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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Prevnar 13® / Prevenar 13® / 13-Valent pneumococcal conjugate vaccine

PROTOCOL NO.: 6115A1-3008 (B1851074)

PROTOCOL TITLE: A Phase 3, Randomized, Double-Blind Trial to Evaluate the Safety, Tolerability, and Immunogenicity of a 13-Valent Pneumococcal Conjugate Vaccine When Administered Concomitantly With Trivalent Inactivated Influenza Vaccine in Healthy Adults 65 Years of Age or Older Who Are Naive to 23-Valent Pneumococcal Polysaccharide Vaccine

Study Centers: A total of 39 centers took part in the study and enrolled subjects; 1 in Belgium, 21 in Germany, 15 in Hungary, and 2 in the Netherlands.

Study Initiation and Final Completion Dates: 12 October 2007 to 13 February 2008

Phase of Development: Phase 3

Study Objectives:

Primary Objectives:

- To demonstrate that the immune responses induced by trivalent inactivated influenza vaccine (TIV) when administered concomitantly with 13-valent pneumococcal conjugate vaccine (13vPnC) are noninferior to the immune responses induced by TIV alone as measured by the standard hemagglutination inhibition assays (HAIs) for the A/H1, A/H3, and B vaccine strains 1 month after vaccination with TIV.

- To demonstrate that the immune responses to the 13vPnC serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) induced by 13vPnC when administered concomitantly with TIV are noninferior to the immune responses induced by 13vPnC administered 1 month after TIV, as measured by serotype-specific immunoglobulin G (IgG) concentrations in a subset of subjects.

Safety Objective:

- To evaluate the acceptability of the safety profile of 13vPnC + TIV given concomitantly and 13vPnC given alone as measured by the incidence rates of local reactions, systemic events, and adverse events (AEs).

METHODS

Study Design: This was a phase 3, parallel-group, randomized, double-blind, multicenter trial to evaluate the safety, tolerability, and immunogenicity of 13vPnC when administered concomitantly with TIV (13vPnC + TIV) in healthy adults aged 65 years or older who were naive to 23-Valent Pneumococcal Polysaccharide Vaccine (23vPS). The study completed in approximately 5 months.

Subjects were randomized (1:1 ratio) to 2 treatment groups: Group 1 received 13vPnC + TIV followed 1 month later by placebo (ie, 13vPnC + TIV/placebo); Group 2 received placebo and TIV (placebo + TIV) administered concomitantly followed 1 month later by 13vPnC (ie, placebo + TIV/13vPnC). Duration of subjects participation in the study was approximately 2 months.

The study flow chart is presented in Table 1.

Table 1. Study Flowchart

Visit Identification Number	**1**	**2**	**3**
Visit Window	**Day 1**	**Days 29 to 43 After Visit 1**	**Days 29 to 43 After Visit 2**
Informed consent	X		
Review inclusion/exclusion criteria	X		
Demography	X		
Mini-mental state examination	X		
Medical history including tobacco usage	X		
Physical examination	X		
Obtain blood sample	X	X	X
Prevaccination body temperature (oral)	X	X	
Randomization	X		
Assess left arm movement before test article administration	X	X	
Administration of test articles	X	X	
Assess acute reactions (including pain at the injection site) for 30 minutes after vaccination	X	X	
Provide electronic-diary, thermometer, caliper, and appointment card	X	X	
Subjects collect electronic-diary reactogenicity (Days 1 to 14 after vaccination)[a]	X	X	
Electronic-diary review		X	X
Collect electronic-diary			X
Adverse event collection	x----------x----------x		
Serious adverse event reporting	x----------x----------x		

a. Subjects were requested to contact the study staff to arrange an additional visit if they experience redness or swelling >10 cm (21/21+ caliper units) or severe limitation of arm movement so the local reaction(s) would be assessed by the Investigator or medically qualified member of the study staff.

Number of Subjects (Planned and Analyzed): The planned number of subjects for this study was approximately 1100 (ie, 550 subjects in each vaccine group) at approximately 55 sites in Germany, the Netherlands, Belgium, and Hungary.

A total of 1185 subjects were screened/enrolled (381 in Netherlands, 55 in Belgium, 386 in Germany and 339 in Hungary), and 1160 subjects were randomized, 580 subjects in each Group 1 and Group 2.

Diagnosis and Main Criteria for Inclusion: Male and female healthy subjects, ≥65 years old and able to complete an electronic diary and follow study procedures in the opinion of the Investigator were included.

Excluded were subjects with previous vaccination with any pneumococcal vaccine, or TIV vaccination within 6 months before study vaccination.

Study Vaccine: Each subject received 1 dose of 13vPnC and 1 dose of TIV. TIV was administered only at Visit 1. Depending on treatment assignment, 13vPnC (or matching placebo) was given concomitantly with TIV at Visit 1 or given 1 month after administration of TIV.

The study vaccines were as follows:

13vPnC contains saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to nontoxic diphtheria cross-reactive material 197 (CRM_{197}). The vaccine was formulated to contain 2.2 μg of each saccharide, except for 4.4 μg of 6B, per 0.5-mL dose. The final vaccine was formulated at pH 5.8 with 5 mM succinate buffer, 0.85% sodium chloride, 0.02% polysorbate 80, and 0.125 mg aluminum as aluminum phosphate ($AlPO_4$), per 0.5-mL dose.

The 13vPnC placebo was formulated at pH 5.8 with 5 mM succinate buffer, 0.15 M sodium chloride, and 0.02% polysorbate 80, and contains 0.125 mg of aluminum phosphate per 0.5-mL dose. The vaccine was filled in containers that were identical to those containing 13vPnC.

TIV contains strains of influenza viruses that are antigenically equivalent to the annually recommended strains: 1 A/H1N1 virus, 1 A/H3N2 virus, and 1 B virus per 0.5-mL dose of vaccine.

All study vaccines were to be administered intramuscularly by a medically qualified member of the Investigator's staff.

Immunogenicity Endpoints:

- The primary endpoints for TIV comparisons were the proportion of subjects (ie, responders) who achieved at least a 4-fold increase in the titer of the HAI (ie, seroconvert) for each influenza virus subtype from Visit 1 to 1 month after TIV vaccination.

- The primary endpoints for the pneumococcal comparisons were the serotype-specific pneumococcal IgG antibody concentrations measured 1 month after 13vPnC vaccination in a subset of 605 subjects.

No efficacy evaluations were performed for this study.

Safety Evaluations: To evaluate the acceptability of the safety profile of 13vPnC + TIV given concomitantly and 13vPnC given alone as measured by the incidence rates of local reactions, systemic events, and AEs.

Statistical Methods: For immunogenicity analyses, 2 analysis populations were defined as follows: evaluable immunogenicity and all-available immunogenicity.

