

FDA Statistical Review and Evaluation

**Document for the Vaccines and Related Biological Products Advisory  
Committee (VRBPAC)**

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**BOOSTRIX™:** Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular  
Pertussis Vaccine, Adsorbed (Tdap)

**Indication:** Single-dose booster immunization against tetanus, diphtheria  
and pertussis in adolescents

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## **Study Title**

Study 776423/001: A phase III, observer-blinded, randomized, multicenter, clinical study of the safety, immunogenicity and consistency of three manufacturing lots of GlaxoSmithKline Biologicals' candidate Tdap vaccine as compared to a US-licensed Td vaccine (Massachusetts Public Health Biologic Laboratories) when given as a booster dose to healthy adolescents (10-18 years of age)

## **Primary Objectives**

1. To demonstrate lot-to-lot consistency of three production lots of GlaxoSmithKline (GSK) Biologicals' candidate tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed (Tdap) vaccine in terms of immunogenicity of each antigen.
2. To demonstrate non-inferiority of GSK Biologicals' candidate Tdap vaccine compared to the control combined tetanus and diphtheria (Td) vaccine in immunogenicity with respect to antidiphtheria toxoid (anti-D) and anti-tetanus toxoid (anti-T) seroprotection (SP) rates.
3. To demonstrate non-inferiority of GSK Biologicals' candidate Tdap vaccine compared to the control Td vaccine in immunogenicity with respect to anti-D and anti-T booster immune responses.
4. To demonstrate that the pertussis booster responses – anti-pertussis toxoid (anti-PT), anti-filamentous hemagglutinin (anti-FHA), and anti-pertactin (anti-PRN) – occur in at least 80% of vaccinees administered GSK Biologicals' candidate Tdap vaccine.
5. To demonstrate non-inferiority of GSK Biologicals' candidate Tdap vaccine compared to the control Td vaccine in safety with respect to Grade 3 pain at the injection site.

## **Study Design**

This was a prospective, randomized, comparative, multi-center study with four groups vaccinated with a single dose of vaccine as follows:

- GSK Biologicals Tdap lot 1,
- GSK Biologicals Tdap lot 2,
- GSK Biologicals Tdap lot 3,
- Massachusetts Public Health Biologic Laboratories (MPHBL) Td.

The study was double-blind for the evaluation of lot-to-lot consistency of Tdap and observer-blind for the comparison between Tdap and MPHBL's Td vaccine. Two blood samples were taken from all subjects (prior to and one month after vaccination). The subjects or their parents/guardians recorded on diary cards any solicited local and general adverse events (AEs) occurring on Days 0-14 after vaccination and unsolicited adverse events occurring on Days 0-30 after vaccination. Serious adverse events were reported for a 6-month follow-up period after vaccination. Subjects experiencing a large injection

site reaction were to be examined by study personnel. Subjects were followed for five months after Visit 2 (Month 1) to record new onset of chronic illnesses, events that led to emergency room visits or physician office visits that were not routine or related to common illnesses, and serious adverse events (SAEs).

**Evaluation Criteria for Primary objectives:**

1. To demonstrate lot-to-lot consistency of three production lots of Tdap vaccine:

**Endpoint:**

Anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibody geometric mean concentrations (GMCs)

**Criteria for evaluating consistency (one month after Tdap dose):**

For all antigens and all pairs of lots, the two-sided 90% confidence interval (CI) for the GMC ratio between lots is within the [0.67; 1.5] interval.

2. To demonstrate non-inferiority of Tdap vaccine compared to the Td vaccine:

**Endpoint:**

Percentage of subjects with anti-D and percentage of subjects with anti-T antibody concentrations  $\geq 0.1$  IU/mL – seroprotection rate (SP) – by enzyme-linked immunosorbent assay (ELISA)

**Criteria for non-inferiority (one month after Tdap dose):**

For both anti-D and anti-T SP rates, the upper limit of the two-sided 95% CI for the treatment difference (Td group minus the pooled Tdap group) in the percentage of subjects with SP antibody concentrations is  $\leq 10\%$ .

