



# STATISTICAL REVIEW AND EVALUATION

## BLA 125324/767

**BLA/Supplement Number:** 125324/767.0 (3/28/2012), 767.2 (8/6/2012), 767.3 (9/7/2012), 767.4 (10/1/2012)

**Product Name:** *Prevnar 13*<sup>®</sup>

**Indication(s):** To expand the use in children 6 through 17 years of age for:

- active immunization for the prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.
- active immunization for the prevention of otitis media caused by *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F.

**Applicant:** Wyeth Pharmaceuticals Inc. (wholly owned subsidiary of Pfizer Inc.)

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## 1. EXECUTIVE SUMMARY

The applicant submitted a biologics license application supplement (sBLA 125324/767) to support the approval for expanding the age indication for *Prevnar 13* to include children ages 6 through 17 years of age. In the submission, the applicant included data and results from their post marketing study 6096A1-3011 (referred to as Study 3011), which also fulfills Post Marketing Commitment (Deferred pediatric study (6096A1-3011) under PREA to evaluate the safety and immunogenicity of *Prevnar 13*<sup>TM</sup> in pediatric patients 6 through 16 years of age) from the *Prevnar 13* approval letter, dated February 24, 2010.

### 1.1 Brief Overview of Clinical Studies

There is one study included in the application to support the proposed age expansion of the indication, which is for active immunization for the prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. Study 6096A1-3011 (referred to as Study 3011) was an open-label study designed to evaluate the safety, tolerability, and immunogenicity of *Prevnar 13* (or 13vPnC) administered to healthy children in four age groups: ages >15 months to <2 years (Group 1); ages  $\geq 2$  years to <5 years (Group 2); ages  $\geq 5$  years to <10 years (Group 3); and ages  $\geq 10$  years to <18 years (Group 4). Children were offered 1 or 2 doses of the study vaccine depending on their age. The application included the data in Groups 3 and 4, consisting of children 5 through 17 years of age from 29 clinical sites in the United States. The study duration for these two groups was from November 18, 2008 to August 10, 2010. During the study, the original primary endpoint (the proportion of subjects achieving a serotype-specific IgG concentration of  $\geq 0.35$   $\mu\text{g/mL}$  measured 1 month after the last scheduled study vaccination) was considered to be inappropriate as the primary endpoint for these age groups. The primary analysis objectives were then modified as agreed by the agency and described in the review below. Because of this modification, the study subjects were divided into two cohorts: the exploratory cohort (N=100 per age group) and the confirmatory cohort (N=200 per age group). The primary immunogenicity analyses were based on the confirmatory cohort whereas the safety analyses were based on the exploratory and confirmatory cohorts combined.

Study 6096A1-3005 (referred to as Study 3005) was a parallel-group, randomized, active-controlled, double-blind, multi-center trial to evaluate the safety, tolerability, and immunogenicity of 13vPnC in healthy infants. The study was initiated in August 2007 and ended in June 2009. Subjects were randomly assigned in a 2:2:2:1 ratio to receive 13vPnC pilot scale lot 1, 13vPnC pilot scale lot 2, 13vPnC manufacturing scale lot, or 7vPnC (or *Prevnar*). The immunogenicity data at post toddler dose (dose 4) were used as a historical control for the primary analysis objectives for children 5 through 9 years of age (Group 3) in Study 3011. Approximately 1050 13vPnC-vaccinated subjects and 170 7vPnC-vaccinated subjects contributed data to the evaluable post-toddler immunogenicity analyses.

## 1.2 Major Statistical Findings, Conclusions, and Recommendations

In Study 3011, the primary immunogenicity objectives were evaluated based on the following comparisons for children 5 through 9 years of age (Group 3) and 10 through 17 years of age (Group 4):

1. Comparison of the IgG geometric mean concentrations (GMCs) with regard to the 7 common serotypes (Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) between Group 3 of Study 3011 and the Prevnar control group in Study 3005
2. Comparison of the IgG GMCs with regard to the 6 additional serotypes (Serotypes 1, 3, 5, 6A, 7F, and 19A) between Group 3 of Study 3011 and subjects who received 13nPnC in Study 3005
3. Comparison of OPA geometric mean titers (GMTs) with regard to all 13 serotypes between Group 4 and Group 3 in Study 3011

The success criterion for all these objectives was based on the demonstration of non-inferiority for each serotype, which was defined as the lower bound of the two-sided 95% CI for the GMC or GMT ratio (Group 3 in Study 3011 versus specified group in Study 3005 for the IgG comparisons, Group 4 versus Group 3 for the OPA comparisons) being greater than 0.5. As shown in Table 4 and Table 5, the non-inferiority criterion for the first and second objectives, which focused on children 5 through 9 years of age, was met. The lower bounds of the two-sided 95% CI of the IgG GMC ratios were between 1.07 and 4.57, exceeding the non-inferiority margin of 0.5. As for the third objective, which focused on children 10 through 17 years of age, the non-inferiority criterion was met for 12 of the 13 serotypes, but not met for Serotype 3 (see Table 7.) The lower bound of the two-sided 95% CI of the OPA GMT ratio between Group 4 and Group 3 for Serotype 3 was 0.48, slightly below the non-inferiority margin of 0.5.

Regarding the safety data collected within this study, approximately 90% of the subjects experienced local symptoms and 50% of the subjects experienced systemic symptoms within 7 days after the *Prevnar 13* vaccination. The adverse events rates were 19% and 24% from Group 3 and Group 4, respectively. Additional safety analysis and discussions can be found in the medical officer's review.

### Conclusions and Recommendations

The results in Study 3011 met all the pre-specified co-primary non-inferiority objectives for the immunogenicity endpoints, except for one serotype in the OPA analyses for children 10 through 17 years of age. The findings support the proposed age expansion of the label indication to include children 6 through 17 years of age. The reviewer has the following additional comments:

- The results presented in this submission included data from 5-year-old children (in Group 3), for whom *Prevnar 13* has already been approved. Nevertheless, the study conclusions did not change for children in this age group regardless of the inclusion or exclusion of subjects 5 years of age.

- The comparisons between Group 3 in Study 3011 and the specified group in Study 3005 suggested higher IgG responses at post *Prevnar 13* vaccination in children 5 through 9 years of age when compared with the specified toddler group in Study 3005. It should be noted that when comparing the pre-vaccination IgG results in Group 3 of Study 3011 with the specified group in Study 3005, the pre-specified non-inferiority criterion was met for 7 (3 of the original types and 4 of the additional types) of the 13 serotypes.
- Based on preliminary subgroup analysis of the immunogenicity results according to whether or not subjects received any non-study vaccination(s) concomitantly with the *Prevnar 13* vaccination, it appears that the immunogenicity responses (for both IgG and OPA) tended to be lower in subjects who received one or more non-study vaccinations concomitantly. The non-inferiority criterion was met in the subgroup where the subjects received *Prevnar 13* only. The sample size in the concomitant vaccination subgroup was small (between 30-40 subjects) and therefore resulted in insufficient statistical power to make non-inferiority comparisons. It should be noted that the data collected in the study might be incomplete due to different data collection procedures across the sites. Therefore, based on results provided in this submission, it is premature to draw any conclusion with regard to the impact or interference of other vaccine(s) when administered concomitantly with *Prevnar 13*. The reviewer defers to the review committee to determine whether there may be a need for further investigation of the interference of the administration of other vaccines with *Prevnar 13* vaccination in this particular age group.

Recommendation:

Based on the statistical results, the statistical reviewer recommends approval of the proposed age expansion of the label indication for the prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.

## **2. INTRODUCTION**

### **2.1 Overview**

There is one study included in the application to support the proposed age expansion of the indication for the prevention of invasive pneumococcal disease caused by strains present in the vaccine. Study 6096A1-3011 was an open-label study designed to evaluate the safety, tolerability, and immunogenicity of *Prevnar 13* (or 13vPnC) administered to healthy children in four age groups: ages >15 months to <2 years (Group 1); ages  $\geq$ 2 years to <5 years (Group 2); ages  $\geq$ 5 years to <10 years (Group 3); and ages  $\geq$ 10 years to <18 years (Group 4). Children were offered 1 or 2 doses of the study vaccine depending on their age. The application included the data in Groups 3 and 4, consisting of children 5 through 17 years of age from 29 clinical sites in the United States. The study duration for these two groups was from November 18, 2008 to August 10, 2010. When the study was amended with a modified protocol analysis objective, as agreed upon with the FDA, the enrolled subjects were considered as the exploratory cohort and the subjects to be enrolled were to address the modified analysis objective and would be referred to as the confirmatory cohort. The primary immunogenicity analyses were based on the

confirmatory cohort whereas the safety analyses were based on the exploratory and confirmatory cohorts combined.

## **2.2 Data Sources**

This review is based on the clinical study reports (CSRs) for Study 6096A1-3011. Various SAS transport datasets are used for verification of the results and the statistical reviewer's independent analyses. The CSRs and SAS datasets as well as other related materials were provided by the applicant at the time of the sBLA submission (STN 125324/767) dated April 27, 2012 and were primarily located in Module 5 of the eCTD submission package ("m5-clinical-study-reports").

Since the immunogenicity data from Study 6096A1-3005 were used as historical control in the analysis, these data, which were submitted under STN Study 3005 in prior supplements STN 125324/0 and STN 125324/460, were also used in the confirmation of the results in this review.

