CVI Accepts, published online ahead of print on 10 December 2014
Clin. Vaccine Immunol. doi:10.1128/CVI.00711-14

Immunogenicity and Safety of 13-valent Pneumococcal Conjugate Vaccine in Adults ≥ 50 Years of Age in Mexico: An Open-Label Trial

Juan Carlos Tinoco,[a#] Christine Juergens,[b] Guillermo M. Ruiz Palacios,[c] Jorge Vazquez-Narvaez,[d] Hermann Leo Enkerlin-Pauwells,[e] Vani Sundaraiyer,[f] Sudam Pathirana,[g] Elena Kalinina,[g] William C. Gruber,[g] Daniel A. Scott,[g] Beate Schmoele-Thoma[b]

Hospital General de Durango, Durango, Mexico[a]; Pfizer Pharma GmbH, Berlin, Germany[b];Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico[c]; Star Medica, Michoacan, Mexico[d]; Mexico Centre for Clinical Research, Mexico City, Mexico[e]; inVentiv Health Clinical, LLC, Princeton, NJ, USA[f]; Pfizer Inc, Pearl River, NY, USA[g]

Running Head: Immunogenicity and Safety of PCV13 in Adults in Mexico

[#]Address correspondence to Juan Carlos Tinoco jctinoco@prodigy.net.mx

Abstract: Current count: 174 words; 250 words allowed

This open-label multicenter clinical trial conducted in Mexico assessed the immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine (PCV13) in adults aged ≥50 years not previously vaccinated with the 23-valent pneumococcal polysaccharide vaccine (PPSV23). PCV13 elicited a robust immune response in this study population, as reflected by the magnitude of fold rises in functional antibody levels measured by serotype-specific opsonophagocytic activity (OPA) assays before and one month after vaccination. Although prevaccination OPA GMTs for the majority of serotypes were significantly lower in the 50–64 years age group compared with the ≥65 years age group, post vaccination immune responses were generally similar. Overall immune responses were higher for the majority of serotypes in the Mexico study population than in similar adult study populations who received PCV13 in Europe and United States. PCV13 was well tolerated and there were no vaccine-related serious adverse events. In conclusion, PCV13 is safe and immunogenic when administered to adults aged ≥50 years in Mexico and has the potential to protect against vaccine-type pneumococcal disease. This trial was registered at www.ClinicalTrials.gov (NCT01432262).

Word Count: 3030

Introduction

Diseases caused by *Streptococcus pneumoniae* are a major worldwide public health problem affecting all age groups, with the highest mortality rates in elderly adults aged >65 years and in individuals with underlying disease [1,2]. In adults aged ≥50 years in Latin American countries, including Mexico, community acquired pneumonia (CAP) caused mainly by *S. pneumoniae* is associated with a high incidence of morbidity and mortality, with the incidence increasing substantially with age [3,4]. Worldwide, 20 serotypes account for more than 70% of invasive pneumococcal disease (IPD) in children <5 years of age, although the prevalence of each varies by region [5]. In Latin America and Caribbean countries, the 21 most common serotypes causing IPD in young children, in order of frequency, were serotypes 14, 6B, 5, 1, 23F, 6A, 18C, 19F, 19A, 9V, 7F, 3, and 4, included in the 13-valent pneumococcal conjugate vaccine (PCV13), and non-vaccine serotypes 8, 15B, 12F, 2, 12A, 9A, 45, and 46 [5]. Castañeda et al reported similar findings from SIREVA surveillance data from Latin America and the Caribbean from 2007–2009 in children <5 years of age; since the introduction of PCV7, serotype replacement with non-vaccine serotypes, especially 19A, has been observed [6]. The Mexico-specific SIREVA II data from 2011 in children aged <6 years and adults aged ≥50 years reported that the PCV13 serotypes were the most frequently isolated, in particular serotype 19A[7].

Vaccination is considered an important preventive strategy for adults and children, in part because of the increased prevalence of *S. pneumoniae* strains resistant to antibiotics [1]. In a study examining antimicrobial susceptibility patterns of *S. pneumoniae*, Quiñones–

Falconi and colleagues concluded that pneumococci isolated from children and adults with community-acquired acute respiratory infections in Mexico City have one of the world's highest rates of penicillin resistance. In addition, these penicillin-nonsusceptible strains were usually resistant to other antimicrobial agents commonly used to treat these infections [8].

