In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

The following guiding principles have been applied to the disclosure:

- Information will be excluded in order to protect the privacy of patients and all named persons associated with the study
- Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the GSK Clinical Study Register.
- Aggregate data will be included; with any direct reference to individual patients excluded

*Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered
GlaxoSmithKline Biologicals, SA

Study detailed title
An open, phase III, non-randomized, multi-center study to assess the immunogenicity and safety of a booster dose of GlaxoSmithKline (GSK) Biologicals’ combined reduced antigen content diphtheria-tetanus toxoids and acellular pertussis vaccine (Boostrix), when administered in young adults, 10 years after previous booster vaccination in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001]

Clinical Study Report for Study 116570 [DTPA 0.3 (BOOSTRIX)-012 EXT:001]

Development Phase: III

IND Number: BB-IND 8461

Name of Investigational Product: GlaxoSmithKline (GSK) Biologicals’ combined reduced antigen content diphtheria-tetanus toxoids and acellular pertussis vaccine (Boostrix).

Indication Studied: Booster vaccination against diphtheria, tetanus and pertussis diseases in adults.

Study initiation date: 31-January-2013

Study completion date: 02-April-2014

Data lock point (Date of database freeze): 10-May-2017

Date of report: Final: 14-September-2017

Sponsor Signatory: Narcisa Mesaros
Clinical and Epidemiology R&D Project Leader, DTP, Polio and Hib containing vaccines R&D Centre Belgium GlaxoSmithKline Biologicals

This study was performed according to the principles of GCP including the archiving of essential documents.

Based on GSK Biologicals’ Study Report INS-BIO-CLIN-1010 v05

© [2017] GSK group of companies or its licensor.
- **Name of company:** GlaxoSmithKline Biologicals, SA, Rixensart, Belgium  
- **Name of finished product:** Boostrix  
- **Name of active substance:** Diphtheria (D) and tetanus toxoids (T), pertussis toxin (PT), filamentous haemagglutinin (FHA) and pertactin (PRN)

### Study No.:

116570 [DTPA 0.3 (BOOSTRIX)-012 EXT:001]

### Title of the study:

An open, phase III, non-randomized, multi-center study to assess the immunogenicity and safety of a booster dose of GlaxoSmithKline (GSK) Biologicals’ combined reduced antigen content diphtheria-tetanus toxoids and acellular pertussis vaccine (Boostrix), when administered in young adults, 10 years after previous booster vaccination in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001]

### Investigators and study centers:

This study was conducted at multiple centers in the United States. The contributing PI for this study was Dr. Meera Varman, (affiliated to Department of Pediatrics, Creighton University School of Medicine) 2412 Cummings Street, Suite 100, Room 1022, Omaha, Nebraska 68131, United States.

### Publication (reference):

None at the time of this report.

### Study period:

- **Study initiation date:** 31-January-2013  
- **Study completion date:** 02-April-2014  
- **Data lock point (Date of database freeze):** 10-May-2017

### Indication:

Booster vaccination against diphtheria, tetanus and pertussis diseases in adults.

### Objectives:

**Co-Primary:**

- To demonstrate that a second dose of Tdap vaccine (administered to the Tdap Group) was non-inferior to a first dose of Tdap vaccine (administered to the Td Group), with respect to immune response to diphtheria and tetanus antigens.
  
  *The criterion for meeting the above objective was defined as:*
  
  - One month after vaccination, the lower limits of the 95% CI on the difference of the seroprotection rates [second dose of Tdap (Tdap Group) minus first dose of Tdap (Td Group)] for anti-diphtheria, anti-tetanus antibody concentrations were greater than or equal to -10% (clinical limit for non-inferiority).
  
- To demonstrate that a second dose of Tdap vaccine, (administered to the Tdap group) was non-inferior to a three dose series of Infanrix vaccine in infants who received this vaccine in German household contact efficacy study APV-039, with respect to antibodies against pertussis toxin (anti-PT), antibodies against filamentous hemagglutinin (anti-FHA) and antibodies against pertactin (anti-PRN) antibody concentrations.
  
  *The criterion for meeting the above objective was defined as:*
  
  - One month after vaccination, the lower limits of the 95% CI on the anti-PT, anti-FHA and anti-PRN GMC ratios (Tdap Group divided by Infanrix Group in APV-039) were greater than or equal to 0.67.

**Secondary:**

- To assess the persistence of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 10 years after the previous booster dose of the Tdap vaccine in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].
  
- To assess the immunogenicity of the Tdap vaccine in terms of seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies, one month after vaccination.
  
- To explore the potential difference in terms of booster response to anti-D, anti-T, anti-PT, anti-FHA and anti-PRN between the second dose of Tdap vaccine (administered to the Tdap Group) and the first dose of Tdap vaccine (administered to the Td Group).
  
- To explore the potential difference in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations.
<table>
<thead>
<tr>
<th>Name of company:</th>
<th>GlaxoSmithKline Biologicals, SA, Rixensart, Belgium</th>
<th>Name of finished product:</th>
<th>Boostrix</th>
<th>Name of active substance: Diphtheria (D) and tetanus toxoids (T), pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN)</th>
</tr>
</thead>
</table>

Antibody concentrations between a second dose of Tdap vaccine (administered to the Tdap Group) and a first dose of Tdap vaccine (administered to the Td Group).

- To evaluate and compare the safety of a second dose of Tdap vaccine (administered to the Tdap group) and a first dose of Tdap vaccine (administered to the Td group), with respect to solicited symptoms (local and general), unsolicited symptoms and serious adverse events (SAEs).

**Methodology:** Phase III, open-label, non-randomized, multi-center, single-country study with two parallel groups.

- Tdap Group: Subjects randomized to the Lot A, Lot B or Lot C groups in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001] were pooled and received a second dose of the Tdap vaccine in this study.
- Td Group: Subjects who had received Td vaccine in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001] received the first dose of Tdap vaccine in this study.

A blood sample of approximately 5 mL was collected from all subjects before vaccination (Pre-Bst) and one month after vaccination (Post-Bst).

**Study vaccine, dose, mode of administration, lot no.:**

**Vaccination schedule /site:** Subjects in both the groups received a single dose of the Tdap vaccine as a deep intramuscular injection into the deltoid muscle of the non-dominant arm.

**Vaccine composition /dose /lot number:** Tdap: Diphtheria toxoid: 2.5 Limits of flocculation (Lf), Tetanus toxoid: 5 Lf, PT: 8 μg, FHA: 8 μg, PRN: 2.5 μg, Aluminum as Al(OH)₃: ≤ 0.39 mg, Sodium chloride.

**Lot numbers:** Tdap: AC52B087BC

Reference vaccine /Comparator, dose and mode of administration, lot no.: Not applicable.

**Study Population:**

A total of 165 subjects (37 subjects in the Td group and 128 subjects in the Tdap group) were vaccinated in this study, of which a total of 160 subjects (36 subjects in the Td group and 124 subjects in the Tdap group) completed this study. Subjects who had received a dose of Tdap or Td vaccines 10 years earlier in the study 776423/001 [DTPA 0.3 (BOOSTRIX)-001] were included in this study. Written informed consent was obtained from all subjects. Subjects who had received diphtheria, tetanus or pertussis vaccination since the last dose received in the study 776423/001 [DTPA 0.3 (BOOSTRIX) -001] or who have encountered diphtheria, tetanus or pertussis disease were ineligible and excluded from the ATP analyses.

**Duration of treatment:**

The duration of the study, for each subject, was approximately one month.

**Criteria for evaluations:**

**Co-Primary endpoints:**

- Immunogenicity with respect to components of the study vaccine.
  - Anti-D and anti-T antibody concentrations ≥ 0.1 IU/mL by ELISA, one month after vaccination.
  - Anti-pertussis (PT, FHA and PRN) antibodies GMCs one month after vaccination.
  - Anti-pertussis (PT, FHA and PRN) antibodies GMCs one month after the third dose of Infanrix in Study APV-039 Total Vaccinated cohort (TVC).

**Secondary endpoints:**

- Immunogenicity with respect to components of the study vaccine.
  - Anti-D* and anti-T antibody concentrations ≥ 0.1 IU and ≥ 1.0 IU/mL by ELISA or ≥ 0.01 IU/mL by Vero cell testing for subjects with post-vaccination ELISA anti-D toxoid antibody concentration < 0.1 IU/mL, prior to and one month after vaccination.
  - Anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ assay cut-off**, anti-D,anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations prior to and one month after
Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium
Name of finished product: Boostrix
Name of active substance: Diphtheria (D) and tetanus toxoids (T), pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN)

vaccination.
- Booster response to the diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens one month after vaccination.

* Sera with ELISA concentrations < 0.1 IU/mL were tested for neutralizing antibodies using a Vero-cell neutralization assay.

** During the course of the study, the assays used to measure the anti-D, anti-T, anti-PT, anti-FHA and anti-PRN IgG concentrations were re-developed and re-validated and both assay units and assay cut-offs were adapted. The new ELISA’s for PT, FHA and PRN were calibrated against the WHO International Standard (NIBSC 06/140). This allowed the expression of concentrations measured with the new ELISA’s in international units per millilitre (IU/mL) instead of the formerly used ELISA units per millilitre (ELU/mL). The newly validated DTPa ELISA’s used in the study have a lower assay cut-off as compared to the one described in the protocol. The current assay cut-off is 0.057 IU/mL for anti-D, 0.043 IU/mL for anti-T, 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA and 2.187 IU/mL for anti-PRN.

• Solicited local and general symptoms.
  - Occurrence of each solicited local and general symptoms (any and Grade 3) within 4-day (Days 0-3) after vaccination.
  - Occurrence of large injection site reactions (defined as swelling with a diameter > 100 mm, noticeable diffuse swelling or noticeable increase of limb circumference) within 4-day (Days 0-3) after vaccination.

• Unsolicited adverse events.
  - Occurrence of unsolicited AEs within 31-day (Days 0-30) after vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.

• Serious adverse events (SAEs).
  - Occurrence of SAEs from the administration of the vaccine dose up to 31 days following vaccination.

Statistical methods: Analyses were performed as per protocol amendment 2 dated 03-October-2013 and Statistical Analysis Plan amendment dated 20-April-2017.

Analysis of demographics
Demographic characteristics (age at vaccination visit in years, gender, geographical ancestry and ethnicity) were summarized by group using descriptive statistics:
- Frequency tables were generated for categorical variable such as center.
- Mean, median, standard deviation was provided for continuous data such as age.

In addition, a summary of the tracking log-sheet documenting outcomes of the contacts made with subjects for enrolment were provided.

Analysis of immunogenicity:
The primary analysis was based on the according to protocol (ATP) cohort for analysis of immunogenicity. Since the percentage of vaccinated subjects with serological results excluded from the ATP cohort for analysis of immunogenicity was 5% or more, a second analysis based on the TVC was performed to complement the ATP analysis.

Within group assessment
For each group and each antigen:
- Seropositivity/seroprotection rate at pre-vaccination, one month post-vaccination was calculated with exact 95% confidence intervals (CIs).
- Geometric mean concentrations (GMCs) or at pre-vaccination, one month post-vaccination were tabulated with 95% CIs.
- Booster response rate one month post-vaccination was calculated with exact 95% CIs.
- Antibody concentrations distribution at pre-vaccination and one month post-vaccination was displayed using reverse cumulative curves (RCC).
Between groups assessment

- For anti-D, anti-T seroprotection rates, the two-sided standardized asymptotic 95% CI for the group differences (Tdap Group minus Td Group) was calculated.
- For anti-D, anti-T antibody response, the two-sided 95% CIs of the GMC ratios between subjects in the Tdap Group and (divided by) the Td Group one month after vaccination was computed using an analysis of covariance (ANCOVA) model on the logarithm10 transformation of the concentrations adjusted to pre-vaccination concentration in 776423/001 [DTPA 0.3 (BOOSTRIX)-001] study.
- For anti-PT, anti-FHA and anti-PRN antibody response, the two-sided 95% CIs of the GMC ratios between subjects in the Tdap Group and (divided by) the Infanrix Group in APV-039 one month after vaccination (one month after vaccination for Tdap Group, one month after the third dose of Infanrix for Infanrix group in APV-039) was computed using the method proposed by G.Y. Zou and A. Donner (Zou, 2008) in order to account heterogeneity of variance between this study and APV-039. Note that the APV-039 reference for this comparison was the results converted into the revalidated assays by using multiple imputation techniques (GlaxoSmithKline Biologicals Annex Report 208355 (APV) 022).
- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN booster response, the two-sided standardized asymptotic 95% CI for the group differences (Tdap Group minus Td Group) was calculated.
- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN alternative booster response, the two-sided standardized asymptotic 95% CI for the group differences (Tdap Group minus Td Group) was calculated.

Interpretation of analyses:
Except for analyses addressing criteria specified in the objectives, comparative analyses were exploratory with the aim to characterize the difference between groups in immunogenicity. These exploratory analyses were not used to conclude since there was no adjustment for multiplicity of endpoints.

With respect to the two co-primary objectives, the interpretation was done according to a hierarchical procedure. More specifically, the second primary objective could be reached only if all the associated criteria were met and the first primary objectives were reached.

Sensitivity analysis
An analysis of persistence was carried out in order to evaluate the robustness of the results with respect to dropout, by using a repeated generalised linear model. This model used results from 776423/001 [DTPA 0.3 (BOOSTRIX)-001] post-vaccination visit and pre-booster results of the current study.

Analysis of safety:
Within groups assessment
The primary analysis was based on the TVC. There were no subjects excluded from the ATP cohort for analysis of safety, hence a second analysis based on this ATP cohort was not performed to complement the analysis of the TVC.

Safety data was analyzed by subject incidence rates of solicited and unsolicited adverse events in the vaccine schedules treatment groups by solicited local and general symptom terms, and, for unsolicited AEs, by MedDRA preferred term and system organ class. Safety data was summarized for all subjects by treatment group.

The incidence of solicited local and general symptoms occurring during 4 days after vaccination was tabulated with exact 95% CI for each treatment group. The same calculations were performed for symptoms of any intensity, those with intensity Grade ≥ 2, and those with intensity of Grade 3, as well as
for solicited general events with relationship to vaccination and events requiring medical attention, respectively. Note that all solicited local adverse events were considered to be causally related. The percentage of subjects with at least one report of an unsolicited adverse event classified by MedDRA up to 31 days after vaccine was tabulated with exact 95% CI for each treatment group. The same tabulation was performed for Grade 3 unsolicited adverse events, AEs resulting in a medically attended visit and for unsolicited adverse events that were considered by the investigator to be possibly related to vaccination. SAEs were summarized from Day 0 to 31 days post-vaccination. SAEs, large injection site reaction (defined as swelling with a diameter > 100 mm, noticeable diffuse swelling or noticeable increase of limb circumference) and withdrawals due to adverse event(s) were described in detail.

**Between groups assessment**

The standardized asymptotic 95% CI for the difference between the two groups and the associated 2-sided p-value to detect group difference (Newcombe, 1998) was computed for the following endpoints:

- For each solicited symptom, the percentage of subjects reporting the symptom within 4 days after vaccination (any Grade, Grade 3, causally related, respectively).
- The percentage of subjects reporting adverse events within 31 days post-vaccination (any, Grade 3, causally related, requiring medical attention).
- The percentage of subjects reporting SAEs (any, causally related) during the study period.

P-value below 5% was used to identify events that were recognized as worthy of further investigation. It was to be noted that the use of such analyses had the potential to identify a large number of events which may or may not have a causal relationship to treatment due to unadjustment for multiplicity. In order to put these in perspective, the analysis was complemented by a permutation test that quantified the probability of identifying erroneously an event according to the threshold p-value. In addition, clinical judgment and biological plausibility was taken into account when performing overall assessment.

**Study population (Total vaccinated cohort)**

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>Td group</th>
<th>Tdap group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planned, N</td>
<td>125</td>
<td>375</td>
<td>500</td>
</tr>
<tr>
<td>Enrolled, N (Total Vaccinated Cohort)</td>
<td>37</td>
<td>128</td>
<td>165</td>
</tr>
<tr>
<td>Completed, n (%)</td>
<td>36 (97.3)</td>
<td>124 (96.9)</td>
<td>160 (97.0)</td>
</tr>
<tr>
<td>Demographics</td>
<td>Td group</td>
<td>Tdap group</td>
<td>Total</td>
</tr>
<tr>
<td>Enrolled, N (Total Vaccinated Cohort)</td>
<td>37</td>
<td>128</td>
<td>165</td>
</tr>
<tr>
<td>Females: Males</td>
<td>18:19</td>
<td>57:71</td>
<td>75:90</td>
</tr>
<tr>
<td>Mean Age, years (SD)</td>
<td>23.3 (2.4)</td>
<td>23.5 (2.1)</td>
<td>23.5 (2.1)</td>
</tr>
<tr>
<td>Median Age, years (minimum, maximum)</td>
<td>23 (20, 29)</td>
<td>23 (20, 29)</td>
<td>23 (20, 29)</td>
</tr>
<tr>
<td>White/Caucasian, n (%)</td>
<td>31 (83.8)</td>
<td>114 (89.1)</td>
<td>145 (87.9)</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>5 (13.5)</td>
<td>7 (5.5)</td>
<td>12 (7.3)</td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>1 (2.7)</td>
<td>6 (4.7)</td>
<td>7 (4.2)</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
N = total number of subjects
n/% = number/percentage of subjects
SD = standard deviation

---

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium
Name of finished product: Boostrix
Name of active substance: Diphtheria (D) and tetanus toxoids (T), pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN)
Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium
Name of finished product: Boostrix
Name of active substance: Diphtheria (D) and tetanus toxoids (T), pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN)

Summary:

Immunogenicity results:
- The primary objectives of the study were met.
  - One month after vaccination, the seroprotection rate for anti-diphtheria and anti-tetanus was 100% in both groups, leading to a lower limit of the 95% CI on the group difference [second dose of Tdap (Tdap Group) minus first dose of Tdap (Td Group)] greater than -10%.
  - One month after vaccination, the lower limits of the 95% CI on the anti-PT (1.69), anti-FHA (5.14) and anti-PRN (3.22) GMC ratios (Tdap Group divided by Infanrix Group in APV-039) were greater than 0.67.
- There were no confirmatory secondary objectives.
- Sensitivity analysis: From modeling, there was no apparent bias related to dropout.
- The observed booster response rates to diphtheria and tetanus antigens were similarly low in both groups (the rates were below 41% for anti-D and below 60% for anti-T). This might be explained by high concentration values at pre-vaccination. Indeed, the alternative booster response adjusted for high concentration at pre-vaccination provided higher value (rate above 58% for anti-D, rate above 82% for anti-T).
- There was at least a 3-fold rise in the GMC value for anti-D and anti-T antibodies in both the groups indicating a good response to vaccination even though the booster response rates were low. This could be due to the high concentration values observed at the pre-vaccination.
- There was at least a 6-fold rise in the GMC value for anti-PT, anti-FHA and anti-PRN antibodies in both the groups. There was a good booster response rate observed.
- The percentage in booster response rates to PT, FHA and PRN antigens were similar in both groups (rate above 90% for PT and FHA, and rate above 68% for PRN).

