Statistical Review and Evaluation

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Subject STN: BL 125260/0
Kinrix™ (DTaP-IPV Combined)
GlaxoSmithKline Biologicals

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1. BACKGROUND

This Biologics License Application was submitted by GlaxoSmithKline (GSK) for the Diphtheria and Tetanus Toxoids, Acellular Pertussis Vaccine Adsorbed and Inactivated Poliovirus Vaccine Combined (referred to as DTaP-IPV). The proposed proprietary name is Kinrix™. The candidate vaccine has been investigated under BB-IND ---------, initially submitted to CBER on September 6, 2002.

The DTaP-IPV vaccine combines GSK's Diphtheria and Tetanus Toxoids and Acellular Pertussis (DTaP) vaccine (Infanrix®; STN 103647, approved January 29, 1997) and inactivated poliovirus vaccine (IPV). The DTaP and IPV components are the same as that found in GSK's Pediarix® which was approved on December 13, 2002 (STN 103907). Pediarix® is Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined.

The candidate DTaP-IPV vaccine will be indicated for active immunization against diphtheria, tetanus, pertussis, and poliomyelitis, administered as the 5th dose of DTaP and as the 4th dose of IPV in children 4 to 6 years of age.

To support this indication, three clinical studies have been conducted and results of these studies are presented in this application. Table 1 presents an overview of these three clinical studies.

Table 1 An overview of the clinical studies for licensure of the DTaP-IPV vaccine

Study	Country	Pivotal/Supportive Phase	Objective	Groups
213503/048	US	Pivotal Phase III	1): Lot-to-lot consistency w.r.t. GMCs (GMTs) to vaccine antigens; non-inferiority of DTaP-IPV to Infanrix+IPOL w.r.t. immunogenicity of vaccine components and incidence of increased circumferential swelling at the DTaP-based injection site 2): Lot-to-lot consistency w.r.t. booster responses to vaccine antigens; Reactogenicity/safety in both groups; Immune response to influenza vaccination	4 parallel groups: DTaP-IPV lot 1 + MMR DTaP-IPV lot 1 + MMR DTaP-IPV lot 1 + MMR Infanrix +IPOL + MMR
213503/047	US	Supportive Phase II	1): Non-inferiority of DTaP-IPV to DTaP+IPV w.r.t. immunogenicity of vaccine antigens 2): Reactogenicity/safety in both groups; Immunogenicity of MMR vaccination in both groups	2 parallel groups: DTaP-IPV + MMR Infanrix +IPOL +MMR
213503/046	Australia	Supportive Phase IIIb	1): non-inferiority of DTaP-IPV to DTaP+IPV w.r.t. immunogenicity of vaccine antigens 2): Reactogenicity/safety in both groups; Immunogenicity of MMR vaccination in both groups	2 parallel groups: DTaP-IPV + Priorix Infanrix +IPOL + Priorix

2. STATISTICAL REVIEW

This statistical review focuses on the two US studies: 213503/048 and 213503/047.

2. 1 Statistical Methods Common to Studies 213503/048 and 213503/047

Analysis Populations

Two populations for analysis of immunogenicity were defined for both studies:

1. The According-to-Protocol (ATP) cohort for analysis of immunogenicity included all eligible subjects who received study vaccines according to protocol, did not receive a vaccine forbidden in the protocol, who had received 4 doses of Infanrix and 3 doses of poliovirus-containing vaccine before 2 years of age, who had met all eligibility criteria,

had complied with the procedures defined in the protocol and had fulfilled the requirement for analysis, and whose assay results were available for antibodies against at least one study vaccine antigen component after vaccination.

2. The Total Vaccinated cohort included all enrolled and vaccinated subjects for whom data were available. Thus, for analysis of immunogenicity, vaccinated subjects for whom data concerning immunogenicity endpoint measures were available were included.

The ATP cohort was the primary cohort for immunogenicity analyses. If 5% or more of the Total Vaccinated subjects were excluded from the ATP cohort for immunogenicity, a secondary analysis of immunogenicity using the Total Vaccinated cohort would be conducted to evaluate whether exclusion from the cohort could have biased the results.

Descriptive Analysis

For each DTaP-IPV vaccine lot, pooled lots, and each group and at each time-point that a blood-sample result was available, the following descriptive analyses were performed for both studies:

- Seroprotection rates against diphtheria and tetanus toxoids (anti-D and anti-T antibody concentrations ≥0.1 IU/mL) and against poliovirus types 1, 2, and 3 (antibody titers ≥1:8) with exact 95% confidence intervals (CIs) were calculated per group.
- The percentage of subjects with anti-D antibody concentrations ≥1.0 IU/mL and anti-T antibody concentrations ≥1.0 IU/mL calculated per group.
- Anti-PT, anti-FHA, and anti-PRN seropositivity rates (antibody concentrations ≥5 EL.U./mL) with exact 95% CI were calculated by group.

- GMCs (GMTs) with 95% CIs were reported for each antigen. GMCs or GMTs were calculated by taking the anti-$\log_{10}$ of the mean of the $\log_{10}$ concentration or titer transformations. Values below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of the calculation.

In addition, for serology results one month after vaccination:

- Distributions of antibody concentrations against each antigen were displayed using reverse cumulative distribution curves.
- Booster response rates to all DTaP-IPV vaccine antigens with exact 95% CIs were calculated per group.

The following statistical review is organized by study.

2. 2 Pivotal Study 213503/048

Study Design

Study 213503/048 was a Phase III randomized, controlled, multicenter study conducted in 4209 children 4-6 years of age who had previously received four doses of *Infanrix*, three doses of *IPOL*, and a single dose of MMR vaccine, as scheduled and according to local guidelines.

Subjects were randomized 1:1:1:1 into four groups. On Day 0, three groups (DTaP-IPV) received one of three manufacturing lots of GSK Biologicals' DTaP-IPV vaccine in the left deltoid co-administered with *M-M-RII* in the right deltoid, and one group received the separately administered vaccines (designated as DTaP+IPV): *Infanrix* in the left deltoid and *IPOL* and *M-M-RII* in separate sites in the right deltoid. In addition to the study vaccines, concomitant vaccination with influenza vaccine was permitted in study 213503/048. Influenza vaccine was not provided as a study vaccine but could be administered at the investigator's discretion.