A 23-valent pneumococcal polysaccharide vaccine (PPSV23) is widely available for the prevention of vaccine-type pneumococcal disease for adults aged ≥50 years and for high-risk younger adults; however, PPSV23 has not been widely implemented in Latin American countries [4]. PPSV23 is efficacious in preventing IPD, although reports on efficacy against CAP have been inconsistent and the duration of protection is limited [1,9,10]. Recently, a 13-valent PCV (PVC13) was licensed for adults in the Unites States, Europe, and many other countries including Mexico for the prevention of pneumococcal disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. Licensing was based on immunological and safety comparisons with PPSV23 in clinical studies performed in the United States and in several European countries as part of the PCV13 clinical development program [11]. The Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) 65 years of age and older was recently completed in the Netherlands with approximately 85,000 subjects, demonstrating that PCV13 is efficacious against vaccine-type CAP including non-bacteremic CAP and vaccine-type IPD [12,13].

In contrast to PPSV23, PCV13 is manufactured by conjugating the capsular saccharides of *S. pneumoniae* to an immunogenic protein carrier (cross-reacting material 197 [CRM_{197}], a nontoxic diphtheria toxin cross-reactive material) in order to elicit a T cell-

dependent immune response. As T cells provide the signals required for the generation of B cell memory [14], PCV13 has the potential to elicit a memory response on subsequent natural exposure to vaccine type pneumococcal strains and provide protection over a prolonged period of time [15].

The aim of the current study was to assess the immunogenicity and safety of PCV13 when administered to adults aged ≥50 years in Mexico who had not previously been vaccinated with PPSV23. In addition, the immunogenicity data from this study were compared post hoc with those of two other PCV13 studies that assessed similar populations of PPSV23-naïve adults [16-18]. These studies were part of the adult clinical development program for the licensing of PCV13 [11].

Materials and Methods

Trial design. This open-label study was conducted at 4 sites in Mexico from 29 July 2011 to 5 December 2011. Subjects were stratified into 2 age groups: 50–64 years and ≥65 years. The study was conducted in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice and the ethical principles that have their origins in the Declaration of Helsinki.

Study population. Eligible study participants included male and female subjects ≥50 years of age, including those with underlying diseases that were stable for ≥6 weeks before vaccination (ie, disease not requiring significant change in therapy or hospitalization for worsening disease 6 weeks before vaccination), and had: no history of *S. pneumoniae* infection within the past 5 years; no previous vaccination with any licensed or investigational pneumococcal vaccine; no history of severe vaccine-

106 associated adverse reactions or receipt of plasma products or immunoglobulins within 60
107 days before vaccination; and no immune deficiency or suppression, or severe chronic
108 disease associated with pulmonary, cardiac, or renal failure.

109 **Comparator study populations.** One of the comparator studies enrolled a PPSV23-
110 naive study population aged 50–64 years from the United States to compare the safety
111 and immunogenicity of PCV13 versus PPSV23 [18]. The other comparator study enrolled
112 a PPSV23-naive population aged ≥65 years from Europe to compare the safety and
113 immunogenicity of PCV13 administered concomitantly with trivalent inactivated
114 influenza vaccine versus PCV13 administered alone one month after trivalent inactivated
115 influenza vaccine [16,17]; data from the latter group were used for the comparison in this
116 manuscript. Inclusion and exclusion criteria for the study populations in the comparator
117 studies were similar to those described above.

118 **Vaccine and administration.** PCV13 contains capsular polysaccharides from
119 pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F (contains
120 2.2 μg of each saccharide, except for 4.4 μg of 6B) individually conjugated to nontoxic
121 diphtheria toxin cross-reactive material 197 (CRM_{197}), 5 mM succinate buffer,
122 0.85% sodium chloride, 0.02% polysorbate 80, and 0.125 mg aluminum as aluminum
123 phosphate per 0.5-mL dose. PCV13 was manufactured by Wyeth, a Pfizer Company (Lot
124 number 10-089561). The vaccine was supplied in single-dose syringes without
125 preservatives and stored at 2°C–8°C. All eligible participants received one dose of
126 PCV13 intramuscularly into the deltoid muscle.

Immunogenicity assessments. Two 15-mL blood samples were taken: one before and one approximately 1 month after vaccination. Functional activity of the antibodies was measured using serotype-specific validated microcolony opsonophagocytic activity (OPA) assays and expressed as OPA titres. OPA titers were defined as the interpolated reciprocal serum dilution that resulted in complement-mediated killing of 50% of the assay bacteria. OPA assay procedures were based on previously described methods [19]. Standardized OPA assays from this PCV13 study and the comparator studies were performed in the same central laboratory by the sponsor, thus allowing comparisons.