Group differences in the percentage of subjects with anti-Diphtheria and anti-Tetanus antibody concentrations ≥ 0.1 IU/mL [Tdap Group minus Td Group], one month after booster vaccination and their standardized asymptotic 95% CIs (ATP cohort for analysis of immunogenicity)

<table>
<thead>
<tr>
<th>Antibody Type</th>
<th>Td group</th>
<th>Tdap group</th>
<th>Difference in percentage of subjects (Tdap group minus Td group)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-D antibody</td>
<td>0.1 IU/mL</td>
<td>35 35 100</td>
<td>115 115 100</td>
<td>0.00</td>
</tr>
<tr>
<td>anti-T antibody</td>
<td>0.1 IU/mL</td>
<td>35 35 100</td>
<td>115 115 100</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
N = number of subjects with available results
n/% = number/percentage of subjects with antibody concentrations above the specified cut-off (≥ 0.1IU/mL)
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
### Name of company:
GlaxoSmithKline Biologicals, SA, Rixensart, Belgium

### Name of finished product:
Boostrix

### Name of active substance:
Diphtheria (D) and tetanus toxoids (T), pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN)

---

GMC ratio between groups [Tdap Group divided by Infanrix Group in APV-039] and their 95% CIs for anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Tdap</th>
<th>Infanrix Group in APV-039</th>
<th>GMC Ratio (Tdap / Infanrix in APV-039)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-PT (Assay cut-off = 2.693 IU/mL)</td>
<td>124</td>
<td>83.5</td>
<td>2884</td>
<td>41.7</td>
</tr>
<tr>
<td>anti-FHA (Assay cut-off = 2.046 IU/mL)</td>
<td>124</td>
<td>265.5</td>
<td>685</td>
<td>47.2</td>
</tr>
<tr>
<td>anti-PRN (Assay cut-off = 2.187 IU/mL)</td>
<td>124</td>
<td>442.6</td>
<td>631</td>
<td>113.0</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
Infanrix Group in APV-039 = Infanrix group of the German household contact study APV-039
N = Number of subjects with available results
95% CI = 95% confidence interval for the adjusted GMC ratio LL = lower limit, UL = upper limit.
The associated CI was derived using the method proposed by G.Y. Zou and A. Donner (Zou, 2008) GMC = geometric mean antibody concentration calculated on all subjects

---

Number and percentage of subjects with anti-Diphtheria and anti-Tetanus antibody concentration ≥ 0.1 IU/mL, ≥ 1 IU/mL and GMCs at pre and post booster vaccination time points (ATP cohort for analysis of immunogenicity)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group</th>
<th>Timing</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
<th>n</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
<th>value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-D antibody (Assay cut-off = 0.057 IU/mL)</td>
<td>Td group</td>
<td>PRE</td>
<td>35</td>
<td>35</td>
<td>100</td>
<td>90.0</td>
<td>100</td>
<td>23</td>
<td>65.7</td>
<td>47.8</td>
<td>80.9</td>
<td>1.6</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>35</td>
<td>35</td>
<td>100</td>
<td>90.0</td>
<td>100</td>
<td>34</td>
<td>97.1</td>
<td>85.1</td>
<td>99.9</td>
<td>6.8</td>
<td>5.4</td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>PRE</td>
<td>115</td>
<td>115</td>
<td>100</td>
<td>96.8</td>
<td>100</td>
<td>70</td>
<td>60.9</td>
<td>51.3</td>
<td>69.8</td>
<td>1.6</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>115</td>
<td>115</td>
<td>100</td>
<td>96.8</td>
<td>100</td>
<td>115</td>
<td>96.8</td>
<td>100</td>
<td>96.8</td>
<td>100</td>
<td>6.0</td>
<td>5.3</td>
</tr>
<tr>
<td>anti-T antibody (Assay cut-off = 0.043 IU/mL)</td>
<td>Td group</td>
<td>PRE</td>
<td>35</td>
<td>35</td>
<td>100</td>
<td>90.0</td>
<td>100</td>
<td>27</td>
<td>77.1</td>
<td>59.9</td>
<td>89.6</td>
<td>1.8</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>35</td>
<td>35</td>
<td>100</td>
<td>90.0</td>
<td>100</td>
<td>35</td>
<td>100</td>
<td>90.0</td>
<td>100</td>
<td>9.9</td>
<td>7.9</td>
<td>12.9</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>PRE</td>
<td>115</td>
<td>115</td>
<td>100</td>
<td>96.8</td>
<td>100</td>
<td>86</td>
<td>74.8</td>
<td>65.8</td>
<td>82.4</td>
<td>1.8</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>115</td>
<td>115</td>
<td>100</td>
<td>96.8</td>
<td>100</td>
<td>115</td>
<td>96.8</td>
<td>100</td>
<td>96.8</td>
<td>100</td>
<td>9.7</td>
<td>8.5</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre =Pre booster vaccination blood sampling time-point
Post = Post booster vaccination blood sampling time-point
**Name of company:**
GlaxoSmithKline Biologicals, SA, Rixensart, Belgium

**Name of finished product:**
Boostrix

**Name of active substance:**
Diphtheria (D) and tetanus toxoids (T), pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN)

---

Number and percentage of subjects with an anti-PT, anti-FHA, anti-PRN antibody concentration ≥ assay cut-off and GMCs at pre and post booster vaccination time points (ATP cohort for analysis of immunogenicity)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group</th>
<th>Timing</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
<th>value</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-PT</td>
<td>Td group</td>
<td>PRE</td>
<td>35</td>
<td>21</td>
<td>60.0</td>
<td>42.1</td>
<td>76.1</td>
<td>5.3</td>
<td>3.4</td>
<td>8.2</td>
</tr>
<tr>
<td>(Assay cut-off = 2.693 IU/mL)</td>
<td>Post</td>
<td>35</td>
<td>35</td>
<td>100</td>
<td>90.0</td>
<td>100</td>
<td>66.2</td>
<td>50.8</td>
<td>86.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>PRE</td>
<td>115</td>
<td>101</td>
<td>87.8</td>
<td>80.4</td>
<td>93.2</td>
<td>9.9</td>
<td>8.1</td>
<td>12.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post</td>
<td>115</td>
<td>115</td>
<td>100</td>
<td>96.8</td>
<td>100</td>
<td>87.3</td>
<td>74.5</td>
<td>102.4</td>
</tr>
<tr>
<td>anti-FHA</td>
<td>Td group</td>
<td>PRE</td>
<td>35</td>
<td>34</td>
<td>97.1</td>
<td>85.1</td>
<td>99.9</td>
<td>21.7</td>
<td>13.4</td>
<td>35.4</td>
</tr>
<tr>
<td>(Assay cut-off = 2.046 IU/mL)</td>
<td>Post</td>
<td>35</td>
<td>35</td>
<td>100</td>
<td>90.0</td>
<td>100</td>
<td>336.2</td>
<td>250.0</td>
<td>452.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>PRE</td>
<td>115</td>
<td>115</td>
<td>100</td>
<td>96.8</td>
<td>100</td>
<td>36.9</td>
<td>31.5</td>
<td>43.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post</td>
<td>115</td>
<td>115</td>
<td>100</td>
<td>96.8</td>
<td>100</td>
<td>290.5</td>
<td>252.5</td>
<td>334.2</td>
</tr>
<tr>
<td>anti-PRN antibody</td>
<td>Td group</td>
<td>PRE</td>
<td>35</td>
<td>33</td>
<td>94.3</td>
<td>80.8</td>
<td>99.3</td>
<td>27.8</td>
<td>13.7</td>
<td>56.3</td>
</tr>
<tr>
<td>(Assay cut-off = 2.187 IU/mL)</td>
<td>Post</td>
<td>35</td>
<td>35</td>
<td>100</td>
<td>90.0</td>
<td>100</td>
<td>425.5</td>
<td>281.9</td>
<td>642.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>PRE</td>
<td>115</td>
<td>115</td>
<td>100</td>
<td>96.8</td>
<td>100</td>
<td>71.6</td>
<td>56.7</td>
<td>90.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post</td>
<td>115</td>
<td>115</td>
<td>100</td>
<td>96.8</td>
<td>100</td>
<td>463.3</td>
<td>390.8</td>
<td>549.3</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre = Pre booster vaccination blood sampling time-point
Post = Post booster vaccination blood sampling time-point

Group difference in booster response to anti-diphtheria and anti-tetanus antigens [Tdap Group minus Td Group], one month after booster vaccination and their standardized asymptotic 95% CIs (ATP cohort for analysis of immunogenicity)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Tdap group</th>
<th>Td group</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-D antibody (IU/mL)</td>
<td>115</td>
<td>47</td>
<td>40.9</td>
</tr>
<tr>
<td>anti-T antibody (IU/mL)</td>
<td>115</td>
<td>64</td>
<td>55.7</td>
</tr>
</tbody>
</table>
**Name of company:** GlaxoSmithKline Biologicals, SA, Rixensart, Belgium  
**Name of finished product:** Boostrix  
**Name of active substance:** Diphtheria (D) and tetanus toxoids (T), pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN)

Td group = Subjects received the first dose of Tdap vaccine  
Tdap group = Subjects received a second dose of Tdap vaccine  
Booster response defined as:
- for subjects with pre-vaccination concentration < 0.1 IU/mL, antibody concentrations at least ≥ 0.4 IU/mL, one month after vaccination,
- for subjects with pre-vaccination concentration ≥ 0.1 IU/mL, an increase in antibody concentrations of at least four times the pre-vaccination concentration one month after vaccination

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

### Group difference in booster response to anti-PT, anti-FHA and anti-PRN antigens [Tdap Group minus Td Group], one month after booster vaccination and their standardized asymptotic 95% CIs (ATP cohort for analysis of immunogenicity)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Tdap group</th>
<th>Td group</th>
<th>Difference in booster response rate (Tdap group minus Td group)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>anti-FHA antibody (IU/mL)</td>
<td>115</td>
<td>104</td>
<td>90.4</td>
<td>35</td>
</tr>
<tr>
<td>anti-PRN antibody (IU/mL)</td>
<td>115</td>
<td>79</td>
<td>68.7</td>
<td>35</td>
</tr>
<tr>
<td>anti-PT antibody (IU/mL)</td>
<td>115</td>
<td>106</td>
<td>92.2</td>
<td>35</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine  
Tdap group = Subjects received a second dose of Tdap vaccine  
Booster response to pertussis antigens is defined as:
- initially seronegative subjects (pre-booster antibody concentration below the assay cut-off) with an increase of at least four times the assay cut-off one month after vaccination,
- initially seropositive subjects with anti-body concentration < four times the assay cut-off with an increase of at least four times the pre-booster antibody concentration one month after vaccination
- initially seropositive subjects with anti-body concentration ≥ four times the assay cut-off with an increase of at least two times the pre-booster antibody concentration one month after vaccination

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

### Alternative booster response to anti-Diphtheria and anti-Tetanus antibodies one month after booster vaccination (ATP cohort for analysis of immunogenicity - excluding subjects with pre-vaccination concentration greater than or equal to 6 IU/mL)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group</th>
<th>Pre-vaccination status</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-D antibody (IU/mL)</td>
<td>Td group</td>
<td>S-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (&lt;1 IU/mL)</td>
<td>12</td>
<td>10</td>
<td>83.3</td>
<td>51.6</td>
<td>97.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (≥1 IU/mL)</td>
<td>18</td>
<td>11</td>
<td>61.1</td>
<td>35.7</td>
<td>82.7</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td>30</td>
<td>21</td>
<td>70.0</td>
<td>50.6</td>
<td>85.3</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>S-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (&lt;1 IU/mL)</td>
<td>45</td>
<td>40</td>
<td>88.9</td>
<td>75.9</td>
<td>96.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (≥1 IU/mL)</td>
<td>53</td>
<td>18</td>
<td>34.0</td>
<td>21.5</td>
<td>48.3</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td>98</td>
<td>58</td>
<td>59.2</td>
<td>48.8</td>
<td>69.0</td>
</tr>
</tbody>
</table>
**Name of company:**
GlaxoSmithKline Biologicals, SA, Rixensart, Belgium

**Name of finished product:**
Boostrix

**Name of active substance:**
Diphtheria (D) and tetanus toxoids (T), pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN)

### Booster response

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group</th>
<th>Pre-vaccination status</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>anti-T antibody (IU/mL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Td group</td>
<td>S-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (&lt;1 IU/mL)</td>
<td>8</td>
<td>8</td>
<td>100</td>
<td>63.1</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (≥1 IU/mL)</td>
<td>24</td>
<td>19</td>
<td>79.2</td>
<td>57.8</td>
<td>92.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>32</td>
<td>27</td>
<td>84.4</td>
<td>67.2</td>
<td>94.7</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>S-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (&lt;1 IU/mL)</td>
<td>29</td>
<td>28</td>
<td>96.6</td>
<td>82.2</td>
<td>99.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (≥1 IU/mL)</td>
<td>76</td>
<td>59</td>
<td>77.6</td>
<td>66.6</td>
<td>86.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>105</td>
<td>87</td>
<td>82.9</td>
<td>74.3</td>
<td>89.5</td>
</tr>
</tbody>
</table>

**Td group** = Subjects received the first dose of Tdap vaccine

**Tdap group** = Subjects received a second dose of Tdap vaccine

Total = subjects either seropositive or seronegative

**Alternative Booster response to Anti D and T antigens is defined as:**
- Initially seronegative subjects (pre-vaccination concentration below the 0.1 IU/mL): antibody concentrations at least four times the 0.1 IU/mL one month after vaccination, and
- Initially seropositive subjects with pre-vaccination concentration < 1.0 IU/mL: antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.
- Initially seropositive subjects with pre-vaccination concentration ≥ 1.0 IU/mL and < 6.0 IU/mL: antibody concentrations of at least two times the pre-vaccination concentration, one month after vaccination.
- Subjects with pre-vaccination concentration ≥ 6.0 IU/mL are not evaluable for vaccine response.

N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of responders

95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

### Alternative booster responses to anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (ATP cohort for analysis of immunogenicity)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group</th>
<th>Pre-vaccination status</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>anti-PT antibody</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Td group</td>
<td>S-</td>
<td>14</td>
<td>14</td>
<td>100</td>
<td>76.8</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ assay cut-off and &lt; 60 IU/mL</td>
<td>20</td>
<td>17</td>
<td>85.0</td>
<td>62.1</td>
<td>96.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 60 IU/mL</td>
<td>1</td>
<td>1</td>
<td>100</td>
<td>2.5</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>35</td>
<td>32</td>
<td>91.4</td>
<td>76.9</td>
<td>98.2</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>S-</td>
<td>14</td>
<td>14</td>
<td>92.9</td>
<td>66.1</td>
<td>99.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ assay cut-off and &lt; 60 IU/mL</td>
<td>96</td>
<td>86</td>
<td>89.6</td>
<td>81.7</td>
<td>94.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 60 IU/mL</td>
<td>5</td>
<td>5</td>
<td>100</td>
<td>47.8</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>115</td>
<td>104</td>
<td>90.4</td>
<td>83.5</td>
<td>95.1</td>
</tr>
<tr>
<td></td>
<td>anti-FHA antibody</td>
<td>Td group</td>
<td>S-</td>
<td>1</td>
<td>1</td>
<td>100</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ assay cut-off and &lt; 60 IU/mL</td>
<td>25</td>
<td>24</td>
<td>96.0</td>
<td>79.6</td>
<td>99.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 60 IU/mL</td>
<td>9</td>
<td>8</td>
<td>88.9</td>
<td>51.8</td>
<td>99.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>35</td>
<td>33</td>
<td>94.3</td>
<td>80.8</td>
<td>99.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tdap group</td>
<td>S-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ assay cut-off and &lt; 60 IU/mL</td>
<td>82</td>
<td>82</td>
<td>100</td>
<td>95.6</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 60 IU/mL</td>
<td>33</td>
<td>28</td>
<td>84.8</td>
<td>68.1</td>
<td>94.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>115</td>
<td>110</td>
<td>95.7</td>
<td>90.1</td>
<td>98.6</td>
</tr>
<tr>
<td>Antibody Group</td>
<td>Pre-vaccination status</td>
<td>N</td>
<td>n</td>
<td>%</td>
<td>LL</td>
<td>UL</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>-----------------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>----</td>
<td>----</td>
<td></td>
</tr>
<tr>
<td>anti-PRN antibody</td>
<td>Td group</td>
<td>S-</td>
<td>2</td>
<td>2</td>
<td>100</td>
<td>15.8</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ assay cut-off and &lt; 60 IU/mL</td>
<td>24</td>
<td>23</td>
<td>95.8</td>
<td>78.9</td>
<td>99.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 60 IU/mL</td>
<td>9</td>
<td>4</td>
<td>44.4</td>
<td>13.7</td>
<td>78.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>35</td>
<td>29</td>
<td>82.9</td>
<td>66.4</td>
<td>93.4</td>
</tr>
<tr>
<td>Tdap group</td>
<td>S-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ assay cut-off and &lt; 60 IU/mL</td>
<td>43</td>
<td>42</td>
<td>97.7</td>
<td>87.7</td>
<td>99.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 60 IU/mL</td>
<td>72</td>
<td>52</td>
<td>72.2</td>
<td>60.4</td>
<td>82.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>115</td>
<td>94</td>
<td>81.7</td>
<td>73.5</td>
<td>88.3</td>
<td></td>
</tr>
</tbody>
</table>

- **Td group** = Subjects received the first dose of Tdap vaccine
- **Tdap group** = Subjects received a second dose of Tdap vaccine
- **Total** = subjects either seropositive or seronegative

Alternative Booster response to pertussis antigens is defined as:
- Initially seronegative subjects (pre-vaccination concentration below the assay cut-off): antibody concentrations at least four times the assay cut-off one month after vaccination.
- Initially seropositive subjects with pre-vaccination antibody concentration ≥ assay cut-off and < 60 IU/mL: antibody concentration increase of at least 30 IU/mL from the pre-vaccination concentration, one month after vaccination.
- Initially seropositive subjects with pre-vaccination antibody concentration ≥ 60 IU/mL: a 1.5-fold increase of antibody concentration from the pre-vaccination concentration, one month after vaccination.

N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of responders
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

**Safety results:**

- **Any symptom (solicited and unsolicited):** During the 4-day (Days 0-3) post-vaccination period, any symptom (solicited and unsolicited) was reported for 80.6% of subjects in the Td group and 85.6% of subjects in the Tdap group. Any Grade 3 symptom (solicited and unsolicited) was reported for 5.6% of subjects in the Td group and 8.8% of subjects in the Tdap group.
- **Solicited local symptom:** During the 4-day (Days 0-3) post-vaccination period, pain was the most frequently reported solicited local symptom, reported for 58.3% of subjects in the Td group and 77.6% of subjects in the Tdap group. Pain was also the most frequently reported Grade 3 solicited local symptom, reported for 5.6% of subjects in the Td group and 4.8% of subjects in the Tdap group.
- **Solicited general symptom:** During the 4-day (Days 0-3) post-vaccination period, fatigue and headache were the most frequently reported solicited general symptom, reported for 22.2% of subjects in the Td group. Headache was the most frequently reported solicited general symptom, reported for 32.0% of subjects in the Tdap group. None of the subjects reported fatigue and headache of Grade 3 intensity in the Td group. Headache and fatigue were the most frequently reported Grade 3 solicited general symptom, reported for 2.4% of subjects in the Tdap group.
- **Unsolicited symptoms:** During the 31-day (Days 0-30) post-vaccination period, at least one unsolicited symptom was reported for 27.0% of subjects in the Td group and 25.8% of subjects in the Tdap group. Headache was the most frequently reported unsolicited symptom, reported for 13.5% of subjects in the Td group and for 9.4% of subjects in the Tdap group. At least one Grade 3 unsolicited symptom was reported for 5.4% of subjects in the Td group and for 2.3% of subjects in the Tdap group. Nausea, vomiting and bronchitis, reported for one subject each (2.7%) were the most frequently reported Grade 3 unsolicited symptom in the Td group while influenza, headache and migraine reported for one subject each (0.8%) were the most frequently reported Grade 3 unsolicited symptom in the Tdap group. Myalgia, reported for one subject (2.7%) was the most
frequently reported unsolicited symptom with causal relationship to vaccination in the Td group while influenza like illness, injection site pruritus, pain in extremity paraesthesia, rash and rash macula-papular reported for one subject each (0.8%) were the most frequently reported unsolicited symptom with causal relationship to vaccination in the Tdap group.

• There was no difference observed with respect to the safety profile (solicited [local and general] and unsolicited symptoms) between the two study groups.
• SAEs: No SAEs were reported in this study.
• Withdrawals due to AEs/SAEs: None of the subjects were withdrawn due to an AE or SAE, during the study period. There were also no large injection site reactions reported.
• Pregnancy: No pregnancies were reported in this study.

Conclusion:
All subjects were protected for anti-Diphtheria and anti-Tetanus ten years after previous booster vaccination of Boostrix. However, with respect to pertussis antigens low GMTs were observed in both groups.
Boostrix when administered in young adults, 10 years after previous booster vaccination was immunogenic and well tolerated. No safety concern was identified.
There were no SAEs reported in this study.