- The evaluable immunogenicity adhered to the protocol requirements included those subjects who had valid and determinate assay results, and had no other major protocol violations.
- The all-available immunogenicity population included all participants who had ≥1 valid and determinate assay result.
- The safety population included all subjects who received at least 1 dose of the study vaccine.

Immunogenicity analyses:

For the 3 influenza virus subtypes contained in TIV, exact, 2-sided 95% confidence intervals (CIs) based on the procedure of Chan and Zhang were computed on the difference in proportions of subjects achieving a 4-fold increase in HAI titers from prevaccination to 1 month postvaccination (13vPnC + TIV]-[Placebo + TIV]). Non-inferiority was declared if the lower bound of the 2-sided CI for the difference is greater than -0.10.

For the comparison of 13vPnC + TIV to 13vPnC, IgG concentrations for each vaccine group and serotype were logarithmically transformed for analysis, and geometric mean concentration (GMC) was computed. Corresponding 2-sided 95% CIs for the GMCs were constructed by back transformation of the CI for the mean of logarithmically transformed assay results, which were computed using the Student t-distribution. For the GMC ratio, the CI was computed by back transforming the CI for the mean difference of the measures on the natural log scale which used the Student t-distribution. Noninferiority was evaluated using the ratio of postvaccination GMCs (13vPnC + TIV: 13vPnC) and corresponding 2-sided 95% CIs, and was declared if the lower limit of the 2-sided 95% CI for the GMC ratio was >0.5.

Safety comparisons between groups were based on the 95% CI using Chan and Zhang methodology, with a difference noted between the 2 groups if the 95% CI for the difference excluded zero.

RESULTS

Subject Disposition and Demography: A total of 1185 subjects were consented and 1160 subjects were randomly assigned in a 1:1 ratio to either Group 1, 13vPnC + TIV/placebo number of subjects (N) (N=580), or Group 2, placebo + TIV/13vPnC (N=580). The subject disposition is presented in Table 2. The evaluable immunogenicity

population included 1096 participants (13vPnC + TIV/Placebo group N=549, and Placebo + TIV/13vPnC group N=547).

Table 2. Disposition of Subjects

	Vaccine Group (as Randomized)			
	Screened Only[a] N=30	13vPnC + TIV/Placebo N=580	Placebo + TIV/13vPnC N=580	Total N=1190
	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)
Consented[c]	29 (100.0)	578 (100.0)	578 (100.0)	1185 (100.0)
Randomized	0 (0.0)	580 (100.3)	580 (100.3)	1160 (97.9)
Not randomized	30 (103.4)	0 (0.0)	0 (0.0)	30 (2.5)
Vaccinated				
Dose 1	0 (0.0)	577 (99.8)	575 (99.5)	1152 (97.2)
Dose 2	0 (0.0)	560 (96.9)	558 (96.5)	1118 (94.3)
Completed	0 (0.0)	556 (96.2)	557 (96.4)	1113 (93.9)
Withdrawn	1 (3.4)	24 (4.2)	23 (4.0)	48 (4.1)
Reasons for withdrawal				
Subject request	1 (3.4)	12 (2.1)	11 (1.9)	24 (2.0)
Protocol violation	0 (0.0)	7 (1.2)	8 (1.4)	15 (1.3)
Other	0 (0.0)	2 (0.3)	2 (0.3)	4 (0.3)
Death	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.2)
Adverse event	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Failed to return	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Lost to follow-up	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)

Eight (8) subjects were reported as randomized but not vaccinated for the following reasons: 3 of these were duplicate randomization numbers; 2 subjects withdrew consent; 2 subjects did not meet eligibility criteria; and 1 subject was randomly assigned in error as consent was not provided.
13vPnC = 13-valent pneumococcal conjugate vaccine; N = number of subjects; TIV = trivalent inactivated influenza vaccine.

a. One subject withdrew consent, and was classified in the screened only category.
b. n = number of subjects in the specified category.
c. The values in this row are used as the denominators for percentages.

The demographics of evaluable immunogenicity population are presented in Table 3.

Table 3. Demographic Characteristics - Safety Population

	Vaccine Group (as Randomized)		
	13vPnC + TIV/Placebo N[a]=576	Placebo + TIV/13vPnC N[a]=575	Total N[a]=1151
	n[b] (%)	n[b] (%)	n[b] (%)
Sex			
Female	289 (50.2)	290 (50.4)	579 (50.3)
Male	287 (49.8)	285 (49.6)	572 (49.7)
Race			
White	570 (99.0)	571 (99.3)	1141 (99.1)
Asian	3 (0.5)	2 (0.3)	5 (0.4)
Other	2 (0.3)	1 (0.2)	3 (0.3)
Black or African American	1 (0.2)	1 (0.2)	2 (0.2)
Age at vaccination (years)			
Mean (SD)	72.1 (5.6)	72.1 (5.5)	72.1 (5.5)
Median	70.8	71.2	71.1
Min, max	65.1, 93.0	62.9, 93.1	62.9, 93.1

13vPnC = 13-valent pneumococcal conjugate vaccine; Max = maximum; Min = minimum; SD = standard deviation; TIV = trivalent inactivated influenza vaccine.

a. N = number of subjects in the specified group, or total sample.

b. n = number of subjects in the specified category.

The all-available and evaluable immunogenicity populations are presented in Table 4.

Table 4. All-Available and Evaluable Immunogenicity Populations

	Vaccine Group (as Randomized)					
	13vPnC + TIV/Placebo		Placebo + TIV/13vPnC		Total	
	n[a]	%	n[a]	%	n[a]	%
Randomized	580	100.0	580	100.0	1160	100.0
All-available immunogenicity population	569	98.1	569	98.1	1138	98.1
Subjects excluded from the all-available immunogenicity population	11	1.9	11	1.9	22	1.9
No predose or postdose assay result for any serotype/antibody	10	1.7	10	1.7	20	1.7
Blood draw before informed consent	1	0.2	1	0.2	2	0.2
Evaluable immunogenicity population	549	94.7	547	94.3	1096	94.5
Subjects excluded from the evaluable immunogenicity population[b]	31	5.3	33	5.7	64	5.5
Did not receive all pneumococcal study vaccinations	11	1.9	13	2.2	24	2.1
Not in all-available immunogenicity population	11	1.9	11	1.9	22	1.9
Other: Forced randomization	3	0.5	4	0.7	7	0.6
Not eligible for the study	2	0.3	3	0.5	5	0.4
Received prohibited vaccines	1	0.2	3	0.5	4	0.3
Postdose 1 sample <28 days after Dose 1	1	0.2	2	0.3	3	0.3
Received vaccine other than randomized	2	0.3	1	0.2	3	0.3
Other: (Per MM) Received previous pneumococcal vaccination	2	0.3	0	0.0	2	0.2
Age <65 years on day of first dose	0	0.0	1	0.2	1	0.1
Other: Subject unblinded	1	0.2	0	0.0	1	0.1
Postdose 1 sample >57 days after Dose 1	1	0.2	0	0.0	1	0.1

13vPnC = 13-valent pneumococcal conjugate vaccine; TIV = trivalent inactivated influenza vaccine.
a. n = number of subjects with specified characteristic.
b. Subjects may have been excluded for >1 reason.