A subset of subjects, equally distributed between the treatment groups, provided blood samples for serological analysis prior to vaccination and 31-48 days following vaccination. This subset was referred to as the "**safety and immunogenicity**" subset and was planned to consist of the first 1340 subjects enrolled into the study who agreed to be part of the subset. Actual enrollment into this subset was 1331 subjects.

Study Objectives and Endpoints

Three co-primary objectives and corresponding endpoints and evaluating criteria are summarized in Table 2.

Table 2 Primary objectives, endpoints, and evaluating criteria

Objective	Endpoint	Criteria
To demonstrate the lot-to-lot consistency of three manufacturing lots of the DTaP-IPV vaccine in terms of immunogenicity of each antigen	immunogenicity **one month** post- vaccination: • Anti-D antibody concentrations (ELISA) • Anti-T antibody concentrations (ELISA) • Anti-PT antibody concentrations (ELISA) • Anti-FHA antibody concentrations (ELISA) • Anti-PRN antibody concentrations (ELISA) • Anti-poliovirus type 1 antibody titers (Neutralization) • Anti-poliovirus type 2 antibody titers (Neutralization) • Anti-poliovirus type 3 antibody titers (Neutralization)	for each pair of lots and for each antigen, the lower and upper limits of the 95% confidence interval [CI] for the geometric mean antibody concentration [titer] ratio are within the predefined clinical limits of [0.67, 1.5]
To demonstrate the non-inferiority of the DTaP-IPV vaccine compared to DTaP + IPV vaccines in terms of immunogenicity	Immunogenicity one month post-vaccination: **Booster responses are defined as follows:** ***For Anti-D and Anti-T:*** • initially seronegative subjects (pre-booster antibody concentration below cut-off of **<0.1** IU/mL) with an increase of at least four times the cut-off one month after vaccination (post-booster antibody concentration **≥0.4** IU/mL) • initially seropositive subjects (pre-booster antibody concentration ≥0.1 IU/mL) with an increase of at least 4 times the pre-booster antibody concentration one month after vaccination ***For Anti-PT, Anti-FHA and Anti-PRN:*** • initially seronegative subjects (pre-booster antibody concentration below cut-off of <5 EL.U/mL) with an increase of at least 4 times the cut-off one month after vaccination (post-booster antibody concentration ≥20 EL.U/mL) • initially seropositive subjects with pre-booster antibody concentration ≥5 EL.U/mL and <20 EL.U/mL with an increase of at least 4 times the pre-booster antibody concentration one month after vaccination • initially seropositive subjects with pre-booster antibody concentration ≥20 EL.U/mL with an increase of at least 2 times the pre-booster antibody concentration one month after vaccination Anti-poliovirus type 1 antibody titers Anti-poliovirus type 2 antibody titers Anti-poliovirus type 3 antibody titers	For **DTaP** antigens, the upper limit of the 2-sided standardized asymptotic 95% CI for the difference between the DTaP + IPV group and [minus] the DTaP-IPV group in the percentage of subjects with a booster response is less than or equal to the pre-defined clinical limit of **10%**. For **poliovirus types 1, 2, and 3**, the upper limit of the 2-sided 95% CI for the GMT ratio [DTaP + IPV group over DTaP-IPV group] is less than or equal to the predefined clinical limit of 1.5
To demonstrate the non-inferiority of the DTaP-IPV vaccine compared to DTaP + IPV vaccines in terms of safety, with respect	Incidence of increased circumferential swelling at the DTaP-containing vaccine injection site within 4 days (Day 0 through Day 3) after vaccination. Increased circumferential swelling was defined as an injection site swelling diameter that involves >50% of the length of the	The upper limit of the 2-sided standardized asymptotic 95% CI for the difference between the DTaP-IPV group and [minus] the DTaP + IPV group in the

to increased circumferential swelling at the DTaP-based injection site	upper arm that also is associated with a >30 mm increase of the mid-upper arm circumference compared to the baseline measurement.	percentage of subjects with increased circumferential swelling is less than or equal to the pre-defined clinical limit of 2%

Secondary objectives include:

- To evaluate the lot-to-lot consistency of three manufacturing lots of DTaP-IPV vaccine in terms of D, T, PT, FHA, PRN, and poliovirus booster responses one month after vaccination.
- To evaluate DTaP-IPV vaccine compared to *Infanrix* + *IPOL* administered separately in terms of D, T, PT, FHA, and PRN GMCs and poliovirus booster responses one month after vaccination.
- To assess the safety and reactogenicity of the study vaccines administered in all groups.
- To evaluate the immune response to influenza vaccine in subjects who received influenza vaccine concomitantly with DTaP-IPV vaccine compared to those who received influenza concomitantly with *Infanrix* + *IPOL*.

Statistical Methods

Comparison between lots and between the pooled lots and the control group was made for each antigen by:

- 95% CIs of the group GMC/GMT ratios using an analysis of co-variance (ANCOVA) model on the $\log_{10}$ transformation of the concentrations one month after booster vaccination. The ANCOVA model included the vaccine group as fixed effect and the pre-vaccination titer as dependent variable.
- Standardized asymptotic 95% CIs for the difference between vaccine groups in the booster response rates and the seroprotection rates.

Immunogenicity Results

Primary objective: lot-to-lot consistency

For each pair of lots and for each vaccine antigen, the lower and upper limits of the 95% CIs for the GMC and GMT ratios are within the pre-defined clinical limits of (0.67, 1.5). Thus, the lot-to-lot consistency of the three manufacturing lots of DTaP-IPV vaccine was demonstrated (Table 3: Table 8 in the applicant's Summary of Clinical Efficacy).