Safety assessments. Participants recorded local reactions and systemic events on an electronic (e)-diary every evening within a fixed time window for 14 days after vaccination. The e-diary prompted reporting of vaccine-associated signs and symptoms through a checklist, providing an accurate representation of each participant's experience. Severity was assessed using the US Food and Drug Administration's "Toxicity Grading Scale" [20]. The largest diameter of any redness or swelling was measured using a caliper. Oral temperature was measured using a digital thermometer, and fever was defined as a temperature of ≥38.0 °C (100.4 °F). The highest daily temperature was recorded. Diary data were transmitted by the participants to the central vendor and thereafter could not be altered. The data were reviewed by the investigator via an internet-based portal to monitor vaccine reactogenicity and compliance with e-diary completion.

Other adverse events (AEs), which were not prompted by the e-diary, were collected by the investigator on an electronic AE case report form at each visit in response to non-specific questions.

Statistical methods

Sample size estimation. Sample size estimation was based on pneumococcal OPA GMTs and associated variability observed in two previous Pfizer studies [21,22]. Assuming a dropout rate of no more than 7%, a sample size of 150 evaluable subjects in each age group was sufficient to provide adequate precision in the study results for descriptive assessment. Thus, 324 subjects (162 per group) were to be vaccinated.

Analysis populations. The evaluable immunogenicity population consisted of eligible subjects who adhered to the protocol requirements, received the study vaccine, had valid and determinate assay results, and had no major protocol violations. The all-available immunogenicity population included all subjects who had at least one valid and determinate assay result (data not presented). The safety population included all subjects who received the study vaccine.

Immunogenicity analysis. The endpoints for the study included measuring functional antibody OPA titers elicited by the 13 pneumococcal serotypes contained in PCV13 at two time points before vaccination and at 1 month (28 to 42 days) after vaccination. The serotype-specific OPA titers were logarithmically transformed for the analysis. The OPA GMTs were calculated at each time point. Two-sided 95% confidence intervals (CIs) were constructed by back transformation of the CIs based on the Student t distribution for the mean logarithm of the titers. For each serotype, geometric mean fold rises (GMFRs) from before to 1 month after vaccination were computed and 2-sided 95% CIs constructed using logarithmically transformed assay results.

Post hoc analyses included comparisons of GMT ratios between age groups within this study and across studies with study populations of comparable ages [16-18]. GMT ratios were calculated by back transforming the mean difference between the groups on the logarithmic scale. The 95% CIs for the ratios are back transformations of a CI based on the Student *t* distribution for the mean difference of the logarithms of the measures. For comparisons between vaccine groups, immune responses were statistically significantly lower when the upper limit of the 2-sided, 95% CI for the GMT ratio was <1 and were statistically significantly higher when the lower limit of the 2-sided, 95% CI for the GMT ratio was >1.

Safety analysis. AEs were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA). The proportion of subjects with local reactions, systemic events, and AEs were summarized with corresponding exact 2-sided 95% CI [23]. Difference in proportions of adults 50–64 years of age versus ≥65 years of age were expressed as a percentage with exact 2-sided CI and corresponding *P*-value [24].

Results

Disposition of subjects and baseline demographics. A total of 324 subjects were enrolled, with 162 subjects in each age group. In the ≥65 years group, 1 subject was withdrawn before vaccination. In the 50–64 years age group, 1 subject was excluded from the evaluable immunogenicity population because of an eligibility violation. The baseline demographic characteristics of the evaluable immunogenicity populations are shown in Table 1. Of note, in the 50–64 years age group (mean age, 55.8 years) and in

192 the ≥65 years age group (mean age, 73.4 years), there was a greater percentage of females
193 (59% and 52.2%, respectively).

194 **Immunogenicity.** For all serotypes in both age groups, OPA GMTs increased
195 significantly from immediately before to one month after vaccination, as reflected by the
196 GMFRs (lower limit of the 2-sided, 95% CI for the GMFRs >1). OPA GMFRs were
197 higher in the 50–64 years age group (GMFR range, 5.3–63.6) compared with the ≥65
198 years age group (GMFR range, 3.4–35.8; Table 2). Prevaccination OPA GMTs in the
199 50–64 year age group were statistically significantly lower (upper limit of the 2-sided,
200 95% CI for the GMT ratio <1) than those in the ≥65 year age group for 8 of 13 serotypes
201 and were similar to those in the ≥65 year age group for the 5 other serotypes (1, 4, 6B,
202 9V, and 14), whereas post vaccination OPA GMTs in the 50–64 year age group were
203 similar to those in the ≥65 year age group for 10 of 13 serotypes but statistically
204 significantly higher for serotypes 4, 7F and 9V (Table 3).