Date of report: Final: 14-September-2017
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYNOPSIS</td>
<td>2</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>24</td>
</tr>
<tr>
<td>GLOSSARY OF TERMS</td>
<td>26</td>
</tr>
<tr>
<td>TRADEMARKS</td>
<td>30</td>
</tr>
<tr>
<td>1. ETHICS</td>
<td>31</td>
</tr>
<tr>
<td>1.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)</td>
<td>31</td>
</tr>
<tr>
<td>1.2. Ethical conduct of the study</td>
<td>31</td>
</tr>
<tr>
<td>1.3. Subject information and consent</td>
<td>31</td>
</tr>
<tr>
<td>2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE</td>
<td>31</td>
</tr>
<tr>
<td>3. INTRODUCTION</td>
<td>31</td>
</tr>
<tr>
<td>3.1. Background</td>
<td>31</td>
</tr>
<tr>
<td>4. STUDY OBJECTIVES</td>
<td>32</td>
</tr>
<tr>
<td>4.1. Co-Primary objectives</td>
<td>32</td>
</tr>
<tr>
<td>4.2. Secondary objectives</td>
<td>33</td>
</tr>
<tr>
<td>5. INVESTIGATIONAL PLAN</td>
<td>34</td>
</tr>
<tr>
<td>5.1. Study design</td>
<td>34</td>
</tr>
<tr>
<td>5.1.1. Overall study design – Description</td>
<td>34</td>
</tr>
<tr>
<td>5.2. Study procedures</td>
<td>36</td>
</tr>
<tr>
<td>5.3. Selection of study population</td>
<td>37</td>
</tr>
<tr>
<td>5.3.1. Inclusion criteria for enrolment</td>
<td>37</td>
</tr>
<tr>
<td>5.3.2. Exclusion criteria</td>
<td>38</td>
</tr>
<tr>
<td>5.3.3. Withdrawal criteria</td>
<td>39</td>
</tr>
<tr>
<td>5.3.3.1. Subject completion</td>
<td>39</td>
</tr>
<tr>
<td>5.3.3.2. Subject withdrawal from the study</td>
<td>39</td>
</tr>
<tr>
<td>5.4. Composition and administration of vaccine</td>
<td>40</td>
</tr>
<tr>
<td>5.4.1. Description of vaccine</td>
<td>40</td>
</tr>
<tr>
<td>5.4.2. Dosage and administration of study vaccine</td>
<td>40</td>
</tr>
<tr>
<td>5.4.3. Treatment allocation</td>
<td>41</td>
</tr>
<tr>
<td>5.4.3.1. Numbering of supplies</td>
<td>41</td>
</tr>
<tr>
<td>5.4.3.2. Treatment allocation to the subject</td>
<td>41</td>
</tr>
<tr>
<td>5.4.3.2.1. Study group and treatment number allocation</td>
<td>41</td>
</tr>
<tr>
<td>5.5. Blinding</td>
<td>41</td>
</tr>
<tr>
<td>5.6. Prior and concomitant medication /vaccinations</td>
<td>42</td>
</tr>
<tr>
<td>5.7. Assessment of immunogenicity variables</td>
<td>42</td>
</tr>
<tr>
<td>5.7.1. Laboratory assays</td>
<td>42</td>
</tr>
<tr>
<td>5.7.2. Immunological read-outs</td>
<td>43</td>
</tr>
<tr>
<td>5.7.3. Immunological correlates of protection</td>
<td>44</td>
</tr>
<tr>
<td>5.8. Assessment of safety variables</td>
<td>45</td>
</tr>
</tbody>
</table>
5.8.1. Adverse events ................................................................. 45
  5.8.1.1. Solicited adverse events ............................................ 46
  5.8.1.2. Assessment of AEs ................................................. 46
    5.8.1.2.1. Assessment of intensity .................................... 46
    5.8.1.2.2. Assessment of causality .................................... 48
  5.8.1.3. Assessment of outcomes .......................................... 50
  5.8.1.4. Medically attended visits ....................................... 50
5.8.2. Serious adverse events .................................................. 50
5.8.3. Pregnancy ........................................................................ 51
5.8.4. Time period for detecting and recording adverse events,
  serious adverse events and pregnancies ................................. 52
5.8.5. Follow-up of adverse events, serious adverse events, and
  pregnancies ........................................................................... 52
  5.8.5.1. Follow-up of adverse events and serious
    adverse events .................................................................... 52
    5.8.5.1.1. Follow-up during the study .................................. 52
    5.8.5.1.2. Follow-up after the subject is
      discharged from the study .............................................. 53
  5.8.5.2. Active questioning to detect adverse events
    and serious adverse events .............................................. 53
  5.8.5.3. Follow-up of pregnancies .......................................... 53
5.9. Statistical methods ................................................................ 54
  5.9.1. Co-Primary endpoint .................................................... 54
  5.9.2. Secondary endpoints ..................................................... 54
  5.9.3. Determination of sample size ........................................ 55
  5.9.4. Study cohorts/data sets analyzed ..................................... 56
    5.9.4.1. Total vaccinated cohort ......................................... 56
    5.9.4.2. According-to-protocol cohort for analysis of
      safety .............................................................................. 57
    5.9.4.3. According-to-protocol cohort for analysis of
      immunogenicity ............................................................ 57
  5.9.5. Derived and transformed data ........................................ 57
  5.9.6. Analysis of demographics ............................................. 59
  5.9.7. Analysis of immunogenicity .......................................... 60
    5.9.7.1. Within groups assessment ..................................... 60
    5.9.7.2. Between groups assessment ................................... 60
    5.9.7.3. Interpretation of analyses ...................................... 61
    5.9.7.4. Sensitivity analysis ............................................... 61
  5.9.8. Analysis of safety ........................................................ 61
    5.9.8.1. Within groups assessment ..................................... 61
    5.9.8.2. Between groups assessment ................................... 62
  5.9.9. Sequence of analyses .................................................. 62
  5.9.10. Interim analysis .......................................................... 62
5.10. Data quality assurance at study level ..................................... 63
5.11. Changes in the conduct of the study or planned analyses ........... 63
  5.11.1. Protocol amendments .................................................. 63
  5.11.2. Changes from planned analyses .................................... 64
6. STUDY POPULATION RESULTS .................................................... 65
  6.1. Study dates ....................................................................... 65
  6.2. Subject disposition ........................................................... 65
  6.3. Important Protocol deviations at subject level ....................... 66
6.3.1. Protocol Deviations leading to elimination from ATP analyses ........................................ 66
6.3.2. Protocol Deviations not leading to elimination from ATP analyses ................................ 66
6.4. Demographic characteristics and other baseline characteristics ................................. 67
7. IMMUNOGENICITY RESULTS ...................................................................................... 68
   7.1. Sensitivity analysis ............................................................................................. 77
   7.2. Immunogenicity summary .................................................................................. 78
8. SAFETY RESULTS ..................................................................................................... 79
   8.1. Total vaccinated cohort analysis ...................................................................... 79
   8.1.1. Overall incidence of adverse events ................................................................. 79
   8.1.2. Solicited local symptoms ............................................................................... 80
   8.1.3. Solicited general symptoms .......................................................................... 81
   8.1.4. Unsolicited adverse events .......................................................................... 84
   8.2. Serious adverse events ...................................................................................... 92
   8.2.1. Fatal events .................................................................................................. 92
   8.2.2. Non-fatal events ............................................................................................ 92
   8.3. Adverse events leading to premature discontinuation of study vaccine and/or study ................................................................. 92
   8.4. Safety summary ............................................................................................... 93
9. OVERALL CONCLUSIONS ........................................................................................ 94
10. POST-TEXT TABLES AND FIGURES .................................................................... 95
    10.1. Study population ............................................................................................ 95
    10.2. Immunogenicity .............................................................................................. 99
        10.2.1. ATP cohort for immunogenicity ................................................................. 99
        10.2.2. TVC for immunogenicity ...................................................................... 110
    10.3. Safety .............................................................................................................. 125
11. REFERENCES .......................................................................................................... 126
12. STUDY REPORT AUTHORS /CONTRIBUTING AUTHORS ................................ 129
13. SERIOUS ADVERSE EVENTS .............................................................................. 130
MODULAR APPENDICES
LIST OF TABLES

Table 1  Study groups and treatment foreseen in the study .................................. 35
Table 2  List of study procedures ......................................................................... 36
Table 3  Intervals between study visits ................................................................. 37
Table 4  Study vaccine ......................................................................................... 40
Table 5  Dosage and administration ...................................................................... 41
Table 6  Humoral Immunity (Antibody determination) ........................................... 43
Table 7  Immunological read-outs ........................................................................ 44
Table 8  Solicited local adverse events ............................................................... 46
Table 9  Solicited general adverse events ............................................................ 46
Table 10 Intensity scales for solicited symptoms in adults ...................................... 47
Table 11 Power to demonstrate non-inferiority of second dose of Tdap vaccine to first dose of Tdap vaccine with respect to anti-D and anti-T seroprotection rate ............................................................... 56
Table 12 Power to demonstrate non-inferiority of second dose of Tdap vaccine to Infanrix vaccine in APV-039 with respect to anti-PT, anti-FHA and anti-PRN GMCs ........................................................................ 56
Table 13 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Total vaccinated cohort) .......................................................... 65
Table 14 Number of subjects at each visit and list of withdrawn subjects (Total vaccinated cohort) .................................................................................. 66
Table 15 Summary of demographic characteristics (Total vaccinated cohort) .................................................................................. 67
Table 16 Summary of demographic characteristics (ATP cohort for analysis of immunogenicity) .......................................................................... 68
Table 17 Group differences in the percentage of subjects with anti-Diphtheria and anti-Tetanus antibody concentrations ≥ 0.1 IU/mL [Tdap Group Minus Td Group], one month after booster vaccination and their standardized asymptotic 95% CIs (ATP cohort for analysis of immunogenicity) .......................................................... 69
Table 18 GMC ratio between groups [Tdap Group divided by Infanrix Group in APV-039] and their 95% CIs for anti-PT, anti-FHA and
Table 19  Number and percentage of subjects with anti-Diphtheria and anti-Tetanus antibody concentration ≥ 0.1 IU/mL, ≥ 1 IU/mL and GMCs at pre and post booster vaccination time points (ATP cohort for analysis of immunogenicity) .......................................................... 70

Table 20  Number and percentage of subjects with an anti-PT, anti-FHA, anti-PRN antibody concentration ≥ assay cut-off and GMCs at pre and post booster vaccination time points (ATP cohort for analysis of immunogenicity) ........................................ 71

Table 21  Booster response to anti-diphtheria and anti-tetanus antigens one month after booster vaccination (ATP cohort for analysis of immunogenicity) ........................................................................ 72

Table 22  Booster response to anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (ATP cohort for analysis of immunogenicity) ........................................................................ 73

Table 23  Group difference in booster response to anti-diphtheria and anti-tetanus antigens [Tdap Group minus Td Group], one month after booster vaccination and their standardized asymptotic 95% CIs (ATP cohort for analysis of immunogenicity) ........................................ 74

Table 24  Group difference in booster response to anti-PT, anti-FHA and anti-PRN antigens [Tdap Group minus Td Group], one month after booster vaccination and their standardized asymptotic 95% CIs (ATP cohort for analysis of immunogenicity) ........................................ 75

Table 25  Adjusted GMC ratio between groups [Tdap group divided by Td group] and their 95% CIs for anti-diphtheria and anti-tetanus antigens one month after booster vaccination (ATP cohort for analysis of immunogenicity) ........................................ 76

Table 26  Adjusted GMC ratio between groups [Tdap group divided by Td group] and their 95% CIs for anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (ATP cohort for analysis of immunogenicity) ........................................ 76

Table 27  Incidence and nature of symptoms (solicited and unsolicited) reported during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort) ........................................................................ 79

Table 28  Incidence and nature of Grade 3 symptoms (solicited and unsolicited) reported during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort) ........................................ 79

Table 29  Incidence and nature of symptoms (solicited and unsolicited) with causal relationship to vaccination, reported during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort) ........ 80
Table 30  Incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort) ........................................ 80

Table 31  Difference between groups (Td group minus Tdap group) in percentage of subjects reporting solicited local symptom during the 4-day post vaccination period (Total vaccinated cohort) ........................................ 81

Table 32  Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort) ........................................ 82

Table 33  Difference between groups (Td group minus Tdap group) in percentage of subjects reporting solicited general symptom during the 4-day post vaccination period (Total vaccinated cohort) ........................................ 83

Table 34  Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MEDDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort) ........................................ 85

Table 35  Percentage of subjects reporting the occurrence of Grade 3 unsolicited symptoms classified by MEDDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort) ........................................ 86

Table 36  Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MEDDRA Primary System Organ Class and Preferred Term with causal relationship to vaccination, within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort) ........................................ 87

Table 37  Difference between groups (Td minus Tdap) in percentage of subjects reporting unsolicited symptom during the 31-day post vaccination period (Total vaccinated cohort) ........................................ 88

Table 38  Difference between groups (Td minus Tdap) in percentage of subjects reporting Grade 3 unsolicited symptom within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort) ........................................ 90

Table 39  Difference between groups (Td minus Tdap) in percentage of subjects reporting unsolicited symptom with causal relationship to vaccination within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort) ........................................ 91

Table 40  Number of subjects by center (Total vaccinated cohort) ........................................ 95

Table 41  Deviation from specifications intervals between study visits (Total vaccinated cohort) ........................................ 95

Table 42  Demography: age (in years) at vaccination dose: 1 (Total vaccinated cohort) ........................................ 96
Table 43 Demography: age (in years) at vaccination dose: 1 (ATP cohort for safety) ............................................................... 96
Table 44 Summary of demographic characteristics (ATP cohort for safety) ......................... 97
Table 45 Number of subjects enrolled into the study as well as the number excluded from ATP analyses with reasons for exclusion ......................... 97
Table 46 Summary of tracking log-sheets for all subjects initially enrolled in the primary study (Total cohort) .......................................................... 98
Table 47 Alternative booster response to anti-Diphtheria and anti-Tetanus antibodies one month after booster vaccination (ATP cohort for analysis of immunogenicity - excluding subjects with pre-vaccination concentration greater than or equal to 6 IU/mL) ................................ 104
Table 48 Alternative booster responses to anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (ATP cohort for analysis of immunogenicity - excluding subjects with pre-vaccination concentration greater than or equal to 6 IU/mL) ................................ 105
Table 49 Group difference in alternative booster response to the diphtheria and tetanus antigens [ATP cohort for analysis of immunogenicity - excluding subjects with pre-vaccination concentration greater than or equal to 6 IU/mL] ........................................................................ 106
Table 50 Group difference in alternative booster response to anti-PT, anti-FHA and anti-PRN antigens [Tdap Group minus Td Group], one month after booster vaccination and their standardized asymptotic 95% CIs (ATP cohort for analysis of immunogenicity) .......... 106
Table 51 Number of years since the vaccination in primary study (ATP cohort for immunogenicity - adapted for each time point) ..................... 107
Table 52 Observed number and percentage of subjects with an ANTI-D and T concentration equal to or above 0.1 and 1 IU/mL and GMCs in the 001 study (ATP cohort for immunogenicity - adapted for the time point) ........................................................................ 107
Table 53 Estimated antibody D and T GMCs, as predicted by modelling (ATP cohort for immunogenicity - adapted for each time point) .............. 108
Table 54 Observed number and percentage of subjects with an ANTI-PT, ANTI-FHA and ANTI-PRN concentration equal to or above 5 EL.U/mL and GMCs in the 001 study (ATP cohort for immunogenicity - adapted for the time point) .......................................................... 108
Table 55 Estimated antibody pertussis GMCs, as predicted by modelling (ATP cohort for immunogenicity - adapted for each time point) .............. 109
Table 56 Number and percentage of subjects with anti-Diphtheria and anti-Tetanus antibody concentration ≥ 0.1 IU/mL, ≥ 1 IU/mL and
GMCs at pre and post booster vaccination time points (Total vaccinated cohort) ............................ 110

Table 57 Number and percentage of subjects with an anti-PT, anti-FHA, anti-PRN antibody concentration ≥ assay cut-off and GMCs at pre and post booster vaccination time points (Total vaccinated cohort) ........................................................................................................ 110

Table 58 Seronegativity status for anti-Diphtheria antibody concentration by ELISA and VERO NEUTRALISATION at pre booster vaccination time points (Total vaccinated cohort) ........................................................................................................ 111

Table 59 Group differences in the percentage of subjects with anti-Diphtheria and anti-Tetanus antibody concentrations ≥ 0.1 IU/mL [Tdap Group minus Td Group], one month after booster vaccination and their standardized asymptotic 95% CIs (Total vaccinated cohort) ........................................................................................................ 111

Table 60 Group difference in booster response to anti-diphtheria and anti-tetanus antigens [Tdap Group minus Td Group], one month after booster vaccination and their standardized asymptotic 95% CIs (Total vaccinated cohort) ........................................................................................................ 111

Table 61 Group difference in booster response to anti-PT, anti-FHA and anti-PRN antigens [Tdap Group minus Td Group], one month after booster vaccination and their standardized asymptotic 95% CIs (Total vaccinated cohort) ........................................................................................................ 112

Table 62 Group difference in alternative booster response to the diphtheria and tetanus antigens [Tdap Group minus Td Group], one month after booster vaccination and their standardized asymptotic 95% CIs (Total vaccinated cohort - excluding subjects with pre-vaccination concentration greater than or equal to 6 IU/mL) ................................................................................................ 113

Table 63 Group difference in alternative booster response to anti-PT, anti-FHA and anti-PRN antigens [Tdap Group minus Td Group], one month after booster vaccination and their standardized asymptotic 95% CIs (Total vaccinated cohort) ........................................................................................................ 113

Table 64 Booster response to anti-diphtheria and anti-tetanus antigens one month after booster vaccination (Total vaccinated cohort) ........................................................................................................ 115

Table 65 Alternative booster response to anti-Diphtheria and anti-Tetanus antibodies one month after booster vaccination (Total vaccinated cohort - excluding subjects with pre-vaccination concentration greater than or equal to 6 IU/mL) ........................................................................................................ 116

Table 66 Alternative booster responses to anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (Total vaccinated cohort) ........................................................................................................ 117

Table 67 Adjusted GMC ratio between groups [Tdap group divided by Td group] and their 95% CIs for anti-diphtheria and anti-tetanus
antigens one month after booster vaccination (Total vaccinated cohort) ................................................................. 119

Table 68 Adjusted GMC ratio between groups [Tdap group divided by Td group] and their 95% CIs for anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (Total vaccinated cohort) ................................................................. 119

Table 69 Compliance in returning symptom sheets (Total vaccinated cohort) ................................................................. 125

Table 70 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MEDDRA Primary System Organ Class and Preferred Term with medically attended visit, within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort) ................................................................. 125
## LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Probability of False Signal- solicited symptom (Total vaccinated cohort)</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>Probability of False Signal-unsolicited symptom (Total vaccinated cohort)</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>Reverse cumulative distribution curve for anti-Diphtheria antibody concentrations per group at pre and post booster vaccination time point (ATP cohort for analysis of immunogenicity)</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>Reverse cumulative distribution curve for anti-Tetanus antibody concentrations per group at pre and post booster vaccination time point (ATP cohort for analysis of immunogenicity)</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>Reverse cumulative distribution curve for anti-PT antibody concentrations per group at pre and post booster vaccination time point (ATP cohort for analysis of immunogenicity)</td>
<td>101</td>
</tr>
<tr>
<td>6</td>
<td>Reverse cumulative distribution curve for anti-FHA antibody concentrations per group at pre and post booster vaccination time point (ATP cohort for analysis of immunogenicity)</td>
<td>102</td>
</tr>
<tr>
<td>7</td>
<td>Reverse cumulative distribution curve for anti-PRN antibody concentrations per group at pre and post booster vaccination time point (ATP cohort for analysis of immunogenicity)</td>
<td>103</td>
</tr>
<tr>
<td>8</td>
<td>Reverse cumulative distribution curve for anti-Diphtheria antibody concentrations per group at pre and post booster vaccination time point (Total vaccinated cohort)</td>
<td>120</td>
</tr>
<tr>
<td>9</td>
<td>Reverse cumulative distribution curve for anti-Tetanus antibody concentrations per group at pre and post booster vaccination time point (Total vaccinated cohort)</td>
<td>121</td>
</tr>
<tr>
<td>10</td>
<td>Reverse cumulative distribution curve for anti-PT antibody concentrations per group at pre and post booster vaccination time point (Total vaccinated cohort)</td>
<td>122</td>
</tr>
<tr>
<td>11</td>
<td>Reverse cumulative distribution curve for anti-FHA antibody concentrations per group at pre and post booster vaccination time point (Total vaccinated cohort)</td>
<td>123</td>
</tr>
<tr>
<td>12</td>
<td>Reverse cumulative distribution curve for anti-PRN antibody concentrations per group at pre and post booster vaccination time point (Total vaccinated cohort)</td>
<td>124</td>
</tr>
</tbody>
</table>
LIST OF ABBREVIATIONS

AE: Adverse Event
ACIP: Advisory Committee on Immunization Practices
ANCOVA: Analysis of Co-Variance
ATP: According-To-Protocol
CDC: Center for Disease Control and Prevention, USA
D: Diphtheria
eCRF: electronic Case Report Form
EDD: Estimated Date of Delivery
ELISA: Enzyme-Linked Immunosorbent Assay
FHA: Filamentous Hemagglutinin
GMC: Geometric Mean Concentration
GCP: Good Clinical Practice
GSK: GlaxoSmithKline
IB: Investigator Brochure
ICF: Informed Consent Form
ICH: International Conference on Harmonization
IEC: Independent Ethics Committee
IMP: Investigational Medicinal Product
IND: Investigational New Drug
IRB: Institutional Review Board
LSLV: Last Subject Last Visit
MedDRA: Medical Dictionary for Regulatory Activities
PRN: Pertactin
PT: Pertussis Toxoid
RCC: Reverse Cumulative Curve
SAE: Serious Adverse Event
SBIR: Randomization System on Internet
T: Tetanus
Td: Reduced-antigen-content diphtheria–tetanus vaccine
Tdap: Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis
TVC: Total Vaccinated Cohort
US: United States
GLOSSARY OF TERMS

Adequate contraception: Adequate contraception was defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label for example:

- abstinence from penile-vaginal intercourse, when this was their preferred and usual lifestyle,
- oral contraceptives, either combined or progestogen alone,
- injectable progestogen,
- implants of etenogestrel or levonorgestrel,
- estrogenic vaginal ring,
- percutaneous contraceptive patches,
- intrauterine device or intrauterine system,
- male partner sterilization prior to the female subject’s entry into the study, and this male was the sole partner for that subject,
- The information on the male sterility came from the site personnel’s review of the subject’s medical records; or interview with the subject on her medical history.
- male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository),
- male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository).