Table 3 Pivotal Study 213503/048: Ratios of post-vaccination antibody GMCs (GMTs) (adjusted for baseline concentration) between DTaP-IPV lots one month after vaccination (ATP Cohort for immunogenicity)

Lot A	N	Adjusted GMC/GMT	Lot B	N	Adjusted GMC/GMT	GMC/GMT ratio			Lot-to-lot consistency criterion met (Yes/No)
						Lot A/ Lot B	95% CI		
							LL	UL	
Anti-D									
DTaP-IPV Lot 1	280	17.460	DTaP-IPV Lot 2	282	17.996	0.970	0.871	1.080	Yes
DTaP-IPV Lot 1	280	17.460	DTaP-IPV Lot 3	282	18.161	0.961	0.863	1.070	Yes
DTaP-IPV Lot 2	282	17.996	DTaP-IPV Lot 3	282	18.161	0.991	0.890	1.103	Yes
Anti-T									
DTaP-IPV Lot 1	279	9.796	DTaP-IPV Lot 2	283	10.050	0.975	0.866	1.097	Yes
DTaP-IPV Lot 1	279	9.796	DTaP-IPV Lot 3	282	11.160	0.878	0.780	0.988	Yes
DTaP-IPV Lot 2	283	10.050	DTaP-IPV Lot 3	282	11.160	0.901	0.800	1.014	Yes
Anti-PT									
DTaP-IPV Lot 1	272	67.9	DTaP-IPV Lot 2	273	72.4	0.938	0.828	1.063	Yes
DTaP-IPV Lot 1	272	67.9	DTaP-IPV Lot 3	277	70.5	0.963	0.850	1.091	Yes
DTaP-IPV Lot 2	273	72.4	DTaP-IPV Lot 3	277	70.5	1.026	0.906	1.162	Yes
Anti-FHA									
DTaP-IPV Lot 1	281	814.7	DTaP-IPV Lot 2	280	932.2	0.874	0.783	0.976	Yes
DTaP-IPV Lot 1	281	814.7	DTaP-IPV Lot 3	283	860.3	0.947	0.849	1.057	Yes
DTaP-IPV Lot 2	280	932.2	DTaP-IPV Lot 3	283	860.3	1.084	0.971	1.209	Yes
Anti-PRN									
DTaP-IPV Lot 1	280	606.8	DTaP-IPV Lot 2	281	608.0	0.998	0.867	1.148	Yes
DTaP-IPV Lot 1	280	606.8	DTaP-IPV Lot 3	284	581.8	1.043	0.907	1.200	Yes
DTaP-IPV Lot 2	281	608.0	DTaP-IPV Lot 3	284	581.8	1.045	0.909	1.202	Yes
Anti-Poliovirus 1									
DTaP-IPV Lot 1	270	2113.5	DTaP-IPV Lot 2	266	2126.8	0.994	0.836	1.181	Yes
DTaP-IPV Lot 1	270	2113.5	DTaP-IPV Lot 3	273	2142.3	0.987	0.831	1.172	Yes
DTaP-IPV Lot 2	266	2126.8	DTaP-IPV Lot 3	273	2142.3	0.993	0.836	1.180	Yes
Anti-Poliovirus 2									
DTaP-IPV Lot 1	274	2361.8	DTaP-IPV Lot 2	268	2112.9	1.118	0.951	1.314	Yes
DTaP-IPV Lot 1	274	2361.8	DTaP-IPV Lot 3	265	2346.7	1.006	0.856	1.183	Yes
DTaP-IPV Lot 2	268	2112.9	DTaP-IPV Lot 3	265	2346.7	0.900	0.765	1.060	Yes
Anti-Poliovirus 3									
DTaP-IPV Lot 1	269	3754.6	DTaP-IPV Lot 2	255	3376.7	1.112	0.941	1.314	Yes
DTaP-IPV Lot 1	269	3754.6	DTaP-IPV Lot 3	263	3631.4	1.034	0.876	1.220	Yes
DTaP-IPV Lot 2	255	3376.7	DTaP-IPV Lot 3	263	3631.4	0.930	0.787	1.099	Yes

DTaP-IPV lot 1: DTaP-IPV lot 1 + *M-M-R*$_{II}$

DTaP-IPV lot 2: DTaP-IPV lot 2 + *M-M-R*$_{II}$

DTaP-IPV lot 3: DTaP-IPV lot 3 + *M-M-R*$_{II}$

Adjusted GMC (GMT) = geometric mean antibody concentration (titer) adjusted for baseline concentration (titer)

N = Number of subjects with both pre- and post-vaccination results available

95% CI = 95% confidence interval for the adjusted GMC (GMT) ratio (ANCOVA model: adjustment for baseline concentration (titer) - pooled variance with more than 2 groups)

LL = lower limit, UL = upper limit

Criteria for claiming lot-to-lot consistency: 95% CI for the point estimate of the between-lot GMC ratio (GMT ratio) completely within the range (0.67, 1.5)

Because lot-to-lot consistency has been demonstrated, all subsequent presentations will be for the pooled DTaP-IPV lot comparison groups and the DTaP+IPV treatment group.

As an exploratory comparison of D and T antibody levels between the pooled DTaP-IPV groups and the DTaP + IPV group, between-group anti-D and anti-T GMC ratios were calculated. The 95% CIs for the point estimates of both the anti-D and anti-T GMC ratios include 1, indicating (according to the applicant) that post-vaccination GMCs for anti-D and anti-T are **similar** in both groups (Page 95, Clinical Study Report for Study 213503/048).

Reviewer's comments: A 95% CI for the GMC ratio between the pooled DTaP-IPV groups and the DTaP + IPV group containing 1 does not imply that post-vaccination GMCs are similar in both groups. It merely implies that the null hypothesis of GMC ratio equal to one has not been rejected at the $\alpha = 0.05$ level. Such a result could be due to insufficient sample size (lack of power) to reject the null hypothesis.

Co-primary objective: Non-inferiority of DTaP-IPV vaccine vs. DTaP + IPV vaccines with respect to booster responses to DTaP antigens and GMT ratios for anti-poliovirus antigens.

