table 10. Subjects Reporting Local Reactions for 7vPnC – Dose 2 Infant Series

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol			7vPnC Without Paracetamol			
Local Reactions	N[b]	n[c]	%	N[b]	n[c]	%	p-Value[d]
Tenderness							
Any	120	10	8.3	118	17	14.4	0.157
Significant[e]	118	0	0.0	113	0	0.0	>0.99
Induration							
Any	123	21	17.1	125	34	27.2	0.067
Mild[f]	123	20	16.3	124	30	24.2	0.154
Moderate[f]	120	5	4.2	114	9	7.9	0.277
Severe[f]	118	0	0.0	113	0	0.0	>0.99
Erythema							
Any	123	26	21.1	126	44	34.9	0.017
Mild[f]	123	26	21.1	126	41	32.5	0.046
Moderate[f]	118	2	1.7	113	5	4.4	0.272
Severe[f]	118	0	0.0	113	0	0.0	>0.99
Any of the above	125	36	28.8	131	57	43.5	0.019

7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine (DTPa)-hepatitis B virus vaccine (HBV)-inactivated poliovirus vaccine (IPV) solution combined with the lyophilyzed *Haemophilus influenzae* type b (Hib) oligosaccharide conjugate vaccine component.

a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.
b. N = number of subjects reporting "yes" for at least 1 day or "no" for all days.
c. n = number of subjects reporting the specific characteristic.
d. Fisher's exact test, 2-sided.
e. Significant = present and interfered with limb movement.
f. Mild = 0.5-2 cm, moderate = 2.5-7 cm, and severe >7 cm.

Table 11. Subjects Reporting Local Reactions for 7vPnC – Dose 3 Infant Series

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol			7vPnC Without Paracetamol			
Local Reactions	N[b]	n[c]	%	N[b]	n[c]	%	p-Value[d]
Tenderness							
Any	109	6	5.5	107	11	10.3	0.216
Significant[e]	104	0	0.0	103	0	0.0	>0.99
Induration							
Any	107	18	16.8	112	31	27.7	0.074
Mild[f]	107	18	16.8	112	30	26.8	0.102
Moderate[f]	104	1	1.0	103	7	6.8	0.035
Severe[f]	104	0	0.0	103	0	0.0	>0.99
Erythema							
Any	114	29	25.4	112	39	34.8	0.147
Mild[f]	114	29	25.4	112	38	33.9	0.190
Moderate[f]	104	1	1.0	103	4	3.9	0.212
Severe[f]	104	0	0.0	103	0	0.0	>0.99
Any of the above	116	35	30.2	118	52	44.1	0.031

7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine (DTPa)-hepatitis B virus vaccine (HBV)-inactivated poliovirus vaccine (IPV) solution combined with the lyophilyzed *Haemophilus influenzae* type b (Hib) oligosaccharide conjugate vaccine component.

a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.
b. N = number of subjects reporting "yes" for at least 1 day or "no" for all days.
c. n = number of subjects reporting the specific characteristic.
d. Fisher's exact test, 2-sided.
e. Significant = present and interfered with limb movement.
f. Mild = 0.5-2 cm, moderate = 2.5-7 cm, and severe >7 cm.

Table 12. Subjects Reporting Local Reactions for 7vPnC – Toddler Dose

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol			7vPnC Without Paracetamol			
Local Reactions	N[b]	n[c]	%	N[b]	n[c]	%	p-Value[d]
Tenderness							
Any	94	20	21.3	107	35	32.7	0.082
Significant[e]	88	3	3.4	98	5	5.1	0.724
Induration							
Any	95	23	24.2	105	35	33.3	0.164
Mild[f]	95	22	23.2	104	30	28.8	0.420
Moderate[f]	87	3	3.4	99	11	11.1	0.055
Severe[f]	86	0	0.0	98	0	0.0	>0.99
Erythema							
Any	101	35	34.7	108	48	44.4	0.160
Mild[f]	100	34	34.0	107	45	42.1	0.254
Moderate[f]	88	4	4.5	99	5	5.1	>0.99
Severe[f]	86	0	0.0	98	0	0.0	>0.99
Any of the above	106	48	45.3	113	63	55.8	0.138

7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine (DTPa)-hepatitis B virus vaccine (HBV)-inactivated poliovirus vaccine (IPV) solution combined with the lyophilyzed *Haemophilus influenzae* type b (Hib) oligosaccharide conjugate vaccine component.

a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.
b. N = number of subjects reporting "yes" for at least 1 day or "no" for all days.
c. n = number of subjects reporting the specific characteristic.
d. Fisher's exact test, 2-sided.
e. Significant = present and interfered with limb movement.
f. Mild = 0.5-2 cm, moderate = 2.5-7 cm, and severe >7 cm.

DTPa-HBV-IPV+Hib:

Analyses of reactions at the injection site of DTPa-HBV-IPV+Hib after each dose are presented in Table 13, Table 14, Table 15 and Table 16. The incidence of local reactions at the DTPa-HBV-IPV+Hib injection site were similar to those observed with 7vPnC after each dose. As with 7vPnC, in general, the incidence of local reactions to DTPa-HBV-IPV+Hib were lowest after Dose 1 and the highest incidences were noted after Dose 4.

Table 13. Subjects Reporting Local Reactions for DTPa-HBV-IPV+Hib – Dose 1 Infant Series

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol			7vPnC Without Paracetamol			
Local Reactions	N[b]	n[c]	%	N[b]	n[c]	%	p-Value[d]
Tenderness							
Any	114	7	6.1	130	15	11.5	0.180
Significant[e]	114	0	0.0	126	0	0.0	>0.99
Induration							
Any	117	21	17.9	132	24	18.2	>0.99
Mild[f]	117	17	14.5	129	20	15.5	0.860
Moderate[f]	114	4	3.5	129	7	5.4	0.548
Severe[f]	114	0	0.0	126	0	0.0	>0.99
Erythema							
Any	120	25	20.8	131	31	23.7	0.650
Mild[f]	119	22	18.5	130	27	20.8	0.750
Moderate[f]	115	3	2.6	127	5	3.9	0.725
Severe[f]	114	1	0.9	126	0	0.0	0.475
Any of the above	121	42	34.7	135	43	31.9	0.691

7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine (DTPa)-hepatitis B virus vaccine (HBV)-inactivated poliovirus vaccine (IPV) solution combined with the lyophilyzed *Haemophilus influenzae* type b (Hib) oligosaccharide conjugate vaccine component.

a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.
b. N = number of subjects reporting "yes" for at least 1 day or "no" for all days.
c. n = number of subjects reporting the specific characteristic.
d. Fisher's exact test, 2-sided.
e. Significant = present and interfered with limb movement.
f. Mild = 0.5-2 cm, moderate = 2.5-7 cm, and severe >7 cm.