Adequate contraception did not apply to subjects of child bearing potential with same sex partners, when this was their preferred and usual lifestyle.

Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An adverse event (AE) could therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
**Blinding:**
A procedure in which one or more parties to the trial were kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding was maintained throughout the conduct of the trial, and only when the data were cleaned to an acceptable level of quality would appropriate personnel be unblinded or when required in case of a serious adverse event. In an open-label study, no blind is used. Both the investigator and the subject know the identity of the treatment assigned.

**Eligible:**
Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.

**Epoch:**
An epoch was a self-contained set of consecutive timepoints or a single timepoint from a single protocol. Self-contained meant that data collected for all subjects at all timepoints within that epoch allowed to draw a complete conclusion to define or precise the targeted label of the product. Typical examples of epochs are primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.

**eTrack:**
GSK’s tracking tool for clinical trials.

**Evaluable:**
Meeting all eligibility criteria, complied with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis.

**Immunological correlate of protection:**
The defined humoral antibody response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.

**Investigational vaccine/product:**
A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Menarche: Menarche was the onset of menses for the first time in a young female and was preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, thelarche. However, a young female could become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female was a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).

Menopause: Menopause was the age associated with complete cessation of menstrual cycles, menses, and implied the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile at the appropriate age e.g. > 45 years.

Randomization: Process of random attribution of treatment to subjects in order to reduce bias of selection.

Seronegative subject: A seronegative subject was a subject whose antibody concentration/titer was below the assay cut-off.

Seropositive subject: A seropositive subject was a subject whose antibody concentration/titer was greater than or equal to the assay cut-off.

Site Monitor: An individual assigned by the sponsor who was responsible for assuring proper conduct of clinical studies at one or more investigational sites.

Solicited adverse event: AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events was actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Subject: Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the vaccine or as a control.

Subject number: A unique number identifying a subject, assigned to each subject consenting to participate in the study.

Treatment: Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomization or treatment allocation.

Treatment number: A number identifying a treatment to a subject, according to the study randomization or treatment allocation.

Unsolicited adverse event: Any AE reported in addition to those solicited during the clinical study. Also any ‘solicited’ symptom with onset outside the specified period of follow-up for solicited symptoms was to be reported as an unsolicited adverse event.
The following trademarks are used in the present report.

<table>
<thead>
<tr>
<th>Trademarks of the GSK group of companies</th>
<th>Generic description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boostrix</td>
<td>Reduced antigen content Diphtheria and Tetanus toxoids and acellular Pertussis (Tdap) vaccine</td>
</tr>
<tr>
<td>Infanrix</td>
<td>Combined diphtheria, tetanus and acellular pertussis vaccine</td>
</tr>
</tbody>
</table>
1. ETHICS

1.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The study protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by an investigational center IEC or IRB.

1.2. Ethical conduct of the study

This study was conducted in accordance with ethical principles that have their origins in the Declaration of Helsinki, the principles of "good clinical practice" (GCP) and all applicable regulatory requirements.

1.3. Subject information and consent

Written informed consent was obtained from each subject prior to the performance of any study-specific procedures.

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study, sponsored by GSK Biologicals was conducted at multiple centers in the United States. The contributing PI for this study was Dr. Meera Varman, (affiliated to Department of Pediatrics, Creighton University School of Medicine) 2412 Cummings Street, Suite 100, Room 1022, Omaha, Nebraska 68131, United States.

3. INTRODUCTION

3.1. Background

Pertussis (whooping cough) is a highly contagious respiratory tract infection caused by Bordetella pertussis, the etiologic bacterial agent. The disease is characterized by severe coughing and spreads via respiratory droplets. WHO estimates that in 2008 about 16 million cases of pertussis were reported worldwide, 95% of which occurred in developing countries and about 195,000 children died from the disease (Black, 2010). Since the 1980s, there has been an increase in the number of reported cases of pertussis in the US, especially among 10-19 year olds and infants younger than 6 months of age. In 2010, about 27,550 cases of pertussis were reported in the US (CDC, 2011).

Waning immunity over time and the benefit of the ‘cocooning’ strategy warrants a vaccination against pertussis beyond childhood (adolescence and adulthood) (ACIP, 2011a; ACIP, 2006). Reduced antigen content diphtheria, tetanus and acellular pertussis (Tdap) vaccines have been developed predominantly for boosting adolescents and adults (Wendelboe, 2005; ACIP, 2006). According to the recent General Recommendations on Immunization, adolescents and adults ≥ 11 years of age are recommended to receive a single Tdap dose by the Advisory Committee on Immunization Practices (ACIP). It is
also recommended for all adults who have or anticipate having close contact with an infant aged < 12 months, pregnant women and postpartum mothers who have not received Tdap previously (ACIP, 2011b; CDC, 2012).

GSK Biologicals’ Boostrix has been evaluated as a booster dose in adults, adolescents and children with a variety of previous vaccination and/or natural infection histories. Results obtained after immunization with the Tdap vaccine demonstrated that regardless of vaccination or natural infection history and age, local and general reactions were all within clinically acceptable ranges. In addition, the vaccine was shown to be immunogenic, since most subjects developed protective antibody concentrations against diphtheria and tetanus as well as a vaccine response against pertussis after vaccination, (Zepp, 2007; Blatter, 2009) and are comparable to other booster vaccines such as reduced-antigen-content diphtheria–tetanus vaccine (Td) vaccine (Frampton, 2006; Pichichero, 2006).

Research suggests that immunity to pertussis wanes approximately 5-10 years after childhood vaccination (Olin, 2003; Tan, 2005; Wendelboe, 2005). Decennial studies with Boostrix formulation containing 0.5 mg aluminum (Al) per dose have been conducted in Australia and Finland and these studies evaluated the persistence of antibody concentrations against diphtheria, tetanus and pertussis after a previous dose of Tdap. In these studies, the geometric mean concentrations (GMC) to all antigens had returned to pre-vaccination levels 10 years after the first booster dose. Following a decennial booster dose, robust increase in antibody concentrations against all antigens was observed irrespective of vaccination history (Booy, 2010; Mertsola, 2010). These studies were conducted in subjects who received a second dose of Boostrix as decennial booster vaccination (dTpa-039 and dTpa-040) and showed adequate immunogenicity and acceptable safety profile of the vaccine (Booy, 2010; Mertsola, 2010).

Please refer to the Prescribing Information for information regarding the potential risks and benefits of Boostrix.

The purpose of this follow-up study was to evaluate 10 years later, the persistence of antibodies against all the vaccine antigens, and to evaluate the immunogenicity and safety of a second dose of Boostrix. This study was conducted in an open-label manner and was non-randomized since all the subjects received a single dose of Boostrix.

Subjects who were vaccinated in the 776423/001 [DTPA 0.3 (BOOSTRIX)-001] study were invited to participate in this study.

### 4. STUDY OBJECTIVES

#### 4.1. Co-Primary objectives

- To demonstrate that a second dose of Tdap vaccine (administered to the Tdap Group) was non-inferior to a first dose of Tdap vaccine (administered to the Td Group), with respect to immune response to diphtheria and tetanus antigens.
The criterion for meeting the above objective was defined as:

- **One month after vaccination, the lower limits of the 95% CI on the difference of the seroprotection rates [second dose of Tdap (Tdap Group) minus first dose of Tdap (Td Group)] for anti-diphtheria, anti-tetanus antibody concentrations were greater than or equal to -10% (clinical limit for non-inferiority).**

☐ To demonstrate that a second dose of Tdap vaccine, (administered to the Tdap group) was non-inferior to a three dose series of Infanrix vaccine in infants who received this vaccine in German household contact efficacy study APV-039, with respect to antibodies against pertussis toxoid (anti-PT), antibodies against filamentous hemagglutinin (anti-FHA) and antibodies against pertactin (anti-PRN) antibody concentrations.

The criterion for meeting the above objective was defined as:

- **One month after vaccination, the lower limits of the 95% CI on the anti-PT, anti-FHA and anti-PRN GMC ratios (Tdap Group divided by Infanrix Group in APV-039) were greater than or equal to 0.67.**

Refer to Section 5.9.1 for the definition of the co-primary endpoints.

### 4.2. Secondary objectives

☐ To assess the persistence of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 10 years after the previous booster dose of the Tdap vaccine in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].

☐ To assess the immunogenicity of the Tdap vaccine in terms of seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies, one month after vaccination.

☐ To explore the potential difference in terms of booster response* to anti-D, anti-T, anti-PT, anti-FHA and anti-PRN between the second dose of Tdap vaccine (administered to the Tdap Group) and the first dose of Tdap vaccine (administered to the Td Group).

☐ To evaluate and compare the safety of a second dose of Tdap vaccine (administered to the Tdap group) and a first dose of Tdap vaccine (administered to the Td group), with respect to solicited symptoms (local and general), unsolicited symptoms and serious adverse events (SAEs).

Refer to Section 5.9.2 for the definition of the secondary endpoints.

*Refer to Section 5.9.5 for the definition of booster response.
5. INVESTIGATIONAL PLAN

5.1. Study design

5.1.1. Overall study design – Description

N = Number of subjects planned to be enrolled; Pre-BS = Pre-vaccination blood sampling; Post-BS = Post-vaccination blood sampling.

☐ Experimental design: A phase III, open-label, non-randomized, multi-center, single-country study with two parallel groups.

☐ Duration of the study: The intended duration of the study, for each subject was approximately one month.

☐ Study groups:
  - Tdap Group: Subjects randomized to the Lot A, Lot B or Lot C groups in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001] were pooled and received a second dose of the Tdap vaccine in this study.
  - Td Group: Subjects who had received Td vaccine in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001] received the first dose of Tdap vaccine in this study.

Table 1 presents the study groups and the vaccines administered in the study.
Table 1  Study groups and treatment foreseen in the study

<table>
<thead>
<tr>
<th>Treatment name</th>
<th>Vaccine/Product name</th>
<th>Study Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boostrix</td>
<td>Tdap</td>
<td>Tdap Group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>x</td>
</tr>
</tbody>
</table>

- Control: active control, subjects who had received Td vaccine in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001] received the first dose of Tdap vaccine in this study.
- Vaccination schedule: A single dose of Tdap vaccine was administered to all subjects, 10 years after the previous booster vaccination in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].
- Treatment allocation: Non-randomized.
- Blinding: Open-label.
- Sampling schedule: A blood sample of approximately 5 mL was collected from all subjects before vaccination (Pre-Bst) and one month after vaccination (Post-Bst).
- Type of study: Extension of Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].
- Data collection: electronic Case Report Form (eCRF).
5.2. Study procedures

The list of study procedures is presented in Table 2.

Table 2 List of study procedures

<table>
<thead>
<tr>
<th>Type of contact</th>
<th>Booster epoch</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit 1</td>
<td>Visit 2</td>
<td></td>
</tr>
<tr>
<td>Time point</td>
<td>Day 0</td>
<td>Month 1</td>
<td></td>
</tr>
<tr>
<td>Sampling time point</td>
<td>Pre-Bst#</td>
<td>Post-Bst#</td>
<td></td>
</tr>
<tr>
<td>Informed consent</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Check inclusion/exclusion criteria</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Vaccination history</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Record demography data †</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>History directed physical examination</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Urine pregnancy test **</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Pre-vaccination body temperature</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Blood sampling</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Check warnings and precautions</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Study group and treatment number allocation</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Recording of administered treatment number</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Vaccination</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Distribution of diary cards</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily recording of solicited adverse events during the 4-day (Day 0-3) follow-up period post-vaccination, by subject</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Recording of non-serious adverse events within 31 days post-vaccination, by subject</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Return of diary cards</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transcription of diary cards by the investigator</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Recording of any large injection site reactions in the eCRF by the investigator *</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Record any concomitant medication and vaccination</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Record any intercurrent medical conditions</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Recording of SAEs related to study participation or to a concurrent GSK medication/vaccine</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Recording of serious adverse events</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Recording of pregnancies</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Investigator sign-off on data</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Study conclusion</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
</tbody>
</table>

● is used to indicate a study procedure that required documentation in the individual eCRF.
○ is used to indicate a study procedure that did not require documentation in the individual eCRF.
# Pre-Bst: before the administration of study vaccine; Post-Bst: one month after the administration of study vaccine.
† Only for subjects who participated in the study.
* Refer to Section 5.8.1.1 for detailed explanation on the reporting of large injection site reactions
**Applicable to female subjects only.

It was the investigator’s responsibility to ensure that the interval between the two visits was strictly followed.

Table 3 presents the intervals between study visits.
Table 3  Intervals between study visits

<table>
<thead>
<tr>
<th>Interval</th>
<th>Optimal length of interval ¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1 → Visit 2</td>
<td>30-48 days (at least 30 days⁴)</td>
</tr>
</tbody>
</table>

¹Whenever possible the investigator was to arrange study visits within this interval. An interval of 21-48 days between Visit 1 and Visit 2 was considered for the ATP cohort of immunogenicity. Refer to Section 5.9.4 for the definition of the cohorts for analysis.

⁴If subjects returned for the visits prior to 30 days, they should have taken home the diary card and continued to record unsolicited safety information until 30 days post-vaccination and mailed/sent it upon completion. Investigators made an attempt to retrieve diary cards from subjects who had not mailed/sent them in.

5.3. Selection of study population

The target was to enrol 500 subjects to be assigned to two study groups—Tdap group and Td group according to their vaccination in study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].

5.3.1. Inclusion criteria for enrolment

All subjects had to satisfy ALL the following criteria at study entry:

☐ Subjects who, in the opinion of the investigator, could and would comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visit).

• Subjects who had received a dose of Tdap or Td vaccines 10 years (± 300 days) earlier, in study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].

☐ Written informed consent obtained from the subject.

☐ Healthy subjects as established by medical history and clinical examination before entering into the study.

☐ Female subjects of non-childbearing potential were to be enrolled in the study.
  – Non-childbearing potential was defined as pre-menarche, current tubal ligation, hysterectomy, ovariectomy or post-menopause.

Please refer to the GLOSSARY OF TERMS for the definition of menarche and menopause.

☐ Female subjects of childbearing potential were to be enrolled in the study, if the subject
  – had practiced adequate contraception for 30 days prior to vaccination, and
  – had a negative pregnancy test on the day of vaccination, and
  – had agreed to continue adequate contraception during the entire treatment period and for one month after completion of the vaccine dose.

Please refer to the GLOSSARY OF TERMS for the definition of adequate contraception.
5.3.2. Exclusion criteria

The following criteria were to be checked at the time of study entry. If ANY exclusion criterion applied, the subject was not to be included in the study:

☐ Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the dose of study vaccine, or planned use during the study period.

☐ Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs within six months prior to the booster vaccine dose. For corticosteroids, this would mean prednisone (≥ 20 mg/day), or equivalent. Inhaled and topical steroids were allowed.

☐ Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before and ending 31 days after the dose of vaccine, with the exception of influenza vaccine which was allowed throughout the study period.

☐ Concurrently participating in another clinical study, at any time during the study period, in which the subject had been or was exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).

☐ Previous vaccination against diphtheria, tetanus or pertussis since the last dose received in the Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].

☐ History of diphtheria, tetanus or pertussis diseases following the receipt of booster dose in the Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].

☐ Severe allergic reaction (e.g. anaphylaxis) after previous administration of any tetanus toxoid, diphtheria toxoid, or pertussis-antigen containing vaccines, or any component of Boostrix.

☐ Hypersensitivity to latex.

☐ Encephalopathy (e.g. coma, decreased level of consciousness, prolonged seizures) of unknown etiology occurring within 7 days following previous vaccination with pertussis-containing vaccine.

☐ History of any neurological disorders or seizures.

☐ Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).

☐ Acute disease and/or fever at the time of enrolment.
  - Fever was defined as temperature ≥ 99.5°F for oral, axillary or tympanic route, or ≥ 100.4°F for rectal route. The preferred route for recording temperature in this study was oral.
  - Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever might be enrolled at the discretion of the investigator.
Administration of immunoglobulins and/or any blood products within the 3 months preceding the booster dose of study vaccine or planned administration during the study period.

☐ Pregnant or lactating female.

☐ Female planning to become pregnant or planning to discontinue contraceptive precautions up to one month post-vaccination.

5.3.3. Withdrawal criteria

5.3.3.1. Subject completion

A subject who returned for the concluding visit or was available for the concluding contact foreseen in the protocol was considered to have completed the study.

5.3.3.2. Subject withdrawal from the study

From an analysis perspective, a ‘withdrawal’ from the study referred to any subject who did not come back for the concluding visit/was not available for the concluding contact foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject was used for the analysis.

A subject was considered a ‘withdrawal’ from the study when no study procedure had occurred, no follow-up had been performed and no further information had been collected for this subject from the date of withdrawal/last contact.

Investigators were to make an attempt to contact those subjects who did not return for scheduled visits or follow-up.

Information relative to the withdrawal was documented in the eCRF. The investigator documented whether the decision to withdraw a subject from the study was made by the subject himself/herself, or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

☐ Serious adverse event.

☐ Non-serious adverse event.

☐ Protocol violation (was to be specified).

☐ Consent withdrawal, not due to an adverse event*.

☐ Moved from the study area.

☐ Lost to follow-up.

☐ Other (was to be specified).
*In case a subject was withdrawn from the study because he/she had withdrawn consent, the investigator documented the reason for withdrawal of consent, if specified by the subject, in the CRF.

Subjects who were withdrawn from the study because of SAEs/AEs were clearly distinguished from subjects who were withdrawn for other reasons. Investigators followed subjects who were withdrawn from the study as result of a SAE/AE until resolution of the event.

5.4. Composition and administration of vaccine

5.4.1. Description of vaccine

The candidate vaccine used was developed and manufactured by GSK Biologicals.

The Quality Control Standards and Requirements for the candidate vaccine were described in separate Quality Assurance documents (e.g. release protocols, certificate of analysis) and the required approvals were obtained.

The vaccine was labelled and packed according to applicable regulatory requirements.

Commercial vaccine was assumed to comply with the specifications given in the manufacturer’s Summary of Product Characteristics.

Table 4 presents the composition of the study vaccine.