Immunogenicity Results:

Immune Response to Trivalent Inactivated Influenza Vaccine: After Dose 1, the proportion of responders (ie, subjects achieving a ≥4-fold increase in HAI titer to 13vPnC + TIV or placebo + TIV was similar in Group 1 (13vPnC + TIV/Placebo) and in Group 2 (placebo + TIV/13vPnC), respectively. Noninferiority was met for A/H1N1, and B-strains but not for A/H3N2 with a lower limit of the 95% CI of -10.4% (criterion -10.0%) (Table 5).

Table 5. Comparison of Subjects Achieving a ≥4-Fold Increase in Titer for Concomitant Vaccine Antigens After Dose 1 - Evaluable Immunogenicity Population

Concomitant Vaccine	Vaccine Group (as Randomized)							
	13vPnC + TIV/Placebo			Placebo + TIV/13vPnC				
	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])	Difference[d]	(95% CI[e])
TIV: HAIs								
A/H1N1	548	440 (80.3)	(76.7, 83.5)	546	429 (78.6)	(74.9, 81.9)	1.7	(-3.1, 6.5)
A/H3N2	545	316 (58.0)	(53.7, 62.2)	545	341 (62.6)	(58.4, 66.6)	-4.6	(-10.4, 1.3)
B	548	286 (52.2)	(47.9, 56.4)	546	295 (54.0)	(49.7, 58.3)	-1.8	(-7.8, 4.1)

13vPnC = 13-valent pneumococcal conjugate vaccine; CI = confidence interval; HAIs = hemagglutination inhibition assay; TIV = trivalent inactivated influenza vaccine.

a. N = number of subjects with a determinate antibody titer for the given concomitant vaccine antigen.
b. n = number of subjects with an antibody titer that met the prespecified level.
c. Exact 2-sided CI based upon the observed proportion of subjects.
d. Difference in proportions, expressed as a percentage.
e. Exact 2-sided CI for the difference in proportions, 13vPnC + TIV/Placebo – Placebo + TIV/13vPnC, expressed as a percentage.

Immune Response to 13-Valent Pneumococcal Conjugate Vaccine: Comparisons of pneumococcal IgG GMCs measured 1 month after 13vPnC + TIV (Dose 1) relative to 1 month after 13vPnC alone (Dose 2) showed that the non-inferiority criterion was met for all serotypes except serotype 19F. The lower limit of the 95% CI of the geometric mean ratio for 19F was 0.49 (criterion 0.5). When 13vPnC was given concomitantly with TIV, the immune responses to 13vPnC were similar or significantly lower (upper limit of 95%CI <1) compared to when 13vPnC was given alone (Table 6).

Table 6. Comparison of Pneumococcal IgG GMCs (µg/mL) Postdose 1 for 13vPnC + TIV/Placebo and Postdose 2 for Placebo + TIV/13vPnC - Evaluable Immunogenicity Population

	Vaccine Group (As Randomized)					
	Postdose 1 13vPnC + TIV/Placebo		Postdose 2 Placebo + TIV/13vPnC		Vaccine Comparison	
Serotype	n[a]	GMC[b]	n[a]	GMC[b]	Ratio[c]	(95% CI[d])
1	276	2.52	270	3.20	0.79	(0.60, 1.04)
3	272	1.08	273	1.15	0.94	(0.78, 1.13)
4	279	2.15	278	3.24	0.66	(0.51, 0.87)
5	253	4.74	255	6.90	0.69	(0.55, 0.86)
6A	272	4.61	264	6.10	076	(0.61, 0.94)
6B	278	6.24	264	6.43	0.97	(0.75, 1.25)
7F	273	7.63	253	9.04	0.84	(0.67, 1.07)
9V	250	4.97	247	6.21	0.80	(0.63, 1.02)
14	272	8.95	277	12.44	0.72	(0.53, 0.97)
18C	247	8.88	261	11.07	0.80	(0.64, 1.01)
19A	266	11.93	255	17.10	0.70	(0.56, 0.87)
19F	277	4.78	276	7.39	0.65	(0.49, 0.85)
23F	277	5.82	265	6.11	0.95	(0.71, 1.27)

13vPnC = 13-valent pneumococcal conjugate vaccine; CI = confidence interval; GMC = geometric mean concentration; IgG = immunoglobulin G; TIV = trivalent inactivated influenza vaccine.

a. n = number of subjects with a determinate IgG antibody concentration to the given serotype.
b. GMCs were calculated using all subjects with available data for the specified blood draw.
c. Ratio of GMCs 13vPnC + TIV/Placebo to Placebo + TIV/13vPnC (geometric mean concentration ratios) was calculated by back transforming the mean difference between vaccine groups on the logarithmic scale.
d. CIs for the ratio are back transformations of a CI based on the Student t-distribution for the mean difference of the logarithms of the measures (13vPnC + TIV/Placebo – Placebo + TIV/13vPnC).

Immunogenicity results in the all-available immunogenicity populations are not presented, but were similar to results in the evaluable immunogenicity population.

Safety Results:

Local Reactions: The number and percentage of subjects with local reactions reported within 14 days after 13vPnC + TIV compared with 13vPnC alone, after Dose 1 in Group 1 (13vPnC + TIV/placebo) and after Dose 2 in Group 2 (placebo + TIV/13vPnC), respectively, are presented in Table 7. Frequencies of local reactions were similar after 13vPnC was administered with TIV compared to 13vPnC administered alone (with one exception: mild redness, which was significantly higher after 13vPnC + TIV).

Table 7. Comparison of Subjects Reporting Local Reactions Within 14 Days After Dose 1 for 13vPnC + TIV and After Dose 2 for TIV Followed by 13vPnC - Safety Population