Table 14. Subjects Reporting Local Reactions for DTPa-HBV-IPV+Hib – Dose 2 Infant Series

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol			7vPnC Without Paracetamol			
Local Reactions	N[b]	n[c]	%	N[b]	n[c]	%	p-Value[d]
Tenderness							
Any	120	12	10.0	117	18	15.4	0.244
Significant[e]	118	0	0.0	113	0	0.0	>0.99
Induration							
Any	124	29	23.4	127	44	34.6	0.053
Mild[f]	124	28	22.6	127	39	30.7	0.156
Moderate[f]	120	6	5.0	114	11	9.6	0.211
Severe[f]	118	0	0.0	113	0	0.0	>0.99
Erythema							
Any	125	38	30.4	128	52	40.6	0.115
Mild[f]	125	37	29.6	128	49	38.3	0.184
Moderate[f]	118	2	1.7	113	5	4.4	0.272
Severe[f]	118	0	0.0	113	0	0.0	>0.99
Any of the above	128	47	36.7	131	64	48.9	0.060

7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine (DTPa)-hepatitis B virus vaccine (HBV)-inactivated poliovirus vaccine (IPV) solution combined with the lyophilyzed *Haemophilus influenzae* type b (Hib) oligosaccharide conjugate vaccine component.

a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.
b. N = number of subjects reporting "yes" for at least 1 day or "no" for all days.
c. n = number of subjects reporting the specific characteristic.
d. Fisher's exact test, 2-sided.
e. Significant = present and interfered with limb movement.
f. Mild = 0.5-2 cm, moderate = 2.5-7 cm, and severe >7 cm.

Table 15. Subjects Reporting Local Reactions for DTPa-HBV-IPV+Hib – Dose 3 Infant Series

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol			7vPnC Without Paracetamol			
Local Reactions	N[b]	n[c]	%	N[b]	n[c]	%	p-Value[d]
Tenderness							
Any	109	7	6.4	108	11	10.2	0.337
Significant[e]	104	0	0.0	103	0	0.0	>0.99
Induration							
Any	110	24	21.8	114	32	28.1	0.355
Mild[f]	110	22	20.0	114	31	27.2	0.213
Moderate[f]	105	4	3.8	103	7	6.8	0.371
Severe[f]	104	0	0.0	103	0	0.0	>0.99
Erythema							
Any	114	33	28.9	114	39	34.2	0.476
Mild[f]	114	32	28.1	114	38	33.3	0.473
Moderate[f]	104	4	3.8	105	7	6.7	0.538
Severe[f]	104	0	0.0	103	0	0.0	>0.99
Any of the above	119	44	37.0	118	49	41.5	0.507

7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine (DTPa)-hepatitis B virus vaccine (HBV)-inactivated poliovirus vaccine (IPV) solution combined with the lyophilyzed *Haemophilus influenzae* type b (Hib) oligosaccharide conjugate vaccine component.

a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.
b. N = number of subjects reporting "yes" for at least 1 day or "no" for all days.
c. n = number of subjects reporting the specific characteristic.
d. Fisher's exact test, 2-sided.
e. Significant = present and interfered with limb movement.
f. Mild = 0.5-2 cm, moderate = 2.5-7 cm, and severe >7 cm.

Table 16. Subjects Reporting Local Reactions for DTPa-HBV-IPV+Hib – Toddler Dose

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol			7vPnC Without Paracetamol			
Local Reactions	N[b]	n[c]	%	N[b]	n[c]	%	p-Value[d]
Tenderness							
Any	99	21	21.2	107	32	29.9	0.202
Significant[e]	88	3	3.4	98	3	3.1	>0.99
Induration							
Any	102	38	37.3	104	39	37.5	>0.99
Mild[f]	100	30	30.0	103	34	33.0	0.654
Moderate[f]	91	12	13.2	99	13	13.1	>0.99
Severe[f]	86	0	0.0	98	0	0.0	>0.99
Erythema							
Any	104	46	44.2	106	51	48.1	0.583
Mild[f]	102	42	41.2	106	48	45.3	0.578
Moderate[f]	91	11	12.1	98	13	13.3	0.831
Severe[f]	86	0	0.0	98	0	0.0	>0.99
Any of the above	108	55	50.9	111	65	58.6	0.279

7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine (DTPa)-hepatitis B virus vaccine (HBV)-inactivated poliovirus vaccine (IPV) solution combined with the lyophilyzed *Haemophilus influenzae* type b (Hib) oligosaccharide conjugate vaccine component.

a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.
b. N = number of subjects reporting "yes" for at least 1 day or "no" for all days.
c. n = number of subjects reporting the specific characteristic.
d. Fisher's exact test, 2-sided.
e. Significant = present and interfered with limb movement.
f. Mild = 0.5-2 cm, moderate = 2.5-7 cm, and severe >7 cm.

Systemic Events:

Systemic events were recorded after each vaccination at Visit 1 through Visit 4. These are presented in the tables after each dose in the infant series (Table 17, Table 18 and Table 19) and after the toddler dose (Table 20).

Table 17. Subjects Reporting Systemic Events – Dose 1 Infant Series

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol			7vPnC Without Paracetamol			
Systemic Events	N[b]	n[c]	%	N[b]	n[c]	%	p-Value[d]
Fever ≥38°C but ≤39°C	118	11	9.3	134	48	35.8	<0.001
Fever >39°C but ≤40°C	115	0	0.0	124	5	4.0	0.061
Fever >40°C	115	0	0.0	124	0	0.0	>0.99
Rash	119	21	17.6	129	22	17.1	>0.99
Irritability	125	59	47.2	140	87	62.1	0.019
Drowsiness	129	65	50.4	139	90	64.7	0.019
Decreased appetite	122	37	30.3	135	54	40.0	0.118
Persistent inconsolable crying	116	11	9.5	130	26	20.0	0.031
Decreased activity	125	52	41.6	136	63	46.3	0.457
Any systemic event[e]	141	113	80.1	149	134	89.9	0.021

7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine -hepatitis B virus vaccine -inactivated poliovirus vaccine solution combined with the lyophilyzed *Haemophilus influenzae* type b oligosaccharide conjugate vaccine component; N = number of subjects; n = number of subjects with the specified characteristic in a vaccine group.

a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.
b. N = number of subjects reporting "yes" for at least 1 day or "no" for all days.
c. n = number of subjects experiencing the event.
d. Fisher's exact test, 2-sided.
e. Includes fever ≥38°C, rash, irritability, drowsiness, decreased appetite, persistent inconsolable crying, and decreased activity.

Table 18. Subjects Reporting Systemic Events – Dose 2 Infant Series

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol			7vPnC Without Paracetamol			
Systemic Events	N[b]	n[c]	%	N[b]	n[c]	%	p-Value[d]
Fever ≥38°C but ≤39°C	122	24	19.7	126	55	43.7	0.000
Fever >39°C but ≤40°C	117	0	0.0	112	2	1.8	0.238
Fever >40°C	117	0	0.0	110	0	0.0	>0.99
Rash	118	8	6.8	121	19	15.7	0.040
Irritability	128	54	42.2	130	76	58.5	0.013
Drowsiness	127	59	46.5	127	74	58.3	0.078
Decreased appetite	124	33	26.6	124	53	42.7	0.011
Persistent inconsolable crying	118	11	9.3	120	19	15.8	0.171
Decreased activity	126	39	31.0	125	60	48.0	0.007
Any systemic event[e]	133	98	73.7	146	131	89.7	0.001

7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine -hepatitis B virus vaccine -inactivated poliovirus vaccine solution combined with the lyophilyzed *Haemophilus influenzae* type b oligosaccharide conjugate vaccine component; N = number of subjects; n = number of subjects with the specified characteristic in a vaccine group.

a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.
b. N = number of subjects reporting "yes" for at least 1 day or "no" for all days.
c. n = number of subjects experiencing the event.
d. Fisher's exact test, 2-sided.
e. Includes fever ≥38°C, rash, irritability, drowsiness, decreased appetite, persistent inconsolable crying, and decreased activity.