To test for non-inferiority of the DTaP-IPV vaccine vs. separately administered DTaP and IPV vaccines with respect to booster responses to DTaP antigens, the percentage of subjects with booster responses in the pooled DTaP-IPV group was subtracted from the percentage with booster responses in the DTaP + IPV group. The combination DTaP-IPV vaccine was considered non-inferior to the separate vaccinations if the upper limit of the 95% CIs for the differences between the groups was 10% or less (Table 4, Table 17 in the applicant's Summary of Clinical Efficacy).

Table 4 Pivotal Study 213503/048: Difference between groups in percentage of subjects with a booster response to DTaP antigens, one month after vaccination - pooled DTaP-IPV vs. separate injections (ATP cohort for immunogenicity)

Antibody	Pooled DTaP-IPV			DTaP + IPV			Difference between groups (DTaP + IPV minus pooled DTaP-IPV) (%)	95% CI		Non-inferiority criterion met (Yes/No)
	N	n	%	N	n	%		LL	UL	
Anti-D	844	840	99.5	260	260	100	0.47	-0.98	1.21	Yes
Anti-T	844	816	96.7	261	245	93.9	-2.81	-6.55	-0.09	Yes
Anti-PT	822	758	92.2	256	237	92.6	0.36	-3.83	3.71	Yes
Anti-FHA	844	805	95.4	261	251	96.2	0.79	-2.50	3.21	Yes
Anti-PRN	845	826	97.8	261	253	96.9	-0.82	-3.79	1.14	Yes

Pooled DTaP-IPV = DTaP-IPV lots 1, 2, and 3 (pooled) + MMR_{II}
DTaP + IPV = *Infanrix* + *IPOL* + MMR_{II}
N = Total number of subjects with available results at PRE and POST time point.
n/% = number/ percentage of subjects with a booster response at post-vaccination.
95% CI, LL/UL = Standardized asymptotic 95% confidence interval around difference, Lower/Upper limit.
Criteria for claiming non-inferiority – Upper limit of the 95% CI for the point estimate of the difference between groups in percentage of subjects with booster response is 10% or less

To test for non-inferiority of the DTaP-IPV vaccine to separately administered DTaP and IPV vaccines with respect to post-vaccination anti-poliovirus antibody titers, the GMT for each anti-poliovirus antibody in the DTaP + IPV group was divided by the GMT for that antibody in the pooled DTaP-IPV group. The combination DTaP-IPV vaccine was considered non-inferior to separately administered DTaP and IPV vaccines if the upper limit of the 95%CI for the GMT ratio was 1.5 or less (Table 5, Table 18 in the applicant's Summary of Clinical Efficacy).

Table 5 Pivotal study 213503/048: Adjusted ratios of anti-poliovirus type 1, 2, and 3 GMTs between the pooled DTaP-IPV and DTaP plus IPV groups one month after vaccination (ATP cohort for immunogenicity)

Antibody	Pooled DTaP-IPV		DTaP + IPV		Adjusted GMT ratio (DTaP + IPV/ pooled DTaP-IPV)	95% CI		Non-inferiority criterion met (Yes/No)
	N	Adjusted GMT	N	Adjusted GMT		LL	UL	
Anti-poliovirus 1	809	2127.0	249	1684.6	0.792	0.680	0.922	Yes
Anti-poliovirus 2	807	2265.2	252	1817.7	0.802	0.696	0.925	Yes
Anti-poliovirus 3	787	3588.1	237	3365.1	0.938	0.811	1.085	Yes

Pooled DTaP-IPV = DTaP-IPV lots 1, 2, and 3 (pooled) + *MMRII*
DTaP + IPV = *Infanrix* + *IPOL* + *MMR*
N = Total number of subjects with available results at PRE and POST time point.
Adjusted GMT=geometric mean antibody titer adjusted for baseline titer
95% CI = 95% confidence interval for the adjusted GMT ratio (ANCOVA model: adjustment for baseline titer- pooled variance); LL = lower limit, UL = upper limit
Criteria for claiming non-inferiority – Upper limit of the 95% CI for the point estimate of the between-group GMT ratio is 1.5 or less

For all DTaP antigens, the upper limit of the standardized asymptotic 2-sided 95%CI for the difference between the pooled DTaP-IPV group and the DTaP + IPV group for the proportions of subjects with booster responses was less than 10%. For all three vaccine poliovirus types, the upper limit of the 95% CI for the ratio of post-vaccination anti-poliovirus antibody GMTs was less than 1.5. The DTaP-IPV combination vaccine satisfied all pre-defined criteria for non-inferiority to separately-administered DTaP and IPV vaccines. Thus, non-inferiority of DTaP-IPV to DTaP + IPV with respect to DTaP booster responses and poliovirus GMTs was demonstrated.

Safety Analysis

Co-primary Endpoint: Non-inferiority of DTaP-IPV Vaccine to Infanrix + IPOL with Respect to Incidence of Increased Circumferential Swelling

To test for non-inferiority of the DTaP-IPV combination vaccine to separately administered DTaP and IPV (denoted DTaP + IPV or Infanrix + IPOL) with respect to the incidence of increased circumferential swelling at the DTaP injection site, the incidence of increased circumferential swelling in the DTaP + IPV group was subtracted from that observed in the pooled DTaP-IPV groups. The combination DTaP-IPV vaccine would be considered non-inferior to separately administered DTaP and IPV vaccines if the upper limit of the 95% CI for the treatment difference was 2% or less.

The standardized asymptotic 95% CI for the difference between the Pooled DTaP-IPV Group and the *Infanrix + IPOL* Group for the percentages of subjects with increased circumferential swelling was less than the prospectively defined clinical limit of 2%. Therefore, the non-inferiority of DTaP-IPV vaccine to *Infanrix + IPOL* was demonstrated with respect to this endpoint (Table 6, Table 43 in the applicant's Clinical Study Report for Study 213503/048).