205 Post hoc analysis comparing adults 50–64 years of age from this Mexico study with same
206 aged adults from the United States comparator study showed prevaccination OPA GMTs
207 were statistically significantly higher in the Mexico study for 11 of 13 serotypes and
208 similar between studies for serotypes 1 and 3. Post vaccination OPA GMTs were
209 statistically significantly higher in the Mexico study for 8 of 13 serotypes, similar
210 between studies for serotypes 3, 5, and 6A, and statistically significantly lower in the
211 Mexico study for serotypes 1 and 3 (Table 4).

212 Similarly, a post hoc analysis comparing adults ≥65 years of age from this Mexico study
213 with same aged adults from the European comparator study showed prevaccination OPA

GMTs were statistically significantly higher in the Mexico study for the 12 of 13 serotypes and similar between studies for serotype 1. Post vaccination OPA GMTs were statistically significantly higher in the Mexico study for 10 of 13 serotypes and similar between studies for serotypes 1, 4, and 14 (Table 5).

Safety. In both age groups, the majority of local and systemic reactions occurred within 14 days after PCV13 administration and were mild or moderate in intensity. Pain at the injection site was the most common local reaction. Muscle and joint pain, fatigue, and headache were the most common systemic reactions. A significantly higher proportion of subjects in the 50–64 years age group compared with the ≥65 years group reported any local reaction (P=0.008) or any systemic reaction (P=0.003; Table 6). These differences were mainly driven by pain at the injection site (P=0.007) for local reactions and by headache (P=0.049), diarrhea (P=0.030), and muscle pain (P=0.006) for systemic reactions. The exception was fever ≥38°C, which was more frequent in the ≥65 years group (P=0.012). Of note, fever >40°C in 5 subjects aged ≥65 years was reported as data entry errors by the investigator. Other local (redness, swelling) and systemic reactions (fatigue, vomiting, joint pain) did not differ significantly between age groups. The mean durations of events were similar between the age groups and did not exceed 4.5 days for local events, 2.0 days for fever, and 6.6 days for other systemic events

The percentage of subjects reporting any AEs within approximately 1 month after vaccination was 11.1% in the 50–64 years age group and 6.2% in the ≥65 years age group; infections were the most common AE reported (5.6% and 1.9%, respectively). Serious adverse events (SAEs) were only reported in the ≥65 years group (2 subjects

[1.2%]: benign prostatic hyperplasia; gastric ulcer and gastritis). Both were considered to be unrelated to the study vaccine. No deaths were reported during the study. No subjects were withdrawn from the study for safety-related reasons.

Discussion

PCV13 elicited a robust immune response in adults aged ≥50 years in Mexico who had not been previously vaccinated with PPSV23, as reflected by the magnitude of the fold rises in functional antibody levels measured by OPA immediately before to one month after vaccination. Postvaccination OPA GMTs were generally similar between the 50–64 years age group and the ≥65 years age group for most serotypes. Of interest, although the OPA GMFRs were numerically higher in the 50–64 years age group, this was due to the lower prevaccination OPA GMTs in the 50–64 years age group. As discussed previously, numerically higher GMFRs do not always indicate a superior immune response [25]. Generally similar immune responses in the ≥65 years age group compared with the 50–64 years age group was unanticipated. Younger age groups generally have significantly higher immune responses than older age groups [26]

Immune responses elicited in this Mexico study were statistically significantly higher for most serotypes when compared with immune responses elicited by a similar study population aged 50–64 years in the United States (for serotypes 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) and aged ≥65 years in Europe (for serotypes 3, 5, 6A, 6B, 7F, 9V, 18C, 19A, 19F, and 23F) [16-18]. In the Mexico study, the baseline OPA GMTs for these serotypes were generally also significantly higher than baseline OPA GMTs observed in the two comparator studies [16-18]. High baseline pneumococcal GMTs of antibody may

be due to exposure to *S. pneumoniae* in the environment and may reflect the high burden of disease in Mexico [3]. Higher antibody responses after PCV13 in subjects in Mexico compared with those seen in other study populations may reflect a memory response commensurate with this greater degree of exposure.