3. To demonstrate the non-inferiority of Tdap vaccine compared to the Td in booster responses:

**Endpoint:** Anti-D and anti-T booster responses

**Criteria for non-inferiority (one month after Tdap dose):**

For both anti-D and anti-T booster responses, the upper limit of the two-sided 95% CI for the treatment difference (Td group minus the pooled Tdap group) in the percentage of subjects with booster response is  $\leq 10\%$ .

4. To demonstrate that booster responses occur in at least 80% of vaccinees:

**Endpoint:** Anti-PT, anti-FHA, and anti-PRN booster responses

**Criteria (one month after Tdap dose):**

For each of the pertussis antigens, the lower limit of the two-sided 95% CI on the percentage of subjects with a booster response is  $\geq 80\%$ .

5. To demonstrate non-inferiority of Tdap vaccine compared to Td in safety:

Endpoint:

Incidence of Grade 3 injection site pain during the 15-day follow-up period after vaccination.

Criterion for non-inferiority:

The upper limit of the two-sided 95% CI for the treatment difference (pooled Tdap group minus the Td group) in the percentage of subjects with Grade 3 pain is  $\leq 4\%$ .

**Sample Size and Power**

The status of subjects enrolled is summarized as follows:

	Tdap lot 1	Tdap lot 2	Tdap lot 3	Pooled Tdap lots	Td	Total
# of subjects in the Total Vaccinated Cohort*	1024	1024	1032	3080	1034	4114
# of subjects completing the Active Phase (Visit 2)	1008	1009	1020	3037	1014	4051
# of subjects withdrawn:	16	15	12	43	20	63
- for a SAE	0	0	0	0	0	0
- for a non-serious AE	0	0	0	0	0	0
# of subjects in the ATP Cohort for immunogenicity	926	928	946	2800	923	3723
# of subjects in the Total Vaccinated Safety Follow-up	1001	998	1006	3005	1003	4008
# of subjects withdrawn from the Total Vaccinated Safety Follow-up	23	26	26	75	32	107

\* The Total Vaccinated Cohort is the primary cohort for the analysis of safety, which corresponds to the vaccine that was actually administered to the subject.

Td : Massachusetts Public Health Biologic Laboratories' (MPHBL) Td

ATP: According-To-Protocol

Total Vaccinated Safety Follow-up: 5-month safety follow-up after visit 2.

Four thousand (4,000) adolescents were targeted to be enrolled and randomized to receive either one of 3 lots of Tdap vaccine or to receive the Td vaccine in a 1:1:1:1 ratio. Allowing for up to 10% of subjects who may not be evaluable for analysis, 3,600 adolescents (900 in each group) were estimated to be evaluable to satisfy the analyses of the primary objectives.

The power to conclude lot-to-lot consistency for each primary endpoint with the sample size of 900 evaluable subjects in each Tdap lot is shown in Table 1. The global power to conclude consistency for all the antigens (anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN) was estimated to be  $>99\%$ . The sample size was determined by equivalence in means using [redacted] software in a two-sided test at  $\alpha=0.05$  with Bonferroni adjustment of  $\beta$  for 3 lot-to-lot comparisons. Although the study did not plan to demonstrate

consistency in each of the age subgroups (younger and older than 15 years old), a subgroup analysis of the primary objectives was performed. Table 1 also illustrates the power/level of accuracy that could be achieved in the exploratory subgroup analyses.

Table 1: Power To Rule Out Difference By More Than 1.5-fold in GMC Ratio

Endpoints Concentrations	N	Standard deviation [Log <sub>10</sub> (concentration)] <sup>1</sup>	Power
anti-D	900	0.446	>99%
anti-T	900	0.318	>99%
anti-PT	900	0.508	>99%
anti-FHA	900	0.374	>99%
anti-PRN	900	0.627	>99%
Exploratory subgroup analysis (adolescents 10-14 years)			
anti-D	675	0.446	>99%
anti-T	675	0.318	>99%
anti-PT	675	0.508	>99%
anti-FHA	675	0.374	>99%
anti-PRN	675	0.627	>99%
Exploratory subgroup analysis (adolescents 15-18 years)			
anti-D	225	0.446	97%
anti-T	225	0.318	>99%
anti-PT	225	0.508	87%
anti-FHA	225	0.374	>99%
anti-PRN	225	0.627	45%