Table 6 Treatment difference in the incidence of increased circumferential swelling at the DTaP-based injection site within 4 days after vaccination (Total Vaccinated Cohort)

							Difference in percentage (Pooled DTaP-IPV minus *Infanrix + IPOL*)			Non-inferiority criteria met (Yes/No)
	Pooled DTaP-IPV			*Infanrix + IPOL*				95% CI		
	N	n	%	N	n	%	%	LL	UL	
With an increase of > 30 mm in mid upper arm circumference compared to baseline measurement and with swelling >50% of upper arm length	3156	20	0.6	1053	11	1.0	-0.41	-1.26	0.16	Yes

Pooled DTaP-IPV = DTaP-IPV lots 1, 2, and 3 (pooled) + *M-M-RII*
Infanrix + IPOL = Infanrix + IPOL + M-M-RII
N = number of subjects having received at least one dose
n (%) = number (percentage) of subjects in the specified category
95%CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit
Criteria for claiming non-inferiority – upper limit of the 95% CI for the difference between groups in percentage of subjects reporting increased circumferential swelling 2% or less

The upper limit of the 2-sided standardized asymptotic 95% CI for the difference between the pooled DTaP-IPV group and (minus) the *Infanrix + IPOL* group for the percentages of subjects with increased circumferential swelling was less than the pre-defined clinical limit of 2%. Therefore, the non-inferiority of DTaP-IPV to *Infanrix +IPOL* was demonstrated with respect to this endpoint.

The reporting of solicited local, solicited general, and unsolicited adverse events was generally comparable between subjects who received the DTaP-IPV candidate vaccine and separately administered DTaP and IPV vaccines. Injection site pain (grade 3 intensity at any injection site and any or grade 3 pain at the DTaP/DTaP-IPV injection site,) and fever >38°C were observed more frequently in the DTaP-IPV vaccine group than in the group receiving separately administered DTaP and IPV vaccines, while redness of ≥110mm diameter at any injection site and any redness at the MMRII injection site was observed more frequently in the group receiving separately administered DTaP and IPV vaccines than in the DTaP-IPV vaccine group. The difference in the incidence of fever between the treatment groups is not considered to be clinically relevant.

There were few SAEs reported during the 31 day period after vaccination.

In conclusion, the DTaP-IPV vaccine appears comparable, in terms of its safety and reactogenicity profile, to separately administered DTaP and IPV vaccines.

Reviewer's comments: Percentages of subjects reporting injection site pain (grade 3 intensity at any injection site and any or grade 3 pain at the DTaP/DTaP-IPV injection site) and fever >38°C were significantly higher in the DTaP-IPV vaccine group than in the group receiving separately administered DTaP and IPV vaccines (P-value = 0.029, 0.012, and 0.017, respectively). Clinical relevance of these findings is determined by the judgment of Dr. Karen Farizo, the clinical reviewer.

2.3 Supportive Study 213503/047

Study Design

This was a phase II IND study to evaluate the non-inferiority of the DTaP-IPV vaccine as compared to DTaP and IPV vaccines administered separately in terms of D, T, PT, FHA, and PRN booster responses and in terms of poliovirus types 1, 2, and 3 GMTs one month after vaccination, when MMR vaccine was co-administered to both groups. This study included 400 healthy children 4 to 6 years of age who had previously received four doses of GSK Biologicals DTaP vaccine Infanrix, three doses of poliovirus vaccine (two doses of Aventis Pasteur-Merck Sharp and Dohme's poliovirus vaccine IPOL and one dose of Lederle's poliovirus vaccine Orimune, or three doses of IPOL), and Merck's MMR vaccine, M-M-R$_{II}$, according to routine US immunization schedule recommendations. Subjects were randomized 1:1 into two groups. One group (DTaP-IPV) received GSK Biologicals' DTaP-IPV vaccine in the left deltoid co-administered with M-M-R$_{II}$ in the right deltoid on Day 0, and the second group (DTaP+IPOL) received Infanrix in the left deltoid and IPOL and M-M-R$_{II}$ at separate sites in the right deltoid on Day 0.

Study Objectives and Endpoints

The primary objective was to evaluate DTaP-IPV vaccine as compared to DTaP and IPV vaccines administered separately in terms of D, T, PT, FHA, and PRN booster responses and in terms of poliovirus GMTs one month after vaccination.

The secondary objective was to evaluate DTaP-IPV vaccine as compared to DTaP and IPV vaccines administered separately in terms of D, T, PT, FHA, and PRN GMCs and in terms of poliovirus booster response one month after vaccination.

Primary endpoints were defined as: **Immunogenicity one month after vaccination:**

- Anti-D booster response
- Anti-T booster response
- Anti-PT booster response
- Anti-FHA booster response
- Anti-PRN booster response
- Anti-poliovirus type 1 antibody titers
- Anti-poliovirus type 2 antibody titers
- Anti-poliovirus type 3 antibody titers.

Booster responses are defined as follows:

For anti-D and anti-T:

- initially seronegative subjects (pre-booster antibody concentration below cut-off: <0.1 IU/mL) should have an increase of at least four times the cut-off, one month after vaccination (post-booster antibody concentration ≥0.4 IU/mL),
- initially seropositive subjects (pre-booster antibody concentration ≥0.1 IU/mL) should have an increase of at least four times the pre-booster antibody concentration, one month after vaccination.

For anti-PT, anti- FHA, and anti-PRN:

- initially seronegative subjects (pre-booster antibody concentration below cut-off: <5 EL.U./mL) should have an increase of at least four times the cut-off, one month after vaccination (post-booster antibody concentration ≥20 EL.U./mL),
- initially seropositive subjects with pre-booster antibody concentration ≥5 EL.U./mL and <20 EL.U./mL should have an increase of at least four times the pre-booster antibody concentration, one month after vaccination,
- initially seropositive subjects with pre-booster antibody concentration ≥20 EL.U./mL should have an increase of at least two times the pre-booster antibody concentration, one month after vaccination.

Secondary endpoints were defined as: **Immunogenicity one month after vaccination:**

- Anti-poliovirus type 1 booster response
- Anti-poliovirus type 2 booster response
- Anti-poliovirus type 3 booster response.