Per request from CBER, the sponsor submitted amendments to the application (STN 125324/767.2 dated August 6, 2012; STN 125324/767.3 dated September 7, 2012, and STN 125324/767.4 dated October 1, 2012) including subgroup analyses of the primary endpoints for both immunogenicity and safety by the presence of concomitant administration of non-study vaccines. These data are also considered in the review.

## **3. STATISTICAL EVALUATION**

### **3.1 Study Descriptions (Study 6096A1-3011)**

The data submitted to support the proposed label indication age expansion in the label were based on partial data generated in the study, specifically, Groups 3 and 4 which consisted of children 5 through 17 years of age. Therefore, the following descriptions of the study and results are also focused on these two groups.

#### **3.1.1 Study Design and Endpoints**

##### Design

Study 6096A1-3011 was an open-label multi-center study, which was designed for the evaluation of the safety, tolerability, and immunogenicity of 13vPnC when administered to healthy children:

- aged >15 months to <2 years (Group 1) who had been previously vaccinated with at least 3 doses of Prevnar,
- children aged  $\geq 2$  years to <5 years (Group 2) who had been previously vaccinated with at least 3 doses of Prevnar,
- children aged  $\geq 5$  years to <10 years (Group 3) who had been previously vaccinated with at least 1 dose of Prevnar, and
- children aged  $\geq 10$  years to <18 years (Group 4) who had never been vaccinated with Prevnar or any other pneumococcal vaccine.

Subjects were enrolled in one of four age groups based on their age at enrollment. The focus of this application is on the two older age groups (Groups 3 and 4), where subjects received one dose of 13vPnC. There were no control groups. The study dates for these two groups were from November 18, 2008 to August 10, 2010. There were 29 sites in the United States involved for these two groups.

The initial planned enrollment for Groups 3 and 4 was 100 subjects per group. Per request from the agency, the protocol was amended to increase the sample size to 300 subjects per group in order to enhance the precision of the immunogenicity results and provide additional safety data for 13vPnC.

Blood samples were obtained before study vaccine administration at Visit 1 (Day 1) and one month (28 to 42 days) after the vaccination.

### Objectives and Endpoints

#### *Immunogenicity*

The primary objective of this study was to assess the pneumococcal immune responses induced by 13vPnC when measured 1 month after the last scheduled study vaccination in each of 4 age groups.

Immunogenicity measurements included: enzyme-linked immunosorbent assay (ELISA), serum concentration of anticapsular IgG, and functional antibody titers using serum opsonophagocytic activity (OPA) assays determined for each of the 13 pneumococcal serotypes contained in 13vPnC (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F). Originally, the protocol specified that the primary endpoint for each of the pneumococcal serotypes was the proportion of subjects achieving a serotype-specific IgG concentration  $\geq 0.35$   $\mu\text{g/mL}$  measured at one month after the last study scheduled vaccination. Per discussion with the FDA, because the correlation of protection against IPD based on IgG was not considered applicable for children in Groups 3 and 4, this primary endpoint was changed. A revised analysis objective was created to bridge data from children 6 through 17 years of age in this study to a population for which *Prevnar 13* is licensed. Study 6096A1-3005 (referred to as Study 3005) was selected as a historical control for the primary immunogenicity analysis. The primary immunogenicity analyses performed include the following:

- Comparison of IgG geometric mean concentrations (GMCs) with regard to the 7 common serotypes between Group 3 of Study 3011 and the Prevnar control group in Study 3005
- Comparison of IgG GMCs with regard to the 6 additional serotypes between Group 3 of Study 3011 and subjects who received 13nPnC in Study 3005
- Comparison of OPA geometric mean titers (GMTs) between Group 4 and Group 3 in Study 3011

#### *Safety*

The objective of this study was to evaluate the safety profile of 13vPnC as measured by the incidence rates of local reactions, systemic events, and adverse events (AEs).



Safety assessments were based on AEs and data from the daily monitoring and recording of local reactions and systemic events by the parent/legal guardian in an e-diary for 7 days after each vaccination (day 1 through day 7).

### 3.1.2 Patient Disposition, Demographic and Baseline Characteristics

The disposition of the subjects in Groups 3 and 4 exploratory cohorts (“3e” and “4e”, respectively) and confirmatory cohorts (3c and 4c, respectively) is provided in Table 1. A total of 598 subjects (299 in each group) were enrolled in Groups 3 and 4. The majority (N=592) of the subjects were vaccinated. Among the enrolled subjects, 27 subjects were withdrawn due to loss to follow-up (14), protocol violations (6), parental request (5), and other reasons (2).

**Table 1: Disposition of Subjects in Study 3011**

	13vPnC Group 3e+3c		13vPnC Group 4e+4c		Total	
	n	%	n	%	n	%
Consented	299	100.0	299	100.0	598	100.0
Enrolled	299	100.0	299	100.0	598	100.0
Vaccinated	294	98.3	298	99.7	592	99.0
Completed	277	92.6	294	98.3	571	95.5
Withdrawn	22	7.4	5	1.7	27	4.5
Reason for withdrawal						
Failed to return	5	1.7	2	0.7	7	1.2
Lost to follow-up	6	2.0	1	0.3	7	1.2
Protocol violation	5	1.7	1	0.3	6	1.0
Parent/legal guardian request	5	1.7	0	0.0	5	0.8
Other	1	0.3	1	0.3	2	0.3

Source: Table 8-1 on Page 42 of the CSR for Study 6096A1-3011

Demographic characteristics for subjects in Groups 3 and 4 in Study 3011 are provided in Table 2. In Group 3 and Group 4, respectively, the majority of subjects were white (66.9% and 77.9%) and non-Hispanic and non-Latino (91.3% and 91.3%). The percentages of males were 48.2% and 54.5%, respectively, and the percentages of females were 51.8% and 45.5%, respectively. In Group 3, age at enrollment ranged from 5 to 10 years, with the mean age being 7.4 years. In Group 4, age at enrollment ranged from 10 to 18 years, with the mean age being 13.7 years. The distributions of the demographic characteristics in the evaluable immunogenicity, all-available immunogenicity, and safety populations were similar to those of all subjects randomized.

**Table 2: Demographic Characteristics (Study 3011): All Subjects**

		Screened Only (N=36)		13vPnC Group 3e+3c (N=299)		13vPnC Group 4e+4c (N=299)		Total (N=634)	
		N	%	N	%	N	%	N	%
Sex	Male	13	36.1	144	48.2	163	54.5	320	50.5
	Female	23	63.9	155	51.8	136	45.5	314	49.5
Race	White	25	69.4	200	66.9	233	77.9	458	72.2
	Black or African American	5	13.9	79	26.4	53	17.7	137	21.6
	Other	2	5.6	14	4.7	6	2.0	22	3.5
	Asian	2	5.6	5	1.7	4	1.3	11	1.7
	American Indian or Alaska Native	2	5.6	1	0.3	3	1.0	6	0.9
Ethnicity	Non-Hispanic and Non-Latino	34	94.4	273	91.3	273	91.3	580	91.5
	Hispanic or Latino	2	5.6	25	8.4	26	8.7	53	8.4
	Unknown	0	0.0	1	0.3	0	0.0	1	0.2
Age (years)	Mean(SD)	6.8 (3.7)		7.4 (1.3)		13.7 (2.1)		10.3 (3.7)	
	Median	7.5		7.5		13.6		9.6	
	Min, max	1.0, 14.0		5.0, 10.0		10.0, 18.0		1.0, 18.0	
Weight (kg)	n	7		296		297		600	
	Mean(SD)	26.7 (14.3)		28.4 (8.9)		58.3 (18.4)		43.2 (20.8)	
	Median	21.6		26.4		55.8		38.6	
	Min, max	13.8, 53.5		15.2, 66.8		23.1, 130.0		13.8, 130.0	

Source: Table 8-8 on Page 42 of the CSR for Study 6096A1-3011.

### 3.1.3 Statistical Methodologies

#### Primary Immunogenicity analyses

Originally in the protocol, there was no formal hypothesis testing planned in the study. The study was initially sized to allow estimation of the proportion of the responders to be within  $\pm 5\%$  precision in each group. Assuming a dropout rate of 20%, at least 100 subjects should be enrolled to ensure 80 subjects are evaluable.

The study was amended to enroll more subjects in the specific age groups (as confirmatory cohorts) in order to achieve adequate power for a non-inferiority (NI) comparison as the primary analysis. The criterion for NI for a given serotype is defined as the lower limit of the two-sided 95% CI for the GMC ratio (Group 3 confirmatory cohort, noted as G3c, in Study 3011 to specified group in Study 3005) being greater than 0.5.

The Group 4 confirmatory cohort (G4c) is compared with G3c via the OPA geometric mean ratio by serotype. The criterion for non-inferiority for a given serotype will be met if the lower limit of the 2-sided 95% CI for the GMR (G4c relative to G3c) is greater than 0.5 (i.e., greater than half-fold).

Two-sided 95% confidence intervals will be estimated by back-transformation of the confidence intervals for the difference in means of the logarithmically transformed assay results, based on the Student t-distribution.