<sup>1</sup> Reference study = 263855/004 (dTpa-004)

Given the planned sample size, Table 2 presents the power to meet the second objective criterion: ruling out the pre-specified limit of 10% for non-inferiority of the candidate Tdap vaccine to the Td vaccine. Assuming that both vaccines elicit identical seroprotection for the interim analysis, the confirmatory analysis, and the subgroup exploratory analyses, the global power to demonstrate non-inferiority in both anti-D and anti-T seroprotection rates was estimated to be >99%. The power was computed using [REDACTED] under the hypothesis of equal proportions, assuming a one-sided equivalence test (non-inferiority) at alpha = 0.025 and a 10% absolute difference for non-inferiority limit.

Table 2: Power To Rule Out A 10% Decrease In Seroprotection Rates

Number of evaluable Tdap vs. Td	Seroprotection <sup>1</sup>	Power
Interim analysis		
270 (Tdap) vs. 90 (Td) <sup>2</sup>	95%	>99%
	97.5%	>99%
	99%	>99%
Confirmatory analysis		
2430 (Tdap) vs. 810 (Td) <sup>3</sup>	95%	>99%
	97.5%	>99%
	99%	>99%
Exploratory subgroup analysis (adolescents 10-14 years)		
1821 (Tdap) vs. 607 (Td) <sup>4</sup>	95%	>99%
	97.5%	>99%
	99%	>99%
Exploratory subgroup analysis (adolescents 15-18 years)		
606 (Tdap) vs. 202 (Td) <sup>5</sup>	95%	>99%
	97.5%	>99%
	99%	>99%

<sup>1</sup> Seroprotection rate with Tdap:

- in Study 263855/004 (dTpa-004):  
diphtheria: 100% [99.2%;100%], tetanus: 100% [99.2%;100%].
- in Study 263855/029 (dTpa-029, 0.3 mg Al group):  
diphtheria: 100% [98.2%;100%], tetanus: 100% [98.2%;100%].

<sup>2</sup> Subject numbers are based on 400 subjects included in the interim analysis, and assuming 10% are non-evaluable.

<sup>3</sup> Subject numbers are based on 3600 subjects included in the confirmatory analysis (subjects who contributed to the interim analysis were excluded), randomized 3:1 (2400:1200) to the Tdap and Td vaccine groups, and assuming 10% are not evaluable.

<sup>4</sup> Subject numbers are based on a 3:1 ratio of younger to older subjects in each of the vaccine groups (subjects who contributed to the interim analysis were excluded) and assuming 10% are not evaluable.

Given the planned sample size, Table 3 presents the power to meet the third objective criterion: ruling out the pre-specified limit of 10% for non-inferiority of the candidate Tdap vaccine to the Td vaccine in booster responses. The feasibility of this objective was first assessed by an interim analysis that included the first 408 subjects enrolled. The objective was confirmed using the results from all subjects enrolled subsequently.

Assuming that both vaccines elicit identical seroprotection for the interim analysis, the confirmatory analysis, and the subgroup exploratory analyses, the global power to demonstrate non-inferiority in both anti-D and anti-T seroprotection rates in booster response was estimated to be >99%. The power was computed using [REDACTED] under the hypothesis of equal proportions, assuming a one-sided equivalence test (non-inferiority) at alpha = 0.025 and a 10% absolute difference for non-inferiority limit.

Table 3: Power To Rule Out A 10% Decrease In Booster Responses

Number of evaluable Tdap vs. Td	Booster response <sup>1</sup>	Power
Interim analysis		
270 (Tdap) vs. 90 (Td) <sup>2</sup>	80%	53%
	90%	78%
	98%	>99%
Confirmatory analysis		
2430 (Tdap) vs. 810 (Td) <sup>3</sup>	80%	>99%
	90%	>99%
	98%	>99%
Exploratory subgroup analysis (adolescents 10-14 years)		
1821 (Tdap) vs. 607 (Td) <sup>4</sup>	80%	>99%
	90%	>99%
	98%	>99%
Exploratory subgroup analysis (adolescents 15-18 years)		
606 (Tdap) vs. 202 (Td) <sup>4</sup>	80%	90%
	90%	>99%
	98%	>99%

<sup>1</sup> Booster response with Tdap:

- in Study 263855/004 (dTpa-004):

diphtheria: 97.7% [95.9%;98.9%], tetanus: 97.3% [95.4%;98.6%].