Booster responses are defined as follows:

For anti-poliovirus types 1, 2, and 3:

- initially seronegative subjects (pre-booster antibody titers below cut-off: <1:8 by neutralization) should have an increase of at least four times the cut-off, one month after vaccination (post-booster antibody titer ≥1:32 neutralization)
- initially seropositive subjects (pre-booster antibody titers ≥1:8 by neutralization) should have an increase of at least four times the pre-booster antibody titer, one month after vaccination.

Antibody concentrations:

- Anti-diphtheria and anti-tetanus antibody concentrations
- Anti-PT, anti-FHA, and anti-PRN antibody concentrations
- Anti-measles, anti-mumps, and anti-rubella antibody concentrations or titers.

Seroprotection status defined as follows:

- anti-diphtheria toxoid antibody concentration ≥0.1 IU/mL by ELISA
- anti-tetanus toxoid antibody concentration ≥0.1 IU/mL by ELISA
- anti-poliovirus type 1 antibody titer ≥1:8 by neutralization
- anti-poliovirus type 2 antibody titer ≥1:8 by neutralization
- anti-poliovirus type 3 antibody titer ≥1:8 by neutralization
- anti-measles antibody concentration ≥150 mIU/mL by ELISA
- anti-mumps antibody titer ≥1:28 by neutralization
- anti-rubella antibody concentration ≥10 IU/mL by ELISA.

Seropositivity status defined as follows:

- anti-PT antibody concentration ≥5 EL.U./mL by ELISA
- anti-FHA antibody concentration ≥5 EL.U./mL by ELISA
- anti-PRN antibody concentration ≥5 EL.U./mL by ELISA
- anti-rubella antibody concentration ≥4 IU/mL by ELISA.

Safety and reactogenicity:

- Occurrence of solicited local (pain, redness, and swelling) and general (fever, drowsiness, and loss of appetite) symptoms within 4 days (Day 0 through Day 3) and within 15 days (Day 0 through Day 14) after vaccination.
- Increase in the mid-upper arm circumference of the DTaP-containing vaccine administration side within 4 days (Day 0 through Day 3) and within 15 days (Day 0 through Day 14) after vaccination.
- Occurrence of large injection site swellings in the DTaP-containing vaccine administration side within 4 days (Day 0 through Day 3) and within 15 days (Day 0 through Day 14) after vaccination. Large injection site swellings are defined as either swelling with a diameter of >50 mm or a >30 mm increase of the mid-upper arm circumference when compared to the baseline (pre-vaccination) measurement, or any diffuse swelling that interferes with or prevents everyday activities (for example, writing, drawing, active playing, eating, school/day care attendance, sleeping).
- Occurrence of solicited general symptoms specific to MMR vaccination (rash/exanthem, parotid/salivary gland swelling, and any suspected signs of meningism including febrile convulsions) within 15 days (Day 0 through Day 14) and within 43 days (Day 0 through Day 42) after vaccination.
- Occurrence of unsolicited symptoms within 31 days (Day 0 through Day 30) after vaccination.
- Occurrence during the entire study period (from Visit 1 to 6 months [minimum 180 days] post-vaccination) of serious adverse events (SAEs).
- Occurrence during the ESFU phase (from Day 31 to 6 months [minimum 180 days] post-vaccination) of:
    - onset of chronic illness(es) (for example, diabetes, autoimmune diseases, asthma, and allergies)
    - adverse events (AEs) leading to emergency room (ER) visits, AEs leading to physician office visits that were not related to either well-child care or vaccine administration or common acute illnesses such as upper respiratory tract infection, otitis media, pharyngitis, urinary tract infection, and gastroenteritis.

<u>Sample Size Calculation</u>

The target sample size was 400 enrolled subjects to attain 360 subjects evaluable for the ATP analysis of immunogenicity. The enrollment aim was to reach at least 200 subjects who had been primed with 3 doses of IPV prior to enrollment.

Considering 180 evaluable subjects by group and assuming an equal immune response for both vaccine groups:

- an upper limit of the two-sided 95% CI for the absolute group difference in booster response rate being ≤ 10% for each of the D, T, PT, FHA, and PRN antigens

and

- an upper limit of the two-sided 95% CI for the GMT ratio between groups in the three poliovirus antigens being ≤ 2 for each of the poliovirus serotypes.

Table 7 and Table 8 (Tables 6 and 7 in the applicant's Clinical Study Report for Study 213503/047) present the power calculation.

Table 7 Power to rule out a decrease of more than 10% in the proportion of subjects showing a booster response to a given antigen one month after vaccination with DTaP-IPV vaccine as compared to vaccination with DTaP and IPV vaccines (N=180 evaluable subjects per group, one-sided equivalence test, α = 2.5%, power under the alternative of equal proportions in both groups)

Endpoints: booster response to	Booster response rate* (%)	Power	Nominal Type II error
Anti-Diphtheria	97.6	>99%	<1%
Anti-Tetanus	100	>99%	<1%
Anti-PT	95.2	>99%	<1%
Anti-FHA	98.7	>99%	<1%
Anti-PRN	100	>99%	<1%

Booster response with DTaP in 208355/118 (APV-118) for anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN.

Table 8 Power to rule out a 2 times decrease in the GMT ratio for each of the three poliovirus antigens one month after vaccination with DTaP-IPV vaccine as compared to DTaP and IPV vaccines (N=180 evaluable subjects per group, one-sided equivalence test, α = 2.5%, power under the alternative of equal GMT in both groups)

Endpoints	Standard deviation [Log10 (concentration)]*	Power to observe a 95% CI below 2 assuming that both vaccines are identical in terms of expected GMT**	Nominal Type II error
anti-poliovirus type 1	0.530	>99%	<1%
anti-poliovirus type 2	0.468	>99%	<1%
anti-poliovirus type 3	0.523	>99%	<1%

* Reference study: 213503-033 (DTPa-IPV-033)
** One sided non-inferiority test, limit=log10(2), N=180/group

Study Cohorts for Safety

For the total analysis of safety, this cohort included all enrolled and vaccinated subjects for whom post-vaccination safety data were available.

The Extended Safety Follow-up (ESFU) cohort included all vaccinated subjects who had safety follow-up beyond Day 30 as documented by either a 6 month telephone contact or an AE reported after Day 30.