Table 4 Study vaccine

<table>
<thead>
<tr>
<th>Treatment name</th>
<th>Vaccine/product name</th>
<th>Formulation</th>
<th>Presentation</th>
<th>Volume</th>
<th>Number of doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boostrix</td>
<td>Tdap</td>
<td>Diphtheria toxoid: 2.5 Lf, Tetanus toxoid: 5 Lf, Pertussis toxoid: 8 µg, Filamentous hemagglutinin: 8 µg, Pertactin: 2.5 µg, Aluminum as Al(OH)_3: ≤ 0.39 mg, Sodium chloride</td>
<td>Pre-fill syringes, Homogeneous turbid white suspension</td>
<td>0.5 mL</td>
<td>1</td>
</tr>
</tbody>
</table>

5.4.2. Dosage and administration of study vaccine

The vaccine was administered as detailed in Table 5.

The vaccine was administered as a deep intramuscular injection into the deltoid muscle of the non-dominant arm*, i.e. in the left arm if the subject was right-handed or in the right arm if the subject was left-handed. Boostrix was not to be administered intravascularly.

In order to ensure proper intramuscular injection of the vaccine, a needle of 1-1 1/2-inch length, 25 gauge was used (ACIP, 2011b; Zuckerman, 2000).
* Vaccination was performed in dominant arm in case of medical indication preventing vaccination in the non-dominant arm, as judged by the investigator.

Table 5  
Dosage and administration

<table>
<thead>
<tr>
<th>Type of contact and timepoint</th>
<th>Dose</th>
<th>Treatment group</th>
<th>Vaccine/product</th>
<th>Route</th>
<th>Site</th>
<th>Side</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1 (Day 0)</td>
<td>1</td>
<td>Tdap Group and Td Group</td>
<td>Tdap</td>
<td>IM</td>
<td>Deltoid</td>
<td>Non-dominant*</td>
</tr>
</tbody>
</table>

* Intramuscular (IM)

* Vaccination was performed in dominant arm in case of medical indication preventing vaccination in the non-dominant arm, as judged by the investigator.

5.4.3.  Treatment allocation

5.4.3.1.  Numbering of supplies

The numbering of supplies by blocks was performed at GSK Biologicals, using MATerial EXcellence (MATEX), a program developed for use in Statistical Analysis System (SAS®) (Cary, NC, USA) by GSK Biologicals. Entire blocks were shipped to the study centers/warehouse(s).

5.4.3.2.  Treatment allocation to the subject

The treatment numbers were allocated by dose.

5.4.3.2.1.  Study group and treatment number allocation

The target was to enrol approximately 500 eligible subjects to be assigned to two study groups: Tdap Group and Td Group according to the vaccine they received in the previous Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001]. The study group allocation was expected to be similar to previous group allocation ratio 3:1 and the enrolment was monitored using SBIR.

After obtaining the signed and dated ICF from the subject and having checked the eligibility of the subject, the site staff in charge of the vaccine administration accessed SBIR. Upon providing the subject identification number, the randomization system provided the treatment number to be used for the vaccine dose.

The number of each administered treatment was recorded in the eCRF on the Vaccine Administration screen.

5.5.  Blinding

This study was conducted in an open-label manner, where all subjects in the Tdap group and Td group received a single dose of Boostrix.

The laboratory in charge of the laboratory testing was blinded to study group in the primary study 776423/001 [DTPA 0.3 (BOOSTRIX)-001], and codes were used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.
5.6. **Prior and concomitant medication /vaccinations**

At each study visit/contact, the investigator questioned the subject about any medication/product taken and vaccination received by the subject.

All concomitant medications/products, with the exception of vitamins and dietary supplements, administered within 30 days following the dose of study vaccine, were recorded in the eCRF. This also applied to concomitant vaccination administered in the period starting at Visit 1 (Day 0) and ending at Visit 2 (Day 30).

A prophylactic medication was a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic was considered a prophylactic when it was given in the absence of fever and any other symptom, to prevent fever from occurring [fever was defined as temperature ≥ 99.5°F for oral, axillary or tympanic route, or ≥ 100.4°F for rectal route]. The preferred route for recording temperature in this study was oral.

Similarly, any concomitant medication/product/vaccine relevant to a SAE or administered at any time during the study period for the treatment of a SAE was recorded in the eCRF.

5.7. **Assessment of immunogenicity variables**

5.7.1. **Laboratory assays**

- During the course of the study, the assays used to measure the anti-D, anti-T, anti-PT, anti-FHA and anti-PRN IgG concentrations were re-developed and re-validated and both assay units and assay cut-offs were adapted. The new ELISA’s for PT, FHA and PRN were calibrated against the WHO International Standard (NIBSC 06/140). This allowed the expression of concentrations measured with the new ELISA’s in international units per milliliter (IU/mL) instead of the formerly used ELISA units per milliliter (ELU/mL). The newly validated DTPa ELISA’s used in the study have a lower assay cut-off as compared to the one described in the protocol. The current assay cut-off is 0.057 IU/mL for anti-D, 0.043 IU/mL for anti-T, 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA and 2.187 IU/mL for anti-PRN.

- Anti-DI/TE IgG’s are measured to evaluate the immunogenicity of diphtheria toxoid (DI) and tetanus toxoid (TE) containing vaccines. More specifically, the following endpoints are used in GSK’s clinical primary and/or booster studies for inferential evaluation: seroprotection rates (percentage of subjects with concentration ≥ 0.1 IU/mL), booster response rates (percentage of subjects with concentration ≥ 1.0 IU/mL or by evaluation of the four-fold increase pre-vaccination to post-vaccination) and/or GMCs. An agreement between the old and new ELISA’s was shown with regards to the two thresholds of clinical relevance for the DI/TE response (0.1 IU/mL and 1.0 IU/mL) in that the false positivity rate for new versus old ELISA’s was demonstrated to be below the 5% pre-specified acceptance limit with 2.5% type I error. In addition, the new ELISA’s showed having no impact on the booster
response (four-fold increase) and thus the evaluation of the booster response remains unchanged.

- For the computation of the pertussis booster response:
  - for subjects with pre-vaccination antibody concentration below the assay cut-offs, post-vaccination antibody concentration ≥ 4 times the assay cut-offs,
  - for subjects with pre-vaccination antibody concentration between the assay cut-offs and below 4 times the assay cut-offs, post-vaccination antibody concentration ≥ 4 times the pre-vaccination antibody concentration,
  - for subjects with pre-vaccination antibody concentration ≥ 4 times the assay cut-offs, post-vaccination antibody concentration ≥ 2 times the pre-vaccination antibody concentration.

Table 6 presents the laboratory assays used for antibody determination.

**Table 6**  Humoral Immunity (Antibody determination)

<table>
<thead>
<tr>
<th>Blood sample from subjects</th>
<th>Marker</th>
<th>Assay</th>
<th>Assay cut-off (IU/mL)</th>
<th>Laboratory</th>
<th>Laboratory address</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>Anti-D</td>
<td>ELISA</td>
<td>0.057</td>
<td>GSK Biologicals</td>
<td>GSK Rixensart Rue de l'Institut, 89 B-1330 Rixensart – Belgium</td>
</tr>
<tr>
<td>Serum</td>
<td>Anti-D</td>
<td>Neutralization assay on Vero cells*</td>
<td>0.004</td>
<td>GSK Biologicals</td>
<td>GSK Wavre Avenue Fleming, 20 B-1300 Wavre – Belgium</td>
</tr>
<tr>
<td>Serum</td>
<td>Anti-T</td>
<td>ELISA</td>
<td>0.043</td>
<td>GSK Biologicals</td>
<td>GSK Rixensart Rue de l'Institut, 89 B-1330 Rixensart – Belgium</td>
</tr>
<tr>
<td>Serum</td>
<td>Anti-PT</td>
<td>ELISA</td>
<td>2.693</td>
<td>GSK Biologicals</td>
<td>GSK Rixensart Rue de l'Institut, 89 B-1330 Rixensart – Belgium</td>
</tr>
<tr>
<td>Serum</td>
<td>Anti-FHA</td>
<td>ELISA</td>
<td>2.046</td>
<td>GSK Biologicals</td>
<td>GSK Rixensart Rue de l'Institut, 89 B-1330 Rixensart – Belgium</td>
</tr>
<tr>
<td>Serum</td>
<td>Anti-PRN</td>
<td>ELISA</td>
<td>2.187</td>
<td>GSK Biologicals</td>
<td>GSK Rixensart Rue de l'Institut, 89 B-1330 Rixensart – Belgium</td>
</tr>
</tbody>
</table>

*Test on Vero cells was to be performed on pre-vaccination samples with concentrations < 0.1IU/mL by ELISA.

The GSK Biologicals’ clinical laboratories had established a Quality System supported by procedures. The activities of GSK Biologicals’ clinical laboratories were audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

**5.7.2. Immunological read-outs**

In case of insufficient blood sample volume to perform assays for all antibodies, the samples were analyzed according to priority ranking provided in Table 7.
### Table 7 Immunological read-outs

<table>
<thead>
<tr>
<th>Blood sampling timepoint</th>
<th>Type of contact and timepoint</th>
<th>No. of subjects</th>
<th>Components priority rank</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diphtheria (ELISA), Diphtheria (Vero cell*),</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tetanus, PT, FHA, PRN</td>
</tr>
<tr>
<td>Visit 1 (Day 0) Pre-Bst¹</td>
<td></td>
<td>All</td>
<td></td>
</tr>
<tr>
<td>Visit 2 (Month 1) Post-Bst²</td>
<td></td>
<td>All</td>
<td>Diphtheria (ELISA), Tetanus, PT, FHA, PRN</td>
</tr>
</tbody>
</table>

¹ Bst: Booster.  
* Test on Vero cells was performed on pre-vaccination samples with concentrations < 0.1IU/mL by ELISA.

#### 5.7.3 Immunological correlates of protection

The following cut-offs were accepted as immunological correlates of protection:

**Seroprotection for diphtheria and tetanus antigens:**

- Specific antibodies against diphtheria toxoid (anti-diphtheria) and tetanus toxoid (anti-tetanus) were measured by an ELISA developed in-house. The assay cut-off for antibodies against diphtheria was set at 0.057 IU/mL and for tetanus toxoids at 0.043 IU/mL. For both serology a threshold of 0.1 IU/mL (ELISA), provided a conservative estimate of the percentage of subjects deemed to be protected (Camargo, 1984; Melville-Smith, 1983).

- The cut-off for the Vero-cell assay (performed for pre-vaccination serum samples when ELISA anti-diphtheria antibody concentrations is < 0.1 IU/mL) was 0.004 IU/mL. Antibody concentrations ≥ 0.01 IU/mL were considered as protective (Camargo, 1984). The ELISA test defined the seroprotection status for the primary endpoint.

- No correlate of protection has been defined for the immune response to pertussis antigens (Granström, 1987; Karpinsky, 1987). Antibodies against the pertussis components PT, FHA and PRN were measured by an ELISA technique developed in-house. The assay cut-off for anti-PT was 2.693 IU/mL, for anti-FHA was 2.046 IU/mL and for anti-PRN was 2.187 IU/mL. Subjects with antibody concentration below these cut-offs were considered seronegative.

The immunological assay results were communicated to the investigator as soon as they became available.

The investigator was encouraged to share the immunological assay results for non-responders with the study subjects.

For the study subjects identified as non-responders, it remained the responsibility of the study investigator in charge of the subject’s clinical management to determine the medical need for re-vaccination and to re-vaccinate the subjects as per local/regional practices.
5.8. Assessment of safety variables

The investigator or site staff was responsible for the detection, documentation and reporting of events meeting the criteria and definition of an AE or SAE as provided in the protocol.

Each subject was instructed to contact the investigator immediately if they manifested any signs or symptoms they perceived as serious.

5.8.1. Adverse events

An AE was any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE was therefore any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also included failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it could have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose per se was not reported as an AE/SAE).
- Significant failure of expected pharmacological or biological action.
- Signs, symptoms temporally associated with vaccine administration.
- Pre- or post-treatment events that occurred as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject’s previous therapeutic regimen).

Examples of an AE DID NOT include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that lead to the procedure was an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
• AEs included pre- or post-treatment events that occurred as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject’s previous therapeutic regimen).

Example of events to be recorded in the medical history section of the eCRF:

☐ Pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e. prior to the first study vaccination).

5.8.1.1. Solicited adverse events

The following local (injection-site) AEs were solicited:

Table 8 Solicited local adverse events

<table>
<thead>
<tr>
<th>Pain at injection site</th>
<th>Redness at injection site</th>
<th>Swelling at injection site</th>
</tr>
</thead>
</table>

N.B. If subjects observed any large injection site reaction (defined as swelling with a diameter > 100 mm, noticeable diffuse swelling or noticeable increase of limb circumference), they were asked to contact study personnel and to visit the investigator’s office and/or home visit for evaluation as soon as possible. The investigator recorded detailed information describing the AE on a specific large injection site reaction in the eCRF.

The following general AEs were solicited:

Table 9 Solicited general adverse events

<table>
<thead>
<tr>
<th>Fatigue</th>
<th>Fever</th>
<th>Gastrointestinal symptoms †</th>
<th>Headache</th>
</tr>
</thead>
</table>

†Gastrointestinal symptoms include nausea, vomiting, diarrhea and/or abdominal pain.

N.B. Temperature was recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature was recorded.

5.8.1.2. Assessment of AEs

5.8.1.2.1. Assessment of intensity

The intensity scale for assessment of intensity for solicited symptoms in adults is presented in Table 10.
### Table 10  Intensity scales for solicited symptoms in adults

<table>
<thead>
<tr>
<th>Adults</th>
<th>Intensity Grade</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain at injection site</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Mild: Any pain neither interfered with nor prevented normal every day activities.</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Moderate: Painful when limb was moved and interfered with every day activities.</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Severe: Significant pain at rest. Prevented normal every day activities.</td>
</tr>
<tr>
<td>Redness at injection site</td>
<td></td>
<td>Recorded greatest surface diameter in mm</td>
</tr>
<tr>
<td>Swelling at injection site</td>
<td></td>
<td>Recorded greatest surface diameter in mm</td>
</tr>
<tr>
<td>Fever*</td>
<td></td>
<td>Recorded temperature in °C/°F</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Mild: Headache that was easily tolerated</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Moderate: Headache that interfered with normal activity</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Severe: Headache that prevented normal activity</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Mild: Fatigue that was easily tolerated</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Moderate: Fatigue that interfered with normal activity</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Severe: Fatigue that prevented normal activity</td>
</tr>
<tr>
<td>Gastrointestinal symptoms (nausea, vomiting, diarrhea and/or abdominal pain)</td>
<td>0</td>
<td>Gastrointestinal symptoms normal</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Mild: Gastrointestinal symptoms that were easily tolerated</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Moderate: Gastrointestinal symptoms that interfered with normal activity</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Severe: Gastrointestinal symptoms that prevented normal activity</td>
</tr>
</tbody>
</table>

*Fever was defined as temperature ≥ 99.5°F for oral, axillary or tympanic route, or ≥100.4°F for rectal route. The preferred route for recording temperature in this study was oral.

The maximum intensity of local injection site redness/swelling was scored at GSK Biologicals as follows:

<table>
<thead>
<tr>
<th>Intensity Grade</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absent</td>
</tr>
<tr>
<td>1</td>
<td>≤ 20 mm</td>
</tr>
<tr>
<td>2</td>
<td>&gt; 20 mm and ≤ 50 mm</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 50 mm</td>
</tr>
</tbody>
</table>
The maximum intensity of fever was scored at GSK Biologics as follows:

<table>
<thead>
<tr>
<th></th>
<th>Oral/Axillary</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt; 99.5°F</td>
</tr>
<tr>
<td>1</td>
<td>≥ 99.5°F and ≤ 100.4°F</td>
</tr>
<tr>
<td>2</td>
<td>&gt; 100.4°F and ≤ 102.2°F</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 102.2°F</td>
</tr>
</tbody>
</table>

The investigator made an assessment of the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment was based on the investigator’s clinical judgment.

The intensity of each AE recorded in the eCRF or SAE Report Form, as applicable was assigned to one of the following categories:

1 (mild) = An AE which was easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

2 (moderate) = An AE which was sufficiently discomforting to interfere with normal everyday activities.

3 (severe) = An AE which prevented normal, everyday activities (In adults, such an AE would, for example, prevented attendance at work/school and would necessitate the administration of corrective therapy.)

An AE that was assessed as Grade 3 (severe) was not be confused with a SAE. Grade 3 was a category used for rating the intensity of an event; and both AEs and SAEs were assessed as Grade 3. An event was defined as ‘serious’ when it met one of the pre-defined outcomes as described in Section 5.8.2.

5.8.1.2.2. Assessment of causality

The definitions for ‘NO’ and ‘YES’ were written in such a way that all events that were attributed a ‘NO’ could be pooled with events which in the primary vaccination study were determined to be ‘not related’ or ‘unlikely to be related’ to vaccination. Those events that were attributed a ‘YES’ were pooled with those events that in the past were determined to have a ‘suspected’ or ‘probable’ relationship to vaccination in the primary vaccination study.

The investigator was obligated to assess the relationship between investigational vaccine and the occurrence of each AE/SAE. The investigator used clinical judgment to determine the relationship. Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational vaccine/product were considered and investigated. The investigator consulted the IB and PI for marketed products to determine his/her assessment.
There could be situations when a SAE had occurred and the investigator had minimal information to include in the initial report to GSK Biologicals. However, it was very important that the investigator always made an assessment of causality for every event prior to submission of the SAE report to GSK Biologicals. The investigator may have changed his/her opinion of causality in light of follow-up information and updating the SAE information accordingly. The causality assessment was one of the criteria used when determining regulatory reporting requirements.

In case of concomitant administration of multiple vaccines, it was not possible to determine the causal relationship of general AEs to the individual vaccines administered. The investigator, therefore, assessed whether the AE was causally related to vaccination rather than to the individual vaccines/products.

All solicited local (injection site) reactions were considered causally related to vaccination. Causality of all other AEs was assessed by the investigator using the following question:

*Was there a reasonable possibility that the AE might have been caused by the investigational vaccine/product?*

**NO**: There was no reasonable possibility that the AE was causally related to the administration of the study vaccine. There were other, more likely causes and administration of the study vaccine was not suspected to have contributed to the AE.

**YES**: There was a reasonable possibility that the vaccine contributed to the AE.

Non-serious and serious AEs were evaluated as two distinct events. If an event met the criteria to be determined as ‘serious’ (see Section 5.8.2 for definition of SAE), additional examinations/tests were to be performed by the investigator to determine all possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the vaccine, if applicable.
- Erroneous administration.
- Other cause (was to be specified).
5.8.1.3. **Assessment of outcomes**

The investigator was to assess the outcome of all unsolicited AEs (including SAEs) recorded during the study as:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

5.8.1.4. **Medically attended visits**

For each solicited and unsolicited symptom the subject experienced, they were asked if they received medical attention defined as hospitalization, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information was to be recorded in the eCRF.

5.8.2. **Serious adverse events**

A SAE was any untoward medical occurrence that:

a. resulted in death,

b. was life-threatening,

*NOTE:* The term 'life-threatening' in the definition of 'serious' referred to an event in which the subject was at risk of death at the time of the event. It did not refer to an event, which hypothetically might have caused death, if it were more severe.

c. required hospitalization or prolongation of existing hospitalization,

*NOTE:* In general, hospitalization signified that the subject had been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occurred during hospitalization were AEs. If a complication prolonged hospitalization or fulfilled any other serious criteria, the event was serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE was considered serious.

Hospitalization for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline was not considered an AE.

d. resulted in disability/incapacity, or

*NOTE:* The term disability meant a substantial disruption of a person’s ability to conduct normal life functions. This definition was not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea,
influenza like illness, and accidental trauma (e.g. sprained ankle) which could interfere
or prevent everyday life functions but did not constitute a substantial disruption.

e. was a congenital anomaly/birth defect in the offspring of a study subject.

Medical or scientific judgment should be exercised in deciding whether reporting was
appropriate in other situations, such as important medical events that could not be
immediately life-threatening or resulted in death or hospitalization but could jeopardize
the subject or may require medical or surgical intervention to prevent one of the other
outcomes listed in the above definition. These were also considered serious. Examples of
such events were invasive or malignant cancers, intensive treatment in an emergency
room or at home for allergic bronchospasm, blood dyscrasias or convulsions that did not
result in hospitalization.

5.8.3. Pregnancy

Female subjects who became pregnant after the vaccination continued the study at the
discretion of the investigator.