- in Study 263855/029 (dTpa-029, 03 mg Al group):

diphtheria: 84.6% [78.8%;89.3%], tetanus: 80.7% [74.6%;85.9%].

<sup>2</sup> Subject numbers are based on 400 subjects included in the interim analysis, and assuming 10% are non-evaluable.

<sup>3</sup> Subject numbers are based on 3600 subjects included in the confirmatory analysis (subjects who contributed to the interim analysis were excluded), randomized 3:1 (2400:1200) to the Tdap and Td vaccine groups, and assuming 10% are not evaluable.

<sup>4</sup> Subject numbers are based on a 3:1 ratio of younger to older subjects in each of the vaccine groups (subjects who contributed to the interim analysis were excluded) and assuming 10% are not evaluable.

Given the planned sample size, Table 4 presents the power to meet the fourth objective criterion: ruling out the pre-specified 95% lower limit of 80% for anti-pertussis booster response of the candidate Tdap vaccine. It shows that the sample size of 2,700 evaluable subjects receiving Tdap (pooled data from the three Tdap lots) would provide >99% power at  $\alpha = 0.025$  against the alternative of percentage of subjects showing a booster response to PT, FHA, and PRN antigens equal to 88.5%, 96.6%, 98.2%, respectively. The computation was based on [REDACTED] software.

Table 4: Power to Rule Out an Anti-Pertussis Booster Response Rate below 80%

Number of evaluable Tdap	Booster response rate <sup>1</sup>	Power
2700 (Tdap) <sup>2</sup>	88.5%	>99%
	96.6%	>99%
	98.2%	>99%
Exploratory subgroup analysis (adolescents 10-14 years)		
2025 (Tdap) <sup>3</sup>	88.5%	>99%
	96.6%	>99%
	98.2%	>99%
Exploratory subgroup analysis (adolescents 15-18 years)		
675 (Tdap) <sup>3</sup>	88.5%	>99%
	96.6%	>99%
	98.2%	>99%

<sup>1</sup> Booster response rate with Tdap:

- in Study 263855/004 (dTpa-004 Annex Report):

PT: 88.5%, FHA: 96.6%, PRN: 98.2%

- in Study 263855/029 (dTpa-029, 03 mg Al group):

PT: 87.5%, FHA: 96.4%, PRN: 98.0%

<sup>2</sup> Subject numbers are based on 3000 subjects in the Tdap vaccine group and assuming 10% are not evaluable.

<sup>3</sup> Subject numbers are based on a 3:1 ratio of younger to older subjects and assuming 10% are not evaluable.

Given the planned sample-size, Table 5 presents the power to meet the fifth objective criterion: ruling out different increases for a range of adverse event rates. To demonstrate non-inferiority of Tdap vaccine compared to the Td vaccine in safety with respect to Grade 3 pain at the injection site would require the upper limit of the 95% CI for treatment difference in this incidence between subjects receiving Tdap (pooled lots) and (minus) subjects receiving Td was less than or equal to the pre-defined clinical limit of [+4%]. Considering a 4% incidence rate for Grade 3 injection site pain during the 15-day follow-up period in both groups, the study had at least 99% power to meet the objective criterion. The power for the subgroup analyses, based on the same criterion, was at least 83%. The power was computed using [REDACTED] under the hypothesis of equal proportions, assuming a one-sided equivalence test (non-inferiority) at alpha = 0.025.

In addition, the sample size of 3,000 vaccinated subjects in the pooled Tdap group allowed for a conclusion that an AE that was not observed in the study had an incidence rate that was <0.1% with 5% risk of error (alpha = 5%), assuming that the number of AEs follow a Poisson probability distribution with an expected value of 3.