Table 19. Subjects Reporting Systemic Events – Dose 3 Infant Series

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol			7vPnC Without Paracetamol			
Systemic Events	N[b]	n[c]	%	N[b]	n[c]	%	p-Value[d]
Fever ≥38°C but ≤39°C	109	21	19.3	114	52	45.6	0.000
Fever >39°C but ≤40°C	102	1	1.0	103	2	1.9	>0.99
Fever >40°C	102	0	0.0	101	0	0.0	>0.99
Rash	110	14	12.7	107	24	22.4	0.074
Irritability	121	48	39.7	118	59	50.0	0.120
Drowsiness	118	43	36.4	114	52	45.6	0.182
Decreased appetite	113	26	23.0	110	37	33.6	0.101
Persistent inconsolable crying	107	15	14.0	111	17	15.3	0.849
Decreased activity	116	27	23.3	115	46	40.0	0.007
Any systemic event[e]	130	88	67.7	132	110	83.3	0.004

7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine -hepatitis B virus vaccine -inactivated poliovirus vaccine solution combined with the lyophilyzed *Haemophilus influenzae* type b oligosaccharide conjugate vaccine component; N = number of subjects; n = number of subjects with the specified characteristic in a vaccine group.

a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.
b. N = number of subjects reporting "yes" for at least 1 day or "no" for all days.
c. n = number of subjects experiencing the event.
d. Fisher's exact test, 2-sided.
e. Includes fever ≥38°C, rash, irritability, drowsiness, decreased appetite, persistent inconsolable crying, and decreased activity.

Table 20. Subjects Reporting Systemic Events – Toddler Dose

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol			7vPnC Without Paracetamol			
Systemic Events	N[b]	n[c]	%	N[b]	n[c]	%	p-Value[d]
Fever ≥38°C but ≤39°C	103	53	51.5	115	69	60.0	0.221
Fever >39°C but ≤40°C	87	4	4.6	99	13	13.1	0.072
Fever >40°C	84	0	0.0	95	1	1.1	>0.99
Rash	90	12	13.3	106	25	23.6	0.098
Irritability	110	53	48.2	124	75	60.5	0.066
Drowsiness	108	47	43.5	117	59	50.4	0.350
Decreased appetite	102	39	38.2	115	52	45.2	0.336
Persistent inconsolable crying	90	7	7.8	105	18	17.1	0.056
Decreased activity	100	29	29.0	116	56	48.3	0.005
Any systemic event[e]	127	103	81.1	137	116	84.7	0.513

7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine -hepatitis B virus vaccine -inactivated poliovirus vaccine solution combined with the lyophilyzed *Haemophilus influenzae* type b oligosaccharide conjugate vaccine component; N = number of subjects; n = number of subjects with the specified characteristic in a vaccine group.

a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.
b. N = number of subjects reporting "yes" for at least 1 day or "no" for all days.
c. n = number of subjects experiencing the event.
d. Fisher's exact test, 2-sided.
e. Includes fever ≥38°C, rash, irritability, drowsiness, decreased appetite, persistent inconsolable crying, and decreased activity.

All-Causality AEs:

AEs occurring from the first vaccination at Visit 1 through Visit 4 and from the fourth vaccination at Visit 5 through Visit 6, including visits to hospital and Physicians, were recorded. These are presented in the tables after each dose in the infant series (Table 21, Table 22 and Table 23), and after the toddler dose (Table 24).

Table 21. Adverse Events – Dose 1 Infant Series

	Vaccine Group (as Adminstered)[a]						
	7vPnC With Paracetamol N=148			7vPnC Without Paracetamol N=152			
System Organ Class/Preferred Term	No. of Subjects[b]	%	No. of Events[c]	No. of Subjects[b]	%	No. of Events[c]	p-Value[d]
Any event	66	44.6	126	90	59.2	215	0.015
Congenital, familial and genetic disorders	0	0.0	0	1	0.7	1	>0.99
Dacryostenosis congenital	0	0.0	0	1	0.7	1	>0.99
Eye disorders	3	2.0	3	3	2.0	3	>0.99
Conjunctivitis	3	2.0	3	2	1.3	2	0.681
Lacrimation increased	0	0.0	0	1	0.7	1	>0.99
Gastrointestinal disorders	11	7.4	12	14	9.2	16	0.678
Diarrhoea	2	1.4	2	5	3.3	5	0.448
Flatulence	3	2.0	3	3	2.0	3	>0.99
Constipation	2	1.4	2	2	1.3	2	>0.99
Teething	1	0.7	1	2	1.3	2	>0.99
Abdominal distension	1	0.7	1	1	0.7	1	>0.99
Vomiting	1	0.7	1	1	0.7	1	>0.99
Abdominal pain upper	0	0.0	0	1	0.7	1	>0.99
Enteritis	0	0.0	0	1	0.7	1	>0.99
Gastrooesophageal reflux disease	1	0.7	1	0	0.0	0	0.493
Infantile colic	1	0.7	1	0	0.0	0	0.493
General disorders and administration site conditions	25	16.9	40	52	34.2	85	<0.001
Irritability	14	9.5	15	20	13.2	21	0.364
Pyrexia	4	2.7	5	29	19.1	30	<0.001
Injection site swelling	9	6.1	15	15	9.9	20	0.288
Injection site erythema	3	2.0	5	8	5.3	10	0.218
Injection site pain	0	0.0	0	3	2.0	3	0.248
Injection site induration	0	0.0	0	1	0.7	1	>0.99
Infections and infestations	26	17.6	29	31	20.4	41	0.559
Rhinitis	10	6.8	10	8	5.3	8	0.633

Table 21. Adverse Events – Dose 1 Infant Series

	Vaccine Group (as Adminstered)[a]						
	7vPnC With Paracetamol N=148			7vPnC Without Paracetamol N=152			
System Organ Class/Preferred Term	No. of Subjects[b]	%	No. of Events[c]	No. of Subjects[b]	%	No. of Events[c]	p-Value[d]
Upper respiratory tract infection	6	4.1	6	11	7.2	12	0.319
Oral candidiasis	4	2.7	4	4	2.6	4	>0.99
Bronchitis	3	2.0	3	4	2.6	4	>0.99
Nasopharyngitis	2	1.4	2	4	2.6	4	0.685
Gastrointestinal infection	1	0.7	1	2	1.3	2	>0.99
Candida nappy rash	1	0.7	1	1	0.7	1	>0.99
Otitis media	0	0.0	0	2	1.3	2	0.498
Conjunctivitis infective	1	0.7	1	0	0.0	0	0.493
Fungal skin infection	0	0.0	0	1	0.7	1	>0.99
Gastroenteritis	0	0.0	0	1	0.7	1	>0.99
Influenza	0	0.0	0	1	0.7	1	>0.99
Respiratory tract infection	0	0.0	0	1	0.7	1	>0.99
Urinary tract infection	1	0.7	1	0	0.0	0	0.493
Metabolism and nutrition disorders	11	7.4	12	16	10.5	16	0.421
Decreased appetite	10	6.8	10	16	10.5	16	0.306
Feeding disorder neonatal	1	0.7	1	0	0.0	0	0.493
Oral intake reduced	1	0.7	1	0	0.0	0	0.493
Musculoskeletal and connective tissue disorders	0	0.0	0	1	0.7	1	>0.99
Pain in extremity	0	0.0	0	1	0.7	1	>0.99
Nervous system disorders	7	4.7	7	18	11.8	18	0.035
Somnolence	7	4.7	7	18	11.8	18	0.035
Psychiatric disorders	9	6.1	11	18	11.8	21	0.106
Decreased activity	6	4.1	6	12	7.9	12	0.224
Crying	5	3.4	5	9	5.9	9	0.413
Respiratory, thoracic and mediastinal disorders	1	0.7	1	1	0.7	1	>0.99
Cough	1	0.7	1	1	0.7	1	>0.99