A limitation of this study was the absence of a comparison of PCV13 with PPSV23, a pneumococcal vaccine for which efficacy against pneumococcal disease has been in part confirmed [1,10]. However this comparison has been made in other similar PCV13 studies, which showed that PCV13 elicited noninferior responses for all PCV13 vaccine serotypes and superior immune responses for the majority of PCV13 vaccine serotypes when compared with PPSV23 [18,27]. IgG immune responses measured by ELISA were not performed in this study. While ELISAs quantify IgG levels, OPA assays assesses antibody function rather than just quantity. This difference is important because a proportion of antibodies measured by ELISA may have no functional activity. For this reason, particularly in the elderly, OPA assays are recommended as the primary measure of immune response because ELISA may have limited relevance due to the presence of nonfunctional antibodies in older adults [28]. OPAs are considered the best correlate of protection [28,29].

Overall, PCV13 was well tolerated in both age groups. Some local (pain) and systemic (headache, diarrhea, muscle pain) reactions were significantly more frequent among the 50–64 years age group than in the ≥65 years age group, but were mainly mild to moderate in intensity. Because postvaccination immune responses were generally similar between age groups, no conclusions could be drawn regarding higher immune responses

and associations with increased reactogenicity. There were no deaths, no SAEs considered related to PCV13, and no safety related withdrawals from the study.

In conclusion, PCV13 was safe and well tolerated, and elicited robust immune responses in adults aged ≥50 years in Mexico. Taking into consideration the significantly higher immune responses observed in this population compared with PCV13 and PPSV23 responses observed in other studies [16-18], and the efficacy data from the CAPITA study [12,13], PCV13 has the potential to protect adults in Mexico against vaccine-type pneumococcal disease.

Acknowledgments

We would like to thank the B1851048 study group and the participants of the study.

This study was funded by Wyeth, which was acquired by Pfizer Inc in October 2009.

Editorial support was provided by Nicole Gudleski O'Regan and Deborah M. Campoli-Richards of Complete Healthcare Communications, Inc. and was funded by Pfizer Inc.

Each author participated in the preparation of this article, and were involved in: (1) collection and interpretation of data; (2) drafting the article, or revising it critically for important intellectual content, and (3) final approval of the version to be submitted. In addition WCG, DAD, BS-T, CJ contributed to the design of the study, VS to the analysis.

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389 **Table 1.** Demographic Characteristics — Evaluable Immunogenicity Population

	Age Group, %		
	50–64 yr	**≥65 yr**	**Total, %**
	N =161	**N=161**	**N =322**
Sex			
Female	59.0	52.2	55.6
Male	41.0	47.8	44.4
Race/ Ethnicity			
White	100.0	100.0	100.0
Hispanic/Latino	100.0	100.0	100.0
Age at vaccination, yr			
Mean (SD)	55.8 (4.0)	73.4 (5.8)	64.6 (10.1)
Median	55.1	72.6	64.9
Range	50.0-64.7	65.1-92.2	50.0-92.2

390 **Table 2.** Geometric Mean Fold Rises of Pneumococcal OPA GMTs — Evaluable Immunogenicity Population

	Age Group							
	50–64 yr N[a] =137–153				≥65 yr N[a] =137–158			
Serotype	Pre-vaccination GMT[b]	Post vaccination GMT[b]	GMFR[b]	(95% CI[c])	Pre-vaccination GMT[b]	Post vaccination GMT[b]	GMFR[b]	(95% CI[c])
1	6	121	21.3	(16.17,28.16)	7	84	11.7	(8.70, 15.82)
3	7	88	12.5	(9.77, 16.05)	11	89	7.8	(6.03, 10.02)
4	31	1767	57.7	(36.40, 91.36)	58	1159	19.9	(13.23, 29.88)
5	8	281	37.3	(26.06, 53.47)	11	281	26.2	(18.74, 36.72)
6A	56	3512	62.3	(39.00, 99.36)	114	3273	28.7	(19.76, 41.70)
6B	237	4290	18.1	(11.61, 28.15)	392	3691	9.4	(6.61, 13.45)
7F	70	3025	43.2	(26.94, 69.17)	124	1922	15.5	(10.05, 23.80)
9V	268	2347	8.8	(5.72, 13.43)	194	1396	7.2	(4.72, 10.98)

14	286	1518	5.3	(3.73, 7.56)	382	1311	3.4	(2.58, 4.56)
18C	69	3070	44.3	(28.19, 69.51)	154	2152	13.9	(9.21, 21.09)
19A	51	1542	30.0	(21.19, 42.50)	107	1196	11.2	(7.99, 15.69)
19F	25	1078	42.8	(28.33, 64.67)	54	1120	20.8	(13.38, 32.29)
23F	14	881	63.6	(43.16, 93.75)	26	923	35.8	(24.16, 52.95)

CI, confidence interval; GMT, geometric mean titer; GMFR, geometric mean fold rise; OPA, opsonophagocytic activity.