Table 5: Probability To Rule Out An Increase In Adverse Event

	Incidence rate in the Td group <sup>1</sup>	Probability that upper limit of 95% CI for the absolute difference in incidence is below $\Delta$ considering the same incidence in both groups					Incidence in the pooled Tdap group that would lead to a statistically significant increase <sup>2</sup>
		2%	3%	4%	6%	8%	
2700 (Tdap) vs. 900 (Td)	1%	>99%	>99%	>99%	>99%	>99%	2.6%
	2%	96%	>99%	>99%	>99%	>99%	4.0%
	4%	75%	97%	>99%	>99%	>99%	6.6%
	6%	59%	90%	>99%	>99%	>99%	9.0%
	8%	48%	81%	96%	>99%	>99%	11.4%
	10%	40%	73%	94%	>99%	>99%	13.7%
Exploratory subgroup analysis (adolescents 10-14 years)							
2025 (Tdap) vs. 675 (Td)	1%	>99%	>99%	>99%	>99%	>99%	2.9%
	2%	93%	>99%	>99%	>99%	>99%	4.4%
	4%	70%	95%	>99%	>99%	>99%	7.0%
	6%	52%	85%	98%	>99%	>99%	9.5%
	8%	42%	75%	93%	>99%	>99%	11.9%
	10%	35%	66%	88%	>99%	>99%	14.3%
Exploratory subgroup analysis (adolescents 15-18 years)							
675 (Tdap) vs. 225 (Td)	1%	78%	99%	>99%	>99%	>99%	5.3%
	2%	56%	85%	97%	>99%	>99%	7.0%
	4%	33%	60%	83%	98%	>99%	10.0%
	6%	23%	45%	67%	94%	>99%	12.8%
	8%	18%	35%	55%	87%	98%	15.4%
	10%	15%	29%	47%	80%	96%	17.9%

<sup>1</sup> Incidence of Grade 3 pain at the injection site after dTpa in Study 263855/004 (dTpa-004) was 3.8%.

<sup>2</sup> Two-sided Fisher's exact P-value <0.05, 80% power

### Statistical Methods

All summaries were generated by vaccine group and for the pooled Tdap group. The primary objectives were evaluated in a hierarchical manner according to the way they were ordered. Subgroup analyses based on age and vaccination history (i.e., number of doses) were performed for all the primary immunogenicity objectives. In addition, analysis by gender and type of previously administered DTP vaccine was done for all solicited AEs.

An interim analysis was performed when approximately 400 subjects had been enrolled and had completed Visit 2 (Day 30) to compare the Tdap vaccine group (pooled Tdap lots) and the Td vaccine group with respect to the anti-D and anti-T antibody concentrations, booster response rates, and GMC ratios. No interim analysis of immunogenicity of the pertussis antigens or analysis of safety was performed. Immunogenicity data from subjects who contributed to the interim analysis were excluded from the final confirmatory analysis of diphtheria and tetanus responses for the comparison of pooled Tdap and Td vaccine groups. Unblinding by Tdap lot was not done for the interim analysis and did not take place before the final analysis. For the final analysis, the type I error,  $\alpha$ , was not changed due to the interim analysis, because the

objective examined in the interim analysis was to be confirmed in the subjects enrolled subsequently. CBER concurred with this plan.

### Statistical Analysis of Immunogenicity

The according to protocol (ATP) Cohort for immunogenicity included all subjects for whom blinding had been maintained, those who had received a dose of study vaccine, and had the results available for statistical analysis. The descriptive analyses included within-group assessment:

- For each antigen, antibody GMCs with 95% CIs were tabulated. Calculation of the GMCs was performed by taking the anti-log of the mean of the log concentration transformations. Note that antibody concentrations below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMC calculation.
- Booster responses with exact 95% CI were calculated at one month post-vaccination (immunogenicity results in the Td vaccine group were summarized only for diphtheria toxoid and tetanus toxoid).
- The percentages of subjects with anti-D and anti-T antibody concentrations  $\geq 0.1$  IU/mL and  $\geq 1.0$  IU/mL by ELISA were calculated with exact 95% CI.
- Seropositivity rates to pertussis antigens (PT, FHA, and PRN) with exact 95% CIs were calculated. Reverse cumulative curves (RCCs) were generated for antigens present in the vaccine that each group received. For Tdap, RCCs were generated both by lot and for the pooled lots.