Table 21. Adverse Events – Dose 1 Infant Series

	Vaccine Group (as Adminstered)[a]						
	7vPnC With Paracetamol N=148			7vPnC Without Paracetamol N=152			
System Organ Class/Preferred Term	No. of Subjects[b]	%	No. of Events[c]	No. of Subjects[b]	%	No. of Events[c]	p-Value[d]
Skin and subcutaneous tissue disorders	11	7.4	11	11	7.2	12	>0.99
Rash	6	4.1	6	8	5.3	9	0.786
Dermatitis	0	0.0	0	1	0.7	1	>0.99
Dermatitis allergic	1	0.7	1	0	0.0	0	0.493
Dermatitis diaper	1	0.7	1	0	0.0	0	0.493
Dry skin	0	0.0	0	1	0.7	1	>0.99
Eczema	0	0.0	0	1	0.7	1	>0.99
Heat rash	1	0.7	1	0	0.0	0	0.493
Rash erythematous	1	0.7	1	0	0.0	0	0.493
Skin fissures	1	0.7	1	0	0.0	0	0.493

Non-serious adverse events and serious adverse events are not separated out.
7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine -hepatitis B virus vaccine - inactivated poliovirus vaccine solution combined with the lyophilyzed *Haemophilus influenzae* type b oligosaccharide conjugate vaccine component; No. = number; N = number of subjects.

a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.
b. Number of subjects reporting at least 1 event.
c. The total number of events. Multiple events may be reported by 1 subject.
d. Fisher's exact test, 2-sided.

Table 22. Adverse Events – Dose 2 Infant Series

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol N=145			7vPnC Without Paracetamol N=151			
System Organ Class/Preferred Term	No. of Subjects[b]	%	No. of Events[c]	No. of Subjects[b]	%	No. of Events[c]	p-Value[d]
Any event	82	56.6	175	95	62.9	217	0.287
Congenital, familial and genetic disorders	1	0.7	1	0	0.0	0	0.490
Hydrocele	1	0.7	1	0	0.0	0	0.490
Eye disorders	4	2.8	4	2	1.3	2	0.440
Conjunctivitis	4	2.8	4	2	1.3	2	0.440
Gastrointestinal disorders	11	7.6	11	13	8.6	15	0.833
Teething	3	2.1	3	3	2.0	3	>0.99
Flatulence	1	0.7	1	4	2.6	4	0.371
Constipation	2	1.4	2	2	1.3	2	>0.99
Diarrhoea	1	0.7	1	2	1.3	2	>0.99
Infantile colic	2	1.4	2	1	0.7	1	0.616
Aphthous stomatitis	0	0.0	0	2	1.3	2	0.499
Vomiting	2	1.4	2	0	0.0	0	0.239
Abdominal pain	0	0.0	0	1	0.7	1	>0.99
General disorders and administration site conditions	32	22.1	58	61	40.4	98	<0.001
Injection site swelling	18	12.4	25	21	13.9	32	0.734
Pyrexia	4	2.8	4	28	18.5	30	<0.001
Injection site erythema	14	9.7	17	13	8.6	15	0.841
Irritability	9	6.2	9	18	11.9	19	0.107
Injection site pain	1	0.7	2	1	0.7	1	>0.99
Injection site induration	0	0.0	0	1	0.7	1	>0.99
Injection site rash	1	0.7	1	0	0.0	0	0.490
Infections and infestations	44	30.3	57	34	22.5	41	0.147
Upper respiratory tract infection	20	13.8	21	13	8.6	13	0.196
Bronchitis	7	4.8	7	5	3.3	5	0.566
Rhinitis	7	4.8	7	5	3.3	5	0.566

Table 22. Adverse Events – Dose 2 Infant Series

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol N=145			7vPnC Without Paracetamol N=151			
System Organ Class/Preferred Term	No. of Subjects[b]	%	No. of Events[c]	No. of Subjects[b]	%	No. of Events[c]	p-Value[d]
Oral candidiasis	5	3.4	6	4	2.6	4	0.746
Nasopharyngitis	4	2.8	4	4	2.6	5	>0.99
Gastroenteritis	3	2.1	3	3	2.0	3	>0.99
Gastrointestinal infection	1	0.7	1	2	1.3	2	>0.99
Varicella	0	0.0	0	2	1.3	2	0.499
Candida nappy rash	1	0.7	1	0	0.0	0	0.490
Diarrhoea infectious	1	0.7	1	0	0.0	0	0.490
Exanthema subitum	1	0.7	1	0	0.0	0	0.490
Febrile infection	1	0.7	1	0	0.0	0	0.490
Fungal skin infection	1	0.7	1	0	0.0	0	0.490
Herpangina	1	0.7	1	0	0.0	0	0.490
Otitis media	1	0.7	1	0	0.0	0	0.490
Pharyngitis	0	0.0	0	1	0.7	1	>0.99
Tonsillitis	1	0.7	1	0	0.0	0	0.490
Viral infection	0	0.0	0	1	0.7	1	>0.99
Injury, poisoning and procedural complications	1	0.7	1	1	0.7	1	>0.99
Arthropod bite	0	0.0	0	1	0.7	1	>0.99
Joint dislocation	1	0.7	1	0	0.0	0	0.490
Metabolism and nutrition disorders	9	6.2	9	9	6.0	10	>0.99
Decreased appetite	9	6.2	9	9	6.0	10	>0.99
Nervous system disorders	11	7.6	11	11	7.3	11	>0.99
Somnolence	9	6.2	9	10	6.6	10	>0.99
Coordination abnormal	2	1.4	2	1	0.7	1	0.616
Psychiatric disorders	9	6.2	10	16	10.6	17	0.212
Decreased activity	5	3.4	5	8	5.3	8	0.573
Crying	5	3.4	5	5	3.3	5	>0.99
Restlessness	0	0.0	0	3	2.0	3	0.248

Table 22. Adverse Events – Dose 2 Infant Series

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol N=145			7vPnC Without Paracetamol N=151			
System Organ Class/Preferred Term	No. of Subjects[b]	%	No. of Events[c]	No. of Subjects[b]	%	No. of Events[c]	p-Value[d]
Sleep disorder	0	0.0	0	1	0.7	1	>0.99
Respiratory, thoracic and mediastinal disorders	1	0.7	1	1	0.7	1	>0.99
Bronchitis chronic	1	0.7	1	0	0.0	0	0.490
Cough	0	0.0	0	1	0.7	1	>0.99
Skin and subcutaneous tissue disorders	11	7.6	12	19	12.6	21	0.180
Rash	2	1.4	2	8	5.3	9	0.104
Dermatitis diaper	3	2.1	3	5	3.3	5	0.723
Eczema infantile	3	2.1	3	1	0.7	1	0.363
Eczema asteatotic	1	0.7	1	1	0.7	1	>0.99
Seborrhoeic dermatitis	0	0.0	0	2	1.3	2	0.499
Dermatitis	0	0.0	0	1	0.7	1	>0.99
Dermatitis atopic	1	0.7	1	0	0.0	0	0.490
Dermatitis exfoliative	1	0.7	1	0	0.0	0	0.490
Dermographism	1	0.7	1	0	0.0	0	0.490
Dry skin	0	0.0	0	1	0.7	1	>0.99
Hyperhidrosis	0	0.0	0	1	0.7	1	>0.99

Non-serious adverse events and serious adverse events are not separated out.
7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine -hepatitis B virus vaccine (HBV)-inactivated poliovirus vaccine (IPV) solution combined with the lyophilyzed *Haemophilus influenzae* type b (Hib) oligosaccharide conjugate vaccine component; No. = number; N = number of subjects.

a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.
b. Number of subjects reporting at least 1 event.
c. The total number of events. Multiple events may be reported by 1 subject.
d. Fisher's exact test, 2-sided.