The ATP cohort for analysis of safety included all vaccinated subjects for whom administration site of study vaccine/comparator was known and who had not received a vaccine not specified or forbidden in the protocol.

The primary analyses were based on:

- the Total vaccinated cohort for the analysis of safety
- the ATP cohort for immunogenicity for the analysis of immunogenicity

Immunogenicity Results

A total of 368 subjects (181 in the DTaP-IPV + MMR group and 187 in the DTaP + IPV + MMR group) were eligible for inclusion in the ATP analysis for immunogenicity.

Booster responses to diphtheria toxoid were observed in 96.6% of subjects in the DTaP-IPV+ MMR group and 98.9% of subjects in the DTaP + IPV + MMR group. Booster responses to tetanus toxoid were observed in at least 97.2% of subjects in both groups.

Table 9 (Table 19 in the applicant's Clinical Study Report for Study 213503/047) presents the differences in booster responses to diphtheria and tetanus between the DTaP + IPV + MMR group and the DTaP-IPV + MMR group one month after vaccination.

Table 9 Differences in percentage of subjects with booster responses to diphtheria and tetanus toxoids in the DTaP-IPV + MMR and DTaP + IPV + MMR groups one month after vaccination (ATP cohort for immunogenicity)

Antibody	DTaP-IPV + MMR			DTaP + IPV + MMR			Difference in booster response rates (DTaP + IPV + MMR minus DTaP-IPV + MMR)			Clinical limit for non-inferiority
							Value (%)	95% CI		
	N	n	%	N	n	%		LL	UL	
Anti-D	176	170	96.6	185	183	98.9	2.33	-0.87	6.29	10%
Anti-T	176	171	97.2	185	180	97.3	0.14	-3.70	4.11	10%

Booster response defined as:
- For initially seronegative subjects (pre-vaccination antibody concentrations below the cut-off of 0.1 IU/mL by ELISA): post-vaccination antibody concentrations at least four times the cut-off (≥0.4 IU/mL) one month after vaccination
- For initially seropositive subjects (pre-vaccination antibody concentrations (≥0.1 IU/mL by ELISA): at least a four increase in pre-vaccination antibody concentrations one month after vaccination

N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of subjects with a booster response
95% CI = standardized asymptotic two-sided 95% confidence interval for the difference; LL = lower limit, UL = upper limit

Table 10 (Table 21 in the applicant's Clinical Study Report for Study 213503/047) presents the two-sided 95% CIs for the adjusted ratios of anti-PT, anti-FHA, and anti-PRN GMCs between the DTaP + IPV + MMR group and the DTaP-IPV + MMR group one month after vaccination for the ATP immunogenicity cohort.

Table 10 Ratios of anti-PT, anti-FHA and anti-PRN GMCs between the DTaP + IPV + MMR and DTaP-IPV + MMR groups one month after vaccination (ATP cohort for immunogenicity)

Antibody	DTaP-IPV + MMR		DTaP + IPV + MMR		Adjusted GMC ratio	95% CI	
	N	Adjusted GMC	N	Adjusted GMC		LL	UL
Anti-PT	165	101.6	168	92.7	0.913	0.760	1.096
Anti-FHA	170	374.1	179	398.0	1.064	0.918	1.233
Anti-PRN	176	620.4	185	533.8	0.860	0.728	1.017

GMC = geometric mean antibody concentration adjusted for baseline concentration by ANCOVA
Ratio = ratio of the GMC in the DTaP + IPV + MMR group divided by the GMC in the DTaP-IPV + MMR group
N = number of subjects with both pre- and post-vaccination results available
95% CI = 95% two-sided confidence interval for the ratio; LL = lower limit; UL = upper limit

Table 11 and Table 12 (Tables 25 and 26 in the applicant's Clinical Study Report for Study 213503/047) presents the two-sided 95% CIs for the adjusted ratios of anti-poliovirus types 1, 2, and 3 GMTs in the DTaP + IPV + MMR group and the DTaP-IPV + MMR group one month after vaccination for the ATP immunogenicity cohort (regardless of poliovirus vaccine priming history) and for subjects who were primed with three doses of IPV vaccine, respectively.

Table 11 Ratios of anti-poliovirus types 1, 2 and 3 GMTs between the DTaP + IPV + MMR group and the DTaP-IPV + MMR group one month after vaccination (ATP cohort for immunogenicity)

Antibody	DTaP-IPV + MMR		DTaP + IPV + MMR		Adjusted GMT ratio	95% CI		Clinical limit for Non-inferiority
	N	Adjusted GMT	N	Adjusted GMT		LL	UL	
Anti-poliovirus type 1	167	1336.0	169	1320.0	0.988	0.812	1.203	2 times
Anti-poliovirus type 2	166	1226.5	167	1180.5	0.962	0.793	1.168	2 times
Anti-poliovirus type 3	152	2108.7	162	2227.3	1.056	0.827	1.348	2 times

Note: Table includes all subjects in the ATP cohort for immunogenicity, regardless of their poliovirus vaccine priming history.
GMT = geometric mean antibody titer adjusted for baseline titer by ANCOVA
Ratio = ratio of the GMT in the DTaP + IPV + MMR group divided by the GMT in the DTaP-IPV + MMR group
N = number of subjects with both pre- and post-vaccination results available
95% CI = 95% two-sided confidence interval for the ratio; LL = lower limit; UL = upper limit

Table 12 Ratios of anti-poliovirus types 1, 2, and 3 GMTs between the DTaP + IPV + MMR group and the DTaP-IPV + MMR group one month after vaccination (ATP cohort for immunogenicity – subjects who previously received 3 doses of IPV)

Antibody	DTaP-IPV + MMR		DTaP + IPV + MMR		Adjusted GMT ratio	95% CI	
	N	Adjusted GMT	N	Adjusted GMT		LL	UL
Anti-poliovirus type 1	152	1272.0	152	1206.4	0.95	0.77	1.16
Anti-poliovirus type 2	152	1172.9	151	1120.9	0.96	0.78	1.17
Anti-poliovirus type 3	142	1968.1	148	1983.5	1.01	0.79	1.29