	Vaccine Group (as Administered)					
	13vPnC + TIV/Placebo Dose 1		Placebo + TIV/13vPnC Dose 2			
Reaction	N[a]	n[b] (%)	N[a]	n[b] (%)	Difference[c]	(95% CI[d])
Redness[e]						
Any	440	73 (16.6)	432	53 (12.3)	4.3	(-0.4, 9.0)
Mild	438	63 (14.4)	432	42 (9.7)	4.7	(0.3, 9.1)
Moderate	433	26 (6.0)	424	26 (6.1)	-0.1	(-3.4, 3.1)
Severe	429	3 (0.7)	420	4 (1.0)	-0.3	(-1.8, 1.2)
Swelling[e]						
Any	441	61 (13.8)	431	44 (10.2)	3.6	(-0.7, 8.0)
Mild	440	52 (11.8)	430	35 (8.1)	3.7	(-0.3, 7.7)
Moderate	432	18 (4.2)	423	21 (5.0)	-0.8	(-3.7, 2.1)
Severe	428	1 (0.2)	420	0 (0.0)	0.2	(-0.7, 1.3)
Pain[f]						
Any	480	192 (40.0)	470	204 (43.4)	-3.4	(-9.7, 3.0)
Mild	470	161 (34.3)	462	175 (37.9)	-3.6	(-9.8, 2.6)
Moderate	447	66 (14.8)	442	87 (19.7)	-4.9	(-9.9, 0.1)
Severe	429	6 (1.4)	421	11 (2.6)	-1.2	(-3.4, 0.8)
Limitation of arm movement[g]						
Any	445	62 (13.9)	432	64 (14.8)	-0.9	(-5.6, 3.8)
Mild	444	58 (13.1)	432	58 (13.4)	-0.4	(-4.9, 4.2)
Moderate	430	6 (1.4)	420	4 (1.0)	0.4	(-1.2, 2.2)
Severe	429	8 (1.9)	420	6 (1.4)	0.4	(-1.4, 2.4)
Any local reaction[h]	488	229 (46.9)	470	219 (46.6)	0.3	(-6.0, 6.7)

13vPnC = 13-valent pneumococcal conjugate vaccine; CI = confidence interval; TIV = trivalent inactivated influenza vaccine.

a. N = number of subjects with known values.
b. n = number of subjects with the given characteristic.
c. Difference in proportions, expressed as a percentage.
d. Exact 2-sided CI for the difference in proportions, 13vPnC + TIV – Placebo + TIV/13vPnC, expressed as a percentage.
e. Mild = 2.5 to 5.0 cm, moderate = 5.1 to 10.0 cm, and severe is >10.0 cm.
f. Mild = awareness of symptoms but easily tolerated, moderate = discomfort enough to cause interference with usual activity, severe = incapacitating with inability to do usual activity.
g. Mild = some limitation, moderate = unable to move above head but able to move above shoulder, and severe = unable to move above shoulder.
h. Any local reaction = any pain, any swelling, any redness or any limitation of arm movement.

Systemic Events: The number and percentage of subjects with systemic events reported within 14 days after 13vPnC + TIV compared with 13vPnC alone after Dose 1 in Group 1 (13vPnC + TIV/placebo) and after Dose 2 in Group 2 (placebo + TIV/13vPnC), respectively, are presented in Table 8. Higher frequency of some solicited systemic reactions was observed when 13vPnC was administered concomitantly with TIV compared to 13vPnC given alone (fatigue, headache, chills, decreased appetite, new and aggravated joint pain).

Table 8. Comparison of Subjects Reporting Systemic Events Within 14 Days After Dose 1 for 13vPnC + TIV and After Dose 2 for TIV Followed by 13vPnC

	Vaccine Sequence (as Administered)					
	13vPnC + TIV/Placebo Dose 1		Placebo + TIV/13vPnC Dose 2			
Event	N[a]	n[b] (%)	N[a]	n[b] (%)	Difference[c]	(95% CI[d])
Fever ≥38°C but <38.5°C	434	13 (3.0)	423	13 (3.1)	-0.1	(-2.5, 2.3)
Fever ≥38.5°C but <39°C	430	6 (1.4)	421	4 (1.0)	0.4	(-1.2, 2.2)
Fever ≥39°C but ≤40.0°C	428	0 (0.0)	420	0 (0.0)	0.0	(-0.9, 0.9)
Fever >40.0°C	429	6 (1.4)	422	3 (0.7)	0.7	(-0.8, 2.4)
Fatigue	476	178 (37.4)	456	130 (28.5)	8.9	(2.8, 14.9)
Headache	472	154 (32.6)	449	111 (24.7)	7.9	(2.1, 13.8)
Chills	443	61 (13.8)	429	39 (9.1)	4.7	(0.4, 9.0)
Rash	433	30 (6.9)	427	29 (6.8)	0.1	(-3.3, 3.6)
Vomiting	432	13 (3.0)	424	7 (1.7)	1.4	(-0.7, 3.6)
Decreased appetite	450	76 (16.9)	434	49 (11.3)	5.6	(1.0, 10.2)
New muscle pain	468	126 (26.9)	448	105 (23.4)	3.5	(-2.2, 9.1)
Any aggravated muscle pain	454	85 (18.7)	439	66 (15.0)	3.7	(-1.2, 8.7)
New joint pain	452	73 (16.2)	435	50 (11.5)	4.7	(0.1, 9.2)
Any aggravated joint pain	452	71 (15.7)	428	37 (8.6)	7.1	(2.7, 11.4)
Any systemic event[e]	510	307 (60.2)	488	237 (48.6)	11.6	(5.4, 17.8)

13vPnC = 13-valent pneumococcal conjugate vaccine; CI = confidence interval; TIV = trivalent inactivated influenza vaccine.

a. N = number of subjects with known values.
b. n = number of subjects with the given characteristic.
c. Difference in proportions, expressed as a percentage.
d. Exact 2-sided CI for the difference in proportions, 13vPnC + TIV – Placebo + TIV/13vPnC, expressed as a percentage.
e. Any systemic event = any fever ≥38°C, any fatigue, any headache, any chills, any rash, any vomiting, any decreased appetite, any new or aggravated generalized muscle pain, and any new or aggravated joint pain.

The number and percentage of subjects with systemic events reported within 14 days after 13vPnC + TIV compared with placebo + TIV after Dose 1 in Group 1 (13vPnC + TIV/placebo) and in Group 2 (placebo + TIV/13vPnC), respectively, are presented in Table 9. Higher frequency of some solicited systemic reactions was observed when 13vPnC was administered concomitantly with TIV compared to TIV alone (chills, rash, new muscle pain).

Table 9. Comparison of Subjects Reporting Systemic Events Within 14 Days After Dose 1

	Vaccine Group (as Administered)					
	13vPnC + TIV/Placebo		Placebo + TIV/13vPnC			
Event	N[a]	n[b] (%)	N[a]	n[b] (%)	Difference[c]	(95% CI[d])
Fever ≥38°C but <38.5°C	434	13 (3.0)	434	8 (1.8)	1.2	(-1.0, 3.4)
Fever ≥38.5°C but <39°C	430	6 (1.4)	433	5 (1.2)	0.2	(-1.4, 2.0)
Fever ≥39°C but ≤40.0°C	428	0 (0.0)	431	1 (0.2)	-0.2	(-1.3, 0.6)
Fever >40.0°C	429	6 (1.4)	438	10 (2.3)	-0.9	(-2.9, 1.0)
Fatigue	476	178 (37.4)	483	154 (31.9)	5.5	(-0.5, 11.5)
Headache	472	154 (32.6)	468	139 (29.7)	2.9	(-3.0, 8.9)
Chills	443	61 (13.8)	440	40 (9.1)	4.7	(0.5, 8.9)
Rash	433	30 (6.9)	436	15 (3.4)	3.5	(0.4, 6.6)
Vomiting	432	13 (3.0)	437	15 (3.4)	-0.4	(-2.9, 2.0)
Decreased appetite	450	76 (16.9)	452	66 (14.6)	2.3	(-2.5, 7.1)
New muscle pain	468	126 (26.9)	456	76 (16.7)	10.3	(4.9, 15.6)
Any aggravated muscle pain	454	85 (18.7)	449	63 (14.0)	4.7	(-0.2, 9.6)
New joint pain	452	73 (16.2)	451	59 (13.1)	3.1	(-1.6, 7.7)
Any aggravated joint pain	452	71 (15.7)	447	58 (13.0)	2.7	(-1.9, 7.4)
Any systemic event[e]	510	307 (60.2)	505	256 (50.7)	9.5	(3.3, 15.6)