Table 23. Adverse Events – Dose 3 Infant Series

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol N=145			7vPnC Without Paracetamol N=151			
System Organ Class/Preferred Term	No. of Subjects[b]	%	No. of Events[c]	No. of Subjects[b]	%	No. of Events[c]	p-Value[d]
Any event	94	64.8	200	99	65.6	251	0.903
Congenital, familial and genetic disorders	1	0.7	1	0	0.0	0	0.490
Phimosis	1	0.7	1	0	0.0	0	0.490
Eye disorders	6	4.1	6	5	3.3	5	0.766
Conjunctivitis	6	4.1	6	5	3.3	5	0.766
Gastrointestinal disorders	11	7.6	11	16	10.6	17	0.423
Teething	5	3.4	5	7	4.6	7	0.770
Constipation	2	1.4	2	3	2.0	3	>0.99
Diarrhoea	0	0.0	0	3	2.0	3	0.248
Dyspepsia	1	0.7	1	2	1.3	2	>0.99
Abdominal pain	0	0.0	0	1	0.7	1	>0.99
Colitis	0	0.0	0	1	0.7	1	>0.99
Enteritis	1	0.7	1	0	0.0	0	0.490
Flatulence	1	0.7	1	0	0.0	0	0.490
Vomiting	1	0.7	1	0	0.0	0	0.490
General disorders and administration site conditions	36	24.8	54	49	32.5	89	0.159
Injection site swelling	13	9.0	19	22	14.6	30	0.152
Pyrexia	14	9.7	15	18	11.9	20	0.578
Irritability	10	6.9	10	20	13.2	21	0.084
Injection site erythema	6	4.1	9	10	6.6	12	0.443
Injection site pain	0	0.0	0	3	2.0	5	0.248
Hyperpyrexia	1	0.7	1	0	0.0	0	0.490
Injection site rash	0	0.0	0	1	0.7	1	>0.99
Infections and infestations	54	37.2	72	52	34.4	76	0.630
Upper respiratory tract infection	20	13.8	20	25	16.6	26	0.522
Bronchitis	12	8.3	13	11	7.3	12	0.830

Table 23. Adverse Events – Dose 3 Infant Series

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol N=145			7vPnC Without Paracetamol N=151			
System Organ Class/Preferred Term	No. of Subjects[b]	%	No. of Events[c]	No. of Subjects[b]	%	No. of Events[c]	p-Value[d]
Rhinitis	8	5.5	8	11	7.3	11	0.638
Nasopharyngitis	5	3.4	6	6	4.0	7	>0.99
Otitis media	2	1.4	2	4	2.6	4	0.685
Febrile infection	3	2.1	3	2	1.3	2	0.679
Respiratory tract infection	4	2.8	4	1	0.7	1	0.206
Influenza	2	1.4	2	1	0.7	1	0.616
Oral candidiasis	1	0.7	1	2	1.3	2	>0.99
Varicella	2	1.4	2	1	0.7	1	0.616
Candida nappy rash	1	0.7	1	1	0.7	1	>0.99
Conjunctivitis infective	1	0.7	1	1	0.7	1	>0.99
Gastroenteritis	0	0.0	0	2	1.3	2	0.499
Paronychia	2	1.4	2	0	0.0	0	0.239
Abscess	1	0.7	1	0	0.0	0	0.490
Acute tonsillitis	0	0.0	0	1	0.7	1	>0.99
Candidiasis	0	0.0	0	1	0.7	1	>0.99
Ear infection	1	0.7	1	0	0.0	0	0.490
Exanthema subitum	1	0.7	1	0	0.0	0	0.490
Gastrointestinal infection	1	0.7	1	0	0.0	0	0.490
Impetigo	1	0.7	1	0	0.0	0	0.490
Laryngotracheitis	0	0.0	0	1	0.7	1	>0.99
Pharyngotonsillitis	0	0.0	0	1	0.7	1	>0.99
Pneumonia	0	0.0	0	1	0.7	1	>0.99
Rhinolaryngitis	1	0.7	1	0	0.0	0	0.490
Viral rash	1	0.7	1	0	0.0	0	0.490
Metabolism and nutrition disorders	11	7.6	11	10	6.6	10	0.823
Decreased appetite	9	6.2	9	10	6.6	10	>0.99
Anorexia	1	0.7	1	0	0.0	0	0.490
Weight gain poor	1	0.7	1	0	0.0	0	0.490
Nervous system disorders	8	5.5	9	9	6.0	9	>0.99

Table 23. Adverse Events – Dose 3 Infant Series

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol N=145			7vPnC Without Paracetamol N=151			
System Organ Class/Preferred Term	No. of Subjects[b]	%	No. of Events[c]	No. of Subjects[b]	%	No. of Events[c]	p-Value[d]
Somnolence	6	4.1	6	7	4.6	7	>0.99
Coordination abnormal	1	0.7	2	2	1.3	2	>0.99
Convulsion	1	0.7	1	0	0.0	0	0.490
Psychiatric disorders	12	8.3	13	11	7.3	12	0.830
Decreased activity	7	4.8	7	8	5.3	8	>0.99
Crying	4	2.8	4	3	2.0	3	0.718
Sleep disorder	2	1.4	2	1	0.7	1	0.616
Reproductive system and breast disorders	0	0.0	0	1	0.7	1	>0.99
Vulval disorder	0	0.0	0	1	0.7	1	>0.99
Respiratory, thoracic and mediastinal disorders	3	2.1	3	5	3.3	7	0.723
Cough	2	1.4	2	4	2.6	5	0.685
Obstructive airways disorder	1	0.7	1	0	0.0	0	0.490
Respiratory failure	0	0.0	0	1	0.7	2	>0.99
Skin and subcutaneous tissue disorders	17	11.7	20	22	14.6	25	0.496
Dermatitis diaper	3	2.1	3	10	6.6	10	0.086
Rash	5	3.4	5	8	5.3	8	0.573
Eczema	5	3.4	6	2	1.3	2	0.275
Eczema infantile	2	1.4	2	2	1.3	2	>0.99
Dermatitis atopic	0	0.0	0	2	1.3	2	0.499
Dermatitis	1	0.7	1	0	0.0	0	0.490
Drug eruption	1	0.7	1	0	0.0	0	0.490
Intertrigo	1	0.7	1	0	0.0	0	0.490
Neurodermatitis	1	0.7	1	0	0.0	0	0.490
Xeroderma	0	0.0	0	1	0.7	1	>0.99

Table 23. Adverse Events – Dose 3 Infant Series

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol N=145			7vPnC Without Paracetamol N=151			
System Organ Class/Preferred Term	No. of Subjects[b]	%	No. of Events[c]	No. of Subjects[b]	%	No. of Events[c]	p-Value[d]

Non-serious adverse events and serious adverse events are not separated out.

7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine -hepatitis B virus vaccine (HBV)-inactivated poliovirus vaccine solution combined with the lyophilyzed *Haemophilus influenzae* type b oligosaccharide conjugate vaccine component; No. = number; N = number of subjects.

a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.
b. Number of subjects reporting at least 1 event.
c. The total number of events. Multiple events may be reported by 1 subject.
d. Fisher's exact test, 2-sided.