While pregnancy itself was not considered an AE or SAE, any adverse pregnancy
outcome or complication or elective termination of a pregnancy for medical reasons was
recorded and reported as an AE or a SAE.

Note: The pregnancy itself was to be recorded on an electronic pregnancy report.

The following was always considered as SAE and reported:

☐ Spontaneous pregnancy loss, including:
  – spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of
gestation)
  – ectopic and molar pregnancy
  – stillbirth (intrauterine death of fetus after 22 weeks of gestation).

Note: the 22 weeks cut-off in gestational age was based on WHO-ICD 10 noted in
the EMA Guideline on pregnancy exposure (EMA, 2006). It was recognized that
national regulations might be different.

☐ Any early neonatal death (i.e. death of a live born infant occurring within the first 7
days of life).

☐ Any congenital anomaly or birth defect [as per (CDC MACDP) guidelines]
identified in the offspring of a study subject (either during pregnancy, at birth or
later) regardless of whether the fetus was delivered dead or alive. This included
anomalies identified by prenatal ultrasound, amniocentesis or examination of the
products of conception after elective or spontaneous abortion.

Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered
by the investigator to be reasonably related to the investigational vaccine was reported to
GSK Biologicals. While the investigator was not obligated to actively seek this
information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

5.8.4. **Time period for detecting and recording adverse events, serious adverse events and pregnancies**

All AEs starting within 30 days following administration of the dose of study vaccine were recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they were considered vaccination-related.

The time period for collecting and recording SAEs began at the receipt of study vaccine and ended on Day 30 following administration of the dose of study vaccine for each subject.

All AEs/SAEs leading to withdrawal from the study were collected and recorded from the time of the receipt of study vaccine.

In addition to the above-mentioned reporting requirements and in order to fulfill international reporting obligations, SAEs that were related to study participation (i.e. protocol-mandated procedures, invasive tests, a change from existing therapy) or were related to a concurrent GSK medication/vaccine were collected and recorded from the time the subject consents to participate in the study until she/he was discharged from the study.

The time period for collecting and recording pregnancies began at the receipt of study vaccine and ended on Day 30 following administration of the dose of study vaccine.

A post-study AE/SAE was defined as any event that occurs outside of the AE/SAE reporting period. Investigators were not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learned of any SAE at any time after a subject had been discharged from the study, and he/she considered the event reasonably related to the investigational vaccine/product, the investigator was to promptly notify the Study Contact for Reporting SAEs.

5.8.5. **Follow-up of adverse events, serious adverse events, and pregnancies**

5.8.5.1. **Follow-up of adverse events and serious adverse events**

5.8.5.1.1. **Follow-up during the study**

After the initial AE/SAE report, the investigator was required to proactively follow each subject and provide additional relevant information on the subject’s condition to GSK Biologicals.

All SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving were reviewed at subsequent visits/contacts until the end of the study.
All AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving were reviewed at subsequent visits/contacts until 30 days after the vaccination.

5.8.5.1.2. **Follow-up after the subject is discharged from the study**

The investigators had followed up subjects:

- with SAEs, or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilized, disappeared, or until the event was otherwise explained, or the subject was lost to follow-up.

If the investigator received additional relevant information on a previously reported SAE, he/she provided this information to GSK Biologicals using a paper SAE and/or pregnancy report as applicable.

GSK Biologicals requested that the investigator performed or arranged for the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator was obliged to assist. If a subject died during participation in the study or during a recognized follow-up period, GSK Biologicals were provided with any available post-mortem findings, including histopathology.

5.8.5.2. **Active questioning to detect adverse events and serious adverse events**

As a consistent method of collecting AEs, the subjects were asked a non-leading question such as:

> ‘Have you felt different in any way since receiving the vaccine or since the previous visit?’

When an AE/SAE occurred, it was the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator then recorded all relevant information regarding an AE/SAE in the eCRF. The investigator was not allowed to send photocopies of the subject’s medical records to GSK Biologicals instead of appropriately completing the eCRF. However, there may have been instances when copies of medical records for certain cases were requested by GSK Biologicals. In this instance, all subject identifiers were blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator attempted to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis documented as the AE/SAE and not the individual signs/symptoms.

5.8.5.3. **Follow-up of pregnancies**

Pregnant subjects were followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother...
and child was forwarded to GSK Biologicals using the electronic pregnancy report and the SAE report if applicable. Generally, the follow-up period doesn’t need to be longer than six to eight weeks after the estimated date of delivery (EDD).

Regardless of the reporting period for SAEs for this study, if the pregnancy outcome was a SAE, it was always reported as SAE.

5.9. Statistical methods

5.9.1. Co-Primary endpoint

☐ Immunogenicity with respect to components of the study vaccine.
  - Anti-D and anti-T antibody concentrations $\geq 0.1$ IU/mL by ELISA, one month after vaccination.
  - Anti-pertussis (PT, FHA and PRN) antibodies GMCs one month after vaccination.
  - Anti-pertussis (PT, FHA and PRN) antibodies GMCs one month after the third dose of Infantrix in Study APV-039 Total Vaccinated cohort (TVC).

5.9.2. Secondary endpoints

☐ Immunogenicity with respect to components of the study vaccine.
  - Anti-D* and anti-T antibody concentrations $\geq 0.1$ IU and $\geq 1.0$ IU/mL by ELISA or $\geq 0.01$ IU/mL by Vero cell testing for subjects with post-vaccination ELISA anti-D toxoid antibody concentration $< 0.1$ IU/mL, prior to and one month after vaccination.
  - Anti-PT, anti-FHA and anti-PRN antibody concentrations $\geq$ assay cut-off**, anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations prior to and one month after vaccination.
  - Booster response to the diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens one month after vaccination

* Sera with ELISA concentrations $< 0.1$ IU/mL was tested for neutralizing antibodies using a Vero-cell neutralization assay.

**During the course of the study, the assays used to measure the anti-D, anti-T, anti-PT, anti-FHA and anti-PRN IgG concentrations were re-developed and re-validated and both assay units and assay cut-offs were adapted. The new ELISA’s for PT, FHA and PRN were calibrated against the WHO International Standard (NIBSC 06/140). This allowed the expression of concentrations measured with the new ELISA’s in international units per milliliter (IU/mL) instead of the formerly used ELISA units per milliliter (ELU/mL). The newly validated DTPa ELISA’s used in the study have a lower assay cut-off as compared to the one described in the protocol. The current assay cut-off is 0.057 IU/mL for anti-D, 0.043 IU/mL for anti-T, 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA and 2.187 IU/mL for anti-PRN.

☐ Solicited local and general symptoms.
  - Occurrence of each solicited local and general symptoms (any and Grade 3) within 4-day (Days 0-3) after vaccination.
- Occurrence of large injection site reactions (defined as swelling with a diameter > 100 mm, noticeable diffuse swelling or noticeable increase of limb circumference) within 4-day (Days 0-3) after vaccination.

☐ Unsolicited adverse events.

- Occurrence of unsolicited AEs within 31-day (Days 0-30) after vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.

☐ Serious adverse events (SAEs).

- Occurrence of SAEs from the administration of the vaccine dose up to 31 days following vaccination.

5.9.3. Determination of sample size

The sample size estimation for the immunogenicity cohort was based on the co-primary objectives below:

- Non-inferiority of the second dose of Tdap vaccine, administered to young adults 10 years after the previous booster dose of the same vaccine, to the first booster dose of Tdap vaccine administered to young adults 10 years after a previous booster dose of Td vaccine, with respect to anti-D and anti-T seroprotection rates (antibody concentration ≥ 0.1 IU/mL by ELISA);

☐ Non-inferiority of the second dose of Tdap vaccine to the primary *Infanrix* vaccination series in the Study APV-039, with respect to anti-pertussis (PT, FHA and PRN) antibody response.

*Table 11* and *Table 12* show the power to demonstrate non-inferiority between second Tdap and first Tdap/*Infanrix* with respect to each of the five antibodies. With 100 evaluable subjects in the Td Group and 300 evaluable subjects in the Tdap Group, the study would have an overall power of 97% to meet both co-primary objectives simultaneously.

Assuming 20% subjects who gave blood samples might be non-evaluable; the study was to take blood samples from at least 500 young adults, i.e. 125 subjects in Td Group and 375 subjects in Tdap Group assuming group allocation ratio was similar to that of the primary study.
Table 11  Power to demonstrate non-inferiority of second dose of Tdap vaccine to first dose of Tdap vaccine with respect to anti-D and anti-T seroprotection rate

<table>
<thead>
<tr>
<th>Endpoint (antibody concentration &gt; 0.1 IU/mL)</th>
<th>Reference values</th>
<th>Power* to reject H0: LL of 95% CI of difference &lt; -10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTPA 0.3 (BOOSTRIX)-007 (Boostrix sub-group 19-29)</td>
<td>Anti-D 99.4%</td>
<td>LL of 95% CI ≥ -10% &gt;99.99%</td>
</tr>
<tr>
<td>Non-inferiority criterion</td>
<td>Anti-T 99.8%</td>
<td>LL of 95% CI ≥ -10% &gt;99.99%</td>
</tr>
<tr>
<td>Difference (2nd dose - 1st dose)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N =100 (1st dose group)</td>
<td>Overall power**</td>
<td>99.99%</td>
</tr>
<tr>
<td>300 (2nd dose group)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Pass 2005, non-inferiority test on 2 independent proportions (Miettinen & Nurminen), alpha=2.5%; non-inferiority margin=10% power under alternative of equal proportions in both groups; LL= lower limit.

**Overall power is the probability to reject all null hypotheses simultaneously, computed by subtracting the sum of individual type-II errors (beta) from 1.

Table 12  Power to demonstrate non-inferiority of second dose of Tdap vaccine to Infanrix vaccine in APV-039 with respect to anti-PT, anti-FHA and anti-PRN GMCs

<table>
<thead>
<tr>
<th>Endpoint (GMCs)</th>
<th>Reference values (Standard Deviation of log10 transformed concentration)</th>
<th>Power* to reject H0: LL of 95% CI of GMC ratio (Tdap/Infanrix) &lt; 0.67</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTPA 0.3 (BOOSTRIX)-007 (Boostrix sub-group 19-29)</td>
<td>APV-039 Infanrix</td>
<td>N in APV-039 (TVC)</td>
</tr>
<tr>
<td>Anti-PT</td>
<td>0.464</td>
<td>0.306</td>
</tr>
<tr>
<td>Anti-FHA</td>
<td>0.374</td>
<td>0.370</td>
</tr>
<tr>
<td>Anti-PRN</td>
<td>0.645</td>
<td>0.413</td>
</tr>
<tr>
<td>Overall power**</td>
<td></td>
<td>97.02%</td>
</tr>
</tbody>
</table>

*Pass 2005, non-inferiority test on 2 independent means, alpha=2.5%; equivalence margin=log_{10} (0.67), variance from DTPA 0.3 (BOOSTRIX)-007 was considered as common variance for both groups, power under alternative of equal means in both groups; LL= lower limit.

**Overall power is the probability to reject the primary objective and all three null hypotheses simultaneously, computed by subtracting the sum of the three type-II errors (beta) from 1.

5.9.4. Study cohorts /data sets analyzed

Three cohorts were defined for the purpose of analysis:

- The Total vaccinated cohort (TVC).
- According to protocol (ATP) cohort for analysis of safety.
- ATP cohort for analysis of immunogenicity.

5.9.4.1. Total vaccinated cohort

The TVC included all subjects with a study vaccine administration dose documented:

- A safety analysis based on the TVC included all vaccinated subjects.
An immunogenicity analysis based on the TVC included all vaccinated subjects for whom immunogenicity results were available.

5.9.4.2. According-to-protocol cohort for analysis of safety

The ATP cohort for analysis of safety included all eligible and vaccinated subjects,

- Who had received the dose of study vaccine.
- For whom administration site of study vaccine was known.
- Who had not received a vaccine leading to elimination from an ATP analysis.

5.9.4.3. According-to-protocol cohort for analysis of immunogenicity

The ATP cohort for analysis of immunogenicity included all evaluable subjects from the ATP cohort for analysis of safety:

- Who met all eligibility criteria.
- Who complied with the procedures and intervals defined in the protocol (refer to Table 3).
- Who did not meet any of the criteria for elimination from an ATP analysis during the study.
- Who did not receive a product leading to elimination from an ATP analysis.
- Who did not present with a medical condition leading to elimination from an ATP analysis, before the visit 2 blood sample.
- For whom data concerning immunogenicity endpoint measures were available. This included subject for whom assay results were available for antibodies against at least one study vaccine antigen component after vaccination.

5.9.5. Derived and transformed data

- Immunogenicity
  - The cut-off value was defined by the laboratory before the analysis and is described in Section 5.7.
  - A seronegative subject was a subject whose concentration was below the cut-off value.
  - A seropositive subject was a subject whose concentration was greater than or equal to the cut-off value.
- A seroprotected subject was a subject whose antibody concentration was greater than or equal to the level defining clinical protection. The following seroprotection thresholds were applicable:
  - Anti-D antibody concentrations $\geq 0.1$ IU/mL.
  - Anti-T antibody concentrations $\geq 0.1$ IU/mL.
_BOXES incontrovertible:
- Anti-D antibody concentrations ≥ 1.0 IU/mL.
- Anti-T antibody concentrations ≥ 1.0 IU/mL.

Booster response defined as:
- for subjects with pre-vaccination concentration < 0.1 IU/mL, antibody concentrations at least ≥ 0.4 IU/mL, one month after vaccination,
- for subjects with pre-vaccination concentration ≥ 0.1 IU/mL, an increase in antibody concentrations of at least four times the pre-vaccination concentration one month after vaccination.

Booster response for pertussis:
- initially seronegative subjects (pre-booster antibody concentration below the assay cut-off) with an increase of at least four times the assay cut-off one month after vaccination,
- initially seropositive subjects with anti-body concentration < four times the assay cut-off with an increase of at least four times the pre-booster antibody concentration one month after vaccination,
- initially seropositive subjects with anti-body concentration ≥ four times the assay cut-off with an increase of at least two times the pre-booster antibody concentration one month after vaccination.

Alternative Booster response to D and T antigens was defined as:
- for initially seronegative subjects (pre-vaccination concentration below the 0.1 IU/mL): antibody concentrations at least four times 0.1 IU/mL one month after vaccination, and
- for initially seropositive subjects with pre-vaccination concentration <1.0 IU/mL: antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.
- for initially seropositive subjects with pre-vaccination concentration in [1.0; 6.0 IU/mL]: antibody concentrations of at least two times the pre-vaccination concentration, one month after vaccination.
- Subjects with pre-vaccination concentration ≥ 6.0 IU/mL are not evaluable for vaccine response.

Alternative Booster response to PT, FHA and PRN antigens was defined as:
- for initially seronegative subjects (pre-vaccination concentration below the assay cut-off): antibody concentrations at least four times the assay cut-off one month after vaccination, and
- for initially seropositive subjects with pre-vaccination antibody concentration ≥ assay cut-off and < 60 IU/mL: antibody concentration increase of at least 30 EL.U/mL from the pre-vaccination concentration, one month after vaccination.
- for initially seropositive subjects with pre-vaccination antibody concentration ≥ 60 EL.U/mL: at least 1.5 fold increase of antibody concentration from the pre-vaccination concentration, one month after vaccination.

☐ The GMC calculations were performed by taking the anti-log of the mean of the log concentration transformations. 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.

☐ The 95% CI for GMTs/GMCs were obtained within each group separately. The 95% CI for the mean of log-transformed concentration was first obtained assuming that log-transformed values were normally distributed with unknown variance. The 95% CI for the GMTs/GMCs were then obtained by exponential-transformation of the 95% CI for the mean of log-transformed concentration.

**Handling of missing data:**

**Immunogenicity:**

☐ For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements was not to be replaced.

**Reactogenicity and Safety:**

☐ For a given subject and the analysis of solicited symptom within 4 days post-vaccination, missing or non-evaluable measurements was not to be replaced. Therefore, the analysis of the solicited symptoms based on the TVC included only vaccinated subjects and doses with documented safety data (i.e. symptom screen completed).

☐ For analysis of unsolicited adverse events, such as SAEs or AEs by primary MedDRA term, and for the analysis of concomitant medications, all vaccinated subjects were considered. Subjects who did not report the event or the concomitant medication were considered as subjects without the event or the concomitant medication respectively.

☐ For summaries reporting both solicited and unsolicited adverse events, all vaccinated subjects were considered. Subjects who did not report the event or the concomitant medication were considered as subjects without the event or the concomitant medication respectively.

**5.9.6. Analysis of demographics**

Demographic characteristics (age at vaccination visit in years, gender, geographical ancestry and ethnicity) were summarized by group using descriptive statistics:

☐ Frequency tables were generated for categorical variable such as center.

☐ Mean, median, standard deviation was provided for continuous data such as age.

In addition, a summary of the tracking log-sheet documenting outcomes of the contacts made with subjects for enrolment were provided.
5.9.7. Analysis of immunogenicity

The primary analysis was based on the ATP cohort for analysis of immunogenicity. Since the percentage of vaccinated subjects with serological results excluded from the ATP cohort for analysis of immunogenicity was 5% or more, a second analysis based on the TVC was performed to complement the ATP analysis.

5.9.7.1. Within groups assessment

For each group and each antigen:

- Seropositivity/seroprotection rate at pre-vaccination, one month post-vaccination was calculated with exact 95% confidence intervals (CIs).
- GMCs or at pre-vaccination, one month post-vaccination were tabulated with 95% CIs.
- Booster response rate one month post-vaccination was calculated with exact 95% CIs.
- Antibody concentrations distribution at pre-vaccination and one month post-vaccination was displayed using reverse cumulative curves (RCC).

5.9.7.2. Between groups assessment

- For anti-D, anti-T seroprotection rates, the two-sided standardized asymptotic 95% CI for the group differences (Tdap Group minus Td Group) was calculated.
- For anti-D, anti-T antibody response, the two-sided 95% CIs of the GMC ratios between subjects in the Tdap Group and (divided by) the Td Group one month after vaccination was computed using an analysis of covariance (ANCOVA) model on the logarithm_{10} transformation of the concentrations adjusted to pre-vaccination concentration in 776423/001 [DTPa 0.3 (BOOSTRIX)-001] study.
- For anti-PT, anti-FHA and anti-PRN antibody response, the two-sided 95% CIs of the GMC ratios between subjects in the Tdap Group and (divided by) the Infanrix Group in APV-039 one month after vaccination (one month after vaccination for Tdap Group, one month after the third dose of Infanrix for Infanrix group in APV-039) was computed using the method proposed by G.Y. Zou and A. Donner (Zou, 2008) in order to account heterogeneity of variance between this study and APV-039. Note that the APV-039 reference for this comparison was the results converted into the revalidated assays by using multiple imputation techniques (GlaxoSmithKline Biologicals Annex Report 208355 (APV) 022).
- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN booster response, the two-sided standardized asymptotic 95% CI for the group differences (Tdap Group minus Td Group) was calculated.
- For anti-PT, anti-FHA and anti-PRN antibody response, the two-sided 95% CI of the GMC ratios between subjects in the Tdap Group and Td Group one month after vaccination was computed using an ANCOVA model on the logarithm_{10}...
transformation of the concentrations adjusted to pre-vaccination concentration in 776423/001 [DTPA 0.3 (BOOSTRIX)-001] study.

For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN alternative booster response, the two-sided standardized asymptotic 95% CI for the group differences (Tdap Group minus Td Group) was calculated.

### 5.9.7.3. Interpretation of analyses

Except for analyses addressing criteria specified in the objectives, comparative analyses were exploratory with the aim to characterize the difference between groups in immunogenicity. These exploratory analyses were not used to conclude since there was no adjustment for multiplicity of endpoints.

With respect to the two co-primary objectives, the interpretation must be done according to a hierarchical procedure. More specifically, the second primary objective could be reached if all the associated criteria were met and the first primary objectives were reached.

### 5.9.7.4. Sensitivity analysis

An analysis of persistence was carried out in order to evaluate the robustness of the results with respect to dropout, by using a repeated generalised linear model. This model used results from 776423/001 [DTPA 0.3 (BOOSTRIX)-001] post-vaccination visit and pre-booster results of the current study. Analyses was based on the ATP cohort of immunogenicity of 776423/001 [DTPA 0.3 (BOOSTRIX)-001] and 116570 studies respectively.