13vPnC = 13-valent pneumococcal conjugate vaccine; CI = confidence interval; TIV = trivalent inactivated influenza vaccine.

a. N = number of subjects with known values.
b. n = number of subjects with the given characteristic.
c. Difference in proportions, expressed as a percentage.
d. Exact 2-sided CI for the difference in proportions, 13vPnC + TIV/Placebo – Placebo + TIV/13vPnC, expressed as a percentage.
e. Any systemic event = any fever ≥38°C, any fatigue, any headache, any chills, any rash, any vomiting, any decreased appetite, any new or aggravated generalized muscle pain, and any new or aggravated joint pain.

Non-Serious Adverse Events:

The number and percentage of subjects experiencing non-serious AEs after 13vPnC + TIV compared with placebo + TIV, (after Dose 1) are presented in Table 10.

Table 10. Non-Serious Adverse Events Reported After Dose 1 – Safety Population

System Organ Class\ Preferred Term	Vaccine Group (as Administered)					
	13vPnC + TIV/Placebo N=576			Placebo + TIV/13vPnC N=575		
	No. of Subjects[a]	%	No. of Events[b]	No. of Subjects[a]	%	No. of Events[b]
Any event	72	12.5	82	69	12.0	79
Cardiac disorders	2	0.3	2	3	0.5	3
Arrhythmia	1	0.2	1	1	0.2	1
Angina pectoris	0	0.0	0	1	0.2	1
Atrial fibrillation	0	0.0	0	1	0.2	1
Cardiac failure	1	0.2	1	0	0.0	0
Eye disorders	3	0.5	3	1	0.2	1
Glaucoma	2	0.3	2	0	0.0	0
Cataract	0	0.0	0	1	0.2	1
Conjunctivitis	1	0.2	1	0	0.0	0
Gastrointestinal disorders	5	0.9	5	2	0.3	3
Diarrhoea	1	0.2	1	1	0.2	1
Rectal haemorrhage	2	0.3	2	0	0.0	0
Colitis	1	0.2	1	0	0.0	0
Nausea	1	0.2	1	0	0.0	0
Oral pain	0	0.0	0	1	0.2	1
Vomiting	0	0.0	0	1	0.2	1
General disorders and administration site conditions	5	0.9	7	3	0.5	3
Injection site haematoma	2	0.3	2	0	0.0	0
Injection site pain	2	0.3	2	0	0.0	0
Injection site erythema	1	0.2	1	0	0.0	0
Injection site pruritus	0	0.0	0	1	0.2	1
Injection site swelling	1	0.2	1	0	0.0	0
Malaise	0	0.0	0	1	0.2	1
Oedema peripheral	1	0.2	1	0	0.0	0
Sensation of foreign body	0	0.0	0	1	0.2	1
Infections and infestations	19	3.3	21	27	4.7	27
Upper respiratory tract infection	6	1.0	6	8	1.4	8
Nasopharyngitis	7	1.2	7	6	1.0	6
Localised infection	1	0.2	1	2	0.3	2
Cystitis	1	0.2	1	1	0.2	1
Pharyngitis	2	0.3	2	0	0.0	0
Respiratory tract infection	0	0.0	0	2	0.3	2
Bronchitis	0	0.0	0	1	0.2	1
Enterovirus infection	1	0.2	1	0	0.0	0
Eyelid infection	0	0.0	0	1	0.2	1
Gastroenteritis	1	0.2	1	0	0.0	0
Influenza	0	0.0	0	1	0.2	1
Oesophageal candidiasis	0	0.0	0	1	0.2	1
Oral herpes	0	0.0	0	1	0.2	1
Otitis externa	1	0.2	1	0	0.0	0
Tooth infection	0	0.0	0	1	0.2	1
Tracheobronchitis	1	0.2	1	0	0.0	0
Urinary tract infection	0	0.0	0	1	0.2	1
Viral infection	0	0.0	0	1	0.2	1

Table 10. Non-Serious Adverse Events Reported After Dose 1 – Safety Population

System Organ Class\ Preferred Term	Vaccine Group (as Administered)					
	13vPnC + TIV/Placebo N=576			Placebo + TIV/13vPnC N=575		
	No. of Subjects[a]	%	No. of Events[b]	No. of Subjects[a]	%	No. of Events[b]
Injury, poisoning and procedural complications	1	0.2	1	6	1.0	6
Contusion	0	0.0	0	1	0.2	1
Fall	0	0.0	0	1	0.2	1
Injury	0	0.0	0	1	0.2	1
Procedural pain	0	0.0	0	1	0.2	1
Tendon rupture	0	0.0	0	1	0.2	1
Traumatic haematoma	1	0.2	1	0	0.0	0
Wrist fracture	0	0.0	0	1	0.2	1
Investigations	0	0.0	0	1	0.2	1
Total lung capacity decreased	0	0.0	0	1	0.2	1
Metabolism and nutrition disorders	3	0.5	3	3	0.5	3
Hypercholesterolaemia	2	0.3	2	2	0.3	2
Diabetes mellitus	1	0.2	1	0	0.0	0
Gout	0	0.0	0	1	0.2	1
Musculoskeletal and connective tissue disorders	10	1.7	11	12	2.1	13
Pain in extremity	3	0.5	3	1	0.2	1
Arthralgia	2	0.3	2	1	0.2	2
Myalgia	2	0.3	3	1	0.2	1
Osteoarthritis	0	0.0	0	3	0.5	3
Bursitis	0	0.0	0	1	0.2	1
Groin pain	0	0.0	0	1	0.2	1
Joint swelling	0	0.0	0	1	0.2	1
Muscle spasms	0	0.0	0	1	0.2	1
Musculoskeletal pain	0	0.0	0	1	0.2	1
Osteitis	1	0.2	1	0	0.0	0
Spinal osteoarthritis	1	0.2	1	0	0.0	0
Tendonitis	1	0.2	1	0	0.0	0
Tenosynovitis	0	0.0	0	1	0.2	1
Nervous system disorders	4	0.7	4	3	0.5	3
Balance disorder	0	0.0	0	1	0.2	1
Cervicobrachial syndrome	1	0.2	1	0	0.0	0
Dizziness	0	0.0	0	1	0.2	1
Headache	1	0.2	1	0	0.0	0
Memory impairment	1	0.2	1	0	0.0	0
Restless legs syndrome	1	0.2	1	0	0.0	0
Transient ischaemic attack	0	0.0	0	1	0.2	1
Psychiatric disorders	1	0.2	1	1	0.2	1
Post-traumatic stress disorder	1	0.2	1	0	0.0	0
Sleep disorder	0	0.0	0	1	0.2	1
Renal and urinary disorders	1	0.2	1	1	0.2	1
Dysuria	1	0.2	1	0	0.0	0
Urinary incontinence	0	0.0	0	1	0.2	1
Reproductive system and breast disorders	2	0.3	2	0	0.0	0
Bartholin's cyst	1	0.2	1	0	0.0	0
Fibrocystic breast disease	1	0.2	1	0	0.0	0