[a]Number of subjects with valid and determinate assay results for the specified serotype at both the prevaccination and post vaccination blood draws.

[b]GMTs and GMFRs were calculated using all subjects with available data for both the prevaccination and post vaccination blood draws.

[c]CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers, or the mean fold rise.

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393 **Table 3.** Effect of Age on Pneumococcal OPA GMTs — Evaluable Immunogenicity Population

	OPA GMTs Prevaccination				OPA GMTs Post Vaccination			
	50–64 yr	≥65 yr	Comparison		50–64 yr	≥65 yr	Comparison	
	N[a]=142–159	N[a] =146–161			N[a]=148–155	N[a]=150–159		
Serotype	GMT[b]	GMT[b]	Ratio[c]	(95% CI[d])	GMT[b]	GMT[b]	Ratio[c]	(95% CI[d])
1	6	7	0.8	(0.64, 1.00)	120	84	1.4	(0.96, 2.10
3	7	11	0.6	(0.48, **0.86**)	88	89	1.0	(0.74, 1.33)
4	30	53	0.6	(0.32, 1.06)	1729	1209	1.4	(**1.05**, 1.95)
5	7	10	0.7	(0.51, **0.99**)	288	285	1.0	(0.65, 1.58)
6A	57	110	0.5	(0.30, **0.91**)	3380	3343	1.0	(0.73, 1.39)
6B	235	388	0.6	(0.33, 1.10)	3982	3384	1.2	(0.88, 1.58)
7F	66	125	0.5	(0.29, **0.98**)	3130	1929	1.6	(**1.25**, 2.11)
9V	264	173	1.5	(0.81, 2.88)	2416	1402	1.7	(**1.17**, 2.54)
14	291	361	0.8	(0.50, 1.30)	1569	1316	1.2	(0.89, 1.60)
18C	70	155	0.4	(0.24, **0.83**)	3063	2197	1.4	(0.99, 1.96)

19A	52	105	0.5	(0.32, **0.77**)	1542	1196	1.3	(0.98, 1.70)
19F	26	53	0.5	(0.29, **0.85**)	1104	1188	0.9	(0.63, 1.38)
23F	13	25	0.5	(0.34, **0.82**)	879	930	0.9	(0.60, 1.48)

CI, confidence interval; GMT, geometric mean titer; OPA, opsonophagocytic activity.

[a]Number of subjects with a valid and determinate OPA titer to the given serotype.

[b]GMTs were calculated using all subjects with available data for the specified blood draw.

[c]Ratio of GMTs (50–64 yr / ≥65 yr) is calculated by back transforming the mean difference between the age 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 (50–64 years – ≥65 years). Statistically significant differences are bolded.

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396 **Table 4.** Comparison of Pneumococcal OPA GMTs in Subjects Aged 50–64 Years, Mexico Study Versus US Comparator Study —

397 Evaluable Immunogenicity Populations

	OPA GMTs Prevaccination				OPA GMTs Post Vaccination			
	Mexico Study N[a]=142–159	US Study N[a] =672–795	Comparison		Mexico Study N[a]=148–155	US Study N[a]=709–786	Comparison	
Serotype	**GMT[b]**	**GMT[b]**	**Ratio[c]**	**(95% CI[d])**	**GMT[b]**	**GMT[b]**	**Ratio[c]**	**(95% CI[d])**
1	6	5	1.1	(0.94, 1.24)	120	171	0.7	(0.53, **0.94)**
3	7	7	1.0	(0.84, 1.24)	88	92	1.0	(0.76, 1.20)
4	30	16	2.0	(**1.23**, 3.09)	1729	2412	0.7	(0.53, **0.96)**
5	7	6	1.3	(**1.05**, 1.52)	288	231	1.2	(0.88, 1.78)
6A	57	16	3.5	(**2.35**, 5.32)	3380	3331	1.0	(0.75, 1.37)
6B	235	38	6.1	(**3.68**, 10.26)	3982	2516	1.6	(**1.16**, 2.15)
7F	66	7	9.2	(**6.55**, 12.82)	3130	1301	2.4	(**1.75**, 3.30)
9V	264	24	11.0	(**6.81**, 17.86)	2416	1416	1.7	(**1.22**, 2.38)
14	291	35	8.2	(**5.30**, 12.78)	1569	765	2.1	(**1.45**, 2.91)

18C	70	23	3.0	(**1.95**, 4.60)	3063	1828	1.7	(**1.22**, 2.30)
19A	52	25	2.1	(**1.51**, 2.85)	1542	805	1.9	(**1.52**, 2.41)
19F	26	17	1.5	(**1.07**, 2.21)	1104	556	2.0	(**1.41**, 2.80)
23F	13	8	1.6	(**1.20**, 2.14)	879	430	2.0	(**1.38**, 3.03)

CI, confidence interval; GMT, geometric mean titer; OPA, opsonophagocytic activity.