Table 24. Adverse Events – Toddler Dose

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol N=139			7vPnC Without Paracetamol N=147			
System Organ Class/Preferred Term	No. of Subjects[b]	%	No. of Events[c]	No. of Subjects[b]	%	No. of Events[c]	p-Value[d]
Any event	83	59.7	187	102	69.4	265	0.107
Blood and lymphatic system disorders	0	0.0	0	1	0.7	1	>0.99
Iron deficiency anaemia	0	0.0	0	1	0.7	1	>0.99
Ear and labyrinth disorders	1	0.7	1	0	0.0	0	0.486
Middle ear effusion	1	0.7	1	0	0.0	0	0.486
Eye disorders	5	3.6	6	8	5.4	8	0.574
Conjunctivitis	5	3.6	6	8	5.4	8	0.574
Gastrointestinal disorders	6	4.3	7	6	4.1	6	>0.99
Vomiting	1	0.7	1	3	2.0	3	0.623
Constipation	0	0.0	0	2	1.4	2	0.499
Diarrhoea	2	1.4	2	0	0.0	0	0.235
Teething	2	1.4	2	0	0.0	0	0.235
Aphthous stomatitis	0	0.0	0	1	0.7	1	>0.99
Dyspepsia	1	0.7	1	0	0.0	0	0.486
Stomatitis	1	0.7	1	0	0.0	0	0.486
General disorders and administration site conditions	46	33.1	86	68	46.3	117	0.029
Pyrexia	24	17.3	29	38	25.9	41	0.086
Injection site swelling	23	16.5	33	23	15.6	32	0.873
Injection site erythema	10	7.2	13	19	12.9	24	0.120
Irritability	7	5.0	7	17	11.6	17	0.055
Injection site pain	3	2.2	4	2	1.4	3	0.677
Immune system disorders	2	1.4	2	2	1.4	2	>0.99
Food allergy	1	0.7	1	2	1.4	2	>0.99
Seasonal allergy	1	0.7	1	0	0.0	0	0.486

Table 24. Adverse Events – Toddler Dose

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol N=139			7vPnC Without Paracetamol N=147			
System Organ Class/Preferred Term	No. of Subjects[b]	%	No. of Events[c]	No. of Subjects[b]	%	No. of Events[c]	p-Value[d]
Infections and infestations	39	28.1	46	50	34.0	72	0.308
Upper respiratory tract infection	16	11.5	16	13	8.8	15	0.557
Gastroenteritis	6	4.3	6	9	6.1	9	0.600
Nasopharyngitis	3	2.2	3	6	4.1	6	0.502
Bronchitis	1	0.7	1	7	4.8	8	0.067
Otitis media	3	2.2	3	5	3.4	5	0.724
Exanthema subitum	2	1.4	2	3	2.0	3	>0.99
Oral candidiasis	1	0.7	1	4	2.7	4	0.372
Rhinitis	3	2.2	3	2	1.4	2	0.677
Ear infection	1	0.7	1	3	2.0	3	0.623
Febrile infection	3	2.2	3	1	0.7	1	0.359
Tonsillitis	1	0.7	1	2	1.4	2	>0.99
Viral infection	2	1.4	2	1	0.7	1	0.613
Acute tonsillitis	0	0.0	0	2	1.4	2	0.499
Bronchopneumonia	1	0.7	1	1	0.7	1	>0.99
Candidiasis	0	0.0	0	2	1.4	3	0.499
Gastroenteritis salmonella	1	0.7	1	0	0.0	0	0.486
Gastroenteritis viral	0	0.0	0	1	0.7	1	>0.99
Infectious mononucleosis	0	0.0	0	1	0.7	1	>0.99
Localised infection	0	0.0	0	1	0.7	1	>0.99
Myringitis	0	0.0	0	1	0.7	1	>0.99
Oral herpes	1	0.7	1	0	0.0	0	0.486
Pseudocroup	0	0.0	0	1	0.7	1	>0.99
Scarlet fever	0	0.0	0	1	0.7	1	>0.99
Staphylococcal infection	0	0.0	0	1	0.7	1	>0.99
Viral rash	1	0.7	1	0	0.0	0	0.486
Injury, poisoning and procedural complications	3	2.2	3	0	0.0	0	0.114
Contusion	1	0.7	1	0	0.0	0	0.486
Injury	1	0.7	1	0	0.0	0	0.486
Skin laceration	1	0.7	1	0	0.0	0	0.486

Table 24. Adverse Events – Toddler Dose

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol N=139			7vPnC Without Paracetamol N=147			
System Organ Class/Preferred Term	No. of Subjects[b]	%	No. of Events[c]	No. of Subjects[b]	%	No. of Events[c]	p-Value[d]
Metabolism and nutrition disorders	12	8.6	12	16	10.9	16	0.556
Decreased appetite	12	8.6	12	16	10.9	16	0.556
Nervous system disorders	7	5.0	7	7	4.8	7	>0.99
Somnolence	6	4.3	6	7	4.8	7	>0.99
Febrile convulsion	1	0.7	1	0	0.0	0	0.486
Psychiatric disorders	6	4.3	6	11	7.5	14	0.321
Decreased activity	4	2.9	4	9	6.1	9	0.258
Crying	1	0.7	1	4	2.7	4	0.372
Restlessness	1	0.7	1	1	0.7	1	>0.99
Reproductive system and breast disorders	0	0.0	0	1	0.7	1	>0.99
Balanitis	0	0.0	0	1	0.7	1	>0.99
Respiratory, thoracic and mediastinal disorders	0	0.0	0	2	1.4	2	0.499
Cough	0	0.0	0	2	1.4	2	0.499
Skin and subcutaneous tissue disorders	11	7.9	11	19	12.9	19	0.182
Rash	4	2.9	4	11	7.5	11	0.111
Dermatitis diaper	4	2.9	4	3	2.0	3	0.716
Eczema	0	0.0	0	3	2.0	3	0.248
Urticaria	2	1.4	2	0	0.0	0	0.235
Dermatitis atopic	0	0.0	0	1	0.7	1	>0.99
Dry skin	0	0.0	0	1	0.7	1	>0.99
Seborrhoeic dermatitis	1	0.7	1	0	0.0	0	0.486

Table 24. Adverse Events – Toddler Dose

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol N=139			7vPnC Without Paracetamol N=147			
System Organ Class/Preferred Term	No. of Subjects[b]	%	No. of Events[c]	No. of Subjects[b]	%	No. of Events[c]	p-Value[d]

Non-serious adverse events and serious adverse events are not separated out.
7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine -hepatitis B virus vaccine -inactivated poliovirus vaccine solution combined with the lyophilyzed *Haemophilus influenzae* type b (Hib) oligosaccharide conjugate vaccine component; No. = number; N = number of subjects.

a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.
b. Number of subjects reporting at least 1 event.
c. The total number of events. Multiple events may be reported by 1 subject.
d. Fisher's exact test, 2-sided.

All-Causality SAEs:

Seventeen (17) SAEs that occurred in 10 subjects during this study are listed in Table 25.