Table 10. Non-Serious Adverse Events Reported After Dose 1 – Safety Population

System Organ Class\ Preferred Term	Vaccine Group (as Administered)					
	13vPnC + TIV/Placebo N=576			Placebo + TIV/13vPnC N=575		
	No. of Subjects[a]	%	No. of Events[b]	No. of Subjects[a]	%	No. of Events[b]
Respiratory, thoracic and mediastinal disorders	7	1.2	7	7	1.2	7
Cough	2	0.3	2	2	0.3	2
Chronic obstructive pulmonary disease	1	0.2	1	1	0.2	1
Epistaxis	2	0.3	2	0	0.0	0
Nasal congestion	1	0.2	1	1	0.2	1
Diaphragmatic hernia	0	0.0	0	1	0.2	1
Dyspnoea	0	0.0	0	1	0.2	1
Pleural effusion	1	0.2	1	0	0.0	0
Throat irritation	0	0.0	0	1	0.2	1
Skin and subcutaneous tissue disorders	6	1.0	6	4	0.7	4
Erythema	3	0.5	3	2	0.3	2
Pruritus	2	0.3	2	0	0.0	0
Dermatitis bullous	1	0.2	1	0	0.0	0
Drug eruption	0	0.0	0	1	0.2	1
Rash	0	0.0	0	1	0.2	1
Vascular disorders	8	1.4	8	3	0.5	3
Hypertension	8	1.4	8	2	0.3	2
Phlebitis	0	0.0	0	1	0.2	1

13vPnC = 13-valent pneumococcal conjugate vaccine; N = number of subjects; No. = number; TIV = trivalent inactivated influenza vaccine.

a. Number of subjects reporting at least 1 event of type specified. For "Any event", it represents the number of subjects reporting at least 1 event of any kind.

b. The total number of events of the type specified. Subjects were represented more than once. For "Any event", it represents the total number of events.

The number and percentage of subjects experiencing non-serious AEs after 13vPnC compared with placebo alone, (after Dose 2), are presented in Table 11.

Table 11. Non-Serious Adverse Events Reported After Dose 2 – Safety Population

System Organ Class\ Preferred Term	Vaccine Group (as Administered)					
	13vPnC + TIV/Placebo N=559			Placebo + TIV/13vPnC N=558		
	No. of Subjects[a]	%	No. of Events[b]	No. of Subjects[a]	%	No. of Events[b]
Any event	75	13.4	89	83	14.9	94
Cardiac disorders	4	0.7	4	1	0.2	1
Arrhythmia	1	0.2	1	0	0.0	0
Cardiac disorder	1	0.2	1	0	0.0	0
Myocardial ischaemia	0	0.0	0	1	0.2	1
Palpitations	1	0.2	1	0	0.0	0
Tachycardia	1	0.2	1	0	0.0	0
Ear and labyrinth disorders	1	0.2	1	1	0.2	1
Deafness unilateral	0	0.0	0	1	0.2	1
Vertigo	1	0.2	1	0	0.0	0
Eye disorders	2	0.4	2	0	0.0	0
Conjunctival haemorrhage	1	0.2	1	0	0.0	0
Glaucoma	1	0.2	1	0	0.0	0
Gastrointestinal disorders	4	0.7	4	2	0.4	2
Diarrhoea	1	0.2	1	1	0.2	1
Cheilitis	1	0.2	1	0	0.0	0
Constipation	1	0.2	1	0	0.0	0
Dyspepsia	1	0.2	1	0	0.0	0
Haemorrhoids	0	0.0	0	1	0.2	1
General disorders and administration site conditions	3	0.5	3	7	1.3	8
Pyrexia	1	0.2	1	3	0.5	3
Malaise	1	0.2	1	1	0.2	1
Fatigue	0	0.0	0	1	0.2	1
Influenza like illness	1	0.2	1	0	0.0	0
Injection site erythema	0	0.0	0	1	0.2	1
Injection site swelling	0	0.0	0	1	0.2	1
Oedema peripheral	0	0.0	0	1	0.2	1
Infections and infestations	34	6.1	36	43	7.7	47
Nasopharyngitis	10	1.8	10	8	1.4	9
Upper respiratory tract infection	4	0.7	4	9	1.6	9
Cystitis	2	0.4	2	5	0.9	5
Gastroenteritis	3	0.5	3	2	0.4	2
Respiratory tract infection	1	0.2	1	4	0.7	4
Bronchitis	1	0.2	1	3	0.5	3
Sinusitis	2	0.4	2	2	0.4	2
Viral infection	1	0.2	1	3	0.5	3
Pneumonia	1	0.2	1	2	0.4	2
Rhinitis	3	0.5	3	0	0.0	0
Herpes zoster	0	0.0	0	2	0.4	2
Localised infection	2	0.4	2	0	0.0	0
Otitis media	1	0.2	1	1	0.2	1
Urinary tract infection	1	0.2	1	1	0.2	1
Erysipelas	0	0.0	0	1	0.2	1
Fungal infection	0	0.0	0	1	0.2	1
Fungal skin infection	0	0.0	0	1	0.2	1
Gastroenteritis viral	1	0.2	1	0	0.0	0
Influenza	1	0.2	1	0	0.0	0