Inferential analyses are mainly performed according to the five primary hypotheses. The statistical analysis of lot-to-lot consistency of the three production lots of Tdap was based on an analysis of covariance (ANCOVA) model adjusting for baseline antibody concentration. The 90% two-sided confidence intervals were based on the assumption of normality of the log-transformed antibody concentrations. As evidenced by the 90% CI for the GMC ratio lying within the pre-defined limits [0.67; 1.5] for all the vaccine antigens and for all pairs of lots, lot-to-lot consistency was demonstrated. Statistical comparisons of the pooled Tdap lots compared to the Td group were then performed for analysis of the remaining objectives.

The asymptotic 95% CIs for group differences in anti-D and anti-T SP rates were calculated. Note that the data from subjects who contributed to the interim analysis are excluded. Similarly, the asymptotic 95% CIs for the group differences in booster response rates to D and T were computed.

One month after vaccination, the 95% CIs of the anti-D and anti-T GMC ratios were computed using an ANCOVA model on the log<sub>10</sub> transformation of the concentrations. The ANCOVA model included the vaccine group as fixed effect and the pre-vaccination concentration as covariate.

As to efficacy with respect to pertussis, antibody GMCs to PT, FHA, and PRN on the pooled Tdap lots in this study were compared to the GMCs of the pooled consistency lots from Study APV-039 following the primary vaccination series with Infanrix using the 95% CI of the GMC ratio between the Tdap and Infanrix vaccinees. To confirm that the serological method for pertussis testing at GSK Biologicals was consistent over time and experienced no drift, the ratio and its 95% CI were computed between the antibody GMCs obtained from a retest of approximately 100 samples from Study APV-039 (selected through [REDACTED] sampling) and the original antibody GMC values obtained in Study APV-039. Additionally, the absence of drift in the assay was also supported by a scatter plot of log-transformed results and the concordance analysis, which used the estimated regression line of the retest results on the original results.

### Statistical Analysis of Safety

The primary analysis of safety was based on the Total Vaccinated Cohort that included all enrolled and vaccinated subjects in the study for whom safety data were available. A secondary analysis was to be performed according to the ATP Cohort for safety that included all subjects for whom blinding had been maintained and those who had received a dose of study vaccine. For the analyses of safety in the Active Phase of the study (Days 0-30), incidence with two-sided exact 95% CI for each vaccine group was determined for all solicited local and general AEs occurring within 72 hours and within 15 days following vaccination, as well as all unsolicited AEs during the 31-day follow-up period. Reverse cumulative curves were used to present the distribution of the endpoints of redness and swelling.

For the Active Phase of the study, differences among the three Tdap lots and between the pooled Tdap and Td vaccine groups were examined by a two-sided Fisher's exact test. In addition, differences between the pooled Tdap and Td vaccine groups were quantified using asymptotic 95% CIs. For all these analyses, a p-value <0.05 was used to highlight possible statistical differences between groups.

Exploratory subgroup analyses were performed on the incidence of all local and general solicited AEs by age, gender, vaccination history, and type of DTP vaccine. For the analyses of safety in the 5-month extended safety follow-up phase, the incidence with two-sided exact 95% CI of all new onsets of chronic illnesses, AEs requiring an ER visit, and AEs requiring a physician's office was calculated. SAEs, classified by Medical Dictionary for Regulatory Activities, were tabulated and described in detailed narratives.

### Changes in Planned Analyses

As per discussion with the FDA during the conduct of the study, additional analyses included the comparisons of post-vaccination pertussis immune response between this study and Study APV-039. The intention was to demonstrate that the pertussis response following the booster dose with the candidate Tdap vaccine in adolescents was not inferior to that in infants following a three-dose primary series of DTaP (Infanrix). A non-inferiority criterion of 1.5 for the ratio of GMCs was set. In addition, a subset of

samples from Study APV-039 was retested to demonstrate that the serological assay used for pertussis testing in the current study provided the results that were consistent with those obtained at the time that Study APV-039 was conducted.