[a]Number of subjects with a valid and determinate OPA titer to the given serotype.

[b]GMTs were calculated using all subjects with available data for the specified blood draw.

[c]Ratio of GMTs (Mexico study to US study) is calculated by back transforming the mean difference between the studies on the logarithmic scale.

[d]CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (Mexico study to US study). Statistically significant differences are bolded.

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400 **Table 5.** Comparison of Pneumococcal OPA GMTs in Subjects Aged ≥65 Years, Mexico Study Versus European Union Comparator

401 Study — Evaluable Immunogenicity Populations

	OPA GMTs Prevaccination				OPA GMTs Post Vaccination			
	Mexico Study	EU Study	Comparison		Mexico Study	EU Study	Comparison	
	N[a]=146–161	N[a] =212–254			N[a]=150–159	N[a]=234–255		
Serotype	GMT[b]	GMT[b]	Ratio[c]	(95% CI[d])	GMT[b]	GMT[b]	Ratio[c]	(95% CI[d])
1	7	6	1.2	(0.95, 1.47)	84	95	0.9	(0.62, 1.26)
3	11	6	1.9	(**1.50**, 2.45)	89	51	1.8	(**1.29**, 2.37)
4	53	14	3.7	(**2.18**, 6.20)	1209	1486	0.8	(0.58, 1.15)
5	10	6	1.8	(**1.38**, 2.36)	285	112	2.6	(**1.68**, 3.88**)**
6A	110	17	6.4	(**3.99**, 10.11)	3343	1597	2.1	(**1.46**, 2.99)
6B	388	53	7.4	(**4.26**, 12.73)	3384	2017	1.7	(**1.17**, 2.41)
7F	125	9	13.5	(**8.53**, 21.27)	1929	835	2.3	(**1.54**, 3.47)
9V	173	21	8.1	(**4.69**, 14.16)	1402	723	1.9	(**1.22**, 3.08)
14	361	80	4.5	(**2.77**, 7.38)	1316	1088	1.2	(0.86, 1.69)

18C	155	22	6.9	(**4.21**, 11.39)	2197	1415	1.6	(**1.10**, 2.20)
19A	105	21	5.1	(**3.50**, 7.51)	1196	539	2.2	(**1.60**, 3.07)
19F	53	15	3.6	(**2.33**, 5.60)	1188	467	2.5	(**1.72**, 3.76)
23F	25	9	2.7	(**1.83**, 4.01)	930	295	3.1	(**1.98**, 5.00)

CI, confidence interval; GMT, geometric mean titer; OPA, opsonophagocytic activity.

[a]Number of subjects with a valid and determinate OPA titer to the given serotype.

[b]GMTs were calculated using all subjects with available data for the specified blood draw.

[c]Ratio of GMTs (Mexico study to EU study) is calculated by back transforming the mean difference between the studies 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 (Mexico study to EU study). Statistically significant differences are bolded.

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403 **Table 6.** Subjects Reporting Local and Systemic Reactions Within 14 Days Post

404 Vaccination — Safety Population

	Age Group						
	50–64 yr		≥65 yr				
	N[a]=124–155		N[a] =112–145				
	n[b]	%	n[b]	%	Difference[c]	(95% CI[d])	p-value[d]
Local							
Any	117	77.0	87	62.6	14.4	(3.7, 24.9)	**0.008**
Redness[e]							
Any	18	14.4	19	15.8	-1.4	(-10.7, 7.7)	0.832
Mild	12	9.7	16	13.3	-3.7	(-12.1, 4.5)	0.444
Moderate	11	8.8	8	7.0	1.8	(-5.4, 9.2)	0.619
Severe	3	2.4	0	0.0	2.4	(-0.9, 6.9)	0.117
Swelling[e]							
Any	28	21.5	16	13.3	8.2	(-1.4, 17.8)	0.091
Mild	23	18.1	14	11.7	6.4	(-2.6, 15.7)	0.167
Moderate	11	8.7	5	4.4	4.3	(-2.3, 11.2)	0.242
Severe	3	2.4	1	0.9	1.5	(-2.6, 6.0)	0.572
Injection site pain[f]							
Any	114	75.5	83	60.6	14.9	(3.8, 25.6)	**0.007**
Mild	112	74.2	82	60.3	13.9	(2.8, 24.7)	**0.014**