Immunogenicity Data Handling for Values Below LLOQ

For IgG concentrations, enzyme-linked immunosorbent assay (ELISA) lower limit of quantitation (LLOQ) is conservatively defined as the 95% upper bound of the lowest mean titer values established during the validation using precision data sets with at least (b)(4) values that also passed the acceptable precision and linearity criteria shown in the validation protocol, MVP-1015. Therefore, the LLOQ in µg/mL for each serotype was set as follows: -----

----- (b)(4) -----  
----- The limit of detection (LOD) was established as 50% of the LLOQ. Therefore, LOD in µ g/mL for each serotype are set as follows: -----

----- (b)(4) -----  
-----.

OPA LLOQ was defined from the GMT of the lowest titer values established during the validation that demonstrated acceptable linearity (relative accuracy) and precision as defined in the validation protocol MVP-1020. Therefore, the LLOQ in titers for each serotype was set as follows: -----

----- (b)(4) -----  
-----.

Antibody concentrations above the LLOQ are considered accurate and their quantitated values will be reported. Values below the LLOQ or denoted as below the limit of quantitation (BLQ) will be set to 0.5×LLOQ for analysis.

*Reviewer’s comment: In section 7.2.1 (“Immunogenicity Data Handling for Values Below Lower Limit of Quantitation”) of the CSR, it was noted that 0.5×LOD was used for values below the LLOQ. Per FDA request, post hoc sensitivity analyses were performed using different imputation methods: 0.50\*LLOQ, 0.75\*LLOQ, 0.80\*LLOQ, and 1.0\*LLOQ. It is agreed that results using the 0.50\*LLOQ imputations will be presented in the label.*

**3.2 Evaluation of Immunogenicity**

**3.2.1 Primary Immunogenicity Results**

The immunogenicity results of *Prevnar 13* among adolescents 5 through 17 years of age were evaluated in Study 3011. Two immunogenicity analysis populations were defined: evaluable immunogenicity cohort and all-available immunogenicity cohort. The all-available immunogenicity population included subjects who had at least one valid assay result. The evaluable immunogenicity population consisted of subjects who met the study eligibility criteria, received the required study vaccination, had at least 1 valid and determinate assay result before and after vaccination, and did not have any major protocol violations. The description of these two populations is presented in Table 3.

**Table 3: All-Available and Evaluable Immunogenicity Populations**

	Vaccine Group (as Enrolled)					
	13vPnC Group 3e+3c (N=299)		13vPnC Group 4e+4c (N=299)		Total (N=598)	
<b>Enrolled</b>	299	100.0	299	100.0	598	100.0
<b>All-available immunogenicity population</b>	295	98.7	298	99.7	593	99.2
Subjects excluded from the all-available immunogenicity population (No assay results)	4	1.3	1	0.3	5	0.8
<b>Evaluable immunogenicity population</b>	272	91.0	286	95.7	558	93.3
Subjects excluded from the evaluable immunogenicity <sup>a</sup>	27	9.0	13	4.3	40	6.7
No assay result for any pneumococcal serotype before or after vaccination	18	6.0	5	1.7	23	3.8
Not eligible for the study	5	1.7	3	1.0	8	1.3
Not in all-available immunogenicity population	4	1.3	1	0.3	5	0.8
Blood draw < day 1 before the first vaccination	1	0.3	3	1.0	4	0.7
Subject received prohibited vaccine (Varivax) per protocol	0	0.0	2	0.7	2	0.3
Subject was enrolled into Group 3, but had not previously received Prevnar. Subject received investigational 13vPnC as part of another trial and was withdrawn from study.	2	0.7	0	0.0	2	0.3
Blood draw >56 days after vaccination	0	0.0	1	0.3	1	0.2
Did not receive all pneumococcal study vaccinations	1	0.3	0	0.0	1	0.2
Subject received previous dose of Prevnar less than 56 days prior to visit 1	1	0.3	0	0.0	1	0.2
Subject received prohibited vaccine (23-valent) per protocol	1	0.3	0	0.0	1	0.2
Subject received prohibited vaccine (MMR, Varicella) per protocol	1	0.3	0	0.0	1	0.2

<sup>a</sup>Subjects may have been excluded for more than 1 reason.

Source: Table 9-1 on Page 53 of the CSR for Study 6096A1-3011.

*Reviewer's comments:*

- *Subjects who were not vaccinated should be excluded from all analysis populations. It was not clear if these subjects were excluded.*
- *There appear to be more subjects who received varicella or MMR vaccines during the vaccination period (-28 to 6 days of the study vaccination) and were not excluded in the evaluable immunogenicity population. Please see Table 9 for details.*

The primary immunogenicity objective was to demonstrate non-inferiority, based on IgG concentrations one month after 13vPnC vaccination in the Group 3 (subjects  $\geq 5$  years to <10 years) confirmatory cohort, compared to the post-toddler responses in the 7vPnC group from study 6096A1-3005 for the 7 common serotypes and compared to the post-toddler responses in

the combined 13vPnC groups from study 6096A1-3005 for the 6 additional serotypes. The primary immunogenicity results for Group 3 are presented in Table 4 and Table 5 for the seven serotypes in 7vPnC and six other serotypes in 13vPnC, respectively. As shown in Table 4, the geometric mean concentration (GMC) ratios between Group 3c in Study 3011 and the 7vPnC group in Study 3005 ranged from 2.51 for serotype 23F to 5.66 for serotype 6B. The lower bounds of the 95% CI of the ratio exceeded 0.5 for all seven serotypes in 7vPnC. Likewise, the GMC ratios between Group 3c in Study 3011 and the 13vPnC group in Study 3005 ranged from 1.23 for Serotype 7 to 3.17 for serotype 3. The lower bounds of the 95% CI of the ratio exceeded 0.5 for all six additional serotypes in 13vPnC. Therefore, the pre-specified non-inferiority criteria were met.

**Table 4: Comparison of Pneumococcal IgG GMCs ( $\mu\text{g/mL}$ ) After Vaccination for Original 7 Serotypes, 13vPnC Group 3 in Study 3011 Relative to 7vPnC in Study 3005 (Post-toddler) – Evaluable Immunogenicity Population**

Serotype	13vPnC Group 3 (Study 3011)		7vPnC (Study 3005)		Ratio (95% CI)
	n	GMC (95% CI)	n	GMC (95% CI)	
4	169	8.45 (7.24, 9.87)	173	2.79 (2.45, 3.18)	3.03 (2.48, 3.71)
6B	171	53.56 (45.48, 63.07)	173	9.47 (8.26, 10.86)	5.66 (4.57, 6.99)
9V	171	9.51 (8.38, 10.78)	172	1.97 (1.77, 2.19)	4.83 (4.10, 5.70)
14	169	29.36 (24.78, 34.78)	173	8.19 (7.31, 9.18)	3.58 (2.93, 4.39)
18C	171	8.23 (7.13, 9.51)	173	2.33 (2.05, 2.65)	3.53 (2.91, 4.29)
19F	171	17.58 (14.95, 20.67)	173	3.31 (2.87, 3.81)	5.31 (4.29, 6.58)
23F	169	11.26 (9.79, 12.95)	173	4.49 (3.86, 5.23)	2.51 (2.04, 3.08)

Source: Table 9-2 on Page 55 of the CSR for Study 6096A1-3011.

**Table 5: Comparison of Pneumococcal IgG GMCs ( $\mu\text{g/mL}$ ) After Vaccination for Six Additional Serotypes, 13vPnC Group 3c in Study 3011 Relative to Combined 13vPnC in Study 3005 (Post-toddler) – Evaluable Immunogenicity Population**

Serotype	13vPnC Group 3c (Study 3011)		13vPnC (Study 3005)		Ratio (95% CI)
	n	GMC (95% CI)	n	GMC (95% CI)	
1	171	3.57 (3.05, 4.18)	1068	2.90 (2.75, 3.05)	1.23 (1.07, 1.42)
3	171	2.38 (2.07, 2.74)	1065	0.75 (0.72, 0.79)	3.17 (2.78, 3.62)
5	171	5.52 (4.82, 6.32)	1068	2.85 (2.72, 2.98)	1.94 (1.71, 2.20)
6A	169	21.51 (18.15, 25.51)	1063	7.11 (6.78, 7.46)	3.03 (2.64, 3.47)
7F	170	6.24 (5.49, 7.08)	1067	4.39 (4.18, 4.61)	1.42 (1.24, 1.62)
19A	170	17.18 (15.01, 19.67)	1056	8.44 (8.05, 8.86)	2.03 (1.78, 2.32)

Source: Table 9-3 on Page 56 of the CSR for Study 6096A1-3011.