Serology results below cut-off were considered as left censored at the assay cut-off.

The model included the fixed group effect, the fixed effect of time since last vaccination, the random intercept effect for all serology, random slope effect for anti-diphtheria and tetanus, and interaction in slope for pertussis antigens (Thiébaut, 2004).

### 5.9.8. Analysis of safety

#### 5.9.8.1. Within groups assessment

The primary analysis was based on the TVC. There were no subjects excluded from the ATP cohort for analysis of safety, hence a second analysis based on this ATP cohort was not performed to complement the analysis of the TVC.

Safety data was analyzed by subject incidence rates of solicited and unsolicited adverse events in the vaccine schedules treatment groups by solicited local and general symptom terms, and, for unsolicited AEs, by MedDRA preferred term and system organ class. Safety data was summarized for all subjects by treatment group.

The incidence of solicited local and general symptoms occurring during 4 days after vaccination was tabulated with exact 95% CI for each treatment group. The same calculations were performed for symptoms of any intensity, those with intensity Grade
≥ 2, and those with intensity of Grade 3, as well as for solicited general events with relationship to vaccination and events requiring medical attention, respectively. Note that all solicited local adverse events were considered to be causally related.

The percentage of subjects with at least one report of an unsolicited adverse event classified by MedDRA up to 31 days after vaccine was tabulated with exact 95% CI for each treatment group. The same tabulation was performed for Grade 3 unsolicited adverse events, AEs resulting in a medically attended visit and for unsolicited adverse events that were considered by the investigator to be possibly related to vaccination.

SAEs were summarized from Day 0 to 31 days post-vaccination.

SAEs, large injection site reaction (defined as swelling with a diameter > 100 mm, noticeable diffuse swelling or noticeable increase of limb circumference) and withdrawals due to adverse event(s) were described in detail.

### 5.9.8.2. Between groups assessment

The standardized asymptotic 95% CI for the difference between the two groups and the associated 2-sided p-value to detect group difference (Newcombe, 1998) was computed for the following endpoints:

- For each solicited symptom, the percentage of subjects reporting the symptom within 4 days after vaccination (any Grade, Grade 3, causally related, respectively).
- The percentage of subjects reporting adverse events within 31 days' post-vaccination (any, Grade 3, causally related, requiring medical attention).
- The percentage of subjects reporting SAEs (any, causally related) during the study period.

P-value below 5% was used to identify events that were recognized as worthy of further investigation. It was to be noted that the use of such analyses has the potential to identify a large number of events which may or may not have a causal relationship to treatment due to unadjustment for multiplicity. In order to put these in perspective, the analysis was complemented by a permutation test that quantified the probability of identifying erroneously an event according to the threshold p-value. In addition, clinical judgment and biological plausibility was taken into account when performing overall assessment.

### 5.9.9. Sequence of analyses

The immunogenicity analyses of antibody persistence and immune response to the booster dose and safety analysis of the booster dose were performed as soon as all immunogenicity and safety data up to Visit 2 had been cleaned. These analyses were the basis for the study report of the booster phase. Results were not shared with the investigator before study conclusion.

### 5.9.10. Interim analysis

All analyses were conducted on final data and therefore no statistical adjustment for interim analyses was required.
5.10. Data quality assurance at study level

To ensure that the study procedures conformed across all investigator sites, the protocol, electronic case report form and safety reporting were reviewed with the investigators and their personnel responsible for the conduct of the study by the Company representatives prior to study start.

Adherence to the protocol requirements and verification of data generation accuracy were achieved through monitoring visits to each investigator site. Computer checks and blinded review of subject tabulations were performed to ensure consistency of eCRF completion. All procedures were performed according to methodologies detailed in GlaxoSmithKline Biologicals Standard Operating Procedures (SOPs).

All protocol deviations collected during the study were reviewed by the GSK study team in order to identify important protocol deviations. Consistent with ICH E3 guidance, important deviations are defined as deviations that were likely to affect the interpretation of the results and/or led to exclusion of any subject data from an analysis. Important deviations include, but are not limited to, those related to study inclusion or exclusion criteria, adherence to the protocol, conduct of the study, subject management or subject assessment.

No CROs were employed in this study.

Independent Audit statement:

- This study was subject to audit by GlaxoSmithKline’s R&D Global Quality Compliance (GQC) - Clinical Development Quality Assurance (CDQA) department. No major findings with regard to the conduct of the study were identified.

5.11. Changes in the conduct of the study or planned analyses

5.11.1. Protocol amendments

There were two amendments to the study protocol (dated 24-May-2012):

Protocol amendment 1 (dated 12-October-2012) was done to reflect the following changes:

☐ Following consultation with Center for Biologics Evaluation and Research (CBER), the objectives were updated and the endpoints were aligned accordingly. Additionally, extended safety follow-up was removed as it was not applicable to the study.
Protocol Amendment 2 (dated 03-October-2013) was done to reflect the following changes:

- Due to slow enrolment of subjects into the study, the protocol was amended to facilitate enrolment by:
  - Extending the window period for re-vaccination from ± 6 months to ± 300 days from the Year 10 time-point.
  - Extending the recruitment period from 6 months to 14 months.
- The format of non-inferiority criterion of the first co-primary objective was updated to keep it aligned with the format of non-inferiority criterion of the second co-primary objective.
- The list of contributing authors was updated. Typographical errors were corrected throughout the document.

5.11.2. Changes from planned analyses

- The study was conducted according to the protocol amendment 2 dated 03-October-2013 and Statistical Analysis Plan amendment dated 20-April-2017.

- During the course of the study, the assays used to measure the anti-D, anti-T, anti-PT, anti-FHA and anti-PRN IgG concentrations were re-developed and re-validated and both assay units and assay cut-offs were adapted. The new ELISA’s for PT, FHA and PRN were calibrated against the WHO International Standard (NIBSC 06/140). This allowed the expression of concentrations measured with the new ELISA’s in international units per milliliter (IU/mL) instead of the formerly used ELISA units per milliliter (ELU/mL). The newly validated DTPa ELISA’s used in the study have a lower assay cut-off as compared to the one described in the protocol. The current assay cut-off is 0.057 IU/mL for anti-D, 0.043 IU/mL for anti-T, 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA and 2.187 IU/mL for anti-PRN.

- For anti-PT, anti-FHA and anti-PRN antibody response, the two-sided 95% CIs of the GMC ratios between subjects in the Tdap Group and (divided by) the Infanrix Group in APV-039 one month after vaccination (one month after vaccination for Tdap Group, one month after the third dose of Infanrix for Infanrix group in APV-039) was computed using the method proposed by G.Y. Zou and A. Donner (Zou, 2008) in order to account heterogeneity of variance between this study and APV-039. Note that the APV-039 reference for this comparison was the results converted into the revalidated assays by using multiple imputation techniques (GlaxoSmithKline Biologicals Annex Report 208355 (APV) 022).

- The vaccine responses were redefined in light of the change in assay cut-off.

- The alternative booster response defined in the protocol amendment 2 was based on the pre-vaccination antibody concentration in DTPa 0.3 (BOOSTRIX)-001 study. In the context of the protocol amendment 3 for study DTPa 0.3 (BOOSTRIX)-009 EXT 007 the definition was challenged by CBER and replaced by an alternative definition using the pre-vaccination antibody concentration in DTPa 0.3 (BOOSTRIX)-012.
The statistical plan of DTPa 0.3 (BOOSTRIX)-012 was amended to reflect the new definition but the protocol was not amended.

- Sensitivity analysis of persistence data was initially based on imputation method. The method was replaced by a repeated mixed model.
- The incidence of solicited general symptom ‘fever’ was presented in °C instead of °F.

6. STUDY POPULATION RESULTS

6.1. Study dates

The first subject was enrolled in the study on 31-January-2013 and the last study visit was on 02-April-2014.

6.2. Subject disposition

The number of subjects vaccinated, completed and withdrawn in the TVC is presented in Table 13.

Table 13 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Reason for withdrawal</th>
<th>Td group</th>
<th>Tdap group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects vaccinated</td>
<td>37</td>
<td>128</td>
<td>165</td>
</tr>
<tr>
<td>Number of subjects completed</td>
<td>36</td>
<td>124</td>
<td>160</td>
</tr>
<tr>
<td>Number of subjects withdrawn</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Migrated/moved from study area</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lost to follow-up (subjects with complete vaccination course)</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come back for the last visit

Out of a total of 165 vaccinated subjects (37 subjects from the Td group and 128 subjects from the Tdap group), five subjects (one subject from the Td group and four subjects from the Tdap group) were withdrawn from the study.

The number of subjects at each visit and list of withdrawn subjects in the TVC is presented in Table 14.
Table 14  Number of subjects at each visit and list of withdrawn subjects
(Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Td group</th>
<th>Subjects received the first dose of Tdap vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tdap group</td>
<td>Subjects received a second dose of Tdap vaccine</td>
</tr>
<tr>
<td>N</td>
<td>Number of subjects who are still in the study up to the visit</td>
</tr>
<tr>
<td>Withdrawn</td>
<td>Subject who did not return after the visit</td>
</tr>
</tbody>
</table>

The number of subjects by center for the TVC is presented in Table 40.

The number of subjects enrolled into the study as well as the number excluded from ATP analyses with reasons for exclusion is presented in Table 45.

6.3. Important Protocol deviations at subject level

6.3.1. Protocol Deviations leading to elimination from ATP analyses

There were protocol deviations that led to elimination of subjects from ATP analyses.

The deviations from specifications for intervals between study visits for TVC are presented in Table 41.

6.3.2. Protocol Deviations not leading to elimination from ATP analyses

There were no important protocol deviations that did not lead to elimination of subjects from ATP analyses.
6.4. Demographic characteristics and other baseline characteristics

The summary of demographic characteristics for the TVC is presented in Table 15.

Table 15 Summary of demographic characteristics (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Td group N = 37</th>
<th>Tdap group N = 128</th>
<th>Total N = 165</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) at vaccination dose:</td>
<td>Mean 23.3 - 23.5 - 23.5 -</td>
<td>SD 2.4 - 2.1 - 2.1 -</td>
<td>Median 23.0 - 23.0 - 23.0 -</td>
</tr>
<tr>
<td></td>
<td>Minimum 20 - 20 - 20 -</td>
<td>Maximum 29 - 29 - 29 -</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>18</td>
<td>48.6</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>19</td>
<td>51.4</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>American Hispanic or Latino</td>
<td>4</td>
<td>10.8</td>
</tr>
<tr>
<td></td>
<td>Not American Hispanic or Latino</td>
<td>33</td>
<td>89.2</td>
</tr>
<tr>
<td>Geographic Ancestry</td>
<td>Black</td>
<td>1</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>White/Caucasian</td>
<td>31</td>
<td>83.8</td>
</tr>
<tr>
<td></td>
<td>Oriental</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>5</td>
<td>13.5</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

The summary of demographic characteristics for the ATP cohort for immunogenicity is presented in Table 16.
Table 16  Summary of demographic characteristics (ATP cohort for analysis of immunogenicity)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Td group N = 35</th>
<th>Tdap group N = 115</th>
<th>Total N = 150</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameters or Categories</td>
<td>Value or n</td>
<td>Value or n</td>
<td>Value or n</td>
</tr>
<tr>
<td>Age (years) at vaccination dose: 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>23.4</td>
<td>23.5</td>
<td>23.5</td>
</tr>
<tr>
<td>SD</td>
<td>2.4</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Median</td>
<td>23.0</td>
<td>23.0</td>
<td>23.0</td>
</tr>
<tr>
<td>Minimum</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Maximum</td>
<td>29</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>17</td>
<td>52</td>
<td>69</td>
</tr>
<tr>
<td>Male</td>
<td>18</td>
<td>51.4</td>
<td>81</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Hispanic or Latino</td>
<td>4</td>
<td>14.1</td>
<td>15</td>
</tr>
<tr>
<td>Not American Hispanic or Latino</td>
<td>31</td>
<td>88.6</td>
<td>135</td>
</tr>
<tr>
<td>Geographic Ancestry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1</td>
<td>2.9</td>
<td>4</td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>29</td>
<td>82.9</td>
<td>134</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>14.3</td>
<td>11</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

The summary of demographic characteristics for the ATP cohort for safety is presented in Table 44.

The demography of age (in years) at vaccination dose 1 for TVC and ATP cohort for safety is presented in Table 42 and Table 43 respectively.

7. IMMUNOGENICITY RESULTS

The primary analysis of immunogenicity was performed on the ATP cohort for immunogenicity. Refer to Section 5.9.4 for the definition of the cohort identified for analyses.

The group differences in the percentage of subjects with anti-Diphtheria and anti-Tetanus antibody concentrations ≥ 0.1 IU/mL [Tdap Group minus Td Group], one month after booster vaccination and their standardized asymptotic 95% CIs for ATP cohort for analysis of immunogenicity are presented in Table 17.
Table 17  Group differences in the percentage of subjects with anti-Diphtheria and anti-Tetanus antibody concentrations ≥ 0.1 IU/mL [Tdap Group Minus Td Group], one month after booster vaccination and their standardized asymptotic 95% CIs (ATP cohort for analysis of immunogenicity)

<table>
<thead>
<tr>
<th>Antibody Type</th>
<th>Td group</th>
<th>Tdap group</th>
<th>Difference in percentage (Tdap group minus Td group)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N  n/ %</td>
<td>N  n/ %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>anti-D antibody</td>
<td>0.1 IU/mL</td>
<td>35  35/100</td>
<td>115 115/100</td>
<td>0.00</td>
</tr>
<tr>
<td>anti-T antibody</td>
<td>0.1 IU/mL</td>
<td>35  35/100</td>
<td>115 115/100</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine  
Tdap group = Subjects received a second dose of Tdap vaccine  
N = number of subjects with available results  
n/% = number/percentage of subjects with antibody concentrations above the specified cut-off (≥ 0.1IU/mL)  
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

One month after vaccination, the lower limits (LL) of the 95% CI on the difference of the seroprotection rates [second dose of Tdap (Tdap Group) minus first dose of Tdap (Td Group)] for anti-diphtheria and anti-tetanus antibody concentrations was -3.25. Therefore, the co-primary objective of the study was met as the LLs were greater than -10% (clinical limit for non-inferiority).

The group differences in the percentage of subjects with anti-Diphtheria and anti-Tetanus antibody concentrations ≥ 0.1 IU/mL [Tdap Group minus Td Group], one month after booster vaccination and their standardized asymptotic 95% CIs for TVC are presented in Table 59.

The GMC ratio between groups [Tdap Group divided by Infanrix Group in APV-039] and their 95% CIs for anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination for TVC are presented in Table 18.
Table 18  GMC ratio between groups [Tdap Group divided by Infanrix Group in APV-039] and their 95% CIs for anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>N</th>
<th>GMC</th>
<th>N</th>
<th>GMC</th>
<th>GMC Ratio</th>
<th>95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-PT (Assay cut-off = 2.693 IU/mL)</td>
<td>124</td>
<td>83.5</td>
<td>2884</td>
<td>41.7</td>
<td>2.00</td>
<td>1.69</td>
<td>2.37</td>
</tr>
<tr>
<td>anti-FHA (Assay cut-off = 2.046 IU/mL)</td>
<td>124</td>
<td>285.5</td>
<td>685</td>
<td>47.2</td>
<td>6.05</td>
<td>5.14</td>
<td>7.11</td>
</tr>
<tr>
<td>anti-PRN (Assay cut-off = 2.187 IU/mL)</td>
<td>124</td>
<td>442.6</td>
<td>631</td>
<td>113.0</td>
<td>3.92</td>
<td>3.22</td>
<td>4.76</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
Infanrix Group in APV-039 = Infanrix group of the German household contact study APV-039
N = Number of subjects with available results
95% CI = 95% confidence interval for the adjusted GMC ratio LL = lower limit, UL = upper limit.
The associated CI was derived using the method proposed by G.Y. Zou and A. Donner (Zou, 2008) GMC = geometric mean antibody concentration calculated on all subjects

One month after vaccination, the lower limits of the 95% CI on the GMC ratio between the groups [Tdap Group divided by Infanrix Group in APV-039] for anti-PT, anti-FHA and anti-PRN were 1.69, 5.14 and 3.22 respectively. Therefore the co-primary objective of the study was met as the LLs were greater than 0.67.

The number and percentage of subjects with anti-diphtheria and anti-tetanus antibody concentration ≥ 0.1 IU/mL, ≥ 1 IU/mL and GMCs at pre and post-booster vaccination time points for ATP cohort for analysis of immunogenicity are presented in Table 19.

Table 19  Number and percentage of subjects with anti-Diphtheria and anti-Tetanus antibody concentration ≥ 0.1 IU/mL, ≥ 1 IU/mL and GMCs at pre and post booster vaccination time points (ATP cohort for analysis of immunogenicity)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group</th>
<th>Timing</th>
<th>N</th>
<th>%</th>
<th>&gt;= 0.1 IU/mL</th>
<th>%</th>
<th>&gt;= 1 IU/mL</th>
<th>%</th>
<th>GMC</th>
<th>95% CI</th>
<th>95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-D antibody</td>
<td>Td group</td>
<td>PRE</td>
<td>35</td>
<td>100</td>
<td>90.0</td>
<td>100</td>
<td>23</td>
<td>65.7</td>
<td>78.9</td>
<td>1.6</td>
<td>1.1</td>
<td>2.3</td>
</tr>
<tr>
<td>(Assay cut-off = 0.057 IU/mL)</td>
<td></td>
<td>Post</td>
<td>35</td>
<td>100</td>
<td>90.0</td>
<td>100</td>
<td>34</td>
<td>97.1</td>
<td>85.1</td>
<td>6.8</td>
<td>5.4</td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>PRE</td>
<td>115</td>
<td>100</td>
<td>96.8</td>
<td>100</td>
<td>70</td>
<td>60.9</td>
<td>51.3</td>
<td>1.6</td>
<td>1.3</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post</td>
<td>115</td>
<td>100</td>
<td>96.8</td>
<td>100</td>
<td>115</td>
<td>96.8</td>
<td>100</td>
<td>6.0</td>
<td>5.3</td>
<td>6.9</td>
</tr>
<tr>
<td>anti-T antibody</td>
<td>Td group</td>
<td>PRE</td>
<td>35</td>
<td>100</td>
<td>90.0</td>
<td>100</td>
<td>27</td>
<td>77.1</td>
<td>59.9</td>
<td>1.8</td>
<td>1.4</td>
<td>2.4</td>
</tr>
<tr>
<td>(Assay cut-off = 0.043 IU/mL)</td>
<td></td>
<td>Post</td>
<td>35</td>
<td>100</td>
<td>90.0</td>
<td>100</td>
<td>35</td>
<td>100</td>
<td>90.0</td>
<td>100</td>
<td>9.9</td>
<td>7.9</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>PRE</td>
<td>115</td>
<td>100</td>
<td>96.8</td>
<td>100</td>
<td>86</td>
<td>74.8</td>
<td>65.8</td>
<td>1.8</td>
<td>1.5</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post</td>
<td>115</td>
<td>100</td>
<td>96.8</td>
<td>100</td>
<td>115</td>
<td>96.8</td>
<td>100</td>
<td>9.7</td>
<td>8.5</td>
<td>11.0</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre = Pre booster vaccination blood sampling time-point
Post = Post booster vaccination blood sampling time-point
One month after vaccination:

- All subjects reported anti-D and anti-T antibody concentrations ≥ 0.1 IU/mL in both the groups.
- The GMC values for anti-D antibodies were 6.8 and 6.0 in the Td and Tdap groups, respectively. There was at least a 3-fold increase from pre to post-vaccination for anti-D antibodies in both the groups indicating a good booster response.
- The GMC values for anti-T antibodies were 9.9 and 9.7 in the Td and Tdap groups, respectively. There was at least a 5-fold increase from pre to post-vaccination for anti-T antibodies in both the groups indicating a good booster response.

The number and percentage of subjects with anti-Diphtheria and anti-Tetanus antibody concentration ≥ 0.1 IU/mL, ≥ 1 IU/mL and GMCs at pre and post-booster vaccination time points for TVC are presented in Table 56.

The number and percentage of subjects with an anti-PT, anti-FHA, anti-PRN antibody concentration ≥ assay cut-off and GMCs at pre and post-booster vaccination time points for ATP cohort for analysis of immunogenicity are presented in Table 20.