Moderate	28	21.5	10	8.5	13.0	(3.5, 22.2)	**0.005**
Severe	4	3.2	4	3.5	-0.3	(-6.0, 4.9)	0.958
Systemic							
Any	119	76.8	88	60.7	16.1	(5.5, 26.4)	**0.003**
Fever							
≥38°C	3	2.4	12	10.2	-7.8	(-14.8, -1.5)	**0.012**
≥38°C – <38.5°C	2	1.6	4	3.5	-2.0	(-7.3, 2.5)	0.488
≥38.5°C – 39°C	1	0.8	2	1.8	-1.0	(-5.5, 2.8)	0.625
≥39°C – ≤40°C	1	0.8	2	1.8	-1.0	(-5.5, 2.8)	0.629
>40°C[g]	0	0.0	5	4.3	-4.3	(-9.8, -0.9)	**0.019**
Fatigue[f]							
Any	68	47.2	51	38.6	8.6	(-3.3, 20.2)	0.155
Mild	56	39.4	47	36.2	3.3	(-8.3, 14.9)	0.583
Moderate	36	26.9	25	20.0	6.9	(-3.6, 17.2)	0.199
Severe	8	6.3	6	5.3	1.0	(-5.5, 7.6)	0.766
Headache[f]							
Any	62	44.3	42	32.6	11.7	(0.0, 23.3)	**0.049**
Mild	55	39.3	39	30.5	8.8	(-2.7, 20.3)	0.134
Moderate	24	18.6	19	16.0	2.6	(-7.0, 12.3)	0.594

Severe	5	4.0	6	5.2	-1.2	(-7.4, 4.5)	0.744
Vomiting[h]							
Any	5	4.0	2	1.8	2.2	(-2.7, 7.6)	0.341
Mild	4	3.2	2	1.8	1.4	(-3.3, 6.5)	0.576
Moderate	2	1.6	1	0.9	0.7	(-3.3, 4.9)	0.739
Severe	0	0.0	0	0.0	0.0	(-3.3, 3.0)	>.99
Diarrhea[i]							
Any	35	26.1	18	15.0	11.1	(1.1, 21.1)	**0.030**
Mild	30	23.3	17	14.2	9.1	(-0.7, 19.0)	0.068
Moderate	8	6.2	2	1.8	4.4	(-0.9, 10.4)	0.100
Severe	1	0.8	1	0.9	-0.1	(-4.1, 3.6)	>.99
Muscle pain[f]							
Any	89	60.5	58	43.9	16.6	(4.8, 28.3)	**0.006**
Mild	87	59.6	52	40.3	19.3	(7.3, 30.8)	**0.001**
Moderate	31	23.5	24	19.5	4.0	(-6.3, 14.3)	0.448
Severe	7	5.6	7	6.0	-0.4	(-7.1, 6.0)	0.945
Joint pain[f]							
Any	49	35.3	43	33.3	1.9	(-9.5, 13.5)	0.750
Mild	42	30.7	38	29.9	0.7	(-10.5, 12.0)	0.913
Moderate	17	13.1	21	17.1	-4.0	(-13.1, 5.0)	0.415
Severe	5	4.0	6	5.2	-1.2	(-7.3, 4.6)	0.760

CI, confidence interval.

[a]Number of subjects reporting "yes" for ≥1 day or "no" for all days. These values are

used as the denominators for percentages.

[b]n = Number of subjects reporting the specified event.

[c]Difference in proportions, 50–64 years – ≥65 years, expressed as a percentage.

[d]Exact 2-sided CI and corresponding p-value for the difference in proportions, 50–64 years – ≥65 years, expressed as a percentage. Statistically significant differences are bolded.

[e]Mild = 2.5–5.0 cm, moderate = 5.1–10.0 cm, and severe = >10.0 cm.

[f]Mild = does not interfere with activity, moderate = some interference with activity, severe = prevents daily routine activity.

[g]Fever >40°C reported in 5 subjects were data entry errors as confirmed by the investigator.

[h]Mild = 1–2 times in 24 hours, moderate = >2 times in 24 hours, severe = requires IV hydration.

[i]Mild = 2–3 loose stools in 24 hours, moderate = 4–5 loose stools in 24 hours, severe ≥6 loose stools in 24 hours.

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