Table 25. Serious Adverse Events

Serial Number	Event Description	Vaccine Administered[Error! Reference source not found.Error! Reference source not found.]	Dose	Days Since Last Dose	Duration(Days)	Severity[Error! Reference source not found.Error! Reference source not found.]	Relationship[c]
1.	Acute obstructive bronchitis	7vPnC with paracetamol	4	4	172	SE	PN
2.	Inconsolable crying	7vPnC with paracetamol	1	17	2	SE	NO
	Refusal of food		1	17	2	MI	NO
	Upper airways infection		1	17	2	MI	NO
3.	Unspecified seizure	7vPnC with paracetamol	3	6	5	SE	PN
4.	Bronchopneumonia	7vPnC without paracetamol	4	6	5	MO	PN
5.	Febrile convulsion	7vPnC with paracetamol	4	24	5	SE	NO
6.	Bronchitis	7vPnC without paracetamol	3	31	16	SE	NO
	Pneumonia		3	35	11	MO	PN
	Acute obstructive bronchitis		3	25	7	MO	NO
	Respiratory failure		3	31	16	SE	NO
	Respiratory infection		3	25	7	MO	NO
	Respiratory insufficiency		3	25	7	MO	NO
7.	Severe febrile upper airways tract infection	7vPnC without paracetamol	4	15	7	SE	NO
8.	Bronchitis	7vPnC with paracetamol	1	10	2	MO	NO
9.	Salmonella gastroenteritis	7vPnC with paracetamol	4	11	3	MO	NO
10.	Gastroesophageal reflux	7vPnC with paracetamol	1	23	3	MI	NO

7vPnC = 7-valent pneumococcal conjugate vaccine.

a. All previous treatments.

b. Mild (MI), moderate (MO), severe (SE), or life-threatening (LT) as assessed by the Investigator.

c. Based on Investigator assessment: NO = not related, PN = probably not related, PO = possibly related, PR = probably related, or DE = definitely related.

Related AEs:

AEs that were possibly, probably, or definitely related to study treatment after each dose are shown in Table 26, Table 27 and Table 28 for the infant series of vaccinations and Table 29 for the toddler dose.

Table 26. Adverse Events Possibly, Probably, or Definitely Related to Study Treatment – Dose 1 Infant Series

	Vaccine Group (as Aministered)[a]						
	7vPnC With Paracetamol N=148			7vPnC Without Paracetamol N=152			
System Organ Class/Preferred Term	No. of Subjects[b]	%	No. of Events[c]	No. of Subjects[b]	%	No. of Events[c]	p-Value[d]
Any event	31	20.9	56	59	38.8	128	<0.001
Gastrointestinal disorders	2	1.4	2	1	0.7	1	0.619
Diarrhoea	1	0.7	1	0	0.0	0	0.493
Flatulence	0	0.0	0	1	0.7	1	>0.99
Vomiting	1	0.7	1	0	0.0	0	0.493
General disorders and administration site conditions	22	14.9	34	48	31.6	78	<0.001
Irritability	12	8.1	12	17	11.2	18	0.436
Pyrexia	2	1.4	2	26	17.1	26	<0.001
Injection site swelling	9	6.1	15	15	9.9	20	0.288
Injection site erythema	3	2.0	5	8	5.3	10	0.218
Injection site pain	0	0.0	0	3	2.0	3	0.248
Injection site induration	0	0.0	0	1	0.7	1	>0.99
Metabolism and nutrition disorders	6	4.1	6	12	7.9	12	0.224
Decreased appetite	6	4.1	6	12	7.9	12	0.224
Musculoskeletal and connective tissue disorders	0	0.0	0	1	0.7	1	>0.99
Pain in extremity	0	0.0	0	1	0.7	1	>0.99
Nervous system disorders	6	4.1	6	15	9.9	15	0.069
Somnolence	6	4.1	6	15	9.9	15	0.069
Psychiatric disorders	6	4.1	7	15	9.9	17	0.069
Decreased activity	5	3.4	5	10	6.6	10	0.290
Crying	2	1.4	2	7	4.6	7	0.173
Skin and subcutaneous tissue disorders	1	0.7	1	4	2.6	4	0.371
Rash	1	0.7	1	4	2.6	4	0.371

Table 26. Adverse Events Possibly, Probably, or Definitely Related to Study Treatment – Dose 1 Infant Series

	Vaccine Group (as Aministered)[a]						
	7vPnC With Paracetamol N=148			7vPnC Without Paracetamol N=152			
System Organ Class/Preferred Term	No. of Subjects[b]	%	No. of Events[c]	No. of Subjects[b]	%	No. of Events[c]	p-Value[d]

7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine -hepatitis B virus vaccine - inactivated poliovirus vaccine solution combined with the lyophilyzed *Haemophilus influenzae* type b oligosaccharide conjugate vaccine component; No. = number; N = number of subjects.

a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.
b. Number of subjects reporting at least 1 event.
c. The total number of events. Multiple events may be reported by 1 subject.
d. Fisher's exact test, 2-sided.

Table 27. Adverse Events Possibly, Probably, or Definitely Related to Study Treatment – Dose 2 Infant Series

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol N=145			7vPnC Without Paracetamol N=151			
System Organ Class/Preferred Term	No. of Subjects[b]	%	No. of Events[c]	No. of Subjects[b]	%	No. of Events[c]	p-Value[d]
Any event	37	25.5	77	57	37.7	110	0.025
General disorders and administration site conditions	28	19.3	53	51	33.8	85	0.006
Injection site swelling	18	12.4	25	21	13.9	32	0.734
Injection site erythema	14	9.7	17	13	8.6	15	0.841
Irritability	8	5.5	8	14	9.3	14	0.270
Pyrexia	0	0.0	0	21	13.9	22	<0.001
Injection site pain	1	0.7	2	1	0.7	1	>0.99
Injection site induration	0	0.0	0	1	0.7	1	>0.99
Injection site rash	1	0.7	1	0	0.0	0	0.490
Metabolism and nutrition disorders	7	4.8	7	7	4.6	7	>0.99
Decreased appetite	7	4.8	7	7	4.6	7	>0.99
Nervous system disorders	7	4.8	7	6	4.0	6	0.782
Somnolence	7	4.8	7	6	4.0	6	0.782
Psychiatric disorders	8	5.5	8	9	6.0	10	>0.99
Decreased activity	4	2.8	4	5	3.3	5	>0.99
Crying	4	2.8	4	4	2.6	4	>0.99
Restlessness	0	0.0	0	1	0.7	1	>0.99
Skin and subcutaneous tissue disorders	2	1.4	2	1	0.7	2	0.616
Rash	1	0.7	1	1	0.7	2	>0.99
Dermatitis exfoliative	1	0.7	1	0	0.0	0	0.490

7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine -hepatitis B virus vaccine -inactivated poliovirus vaccine solution combined with the lyophilyzed *Haemophilus influenzae* type b oligosaccharide conjugate vaccine component; No. = number; N = number of subjects.

Table 27. Adverse Events Possibly, Probably, or Definitely Related to Study Treatment – Dose 2 Infant Series

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol N=145			7vPnC Without Paracetamol N=151			
System Organ Class/Preferred Term	No. of Subjects[b]	%	No. of Events[c]	No. of Subjects[b]	%	No. of Events[c]	p-Value[d]

a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.
b. Number of subjects reporting at least 1 event.
c. The total number of events. Multiple events may be reported by 1 subject.
d. Fisher's exact test, 2-sided.