*Reviewer's comment: The IgG responses post one dose of Prevnar 13 for Group 3c in Study 3011 were statistically significantly higher than those at Post Dose 4 for those post toddlers in Study 3005 for all serotypes. It is worth noting that the non-inferiority criterion was met for 7 of the 13 serotypes at pre-vaccination for Group 3c in Study 3011 when comparing with the corresponding groups in Study 3005 (see Table 6 below).*

**Table 6: Comparison of Pneumococcal IgG GMCs ( $\mu\text{g/mL}$ ) Pre Vaccination Dose for 13vPnC Group 3c in Study 3011 Relative to Specified Groups in Study 3005 (Post-toddler) – Evaluable Immunogenicity Population**

Serotype	13vPnC Group 3c (Study 3011) vs. 7vPnC (Study 3005): (95% CI)		
	GMC ratio	Lower 95% CI	Upper 95% CI
4	0.15	0.12	0.19
<b>6B</b>	<b>0.65</b>	<b>0.53</b>	<b>0.79</b>
<b>9V</b>	<b>0.89</b>	<b>0.75</b>	<b>1.07</b>
14	0.08	0.06	0.10
18C	0.27	0.22	0.33
<b>19F</b>	<b>1.19</b>	<b>0.94</b>	<b>1.49</b>
23F	0.53	0.43	0.66
	13vPnC Group 3c (Study 3011) vs. 13vPnC (Study 3005): GMC ratio (95% CI)		
1	0.16	0.14	0.19
<b>3</b>	<b>1.68</b>	<b>1.45</b>	<b>1.95</b>
<b>5</b>	<b>1.35</b>	<b>1.19</b>	<b>1.54</b>
<b>6A</b>	<b>0.61</b>	<b>0.54</b>	<b>0.70</b>
7F	0.22	0.19	0.26
<b>19A</b>	<b>0.80</b>	<b>0.70</b>	<b>0.91</b>

*Source: Reviewer's analysis*

For Group 4, the primary immunogenicity objective was to demonstrate non-inferiority of the immune responses to the 13 serotypes in 13vPnC in Group 4 (subjects  $\geq 10$  years to  $< 18$  years) confirmatory cohort compared to the Group 3 (subjects  $\geq 5$  years to  $< 10$  years) confirmatory cohort, as measured by OPA titers 1 month after vaccination. The results are presented in Table 7. The ratio of geometric mean titers (GMTs) between Group 4c and Group 3c in Study 3011 ranged from 0.7 to 1.7. All the lower bounds of the 95% CI of the ratios were above 0.5, except for Serotype 3, with the lower bound being 0.48.

**Table 7: Comparison of Pneumococcal OPA GMTs after Vaccination, 13vPnC Group 4c Relative to 13vPnC Group 3c – Evaluable Immunogenicity Population**

Serotype	13vPnC Group 4c (Study 3011)			13vPnC Group 3c (Study 3011)			Ratio	95% CI
	n	GMT	95% CI	n	GMT	95% CI		
4	188	6912	(6101.2, 7831.4)	181	4629	(4017.2, 5334.3)	1.5	(1.24, 1.80)
6B	183	14224	(12316.4, 16427.3)	178	14996	(13164.1, 17083.1)	0.9	(0.78, 1.15)
9V	186	4485	(4001.1, 5027.5)	180	4733	(4203.3, 5328.4)	0.9	(0.80, 1.12)
14	187	6894	(6028.3, 7884.0)	176	4759	(4120.4, 5497.0)	1.4	(1.19, 1.76)
18C	182	6263	(5436.4, 7215.1)	175	8815	(7738.2, 10041.0)	0.7	(0.59, 0.86)
19F	184	2280	(1949.4, 2667.6)	178	1559	(1293.3, 1878.9)	1.5	(1.15, 1.86)
23F	187	3808	(3354.7, 4322.6)	176	3245	(2818.8, 3735.5)	1.2	(0.97, 1.42)
<b>Additional</b>								
1	189	319	(271.2, 376.0)	179	187	(160.4, 218.6)	1.7	(1.36, 2.13)
3	181	114	(100.4, 129.4)	178	202	(180.9, 226.3)	0.6	(0.48, 0.67)
5	183	336	(270.3, 417.6)	178	491	(426.3, 565.3)	0.7	(0.53, 0.89)
6A	182	9928	(8457.0, 11654.8)	178	7514	(6350.8, 8890.7)	1.3	(1.05, 1.67)
7F	185	6584	(5829.4, 7435.5)	178	10334	(9099.0, 11736.8)	0.6	(0.53, 0.76)
19A	187	1276	(1131.7, 1439.0)	180	1180	(1047.5, 1329.4)	1.1	(0.91, 1.28)

Source: Table 9-3 in the CSR for Study 6096A1-3011.

When using ½\*LLOQ, instead of ½\*LOD for values below serotype specific LLOQ, the results are provided in Table 8. The results are similar to those presented in Table 7.

**Table 8: Comparison of Pneumococcal OPA GMTs after Vaccination, 13vPnC Group 4c Relative to 13vPnC Group 3c – 0.5\*LLOQ: Evaluable Immunogenicity Population**

Serotype	13vPnC Group 4c (Study 3011)			13vPnC Group 3c (Study 3011)			Ratio	95% CI
	n	GMT	95% CI	n	GMT	95% CI		
4	188	6912	(6101.2, 7831.4)	181	4629	(4017.2, 5334.3)	1.5	(1.24, 1.80)
6B	183	14224	(12316.4, 16427.3)	178	14996	(13164.1, 17083.1)	0.9	(0.78, 1.15)
9V	186	4485	(4001.1, 5027.5)	180	4733	(4203.3, 5328.4)	0.9	(0.80, 1.12)
14	187	6894	(6028.3, 7884.0)	176	4759	(4120.4, 5497.0)	1.4	(1.19, 1.76)
18C	182	6263	(5436.4, 7215.1)	175	8815	(7738.2, 10041.0)	0.7	(0.59, 0.86)
19F	184	2280	(1949.4, 2667.6)	178	1591	(1336.1, 1893.4)	1.4	(1.14, 1.81)
23F	187	3808	(3354.7, 4322.6)	176	3245	(2818.8, 3735.5)	1.2	(0.97, 1.42)
<b>Additional</b>								
1	189	322	(274.7, 377.6)	179	191	(164.8, 220.6)	1.7	(1.36, 2.10)
3	181	114	(100.8, 129.5)	178	203	(181.6, 226.4)	0.6	(0.48, 0.67)
5	183	360	(298.4, 435.6)	178	498	(436.8, 567.9)	0.7	(0.57, 0.91)
6A	182	9928	(8457.0, 11654.8)	178	7514	(6350.8, 8890.7)	1.3	(1.05, 1.67)
7F	185	6584	(5829.4, 7435.5)	178	10334	(9099.0, 11736.8)	0.6	(0.53, 0.76)
19A	187	1276	(1131.7, 1439.0)	180	1180	(1047.5, 1329.4)	1.1	(0.91, 1.28)

Source: Table 9-18 in the CSR for Study 6096A1-3011.

Although not included in this review, results for the all-available immunogenicity population were similar to those observed for the evaluable immunogenicity population

*Reviewer's comments: The results supporting the immunogenicity of this product have been verified by the reviewer. At post vaccination, the majority of the OPA responses among the studied age groups were above LLOQ. Therefore, the impact on the results using a different imputation strategy (0.5\*LLOQ vs. 0.5\*LOD) is minimal.*

### 3.2.2 Immunogenicity Results by Concomitant Vaccination(s) Status

Concomitant vaccination(s) were given to some of the subjects in the study. According to the protocol, a delay of the vaccination was implemented if:

- Subject is experiencing a febrile illness (temperature greater than or equal to 100.4°F [38.0°C]) or other acute illness within 48 hours before test article administration.
- Subject has received any non-live vaccine within the previous 14 days or live virus vaccine within the previous 28 days.

Table 9 provides a summary of the number of subjects in the primary evaluable immunogenicity cohort who received one or more non-study vaccine(s) between -14 days (-28 days for live virus vaccines) and 6 days of the study vaccination. There were 37 and 41 subjects in Group 3c and Group 4c, respectively, accounting for about 20% of the subjects. The majority of the subjects received live/non-live influenza vaccines, while some subjects received routine vaccinations such as Hepatitis A, Human papillomavirus, Meningococcal, and varicella vaccines.

**Table 9: Concomitant Vaccination(s)\* in the Evaluable Immunogenicity Confirmatory Cohorts in Study 3011**

Non-Study Vaccine	Confirmatory Cohorts	
	13vPnC Group 3c N	13vPnC Group 4c N
ANY NON-STUDY VACCINE	37	41
DTAP/DTAP-IPV	0	11
HEP A VACCINE	2	3
HPV	0	3
INACTIVED/UNSPECIFIED FLU VACCINE	27	20
KINRIX VACCINE	1	0
LIVE FLU VACCINE	7	13
MENINGOCOCCAL VACCINE	0	10
MMR VACCINE	1	0
VARICELLA VACCINE	6	2

\*Subject received non-study vaccine(s) within the -14 days (-28 day for live vaccine) and 6 days of the *Prevnar 13* vaccination.

Source: Reviewer's analysis



*Reviewer's comment: The tabulated values of concomitant vaccinations in Table 9 are consistent with those presented in Table 1 of the amendment dated September 6, 2012, "Immunogenicity response to Prevnar 13 Age Expansion Supplement STN 125324/767." However, the reviewer has the following comments:*

- *The counts in the applicant's table included all subjects, rather than the immunogenicity evaluable population.*
- *The labels in the table are not clearly defined, although the reviewer was able to interpret them based on the variable names in the dataset.*
- *The title for Table 1 "Frequency of Non Vaccines for Confirmatory Cohorts" is inaccurate. It should read "Frequency of Non-**Study** vaccines for Confirmatory Cohorts"*
- *The counts for live vaccine administration were not given in this table, although the applicant presented results in a later section based on whether the subjects received any live vaccine administration. Based on examination of the applicant's SAS program, it appears that live flu vaccine (FluMist) was not taken into account in the "any live vaccine" category.*

The immunogenicity results for both IgG and OPA are summarized in Table 10 separately for subjects with concomitant vaccinations, and for subjects without concomitant vaccinations in Group 3c. Similarly, the results for Group 4c are presented in Table 11. The point estimates of GMCs for IgG and GMTs for OPA tended to be lower in subjects who received concomitant vaccination(s) when compared to subjects who did not receive any concomitant vaccination. However, due to the small numbers of subjects in each group, the data are insufficient for evaluation with regard to statistical significance.