Table 11. Non-Serious Adverse Events Reported After Dose 2 – Safety Population

System Organ Class\ Preferred Term	Vaccine Group (as Administered)					
	13vPnC + TIV/Placebo N=559			Placebo + TIV/13vPnC N=558		
	No. of Subjects[a]	%	No. of Events[b]	No. of Subjects[a]	%	No. of Events[b]
Otitis externa	1	0.2	1	0	0.0	0
Tonsillitis	1	0.2	1	0	0.0	0
Viral upper respiratory tract infection	0	0.0	0	1	0.2	1
Injury, poisoning and procedural complications	6	1.1	8	8	1.4	8
Contusion	2	0.4	3	2	0.4	2
Concussion	1	0.2	1	0	0.0	0
Corneal abrasion	0	0.0	0	1	0.2	1
Fibula fracture	1	0.2	1	0	0.0	0
Joint dislocation	1	0.2	1	0	0.0	0
Post procedural haematoma	1	0.2	1	0	0.0	0
Procedural pain	0	0.0	0	1	0.2	1
Radius fracture	0	0.0	0	1	0.2	1
Rib fracture	0	0.0	0	1	0.2	1
Traumatic haematoma	0	0.0	0	1	0.2	1
Ulna fracture	1	0.2	1	0	0.0	0
Wrist fracture	0	0.0	0	1	0.2	1
Investigations	1	0.2	1	1	0.2	1
Cardiac murmur	0	0.0	0	1	0.2	1
Weight decreased	1	0.2	1	0	0.0	0
Metabolism and nutrition disorders	1	0.2	1	0	0.0	0
Hypercholesterolaemia	1	0.2	1	0	0.0	0
Musculoskeletal and connective tissue disorders	10	1.8	10	9	1.6	10
Arthralgia	3	0.5	3	3	0.5	3
Myalgia	1	0.2	1	2	0.4	2
Back pain	1	0.2	1	1	0.2	1
Neck pain	0	0.0	0	2	0.4	2
Osteoarthritis	1	0.2	1	1	0.2	1
Bursitis	1	0.2	1	0	0.0	0
Flank pain	1	0.2	1	0	0.0	0
Musculoskeletal pain	0	0.0	0	1	0.2	1
Myositis	1	0.2	1	0	0.0	0
Osteitis	1	0.2	1	0	0.0	0
Nervous system disorders	4	0.7	4	1	0.2	1
Dizziness	1	0.2	1	0	0.0	0
Headache	1	0.2	1	0	0.0	0
Hypoaesthesia	0	0.0	0	1	0.2	1
Sciatica	1	0.2	1	0	0.0	0
Vertebrobasilar insufficiency	1	0.2	1	0	0.0	0
Psychiatric disorders	1	0.2	1	0	0.0	0
Insomnia	1	0.2	1	0	0.0	0
Renal and urinary disorders	3	0.5	3	2	0.4	2
Haematuria	2	0.4	2	0	0.0	0
Nephrocalcinosis	0	0.0	0	1	0.2	1
Urge incontinence	1	0.2	1	0	0.0	0
Urinary incontinence	0	0.0	0	1	0.2	1

Table 11. Non-Serious Adverse Events Reported After Dose 2 – Safety Population

	Vaccine Group (as Administered)					
	13vPnC + TIV/Placebo N=559			Placebo + TIV/13vPnC N=558		
System Organ Class\ Preferred Term	No. of Subjects[a]	%	No. of Events[b]	No. of Subjects[a]	%	No. of Events[b]
Respiratory, thoracic and mediastinal disorders	6	1.1	6	5	0.9	5
Cough	2	0.4	2	2	0.4	2
Chronic obstructive pulmonary disease	1	0.2	1	2	0.4	2
Asthma	1	0.2	1	0	0.0	0
Dyspnoea	1	0.2	1	0	0.0	0
Dyspnoea exertional	0	0.0	0	1	0.2	1
Pharyngolaryngeal pain	1	0.2	1	0	0.0	0
Skin and subcutaneous tissue disorders	2	0.4	2	6	1.1	6
Eczema	1	0.2	1	3	0.5	3
Erythema	1	0.2	1	2	0.4	2
Rash	0	0.0	0	1	0.2	1
Social circumstances	0	0.0	0	1	0.2	1
Dental prosthesis user	0	0.0	0	1	0.2	1
Vascular disorders	3	0.5	3	1	0.2	1
Hypertension	3	0.5	3	0	0.0	0
Haematoma	0	0.0	0	1	0.2	1

13vPnC = 13-valent pneumococcal conjugate vaccine; N = number of subjects; No. = number; TIV = trivalent inactivated influenza vaccine.

a. Number of subjects reporting at least 1 event of type specified. For "Any event", it represents the number of subjects reporting at least 1 event of any kind.

b. The total number of events of the type specified. Subjects were represented more than once. For "Any event", it represents the total number of events.

Serious Adverse Events:

The number and percentage of subjects experiencing serious AEs (SAEs) after 13vPnC + TIV compared with placebo + TIV, (after Dose 1) are presented in Table 12.

Table 12. Serious Adverse Events Reported After Dose 1 - Safety Population

System Organ Class\ Preferred Term	Vaccine Group (as Administered)			
	13vPnC + TIV/Placebo N=576		Placebo + TIV/13vPnC N=575	
	n[a] (%)	No. of Events[b]	n[a] (%)	No. of Events[b]
Any event	4 (0.7)	7	0 (0.0)	0
Cardiac disorders	3 (0.5)	3	0 (0.0)	0
Angina pectoris	1 (0.2)	1	0 (0.0)	0
Cardiac failure	1 (0.2)	1	0 (0.0)	0
Myocardial infarction	1 (0.2)	1	0 (0.0)	0
Gastrointestinal disorders	1 (0.2)	1	0 (0.0)	0
Gastric ulcer	1 (0.2)	1	0 (0.0)	0
Infections and infestations	1 (0.2)	1	0 (0.0)	0
Pneumonia	1 (0.2)	1	0 (0.0)	0
Investigations	1 (0.2)	1	0 (0.0)	0
Endoscopy small intestine	1 (0.2)	1	0 (0.0)	0
Musculoskeletal and connective tissue disorders	1 (0.2)	1	0 (0.0)	0
Spinal column stenosis	1 (0.2)	1	0 (0.0)	0

13vPnC = 13-valent pneumococcal conjugate vaccine; N = number of subjects; No. = number; TIV = trivalent inactivated influenza vaccine.

a. Number of subjects reporting at least 1 event of type specified. For "Any event," it represents the number of subjects reporting at least 1 event of any kind.

b. The total number of events of the type specified. Subjects were represented more than once. For "Any event," it represents the total number of events.

The number and percentage of subjects experiencing SAEs after 13vPnC compared with after placebo, (after Dose 2) are presented in Table 13.