Table 28. Adverse Events Possibly, Probably, or Definitely Related to Study Treatment – Dose 3 Infant Series

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol N=145			7vPnC Without Paracetamol N=151			
System Organ Class/Preferred Term	No. of Subjects[b]	%	No. of Events[c]	No. of Subjects[b]	%	No. of Events[c]	p-Value[d]
Any event	36	24.8	69	48	31.8	108	0.199
Gastrointestinal disorders	1	0.7	1	2	1.3	3	>0.99
Abdominal pain	0	0.0	0	1	0.7	1	>0.99
Constipation	0	0.0	0	1	0.7	1	>0.99
Diarrhoea	0	0.0	0	1	0.7	1	>0.99
Teething	1	0.7	1	0	0.0	0	0.490
General disorders and administration site conditions	29	20.0	45	40	26.5	77	0.216
Injection site swelling	13	9.0	19	22	14.6	30	0.152
Pyrexia	9	6.2	9	15	9.9	16	0.289
Irritability	8	5.5	8	13	8.6	13	0.368
Injection site erythema	6	4.1	9	10	6.6	12	0.443
Injection site pain	0	0.0	0	3	2.0	5	0.248
Injection site rash	0	0.0	0	1	0.7	1	>0.99
Metabolism and nutrition disorders	6	4.1	6	8	5.3	8	0.786
Decreased appetite	6	4.1	6	8	5.3	8	0.786
Nervous system disorders	6	4.1	6	6	4.0	6	>0.99
Somnolence	6	4.1	6	6	4.0	6	>0.99
Psychiatric disorders	7	4.8	8	8	5.3	9	>0.99
Decreased activity	6	4.1	6	6	4.0	6	>0.99
Crying	2	1.4	2	2	1.3	2	>0.99
Sleep disorder	0	0.0	0	1	0.7	1	>0.99
Respiratory, thoracic and mediastinal disorders	0	0.0	0	1	0.7	1	>0.99
Cough	0	0.0	0	1	0.7	1	>0.99
Skin and subcutaneous tissue disorders	3	2.1	3	4	2.6	4	>0.99

Table 28. Adverse Events Possibly, Probably, or Definitely Related to Study Treatment – Dose 3 Infant Series

Rash	3	2.1	3	4	2.6	4	>0.99

7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine -hepatitis B virus vaccine - inactivated poliovirus vaccine solution combined with the lyophilyzed *Haemophilus influenzae* type b oligosaccharide conjugate vaccine component; No. = number; N = number of subjects.

a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.
b. Number of subjects reporting at least 1 event.
c. The total number of events. Multiple events may be reported by 1 subject.
d. Fisher's exact test, 2-sided.

Table 29. Adverse Events Possibly, Probably, or Definitely Related to Study Treatment – Toddler Dose

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol N=139			7vPnC Without Paracetamol N=147			
System Organ Class/Preferred Term	No. of Subjects[b]	%	No. of Events[c]	No. of Subjects[b]	%	No. of Events[c]	p-Value[d]
Any event	48	34.5	99	65	44.2	136	0.116
Gastrointestinal disorders	1	0.7	1	1	0.7	1	>0.99
Diarrhoea	1	0.7	1	0	0.0	0	0.486
Vomiting	0	0.0	0	1	0.7	1	>0.99
General disorders and administration site conditions	38	27.3	75	58	39.5	102	0.034
Injection site swelling	23	16.5	33	23	15.6	32	0.873
Pyrexia	16	11.5	19	27	18.4	27	0.136
Injection site erythema	10	7.2	13	19	12.9	24	0.120
Irritability	6	4.3	6	16	10.9	16	0.046
Injection site pain	3	2.2	4	2	1.4	3	0.677
Infections and infestations	1	0.7	1	1	0.7	1	>0.99
Bronchitis	0	0.0	0	1	0.7	1	>0.99
Gastroenteritis	1	0.7	1	0	0.0	0	0.486
Metabolism and nutrition disorders	11	7.9	11	9	6.1	9	0.645
Decreased appetite	11	7.9	11	9	6.1	9	0.645
Nervous system disorders	6	4.3	6	4	2.7	4	0.532
Somnolence	6	4.3	6	4	2.7	4	0.532
Psychiatric disorders	3	2.2	3	9	6.1	12	0.139
Decreased activity	3	2.2	3	7	4.8	7	0.337
Crying	0	0.0	0	4	2.7	4	0.123
Restlessness	0	0.0	0	1	0.7	1	>0.99
Skin and subcutaneous tissue disorders	2	1.4	2	7	4.8	7	0.174
Rash	2	1.4	2	7	4.8	7	0.174

Table 29. Adverse Events Possibly, Probably, or Definitely Related to Study Treatment – Toddler Dose

	Vaccine Group (as Administered)[a]						
	7vPnC With Paracetamol N=139			7vPnC Without Paracetamol N=147			
System Organ Class/Preferred Term	No. of Subjects[b]	%	No. of Events[c]	No. of Subjects[b]	%	No. of Events[c]	p-Value[d]

7vPnC = 7-valent pneumococcal conjugate vaccine; DTPa-HBV-IPV+Hib = routine diphtheria, tetanus, and acellular pertussis vaccine -hepatitis B virus vaccine - inactivated poliovirus vaccine solution combined with the lyophilyzed *Haemophilus influenzae* type b oligosaccharide conjugate vaccine component; No. = number; N = number of subjects.

a. All subjects were to receive DTPa-HBV-IPV+Hib concomitantly with 7vPnC.
b. Number of subjects reporting at least 1 event.
c. The total number of events. Multiple events may be reported by 1 subject.
d. Fisher's exact test, 2-sided.

Related SAEs:

Of the SAEs reported, none were considered related to the administration of study vaccine and medication. All were of types that are seen in infants of this age.

Safety-Related Subject Withdrawals:

No subject was withdrawn from the study for safety-related reasons.

Deaths:

No deaths were reported in the study.

CONCLUSIONS:

This randomized, controlled, open-label, Phase 4, multicenter study was conducted to determine whether paracetamol administered prophylactically after vaccination with 7vPnC and DTPa-HBV-IPV+Hib was able to reduce the rate of febrile reactions compared with control subjects receiving the same vaccinations with no paracetamol. The study also assessed safety and tolerability in the 2 treatment groups. The ITT population was the primary analysis population.

The efficacy results for the ITT population indicated that paracetamol given as prophylaxis after each dose of 7vPnC and concomitant DTPa-HBV-IPV+Hib in the infant series was 43% efficacious in preventing fever ≥ 38ºC (95% CI: 17.4, 61.2). This result was statistically significant. After the toddler dose, however, paracetamol prevented fever ≥ 38ºC by 15.9%, and statistical significance was not demonstrated (95% CI: -19.9, 41.3).

Efficacy of paracetamol in preventing fever >39ºC after each dose in the infant series could not be determined because too few subjects in the control group had fever >39ºC. After the toddler dose more subjects experienced fever in both groups and the estimate of efficacy was 65.0%, though the CI was wide (95% CI: -13.3, 91.7).

Results in the PP efficacy population were similar to those observed in the ITT population for the prevention of fever ≥ 38ºC. Paracetamol was 52.3% efficacious in preventing fever after the infant series, a statistically significant result (95% CI: 26.3, 69.9). After the toddler dose, however, efficacy was 16.1% (95% CI: -23.1, 43.2).

Efficacy of paracetamol in preventing fever >39ºC in the PP population again could not be determined after Dose 1, Dose 2, or Dose 3 of the infant series because too few subjects experienced this degree of fever in the control group. After the toddler dose, however, paracetamol was 79.0% efficacious in preventing fever (95% CI: 3.9, 97.7), a statistically significant result.

The analyses of safety indicate that paracetamol given prophylactically after vaccination with 7vPnC and DTPa-HBV-IPV+Hib was well tolerated and presented no major safety concerns. The results also suggested a statistically significant reduction, or a trend toward a reduction, of local reactions and most systemic events in subjects receiving prophylactic paracetamol

relative to control subjects who did not receive paracetamol. After each dose of the infant series, the incidence of fever ≥38°C was significantly lower in the prophylaxis group. A significant reduction in the incidence of pyrexia after the first 2 doses, suggested that administration of prophylactic paracetamol also reduced the clinical presentation of fever.