**Table 10: IgG and OPA Results for Subject with and without Concomitant Vaccination(s):  
Group 3c**

Assay Serotype	w/ Concomitant Vaccination(s)				w/o Concomitant Vaccination(s)				Ratio (with/without)		
	N	GMC/ GMT	Lower 95% CI	Upper 95% CI	N	GMC/ GMT	Lower 95% CI	Upper 95% CI	Ratio	Lower 95% CI	Upper 95% CI
IgG 1	33	2.39	1.70	3.35	138	3.93	3.29	4.69	0.61	0.41	0.90
IgG 3	33	2.36	1.63	3.42	138	2.39	2.05	2.78	0.99	0.69	1.42
IgG 4	33	6.06	4.39	8.38	136	9.16	7.69	10.91	0.66	0.45	0.97
IgG 5	33	3.96	2.85	5.51	138	5.97	5.16	6.92	0.66	0.47	0.93
IgG 6A	32	23.08	15.20	35.04	137	21.17	17.53	25.56	1.09	0.71	1.69
IgG 6B	33	59.11	38.68	90.33	138	52.31	43.78	62.50	1.13	0.75	1.71
IgG 7F	33	5.73	4.13	7.96	137	6.36	5.54	7.31	0.90	0.65	1.24
IgG 9V	33	6.79	4.88	9.46	138	10.30	9.02	11.77	0.66	0.48	0.90
IgG 14	33	17.43	11.30	26.89	136	33.31	27.86	39.84	0.52	0.34	0.79
IgG 18C	33	7.11	4.89	10.33	138	8.53	7.29	9.98	0.83	0.58	1.20
IgG 19A	33	11.67	8.29	16.43	137	18.86	16.33	21.78	0.62	0.44	0.87
IgG 19F	33	12.97	8.84	19.03	138	18.90	15.81	22.60	0.69	0.46	1.03
IgG 23F	33	9.16	6.89	12.18	136	11.84	10.09	13.90	0.77	0.54	1.10
OPA 1	36	160.9	116.1	223.0	143	199.0	168.9	234.5	0.81	0.56	1.16
OPA 3	37	185.0	143.2	239.0	141	207.7	183.6	235.0	0.89	0.68	1.15
OPA 4	37	3709	2839	4845	144	4900	4157	5777	0.76	0.53	1.21
OPA 5	35	401.1	284.1	566.3	143	525.2	456.2	604.6	0.76	0.55	1.30
OPA 6A	36	4927	3378	7185	142	8363	6943	10073	0.59	0.39	1.67
OPA 6B	37	12043	8974	16163	141	15884	13732	18374	0.76	0.55	1.24
OPA 7F	36	10103	7603	13426	142	10393	8999	12004	0.97	0.71	1.17
OPA 9V	37	3595	2665	4848	143	5082	4475	5770	0.71	0.53	1.07
OPA 14	37	4011	2904	5538	139	4981	4235	5858	0.81	0.57	1.06
OPA 18C	36	7949	5636	11209	139	9054	7872	10413	0.88	0.64	0.89
OPA 19A	37	1150	849.2	1558	143	1188	1043	1353	0.97	0.72	1.04
OPA 19F	37	1696	1243	2314	141	1564	1273	1922	1.08	0.71	1.34
OPA 23F	35	2904	1998	4223	141	3336	2867	3881	0.87	0.61	0.95

Source: Reviewer's analysis. Results are also provided in Tables 14 and 22 in applicant's amendment STN 125324/767.3 dated September 7, 2012

**Table 11: IgG and OPA Results for Subject with and without Concomitant Vaccination(s):  
Group 4c**

Assay Serotype	w/ Concomitant Vaccination(s)				w/o Concomitant Vaccination(s)				Ratio (with/without)		
	N	GMC/ GMT	Lower 95% CI	Upper 95% CI	N	GMC/ GMT	Lower 95% CI	Upper 95% CI	Ratio	Lower 95% CI	Upper 95% CI
IgG 1	41	4.86	3.30	7.14	147	6.75	5.56	8.20	0.72	0.47	1.09
IgG 3	41	1.89	1.48	2.42	146	1.87	1.62	2.16	1.01	0.75	1.36
IgG 4	41	3.47	2.48	4.86	148	4.79	3.99	5.75	0.72	0.49	1.07
IgG 5	41	7.33	5.40	9.94	147	6.99	5.96	8.20	1.05	0.75	1.47
IgG 6A	41	13.09	9.36	18.31	147	18.10	14.62	22.40	0.72	0.47	1.12
IgG 6B	41	21.88	14.12	33.91	146	27.94	22.41	34.83	0.78	0.49	1.26
IgG 7F	41	5.18	4.13	6.51	147	6.74	5.78	7.85	0.77	0.56	1.05
IgG 9V	41	5.20	3.81	7.11	147	5.39	4.64	6.25	0.97	0.70	1.34
IgG 14	41	13.77	8.15	23.29	147	20.12	15.13	26.77	0.68	0.37	1.25
IgG 18C	40	4.50	2.88	7.04	147	7.28	6.04	8.79	0.62	0.40	0.94
IgG 19A	41	15.71	11.85	20.83	147	18.27	15.76	21.20	0.86	0.63	1.18
IgG 19F	41	10.22	6.78	15.43	144	15.18	12.52	18.41	0.67	0.44	1.02
IgG 23F	40	11.83	7.79	17.96	144	16.58	13.12	20.96	0.71	0.44	1.17
OPA 1	40	245.6	163.5	368.8	149	346.4	292.1	410.8	0.71	0.48	1.04
OPA 3	40	81.16	59.98	109.8	141	125.9	110.1	143.9	0.64	0.48	0.87
OPA 4	40	5291	4021	6961	148	7430	6463	8543	0.71	0.53	0.96
OPA 5	38	336.7	225.7	502.4	145	367.0	295.5	455.8	0.92	0.57	1.46
OPA 6A	39	7031	5092	9707	143	10908	9083	13098	0.64	0.44	0.95
OPA 6B	40	9683	7626	12294	143	15839	13379	18753	0.61	0.43	0.86
OPA 7F	40	5505	4301	7045	145	6917	6014	7956	0.80	0.59	1.07
OPA 9V	40	4106	3105	5430	146	4595	4054	5208	0.89	0.68	1.18
OPA 14	39	5546	4227	7277	148	7301	6259	8515	0.76	0.55	1.06
OPA 18C	39	4597	3415	6187	143	6814	5807	7995	0.67	0.48	0.95
OPA 19A	40	1072	824.8	1393	147	1338	1168	1533	0.80	0.60	1.07
OPA 19F	40	1917	1337	2749	144	2393	2009	2851	0.80	0.55	1.17
OPA 23F	40	2612	2085	3272	147	4219	3647	4882	0.62	0.46	0.84

Source: Reviewer's analysis. Results are also provided in Tables 18 and 26 in applicant's amendment STN 125324/767.3 dated September 7, 2012

In the following tables, subgroup analyses for the primary immunogenicity objectives were performed and presented separately for subjects with and without concomitant vaccination(s). The results for comparing the seven common serotypes as Prevnar (7vPnC) between Group 3c and the post-toddler cohort who received 7vPnC in Study 3005 are presented in Table 12. The lower bounds of the GMC ratios exceeded 0.5 for all seven original serotypes for both subgroups, therefore meeting the pre-specified non-inferiority criterion.

**Table 12: Comparison of Pneumococcal IgG GMCs ( $\mu\text{g/mL}$ ) After Vaccination for Original 7 Serotypes, 13vPnC Group 3c in Study 3011 by Any Non-Study Vaccine Usage Relative to 7vPnC in Study 3005 (Post-Toddler) - Evaluable Immunogenicity Population**

Serotype	13vPnC Group 4c (Study 3011)			7vPnC Post-toddlers (Study 3005)			Ratio	95% CI
	n	GMT	95% CI	n	GMT	95% CI		
<i>Subjects with Concomitant Vaccination(s)</i>								
4	33	6.06	(4.39, 8.38)	173	2.79	(2.45, 3.18)	2.17	(1.57, 3.02)
6B	33	59.11	(38.68, 90.33)	173	9.47	(8.26, 10.86)	6.24	(4.35, 8.95)
9V	33	6.79	(4.88, 9.46)	172	1.97	(1.77, 2.19)	3.45	(2.60, 4.58)
14	33	17.43	(11.30, 26.89)	173	8.19	(7.31, 9.18)	2.13	(1.55, 2.92)
18C	33	7.11	(4.89, 10.33)	173	2.33	(2.05, 2.65)	3.05	(2.18, 4.27)
19F	33	12.97	(8.84, 19.03)	173	3.31	(2.87, 3.81)	3.92	(2.73, 5.63)
23F	33	9.16	(6.89, 12.18)	173	4.49	(3.86, 5.23)	2.04	(1.41, 2.95)
<i>Subjects without Concomitant Vaccinations</i>								
4	136	9.16	(7.69, 10.91)	173	2.79	(2.45, 3.18)	3.28	(2.65, 4.07)
6B	138	52.31	(43.78, 62.50)	173	9.47	(8.26, 10.86)	5.52	(4.43, 6.88)
9V	138	10.30	(9.02, 11.77)	172	1.97	(1.77, 2.19)	5.24	(4.42, 6.20)
14	136	33.31	(27.86, 39.84)	173	8.19	(7.31, 9.18)	4.07	(3.32, 4.98)
18C	138	8.53	(7.29, 9.98)	173	2.33	(2.05, 2.65)	3.66	(2.99, 4.47)
19F	138	18.90	(15.81, 22.60)	173	3.31	(2.87, 3.81)	5.71	(4.57, 7.15)
23F	136	11.84	(10.09, 13.90)	173	4.49	(3.86, 5.23)	2.64	(2.11, 3.29)

Source: Table 2 in applicant's amendment 767.3

The results for comparing the six additional serotypes between Group 3c and the post-toddler cohort who received 13vPnC in Study 3005 are presented in Table 13. The lower bounds of the GMC ratios exceeded 0.5 for all six additional serotypes for both subgroups, therefore meeting the non-inferiority criterion.