The cohort chosen for the ATP analysis of immunogenicity did not exclude those subjects without pre-vaccination serology data, as was originally planned. It was found that the inclusion of data from these subjects would not affect the conclusions regarding post-vaccination seroprotection or seropositivity rates and antibody GMCs. These subjects were not included in the analyses of booster responses or comparisons of GMC ratios in the ANCOVA model.

### Statistical Review Comments

The study protocol was revised and supplemented several times. The study power and sample size are adequate. The statistical analyses are appropriate. There are no major statistical issues in this submission.

In this study the two-sided 90% confidence intervals for the GMC ratios between lots are used in the evaluation of the lot-to-lot manufacturing consistency, as shown in Table 6 below. The results of CIs fall within the pre-defined [0.67; 1.5] limits.

Table 6: Ratios of post-vaccination antibody GMCs (adjusted for baseline concentration) among Tdap lots one month after vaccination (ATP Cohort for immunogenicity)

Lot A	n	GMC	Lot B	n	Adjusted GMC	GMC Ratio		
						Lot A /Lot B	90% CI	
							LL	UL
Anti-D								
Lot 1	913	7.5	Lot 2	905	7.6	0.98	0.92	1.05
Lot 1	913	7.5	Lot 3	926	7.2	1.04	0.98	1.11
Lot 2	905	7.6	Lot 3	926	7.2	1.06	1.00	1.13
Anti-T								
Lot 1	914	15.0	Lot 2	909	16.7	0.90	0.85	0.96
Lot 1	914	15.0	Lot 3	928	16.2	0.93	0.87	0.98
Lot 2	909	16.7	Lot 3	928	16.2	1.03	0.97	1.09
Anti-PT								
Lot 1	886	86.6	Lot 2	883	82.2	1.05	0.99	1.12
Lot 1	886	86.6	Lot 3	908	88.9	0.97	0.92	1.04
Lot 2	883	82.2	Lot 3	908	88.9	0.92	0.87	0.98
Anti-FHA								
Lot 1	912	628.9	Lot 2	907	621.8	1.01	0.95	1.07
Lot 1	912	628.9	Lot 3	925	620.7	1.01	0.95	1.08
Lot 2	907	621.8	Lot 3	925	620.7	1.00	0.94	1.06
Anti-PRN								
Lot 1	913	476.2	Lot 2	912	461.4	1.03	0.94	1.13
Lot 1	913	476.2	Lot 3	927	480.8	0.99	0.91	1.08
Lot 2	912	461.4	Lot 3	927	480.8	0.96	0.88	1.05

As lot-to-lot consistency was demonstrated, the remaining study objectives regarding the non-inferiority of the candidate Tdap vaccine to the Td vaccine were then evaluated using statistical comparisons of the pooled Tdap lots compared to the Td group. As shown in the following Table 7, the differences in immune response rates between the pooled Tdap lots that jointly demonstrate the immune response of the same candidate Tdap vaccine and the comparator Td group are below the pre-specified limit of 10% (the upper 95% confidence limit, UL, is less than .10).

Table 7: Differences In Immune Responses Between Pooled Tdap and Td Groups one-month after vaccination (ATP Cohort for immunogenicity)

	Group				Difference		
	Pooled Tdap		Td		(Td minus Pooled Tdap)		
	n	%	n	%	Difference in Rates (%)	95% CI	
					LL	UL	
<b>Anti-D</b>							
≥0.1 IU/mL	2515	99.9	834	99.9	0.0	-0.6	<b>0.3</b>
≥1.0 IU/mL	2515	97.3	834	99.3	2.0	1.0	2.8
Booster Response	2463	90.6	814	95.9	5.3	3.4	<b>7.0</b>
<b>Anti-T</b>							
≥0.1 IU/mL	2516	100	834	100	0.0	-0.4	<b>0.2</b>
≥1.0 IU/mL	2516	99.5	834	99.8	0.3	-0.4	0.7
Booster Response	2469	89.7	817	92.5	2.9	0.6	<b>4.9</b>