Table 13. Serious Adverse Events Reported After Dose 2 - Safety Population

System Organ Class\ Preferred Term	Vaccine Group (as Administered)			
	13vPnC + TIV/Placebo N=559		Placebo + TIV/13vPnC N=558	
	n[a] (%)	No. of Events[b]	n[a] (%)	No. of Events[b]
Any event	8 (1.4)	11	5 (0.9)	7
Cardiac disorders	3 (0.5)	4	1 (0.2)	1
Cardiac failure	2 (0.4)	2	1 (0.2)	1
Angina pectoris	1 (0.2)	1	0 (0.0)	0
Atrial fibrillation	1 (0.2)	1	0 (0.0)	0
Gastrointestinal disorders	0 (0.0)	0	1 (0.2)	3
Duodenal ulcer perforation	0 (0.0)	0	1 (0.2)	1
Gastrointestinal haemorrhage	0 (0.0)	0	1 (0.2)	1
Peritonitis	0 (0.0)	0	1 (0.2)	1
Hepatobiliary disorders	1 (0.2)	1	0 (0.0)	0
Cholecystitis	1 (0.2)	1	0 (0.0)	0
Infections and infestations	1 (0.2)	1	0 (0.0)	0
Pneumonia	1 (0.2)	1	0 (0.0)	0
Injury, poisoning and procedural complications	1 (0.2)	1	1 (0.2)	1
Femoral neck fracture	1 (0.2)	1	0 (0.0)	0
Sternal fracture	0 (0.0)	0	1 (0.2)	1
Investigations	1 (0.2)	1	0 (0.0)	0
Electrocardiogram ST segment elevation	1 (0.2)	1	0 (0.0)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.2)	1	2 (0.4)	2
Basal cell carcinoma	0 (0.0)	0	1 (0.2)	1
Bladder neoplasm	1 (0.2)	1	0 (0.0)	0
Malignant melanoma	0 (0.0)	0	1 (0.2)	1
Respiratory, thoracic and mediastinal disorders	1 (0.2)	1	0 (0.0)	0
Chronic obstructive pulmonary disease	1 (0.2)	1	0 (0.0)	0
Surgical and medical procedures	1 (0.2)	1	0 (0.0)	0
Cardiac pacemaker insertion	1 (0.2)	1	0 (0.0)	0

13vPnC = 13-valent pneumococcal conjugate vaccine; N = number of subjects; No. = number; TIV = trivalent inactivated influenza vaccine.

a. Number of subjects reporting at least 1 event of type specified. For "Any event," it represents the number of subjects reporting at least 1 event of any kind.

b. The total number of events of the type specified. Subjects were represented more than once. For "Any event," it represents the total number of events.

Related Adverse Events:

Related AEs are defined as AEs where there is a reasonable possibility that the AE is associated with the investigational product according to the assessment of the Investigator.

The related AEs after Dose 1 are presented in Table 14.

Table 14. Adverse Events Related to Study Vaccine Reported After Dose 1 - Safety Population

System Organ Class\ Preferred Term	Vaccine Group (as Administered)			
	13vPnC + TIV/Placebo N=576		Placebo + TIV/13vPnC N=575	
	n[a] (%)	No. of Events[b]	n[a] (%)	No. of Events[b]
Any event	10 (1.7)	13	1 (0.2)	1
General disorders and administration site conditions	4 (0.7)	6	1 (0.2)	1
Injection site haematoma	2 (0.3)	2	0 (0.0)	0
Injection site pain	2 (0.3)	2	0 (0.0)	0
Injection site erythema	1 (0.2)	1	0 (0.0)	0
Injection site pruritus	0 (0.0)	0	1 (0.2)	1
Injection site swelling	1 (0.2)	1	0 (0.0)	0
Musculoskeletal and connective tissue disorders	3 (0.5)	4	0 (0.0)	0
Pain in extremity	2 (0.3)	2	0 (0.0)	0
Myalgia	1 (0.2)	2	0 (0.0)	0
Skin and subcutaneous tissue disorders	3 (0.5)	3	0 (0.0)	0
Erythema	2 (0.3)	2	0 (0.0)	0
Dermatitis bullous	1 (0.2)	1	0 (0.0)	0

13vPnC = 13-valent pneumococcal conjugate vaccine; N = number of subjects; No. = number; TIV = trivalent inactivated influenza vaccine.

a. Number of subjects reporting at least 1 event of type specified. For "Any event," it represents the number of subjects reporting at least 1 event of any kind.

b. The total number of events of the type specified. Subjects were represented more than once. For "Any event," it represents the total number of events.

The related AEs after Dose 2 are presented in Table 15.

Table 15. Adverse Events Related to Study Vaccine Reported After Dose 2 - Safety Population

System Organ Class\ Preferred Term	Vaccine Group (as Administered)			
	13vPnC + TIV/Placebo N=559		Placebo + TIV/13vPnC N=558	
	n[a] (%)	No. of Events[b]	n[a] (%)	No. of Events[b]
Any event	5 (0.9)	5	6 (1.1)	8
Gastrointestinal disorders	1 (0.2)	1	0 (0.0)	0
Cheilitis	1 (0.2)	1	0 (0.0)	0
General disorders and administration site conditions	1 (0.2)	1	3 (0.5)	4
Pyrexia	1 (0.2)	1	2 (0.4)	2
Injection site erythema	0 (0.0)	0	1 (0.2)	1
Injection site swelling	0 (0.0)	0	1 (0.2)	1
Infections and infestations	0 (0.0)	0	2 (0.4)	2
Herpes zoster	0 (0.0)	0	1 (0.2)	1
Upper respiratory tract infection	0 (0.0)	0	1 (0.2)	1
Musculoskeletal and connective tissue disorders	1 (0.2)	1	1 (0.2)	1
Arthralgia	1 (0.2)	1	1 (0.2)	1
Respiratory, thoracic and mediastinal disorders	1 (0.2)	1	0 (0.0)	0
Cough	1 (0.2)	1	0 (0.0)	0
Skin and subcutaneous tissue disorders	1 (0.2)	1	1 (0.2)	1
Erythema	1 (0.2)	1	1 (0.2)	1

13vPnC = 13-valent pneumococcal conjugate vaccine; N = number of subjects; No. = number; TIV = trivalent inactivated influenza vaccine.

a. Number of subjects reporting at least 1 event of type specified. For "Any event," it represents the number of subjects reporting at least 1 event of any kind.

b. The total number of events of the type specified. Subjects were represented more than once. For "Any event," it represents the total number of events.

No SAEs were assessed as related to study vaccine in this study. One (1) SAE (angina pectoris accompanied by ST segment elevation) resulted in the subject's withdrawal from the study and was assessed as not related to study vaccine by the Investigator.

Deaths: Two (2) SAEs resulted in death, and both were assessed as not related to study vaccine by the Investigator. One (1) case of cardiac failure resulted in death on Day 3 after placebo (Dose 2). One (1) case of duodenal ulcer perforation complicated by gastrointestinal hemorrhage and peritonitis led to death on Day 29 after 13vPnC (Dose 2).

CONCLUSION: Overall assessment of the immunogenicity and safety data showed that 13vPnC may be administered concomitantly with seasonal TIV. When 13vPnC was given concomitantly with TIV, the immune responses to TIV were similar to the responses when TIV was given alone. When 13vPnC was given concomitantly with TIV, the immune responses to 13vPnC were lower compared to when 13vPnC was given alone. The clinical significance of this is unknown.