**Table 13: Comparison of Pneumococcal IgG GMCs ( $\mu$  g/mL) After Vaccination for Additional 6 Serotypes, 13vPnC Group 3c in Study 3011 by Any Non-Study Vaccine Usage Relative to 13vPnC in Study 3005 (Post-Toddler) - Evaluable Immunogenicity Population**

Serotype	13vPnC Group 4c (Study 3011)			13vPnC Post-toddlers (Study 3005)			Ratio	95% CI
	n	GMT	95% CI	n	GMT	95% CI		
<i>Subjects with Concomitant Vaccination(s)</i>								
1	33	2.39	(1.70, 3.35)	1068	2.90	(2.75, 3.05)	0.82	(0.61, 1.11)
3	33	2.36	(1.63, 3.42)	1065	0.75	(0.72, 0.79)	3.14	(2.38, 4.15)
5	33	3.96	(2.85, 5.51)	1068	2.85	(2.72, 2.98)	1.39	(1.07, 1.82)
6A	32	23.08	(15.20, 35.04)	1063	7.11	(6.78, 7.46)	3.25	(2.44, 4.31)
7F	33	5.73	(4.13, 7.96)	1067	4.39	(4.18, 4.61)	1.31	(0.98, 1.74)
19A	33	11.67	(8.29, 16.43)	1056	8.44	(8.05, 8.86)	1.38	(1.05, 1.83)
<i>Subjects without Concomitant Vaccination(s)</i>								
1	138	3.93	(3.29, 4.69)	1068	2.90	(2.75, 3.05)	1.36	(1.16, 1.59)
3	138	2.39	(2.05, 2.78)	1065	0.75	(0.72, 0.79)	3.18	(2.75, 3.67)
5	138	5.97	(5.16, 6.92)	1068	2.85	(2.72, 2.98)	2.10	(1.83, 2.41)
6A	137	21.17	(17.53, 25.56)	1063	7.11	(6.78, 7.46)	2.98	(2.56, 3.46)
7F	137	6.36	(5.54, 7.31)	1067	4.39	(4.18, 4.61)	1.45	(1.25, 1.68)
19A	137	18.86	(16.33, 21.78)	1056	8.44	(8.05, 8.86)	2.23	(1.94, 2.58)

Source: Table 3 in applicant's amendment 767.3

Finally, the comparisons of the OPA results between Group 4c and Group 3c are presented in Tables 14 and 15, for subjects with concomitant vaccination(s) and for subjects without concomitant vaccination(s), respectively. Among subjects who received one or more of the non-study vaccines, the GMT ratio between Group 4c and Group 3c (Group4c/Group3c), three (Serotype 18C, 3 and 19A) of the 13 serotypes did not meet the non-inferiority criterion. On the other hand, when the analysis is restricted to subjects who received *Prevnar 13* alone, without concomitant vaccinations, the non-inferiority criterion was met for all serotypes, including Serotype 3, for which the non-inferiority criterion was not met in the primary analysis.

**Table 14: Comparison of Pneumococcal OPA GMTs After Vaccination, 13vPnC Group 4c Relative to 13vPnC Group 3c by Any Non-Study Vaccine Usage - 0.5\*LLOQ - Evaluable Immunogenicity Population: Subjects with Concomitant Vaccination(s)**

Serotype	13vPnC Group 4c (Study 3011)			13vPnC Group 3c (Study 3011)			Ratio	95% CI
	n	GMT	95% CI	n	GMT	95% CI		
4	40	5291	(4021.0, 6960.9)	37	3709	(2839.1, 4845.0)	1.4	(0.98, 2.08)
6B	40	9683	(7626.5, 12294.4)	37	12043	(8973.6, 16162.8)	0.8	(0.56, 1.16)
9V	40	4106	(3104.5, 5429.9)	37	3595	(2665.2, 4847.9)	1.1	(0.76, 1.71)
14	39	5546	(4227.4, 7277.1)	37	4011	(2904.3, 5538.0)	1.4	(0.91, 2.09)
18C	39	4597	(3415.2, 6187.0)	36	7949	(5636.3, 11209.5)	0.6	(0.37, 0.90)
19F	40	1917	(1336.6, 2749.3)	37	1696	(1243.1, 2314.0)	1.1	(0.71, 1.81)
23F	40	2612	(2085.2, 3272.2)	35	2904	(1997.5, 4222.6)	0.9	(0.59, 1.37)
<b>Additional</b>								
1	40	246	(163.5, 368.8)	36	161	(116.1, 223.0)	1.5	(0.91, 2.57)
3	40	81	(60.0, 109.8)	37	185	(143.2, 239.0)	0.4	(0.30, 0.65)
5	38	337	(225.7, 502.4)	35	401	(284.1, 566.3)	0.8	(0.50, 1.42)
6A	39	7031	(5092.3, 9707.1)	36	4927	(3377.8, 7185.3)	1.4	(0.88, 2.32)
7F	40	5505	(4301.1, 7044.8)	36	10103	(7603.1, 13425.7)	0.5	(0.38, 0.79)
19A	40	1072	(824.8, 1393.3)	37	1150	(849.2, 1558.1)	0.9	(0.63, 1.38)

Source: Table 10 in applicant's amendment 767.

**Table 15: Comparison of Pneumococcal OPA GMTs After Vaccination, 13vPnC Group 4c Relative to 13vPnC Group 3c by Any Non-Study Vaccine Usage - 0.5\*LLOQ - Evaluable Immunogenicity Population: Subjects without Concomitant Vaccination(s)**

Serotype	13vPnC Group 4c (Study 3011)			13vPnC Group 3c (Study 3011)			Ratio	95% CI
	n	GMT	95% CI	n	GMT	95% CI		
4	148	7430	(6462.8, 8542.8)	144	4900	(4156.7, 5777.3)	1.5	(1.22, 1.88)
6B	143	15839	(13378.8, 18752.7)	141	15884	(13732.0, 18374.1)	1.0	(0.80, 1.25)
9V	146	4595	(4053.9, 5208.2)	143	5082	(4475.3, 5770.0)	0.9	(0.76, 1.08)
14	148	7301	(6259.3, 8515.1)	139	4981	(4235.0, 5858.5)	1.5	(1.17, 1.83)
18C	143	6814	(5807.4, 7995.4)	139	9054	(7872.0, 10413.5)	0.8	(0.61, 0.93)
19F	144	2393	(2008.6, 2851.1)	141	1564	(1272.8, 1921.7)	1.5	(1.17, 2.00)
23F	147	4219	(3646.5, 4882.3)	141	3336	(2866.8, 3881.0)	1.3	(1.03, 1.56)
<b>Additional</b>								
1	149	346	(292.1, 410.8)	143	199	(168.9, 234.5)	1.7	(1.37, 2.20)
3	141	126	(110.1, 143.9)	141	208	(183.6, 235.0)	0.6	(0.51, 0.73)
5	145	367	(295.5, 455.8)	143	525	(456.2, 604.6)	0.7	(0.54, 0.90)
6A	143	10908	(9083.4, 13098.2)	142	8363	(6943.3, 10073.1)	1.3	(1.01, 1.69)
7F	145	6917	(6013.8, 7955.7)	142	10393	(8999.0, 12004.0)	0.7	(0.54, 0.81)
19A	147	1338	(1168.3, 1532.6)	143	1188	(1043.2, 1352.6)	1.1	(0.93, 1.36)

Source: Table 10 in applicant's amendment 767.

### 3.2.3 Immunogenicity Results by Gender

Analyses of immunogenicity by gender were performed for subsets of the all available immunogenicity population. A summary of the results is provided in Table 16. For Group 3c, the non-inferiority criterion for IgG responses was met for both male and female subgroups when compared with those in the corresponding groups in Study 3005. For Group 4c, when comparing OPA responses with those in Group 3c, the non-inferiority criterion was met for all but one serotype (7F) in males, and was met for 10 of the 13 serotypes in females (the non-inferiority criterion was not met for Serotypes 18C, 3, and 5). It is recognized that the interpretation of these subgroup analysis results are limited because the study was not designed to have sufficient power to address the non-inferiority criterion within different gender subgroups.