Note: Table includes only subjects in the ATP cohort for immunogenicity who had received three previous doses of IPV vaccine.
GMT = geometric mean antibody titer adjusted for baseline titer by ANCOVA
Ratio = ratio of the GMT in the DTaP + IPV + MMR group divided by the GMT in the DTaP-IPV + MMR group
N = number of subjects primed with three doses of IPV vaccine prior to study entry with both pre- and post-vaccination results available
95% CI = 95% two-sided confidence interval for the ratio; LL = lower limit; UL = upper limit

Conclusion for the primary objectives: The upper limit of the standardized asymptotic two-sided 95% CIs for the group differences (DTaP + IPV + MMR minus DTaP-IPV + MMR) in booster response rates was below the pre-defined clinical limit for non-inferiority of 10% for anti-D and for anti-T. Hence, it can be concluded that the primary objective with respect to D and T response has been met.

The upper limits of the standardized asymptotic two-sided 95% CIs for the group differences (DTaP + IPV + MMR minus DTaP-IPV + MMR) in booster response rates were below the predefined clinical limit for non-inferiority of 10% for each of the pertussis antigens. Hence, it can be concluded that the primary objective with respect to PT, FHA, and PRN immune response has been met.

The upper limits of the two-sided 95% CIs for the GMT ratio between groups (DTaP + IPV + MMR divided by DTaP-IPV + MMR) for the three poliovirus antigens in the ATP cohort, regardless of poliovirus vaccine priming history, as well as for the analyses restricted to subjects primed with three doses of IPV vaccine were below the pre-defined clinical limit for noninferiority of 2. Hence, it can be concluded that the immunogenicity of the DTaP-IPV vaccine was non-inferior to that of DTaP and IPV vaccines administered separately in terms of anti-poliovirus type 1, anti-poliovirus type 2, and anti-poliovirus type 3 GMT, when both groups received a separate concomitant injection of MMR vaccine.

Safety Results

The study's objective was to assess the safety and reactogenicity of the study vaccines administered in both groups. No statistically significant differences were observed between the DTaP-IPV + MMR and DTaP + IPV + MMR groups in the incidence of solicited local symptoms or in the incidence of solicited general symptoms. Grade 3 solicited symptoms were reported infrequently by both the DTaP-IPV + MMR and DTaP + IPV + MMR groups. Specifically, in the 4-day period after vaccination, Grade 3 pain, Grade 3 redness, Grade 3 swelling at any injection site, and fever ≥39.5$_{o}$C were reported by 3.1%, 28.6%, 15.8%, and 0.5% of subjects in the DTaP-IPV + MMR group, and 4.1%, 24.6%, 14.4%, and 0% of subjects in the DTaP + IPV + MMR group, respectively. The most frequently reported unsolicited AEs by subjects in the DTaP-IPV + MMR group were upper respiratory infection (6.0%), vomiting (5.0%), cough (4.0%), pyrexia (4.0%), injection site pruritus (3%), and by subjects in the DTaP + IPV + MMR group were cough (7.5%), upper respiratory infection (3.0%), headache (3.0%), and injection site bruising (3.0%).The percentage of subjects reporting Grade 3 unsolicited symptoms in both groups was low (4.5% of subjects in the DTaP-IPV + MMR group and 4.0% of subjects in the DTaP + IPV + MMR group) during the 31-day follow-up period after vaccination.

Serious adverse events were reported for two subjects in the DTaP + IPV + MMR group during the active phase of the study. Neither of the SAEs was considered by the investigator to be related to vaccination.

During the 5-month ESFU phase, the percentages of subjects reporting a new onset of chronic illness, AEs that resulted in an ER visit, or resulted in a physician's office visit that were not related to routine visits for physical examinations or common illnesses were similar between the two vaccine groups. The occurrence of SAEs was low in the DTaPIPV + MMR group (N = 3) and no SAEs were reported in the DTaP + IPV + MMR group. None of the SAEs were considered to be related to vaccination by the investigators.

3. REVIEWER'S RECOMMENDATION

Overall, data presented in this submission support the conclusion that a single booster dose of the candidate DTaP-IPV vaccine is immunogenic for all vaccine components, elicits seroprotective antibody concentrations of antibodies to diphtheria and tetanus toxoids and poliovirus types 1, 2, and 3, and will be as efficacious as *Infanrix* against pertussis disease when administered to children 4 to 6 years of age.

A minor concern regarding safety in Study 213503/048 is addressed below in the Comments and Questions to CBER Review Committee.

Based on the fact that the 95% CIs of GMC ratios included 1, the applicant claimed that post-vaccination GMCs for anti-D and anti-T as well as for anti-PT, anti-FHA, and anti-PRN were "similar" in the pooled DTaP-IPV groups and the DTaP + IPV group. Such a result could be due to insufficient sample size (lack of power) to reject the null hypothesis. Although these statements refer to the exploratory analysis, accurate conclusions still should be made.

4. COMMENTS AND QUESTIONS TO CBER REVIEW COMMITTEE

- Percentages of subjects reporting injection site pain (grade 3 intensity at any injection site and any or grade 3 pain at the DTaP/DTaP-IPV injection site,) and fever >38°C were statistically significantly higher in the DTaP-IPV vaccine group than in the group receiving separately administered DTaP and IPV vaccines (P-value = 0.029, 0.012, and 0.017, respectively). Clinical relevance of these findings should be evaluated by Dr. Karen Farizo, the clinical reviewer.

5. COMMENTS AND QUESTIONS TO APPLICANT

- In the Clinical Study Report for Study 213503/048 (pages 95 and 97), you state that a 95% CI for the GMC ratio between the pooled DTaP-IPV groups and the DTaP + IPV group containing 1 implies that post-vaccination GMCs are **similar** in both groups. Please note that the hypothesis did not test for similarity. Such a result could be due to insufficient sample size (lack of power) to reject the null hypothesis. Please state the conclusion accurately.