**Table 16: Primary Immunogenicity Results by Gender**

Serotype	IgG (Group 3c/Post-toddler in Study 3005): GMC ratio (95% CI)		OPA (Group 4c /Group 3c) GMT ratio (95% CI)	
	Males	Females	Males	Females
4	3.20 (2.40, 4.25)	2.88 (2.19, 3.79)	1.5 (1.10, 1.91)	1.6 (1.22, 2.05)
6B	6.49 (4.77, 8.84)	4.77 (3.62, 6.30)	1.0 (0.75, 1.28)	0.9 (0.70, 1.22)
9V	5.19 (4.11, 6.54)	4.49 (3.58, 5.64)	1.0 (0.74, 1.23)	1.0 (0.79, 1.21)
14	3.93 (2.94, 5.25)	3.29 (2.51, 4.32)	1.3 (1.00, 1.78)	1.6 (1.26, 2.12)
18C	3.81 (2.88, 5.04)	3.30 (2.55, 4.28)	0.7 (0.56, 0.95)	0.6 (0.45, 0.86)
19F	5.60 (4.12, 7.61)	4.89 (3.62, 6.61)	1.7 (1.21, 2.47)	1.3 (0.94, 1.80)
23F	2.40 (1.77, 3.26)	2.63 (2.00, 3.45)	1.4 (1.04, 1.81)	1.0 (0.80, 1.33)
<b>Additional</b>				
1	1.42 (1.16, 1.74)	1.05 (0.86, 1.29)	1.7 (1.26, 2.43)	1.6 (1.20, 2.24)
3	3.88 (3.22, 4.66)	2.67 (2.22, 3.22)	0.6 (0.50, 0.80)	0.5 (0.41, 0.66)
5	2.26 (1.89, 2.71)	1.67 (1.40, 2.00)	0.7 (0.50, 1.11)	0.7 (0.49, 0.95)
6A	2.92 (2.39, 3.56)	2.98 (2.47, 3.60)	1.3 (0.91, 1.77)	1.3 (0.94, 1.81)
7F	1.45 (1.20, 1.75)	1.40 (1.16, 1.70)	0.6 (0.47, 0.77)	0.6 (0.51, 0.83)
19A	2.36 (1.94, 2.87)	1.73 (1.44, 2.07)	1.1 (0.85, 1.40)	1.1 (0.86, 1.36)

Source: Supportive Tables 14-159, 14-160, 14-169, 14-170, 14-181 in the CSR for Study 6096A1-3011.

### 3.2.4 Immunogenicity Results by Race

Analyses of immunogenicity by race (White, Black, and Other) were performed for subsets of the all available immunogenicity population. A summary of the results is provided in Table 17. For Group 3c, the non-inferiority criterion for IgG responses was met for all the racial subgroups when compared with those in the corresponding groups in Study 3005. For Group 4c, when comparing OPA responses with those in Group 3c, the non-inferiority criterion was met for all but one serotype (3) in whites; was met for 10 of the 13 serotypes (not met for Serotypes 18C, 3, and 5) in blacks; and was met for two of the 13 serotypes in the other racial groups combined. It is noted that the sample sizes in the subgroups were small, e.g., in the other racial groups, there were 14 subjects in Group 3c and 10 subjects in Group 4c. These analyses may not have enough power to assess non-inferiority.

**Table 17: Primary Immunogenicity Results by Race**

Sero-type	IgG (Group 3c/Post-toddler in Study 3005): GMC ratio (95% CI)			OPA (Group 4c/Group 3c) GMT ratio (95% CI)		
	White	Black	Other	White	Black	Other
	4	2.75 (2.19, 3.45)	4.17 (2.33, 7.46)	3.96 (1.85, 8.45)	1.4 (1.12, 1.74)	1.5 (0.99, 2.28)
6B	5.13 (4.04, 6.51)	5.27 (2.88, 9.64)	7.12 (3.15, 16.10)	1.0 (0.80, 1.27)	1.0 (0.64, 1.42)	0.6 (0.35, 1.18)
9V	4.36 (3.64, 5.22)	5.66 (3.45, 9.27)	4.10 (2.06, 8.18)	1.0 (0.81, 1.18)	0.9 (0.59, 1.23)	0.7 (0.35, 1.39)
14	3.18 (2.53, 3.99)	4.79 (2.74, 8.35)	5.84 (2.26, 15.07)	1.5 (1.15, 1.85)	1.4 (0.92, 2.01)	1.3 (0.57, 3.18)
18C	3.23 (2.59, 4.04)	3.74 (2.17, 6.45)	3.72 (2.14, 6.46)	0.7 (0.55, 0.92)	0.6 (0.41, 0.93)	0.4 (0.22, 0.87)
19F	4.76 (3.72, 6.09)	6.57 (3.46, 12.48)	5.16 (2.30, 11.57)	1.5 (1.10, 1.94)	1.4 (0.85, 2.46)	1.1 (0.40, 3.15)
23F	2.32 (1.84, 2.94)	3.26 (1.86, 5.71)	1.56 (0.67, 3.63)	1.3 (1.02, 1.64)	0.9 (0.67, 1.32)	0.9 (0.52, 1.62)
<b>Additional</b>						
1	1.20 (1.00, 1.43)	0.97 (0.71, 1.32)	0.96 (0.59, 1.59)	1.6 (1.23, 2.09)	2.3 (1.45, 3.70)	1.2 (0.47, 2.88)
3	3.26 (2.77, 3.83)	2.56 (1.91, 3.41)	3.12 (1.96, 4.98)	0.5 (0.45, 0.66)	0.7 (0.46, 1.00)	0.3 (0.14, 0.53)
5	2.06 (1.77, 2.41)	1.51 (1.13, 2.02)	1.71 (1.09, 2.70)	0.7 (0.51, 0.91)	0.7 (0.39, 1.12)	0.6 (0.11, 3.08)
6A	3.01 (2.56, 3.55)	2.59 (1.86, 3.61)	4.33 (2.69, 6.96)	1.3 (1.01, 1.76)	1.4 (0.88, 2.30)	0.7 (0.30, 1.60)
7F	1.42 (1.20, 1.68)	1.10 (0.86, 1.41)	1.74 (1.06, 2.87)	0.6 (0.53, 0.79)	0.8 (0.52, 1.10)	0.3 (0.18, 0.63)
19A	1.99 (1.70, 2.34)	1.87 (1.38, 2.54)	2.17 (1.27, 3.72)	1.1 (0.92, 1.38)	1.0 (0.68, 1.39)	0.8 (0.45, 1.32)

Source: Tables 14-161, 14-162, 14-163, 14-171, 14-172, 14-173, 14-181, 14-182, 14-183 in the CSR for Study 6096A1-3011.

*Reviewer’s comment: Note that the applicant used the all-available immunogenicity population, rather than the evaluable immunogenicity population, in the subgroup analyses by gender and race. The reviewer performed analyses based on the evaluable immunogenicity population. The results are similar to those based on the all-available immunogenicity population, and conclusions regarding the non-inferiority of this product remain consistent.*

### 3.3 Evaluation of Safety

#### 3.3.1 Primary Safety Results

##### Reactogenicity Symptoms

A summary of the local and systemic reactions within 7 days post vaccination for Group 3 (3e and 3c combined) and Group 4 (4e and 4c combined) is presented in Table 18. In Group 3 and Group 4, respectively, 89.6% (242/270) and 90.5% (258/285) of the subjects experienced at least one local reaction (tenderness, swelling, and redness) whereas 47.2% (118/250) and 51.4% (130/253) of the subjects experienced at least one of the systemic events (fever  $\geq 38^{\circ}\text{C}$ , decreased appetite, irritability, increased sleep, decreased sleep, and hives).



**Table 18: Local and Systemic Reactions within 7 days of Vaccination**

	Group 3		Group 4	
	N <sup>a</sup>	n (%)	N <sup>a</sup>	n (%)
<b>Any Local Symptom</b>	270	242 (89.6)	285	258 (90.5)
Tenderness	265	230 (86.8)	283	252 (89.0)
Swelling	226	85 (37.6)	233	86 (36.9)
Redness	233	100 (42.9)	232	70 (30.2)
<b>Any Systemic Events<sup>b</sup></b>	250	118 (47.2)	253	130 (51.4)
Fever $\geq 38^{\circ}$ C but $\leq 39^{\circ}$ C	212	9 (4.2)	214	11 (5.1)
Fever $> 39^{\circ}$ C but $\leq 40^{\circ}$ C	212	5 (2.4)	212	1 (0.5)
Fever $> 40^{\circ}$ C	210	1 (0.5)	212	1 (0.5)
Decreased appetite	227	52 (22.9)	223	51 (22.9)
Irritability	234	73 (31.2)	234	59 (25.2)
Increased sleep	226	48 (21.2)	229	61 (26.6)
Decreased sleep	212	12 (5.7)	224	42 (18.8)
Hives (urticaria)	213	4 (1.9)	214	3 (1.4)
Use of medication to treat symptoms	232	88 (37.9)	232	66 (28.4)
Use of medication to prevent symptoms	225	58 (25.8)	225	47 (20.9)
Use of medication to treat or to prevent symptoms	237	107 (45.1)	236	78 (33.1)
Use of medication to treat and to prevent symptoms	220	35 (15.9)	221	29 (13.1)

<sup>a</sup>N = number of subjects reporting yes for at least 1 day or no for all days.

<sup>b</sup>Includes any fever  $\geq 38^{\circ}$ C, decreased appetite, irritability, increased sleep, decreased sleep, and hives (urticaria).

Source: Tables 10-1, 10-2, 10-7 and 10-8 in the CSR for Study 6096A1-3011

### Adverse Events

The summary of adverse events reported in Group 3 and Group 4 by system organ class is provided in Table 19. It can be seen that 19% and 24% of the subjects experienced at least one adverse event during the approximately one month follow-up in Group 3 and Group 4, respectively. The most frequently reported individual AEs in Group 3 were cough (10 subjects, 3.4%), vomiting (8 subjects, 2.7%), pyrexia (7 subjects, 2.4%), and pharyngitis streptococcal (6 subjects, 2.0%). The most frequently reported individual AEs in Group 4 were headache (10 subjects, 3.4%), cough (5 subjects, 1.7%), pharyngitis (5 subjects, 1.7%), influenza (5 subjects, 1.7%), oropharyngeal pain (5 subjects, 1.7%), and sinusitis (5 subjects, 1.7%).

**Table 19: Adverse Events by System Organ Class**

System Organ Class	Group 3 (N=294)	Group 4 (N=298)
	n (%)	n (%)
Any Event	57 (19.4)	72 (24.2)
Ear and Labyrinth Disorders	1 (0.3)	1 (0.3)
Eye Disorders	2 (0.7)	0 (0)
Gastrointestinal Disorders	11 (3.7)	11 (3.7)
General Disorders and Administration Site Conditions	7 (2.4)	9 (3.0)
Immune System Disorders	1 (0.3)	0 (0)
Infections and Infestations	30 (10.2)	31 (10.4)
Injury, Poisoning and Procedural Complications	5 (1.7)	9 (3.0)
Investigations	0 (0)	1 (0.3)
Musculoskeletal and Connective Tissue Disorders	3 (1.0)	3 (1.0)
Nervous System Disorders	5 (1.7)	14 (4.7)
Psychiatric Disorders	0 (0)	2 (0.7)
Renal and Urinary Disorders	2 (0.7)	0 (0)
Respiratory, Thoracic and Mediastinal Disorders	14 (4.8)	11 (3.7)
Skin and Subcutaneous Tissue Disorders	1 (0.3)	4 (1.3)

*Source: Tables 10-11 and 10-12 18 in the CSR for Study 6096A1-3011*

*Reviewer's comments:*

- *There were 11 adverse events involving 11 subjects, which were collected beyond the 1-month window. These data are not summarized in the table.*
- *The two serious adverse events that occurred during the study are included in the table.*

Serious Adverse Events

Two (2) subjects in Group 3 experienced severe or life threatening AEs: 1 subject had appendicitis and 1 subject had an eye injury. Neither of these events was considered to be related to study vaccine. There were no severe or life threatening AEs observed or documented in Group 4 after vaccination.

**3.3.2 Gender, Race, Age, and Other Special/Subgroup Populations**

A summary of safety results by gender, race, and concomitant vaccination status for Group 3 (5-10 year olds) and Group 4 (11-17 year olds) is presented in Table 20. It appears that female children had slightly higher local and systemic reaction rates than their male counterparts, and whites had slightly higher rates than blacks. There were no clear patterns of subgroup effect on the safety parameters between subjects who received non-study vaccines concomitantly and those who did not. The reviewer defers to the clinical reviewer to provide a more comprehensive evaluation of potential clinical significance of the differences observed between the subgroups.

**Table 20: Summary of Safety Results by Gender, by Race and by Concomitant Vaccination Status**

	Any Local Symptoms		Any Systemic Symptoms		Any AE	
	Group 3 n/N (%)	Group 4 n/N (%)	Group 3 n/N (%)	Group 4 n/N (%)	Group 3 n/N (%)	Group 4 n/N (%)
<b>Male</b>	110/127 (86.6)	131/153 (85.6)	55/121 (45.5)	69/136 (50.7)	29/140 (20.7)	36/163 (22.1)
<b>Female</b>	132/143 (92.3)	127/132 (96.2)	63/129 (48.8)	61/117 (52.1)	28/154 (18.2)	36/135 (26.7)
<b>White</b>	172/189 (91.0)	209/223 (93.7)	86/177 (48.6)	107/197 (54.3)	39/198 (19.7)	57/233 (24.5)
<b>Black</b>	56/64 (87.5)	37/49 (75.5)	22/55 (40.0)	16/47 (34.0)	16/77 (20.8)	11/52 (21.2)
<b>Other Races</b>	14/17 (82.4)	12/13 (92.3)	10/18 (55.6)	7/9 (77.8)	2/19 (10.5)	4/13 (30.8)
<b>With Con. Vac</b>	42/49 (85.7)	55/59 (93.2)	18/45 (40.0)	23/54 (42.6)	11/53 (20.7)*	17/62 (27.4)*
<b>Without Con. Vac</b>	200/221 (90.5)	203/226 (89.8)	100/205 (48.8)	107/199 (53.8)	46/241 (19.1)*	55/236 (23.3)*

Source: Tables 14-252 through 14-263, 14-374 through 14-383 in the CSR for Study 6096A1-3011 and Tables 38 and 46 in Amendment 767.3 submitted on August 7, 2012.

\*Reviewer's analysis.

Subgroup analysis by clinical site is not performed because it is unlikely to produce meaningful findings with small sample sizes across the 29 sites in the study.

## 4. SUMMARY AND CONCLUSIONS

### 4.1 Major Statistical Findings

In Study 3011, the primary immunogenicity objectives were evaluated based on the following comparisons for children 5 through 9 years of age (Group 3) and 10 through 17 years of age (Group 4):

4. Comparison of the IgG geometric mean concentrations (GMCs) with regard to the 7 common serotypes (Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) between Group 3 of Study 3011 and the Prevnar control group in Study 3005
5. Comparison of the IgG GMCs with regard to the 6 additional serotypes (Serotypes 1, 3, 5, 6A, 7F, and 19A) between Group 3 of Study 3011 and subjects who received 13nPnC in Study 3005
6. Comparison of OPA geometric mean titers (GMTs) with regard to all 13 serotypes between Group 4 and Group 3 in Study 3011

The success criterion for all these objectives was based on the demonstration of non-inferiority for each serotype, which was defined as the lower bound of the two-sided 95% CI for the GMC or GMT ratio (Group 3 in Study 3011 versus specified group in Study 3005 for the IgG comparisons, Group 4 versus Group 3 for the OPA comparisons) being greater than 0.5. As shown in Table 4 and Table 5, the non-inferiority criterion for the first and second objectives, which focused on children 5 through 9 years of age, was met. The lower bounds of the two-sided 95% CI of the IgG GMC ratios were between 1.07 and 4.57, exceeding the non-inferiority

margin of 0.5. As for the third objective, which focused on children 10 through 17 years of age, the non-inferiority criterion was met for 12 of the 13 serotypes, but not met for Serotype 3 (see Table 7.) The lower bound of the two-sided 95% CI of the OPA GMT ratio between Group 4 and Group 3 for Serotype 3 was 0.48, slightly below the non-inferiority margin of 0.5.

Considering safety datasets, approximately 90% of the subjects experienced local symptoms, and 50% of the subjects experienced systemic symptoms within 7 days after the *Prevnar 13* vaccination. Adverse events rates were 19% and 24% from Group 3 and Group 4, respectively. Additional results and discussions related to the safety data can be seen in the clinical review.

## 4.2 Conclusions and Recommendations

The results in Study 3011 met all pre-specified co-primary non-inferiority objectives for the immunogenicity endpoints, except for one serotype in the OPA analyses for children 10 through 17 years of age. The findings support the proposed age expansion of the label indication to children 6 through 17 years of age. The reviewer has the following additional comments:

- All results in the applicant's primary analyses have been verified by the reviewer.
- The results presented in this submission included data from children 5 years of age (in Group 3), for whom *Prevnar 13* has already been approved. Nevertheless, the study conclusions did not change regardless of whether data for children in this age group were included or excluded from the analysis.
- The comparisons between Group 3 in Study 3011 and the specified group in Study 3005 suggested higher IgG responses at post *Prevnar 13* vaccination in children 5 through 9 years of age, when compared with the specified toddler group in Study 3005. It should be noted that when comparing the pre-vaccination IgG results in Group 3 of Study 3011 with the specified group in Study 3005, the pre-specified non-inferiority criterion was met for 7 (3 of the original types and 4 of the additional types) of the 13 serotypes.
- Based on preliminary subgroup analysis of the immunogenicity results, and whether or not subjects received any non-study vaccination(s) concomitantly with the *Prevnar 13* vaccination, it appears that the immunogenicity responses (for both IgG and OPA) tended to be lower in subjects who received one or more non-study vaccinations concomitantly. The non-inferiority criterion was met in the subgroup where the subjects received *Prevnar 13* only. The sample size in the concomitant vaccination subgroup was small (between 30-40 subjects) and therefore resulted in insufficient statistical power to make non-inferiority comparisons. It should be noted that the data collected in the study might be incomplete due to different data collection procedures across the sites. Therefore, based on the results provided in this submission, it is premature to draw any conclusion with regard to the impact or interference of other vaccine(s) when administered concomitantly with *Prevnar 13*. The reviewer defers to the review committee to decide whether there is a need for further investigation of the interference of the administration of other vaccines during the *Prevnar 13* vaccination in this particular age group.

Recommendation:

Based on the statistical results, the statistical reviewer recommends approval of the proposed age expansion of the label indication for the prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.

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