### Table 20 Number and percentage of subjects with an anti-PT, anti-FHA, anti-PRN antibody concentration ≥ assay cut-off and GMCs at pre and post booster vaccination time points (ATP cohort for analysis of immunogenicity)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group</th>
<th>Timing</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
<th>Value</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-PT (Assay cut-off = 2.693 IU/mL)</td>
<td>Td group</td>
<td>PRE</td>
<td>35</td>
<td>21</td>
<td>60.0</td>
<td>42.1</td>
<td>76.1</td>
<td>5.3</td>
<td>3.4</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post</td>
<td>35</td>
<td>35</td>
<td>100</td>
<td>90.0</td>
<td>100</td>
<td>66.2</td>
<td>50.8</td>
<td>86.2</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>PRE</td>
<td>115</td>
<td>115</td>
<td>100</td>
<td>96.8</td>
<td>100</td>
<td>87.3</td>
<td>74.5</td>
<td>102.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post</td>
<td>115</td>
<td>115</td>
<td>100</td>
<td>96.8</td>
<td>100</td>
<td>87.3</td>
<td>74.5</td>
<td>102.4</td>
</tr>
<tr>
<td>anti-FHA (Assay cut-off = 2.046 IU/mL)</td>
<td>Td group</td>
<td>PRE</td>
<td>35</td>
<td>34</td>
<td>97.1</td>
<td>85.1</td>
<td>99.9</td>
<td>21.7</td>
<td>13.4</td>
<td>35.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post</td>
<td>35</td>
<td>35</td>
<td>100</td>
<td>90.0</td>
<td>100</td>
<td>336.2</td>
<td>250.0</td>
<td>452.2</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>PRE</td>
<td>115</td>
<td>115</td>
<td>100</td>
<td>96.8</td>
<td>100</td>
<td>87.3</td>
<td>74.5</td>
<td>102.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post</td>
<td>115</td>
<td>115</td>
<td>100</td>
<td>96.8</td>
<td>100</td>
<td>87.3</td>
<td>74.5</td>
<td>102.4</td>
</tr>
<tr>
<td>anti-PRN antibody (Assay cut-off = 2.187 IU/mL)</td>
<td>Td group</td>
<td>PRE</td>
<td>35</td>
<td>33</td>
<td>94.3</td>
<td>80.8</td>
<td>99.3</td>
<td>27.8</td>
<td>13.7</td>
<td>56.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post</td>
<td>35</td>
<td>35</td>
<td>100</td>
<td>90.0</td>
<td>100</td>
<td>425.5</td>
<td>281.9</td>
<td>642.3</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>PRE</td>
<td>115</td>
<td>115</td>
<td>100</td>
<td>96.8</td>
<td>100</td>
<td>71.6</td>
<td>56.7</td>
<td>90.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post</td>
<td>115</td>
<td>115</td>
<td>100</td>
<td>96.8</td>
<td>100</td>
<td>463.3</td>
<td>390.8</td>
<td>549.3</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre = Pre booster vaccination blood sampling time-point
Post = Post booster vaccination blood sampling time-point

One month after vaccination:

- All subjects were seropositive for anti-PT, anti-FHA and anti-PRN antibodies in both groups.
The GMC values for anti-PT antibodies were 66.2 and 87.3 in the Td and Tdap groups, respectively. There was at least an 8-fold increase from pre to post-vaccination for anti-PT antibodies in both the groups.

The GMC values for anti-FHA antibodies were 336.2 and 290.5 in the Td and Tdap groups, respectively. There was at least a 7-fold increase from pre to post-vaccination for anti-FHA antibodies in both the groups.

The GMC values for anti-PRN antibodies were 425.5 and 463.3 in the Td and Tdap groups, respectively. There was at least a 6-fold increase from pre to post-vaccination for anti-PRN antibodies in both the groups.

The number and percentage of subjects with an anti-PT, anti-FHA, anti-PRN antibody concentration ≥ assay cut-off and GMCs at pre and post-booster vaccination time points for TVC are presented in Table 57.

The booster response to anti-diphtheria, anti-tetanus, anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination for ATP cohort for analysis of immunogenicity are presented in Table 21 and Table 22.

**Table 21** Booster response to anti-diphtheria and anti-tetanus antigens one month after booster vaccination (ATP cohort for analysis of immunogenicity)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group</th>
<th>Pre-vaccination status</th>
<th>N</th>
<th>n %</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-D antibody (IU/mL)</td>
<td>Td group</td>
<td>S-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+</td>
<td>35</td>
<td>14</td>
<td>23.9</td>
<td>57.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>35</td>
<td>14</td>
<td>23.9</td>
<td>57.9</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>S-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+</td>
<td>115</td>
<td>47</td>
<td>31.8</td>
<td>50.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>115</td>
<td>47</td>
<td>31.8</td>
<td>50.4</td>
</tr>
<tr>
<td>anti-T antibody (IU/mL)</td>
<td>Td group</td>
<td>S-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+</td>
<td>35</td>
<td>21</td>
<td>42.1</td>
<td>76.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>35</td>
<td>21</td>
<td>42.1</td>
<td>76.1</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>S-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+</td>
<td>115</td>
<td>64</td>
<td>55.7</td>
<td>64.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>115</td>
<td>64</td>
<td>55.7</td>
<td>64.9</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine  
Tdap group = Subjects received a second dose of Tdap vaccine  
S- = seronegative subjects (antibody concentration < 0.1 IU/mL for anti-Diphtheria and anti-Tetanus)  
S+ = seropositive subjects (antibody concentration ≥ 0.1 IU/mL for anti-Diphtheria and anti-Tetanus)  
Total = subjects either seropositive or seronegative at pre-vaccination  
Booster response to Anti D and T antigens is defined as:  
- initially seronegative subjects with pre-booster antibody concentration below the 0.1 IU/mL, an increase of at least four times the pre-booster antibody concentration one month after vaccination  
- initially seropositive subjects with pre-booster antibody concentration ≥ 0.1 IU/mL, an increase of at least four times the pre-booster antibody concentration one month after vaccination  
N = number of subjects with both pre- and post-vaccination results available  
n%/ = number/percentage of responders  
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
One month after booster vaccination, at least 40% of subjects showed a booster response against diphtheria antigen while at least 55.7% of subjects showed a booster response against tetanus antigen.

Table 22 Booster response to anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (ATP cohort for analysis of immunogenicity)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group</th>
<th>Pre-vaccination status</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-PT antibody (IU/mL)</td>
<td>Td group</td>
<td>S-</td>
<td>14</td>
<td>14</td>
<td>100</td>
<td>76.8</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (&lt;4*cut_off IU/mL)</td>
<td>9</td>
<td>8</td>
<td>88.9</td>
<td>51.8</td>
<td>99.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (≥4*cut_off IU/mL)</td>
<td>12</td>
<td>11</td>
<td>91.7</td>
<td>61.5</td>
<td>99.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>35</td>
<td>33</td>
<td>94.3</td>
<td>80.8</td>
<td>99.3</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>S-</td>
<td>14</td>
<td>12</td>
<td>85.7</td>
<td>57.2</td>
<td>98.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (&lt;4*cut_off IU/mL)</td>
<td>47</td>
<td>45</td>
<td>95.7</td>
<td>85.5</td>
<td>99.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (≥4*cut_off IU/mL)</td>
<td>54</td>
<td>49</td>
<td>90.7</td>
<td>79.7</td>
<td>96.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>115</td>
<td>106</td>
<td>92.2</td>
<td>85.7</td>
<td>96.4</td>
</tr>
<tr>
<td>anti-FHA antibody (IU/mL)</td>
<td>Td group</td>
<td>S-</td>
<td>1</td>
<td>1</td>
<td>100</td>
<td>2.5</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (&lt;4*cut_off IU/mL)</td>
<td>8</td>
<td>8</td>
<td>100</td>
<td>63.1</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (≥4*cut_off IU/mL)</td>
<td>26</td>
<td>25</td>
<td>96.2</td>
<td>80.4</td>
<td>99.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>35</td>
<td>34</td>
<td>97.1</td>
<td>85.1</td>
<td>99.9</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>S-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (&lt;4*cut_off IU/mL)</td>
<td>4</td>
<td>4</td>
<td>100</td>
<td>39.8</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (≥4*cut_off IU/mL)</td>
<td>111</td>
<td>100</td>
<td>90.1</td>
<td>83.0</td>
<td>94.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>115</td>
<td>104</td>
<td>90.4</td>
<td>83.5</td>
<td>95.1</td>
</tr>
<tr>
<td>anti-PRN antibody (IU/mL)</td>
<td>Td group</td>
<td>S-</td>
<td>2</td>
<td>2</td>
<td>100</td>
<td>15.8</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (&lt;4*cut_off IU/mL)</td>
<td>9</td>
<td>9</td>
<td>100</td>
<td>66.4</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (≥4*cut_off IU/mL)</td>
<td>24</td>
<td>18</td>
<td>75.0</td>
<td>53.3</td>
<td>90.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>35</td>
<td>29</td>
<td>82.9</td>
<td>66.4</td>
<td>93.4</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>S-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (&lt;4*cut_off IU/mL)</td>
<td>9</td>
<td>9</td>
<td>100</td>
<td>66.4</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (≥4*cut_off IU/mL)</td>
<td>106</td>
<td>70</td>
<td>66.0</td>
<td>56.2</td>
<td>75.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>115</td>
<td>79</td>
<td>68.7</td>
<td>59.4</td>
<td>77.0</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine  
Tdap group = Subjects received a second dose of Tdap vaccine  
S- = seronegative subjects (antibody concentration < assay cut-off for anti-PT, anti-FHA, anti-PRN)  
S+ = seropositive subjects (antibody concentration ≥ assay cut-off for anti-PT, anti-FHA, anti-PRN)  
Total = subjects either seropositive or seronegative  
Booster response to pertussis antigens is defined as:  
- initially seronegative subjects (pre-booster antibody concentration below the assay cut-off) with an increase of at least four times the assay cut-off one month after vaccination,  
- initially seropositive subjects with antibody concentration < four times the assay cut-off with an increase of at least four times the pre-booster antibody concentration one month after vaccination  
- initially seropositive subjects with antibody concentration ≥ four times the assay cut-off with an increase of at least two times the pre-booster antibody concentration one month after vaccination  
N = number of subjects with both pre- and post-vaccination results available  
n/% = number/percentage of responders  
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

One month after booster vaccination, at least 92.2%, 90.4% and 68.7% of subjects showed a booster response against anti-PT, anti-FHA anti-PRN antigens respectively.
The alternative booster response to anti-Diphtheria, anti-Tetanus, anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination for ATP cohort for analysis of immunogenicity - excluding subjects with pre-vaccination concentration ≥ 6 IU/mL is presented in Table 47 and Table 48.

The booster response to anti-diphtheria and anti-tetanus antigens one month after booster vaccination TVC is presented in Table 64.

The alternative booster response to anti-Diphtheria and anti-Tetanus antibodies one month after booster vaccination for TVC-excluding subjects with pre-vaccination concentration greater than or equal to 6 IU/mL is presented in Table 65.

The alternative booster responses to anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination for TVC are presented in Table 66.

The group difference in booster response to anti-diphtheria, anti-tetanus, anti-PT, anti-FHA and anti-PRN antigens [Tdap Group minus Td Group], one month after booster vaccination and their standardized asymptotic 95% CIs for ATP cohort for analysis of immunogenicity are presented in Table 23 and Table 24.

Table 23  

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Tdap group</th>
<th>Td group</th>
<th>Difference in booster response rate (Tdap group minus Td group)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>anti-D antibody (IU/mL)</td>
<td>115</td>
<td>47</td>
<td>40.9</td>
<td>35</td>
</tr>
<tr>
<td>anti-T antibody (IU/mL)</td>
<td>115</td>
<td>64</td>
<td>55.7</td>
<td>35</td>
</tr>
</tbody>
</table>

Tdap group = Subjects received the first dose of Tdap vaccine
Td group = Subjects received a second dose of Tdap vaccine

Booster response to Anti D and T antigens is defined as:
- initially seronegative subjects with pre-booster antibody concentration below the 0.1 IU/mL, an increase of at least four times 0.1 IU/mL one month after vaccination,
- initially seropositive subjects with pre-booster antibody concentration ≥ 0.1 IU/mL, an increase of at least four times the pre-booster antibody concentration one month after vaccination

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

The observed booster response rates to diphtheria and tetanus antigens were similarly low in both groups (the rates were below 41% for anti-D and below 60% for anti-T). This could be because of the high concentration values at the pre-vaccination.
Table 24

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Tdap group</th>
<th>Td group</th>
<th>Difference in booster response rate (Tdap group minus Td group)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>anti-FHA antibody (IU/mL)</td>
<td>115</td>
<td>104</td>
<td>90.4</td>
<td>35</td>
</tr>
<tr>
<td>anti-PRN antibody (IU/mL)</td>
<td>115</td>
<td>79</td>
<td>68.7</td>
<td>35</td>
</tr>
<tr>
<td>anti-PT antibody (IU/mL)</td>
<td>115</td>
<td>106</td>
<td>92.2</td>
<td>35</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine

Booster response to pertussis antigens is defined as:
- initially seronegative subjects (pre-booster antibody concentration below the assay cut-off) with an increase of at least four times the assay cut-off one month after vaccination,
- initially seropositive subjects with antibody concentration < four times the assay cut-off with an increase of at least four times the pre-booster antibody concentration one month after vaccination
- initially seropositive subjects with antibody concentration ≥ four times the assay cut-off with an increase of at least two times the pre-booster antibody concentration one month after vaccination

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

The percentage in booster response rates for PT, FHA and PRN were similar in both groups (rate above 90% for PT and FHA, and rate above 68% for PRN).

The group difference in booster response to anti-diphtheria, anti-tetanus, anti-PT, anti-FHA and anti-PRN antigens [Tdap Group minus Td Group], one month after booster vaccination and their standardized asymptotic 95% CIs for TVC are presented in Table 60 and Table 61.

The group difference in alternative booster response to the diphtheria and tetanus antigens for ATP cohort for analysis of immunogenicity - excluding subjects with pre-vaccination concentration greater than or equal to 6 IU/mL is presented in Table 49.

The group difference in alternative booster response to anti-PT, anti-FHA and anti-PRN antigens [Tdap Group minus Td Group], one month after booster vaccination and their standardized asymptotic 95% CIs for ATP cohort for analysis of immunogenicity is presented in Table 50.

The group difference in alternative booster response to the diphtheria and tetanus antigens for TVC - excluding subjects with pre-vaccination concentration greater than or equal to 6 IU/mL is presented in Table 62.

The group difference in alternative booster response to anti-PT, anti-FHA and anti-PRN antigens [Tdap Group minus Td Group], one month after booster vaccination and their standardized asymptotic 95% CIs for TVC is presented in Table 63.
The Adjusted GMC ratio between groups [Tdap group divided by Td group] and their 95% CIs for anti-diphtheria, anti-tetanus, anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination for ATP cohort for analysis of immunogenicity is presented in Table 25 and Table 26.

Table 25  **Adjusted GMC ratio between groups [Tdap group divided by Td group] and their 95% CIs for anti-diphtheria and anti-tetanus antigens one month after booster vaccination (ATP cohort for analysis of immunogenicity)**

<table>
<thead>
<tr>
<th>Antibody (IU/mL)</th>
<th>Group description</th>
<th>N</th>
<th>Adjusted GMC</th>
<th>Group description</th>
<th>N</th>
<th>Adjusted GMC</th>
<th>Ratio order</th>
<th>Value</th>
<th>95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-D antibody</td>
<td>Tdap group</td>
<td>113</td>
<td>6.2</td>
<td>Td group</td>
<td>34</td>
<td>6.6</td>
<td>Tdap group /Td group</td>
<td>0.94</td>
<td>0.73</td>
<td>1.21</td>
</tr>
<tr>
<td>anti-T antibody</td>
<td>Tdap group</td>
<td>113</td>
<td>9.7</td>
<td>Td group</td>
<td>34</td>
<td>10.1</td>
<td>Tdap group /Td group</td>
<td>0.96</td>
<td>0.73</td>
<td>1.25</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
Adjusted GMC = geometric mean antibody concentration adjusted for baseline of 001 study
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for baseline concentration - pooled variance); LL = lower limit, UL = upper limit

One month after booster vaccination,

- The adjusted GMC ratio between groups [Tdap group divided by Td group] for anti-D antibody was 0.94 [95% CI; 0.73-1.21].
- The adjusted GMC ratio between groups [Tdap group divided by Td group] for anti-T antibody was 0.96 [95% CI; 0.73-1.25].

Table 26  **Adjusted GMC ratio between groups [Tdap group divided by Td group] and their 95% CIs for anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (ATP cohort for analysis of immunogenicity)**

<table>
<thead>
<tr>
<th>Antibody (IU/mL)</th>
<th>Group description</th>
<th>N</th>
<th>Adjusted GMC</th>
<th>Group description</th>
<th>N</th>
<th>Adjusted GMC</th>
<th>Ratio order</th>
<th>Value</th>
<th>95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-PT antibody</td>
<td>Tdap group</td>
<td>110</td>
<td>86.5</td>
<td>Td group</td>
<td>33</td>
<td>68.3</td>
<td>Tdap group /Td group</td>
<td>1.27</td>
<td>0.94</td>
<td>1.71</td>
</tr>
<tr>
<td>anti-FHA antibody</td>
<td>Tdap group</td>
<td>113</td>
<td>291.6</td>
<td>Td group</td>
<td>34</td>
<td>351.2</td>
<td>Tdap group /Td group</td>
<td>0.83</td>
<td>0.62</td>
<td>1.11</td>
</tr>
<tr>
<td>anti-PRN antibody</td>
<td>Tdap group</td>
<td>113</td>
<td>463.4</td>
<td>Td group</td>
<td>34</td>
<td>437.0</td>
<td>Tdap group /Td group</td>
<td>1.06</td>
<td>0.75</td>
<td>1.51</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
Adjusted GMC = geometric mean antibody concentration adjusted for baseline of 001 study
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for baseline concentration - pooled variance); LL = lower limit, UL = upper limit
One month after booster vaccination,

- The adjusted GMC ratio between groups [Tdap group divided by Td group] for anti-PT antibody was 1.27 [95% CI; 0.94-1.71].
- The adjusted GMC ratio between groups [Tdap group divided by Td group] for anti-FHA antibody was 0.83 [95% CI; 0.62-1.11].
- The adjusted GMC ratio between groups [Tdap group divided by Td group] for anti-PRN antibody was 1.06 [95% CI; 0.75-1.51].

The Adjusted GMC ratio between groups [Tdap group divided by Td group] and their 95% CIs for anti-diphtheria, anti-tetanus, anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination for TVC are presented in Table 67 and Table 68.

### 7.1. Sensitivity analysis

From modelling, there was no apparent bias related to drop out.

- The number of years since the vaccination in primary study for ATP cohort for immunogenicity (adapted for each time point) is presented in Table 51.
- The observed number and percentage of subjects with an anti-D and T concentration equal to or above 0.1 IU/mL and GMCs in the 001 study for ATP cohort for immunogenicity (adapted for the time point) is presented in Table 52.
- The estimated antibody D and T GMCs, as predicted by modelling for ATP cohort for immunogenicity (adapted for each time point) is presented in Table 53.
- The observed number and percentage of subjects with an anti-PT, anti-FHA and anti-PRN concentration equal to or above 5 EL.U/mL and GMCs in the 001 study for ATP cohort for immunogenicity (adapted for the time point) is presented in Table 54.
- The estimated antibody pertussis GMCs, as predicted by modelling for ATP cohort for immunogenicity (adapted for each time point) is presented in Table 55.
7.2. Immunogenicity summary

☐ The primary objectives of the study were met.
- One month after vaccination, the seroprotection rate for anti-diphtheria and anti-tetanus was 100% in both groups, leading to a lower limit of the 95% CI on the group difference [second dose of Tdap (Tdap Group) minus first dose of Tdap (Td Group)] greater than -10%.
- One month after vaccination, the lower limits of the 95% CI on the anti-PT (1.69), anti-FHA (5.14) and anti-PRN (3.22) GMC ratios (Tdap Group divided by Infanrix Group in APV-039) were greater than 0.67.

☐ There were no confirmatory secondary objectives.

☐ Sensitivity analysis: From modeling, there was no apparent bias related to dropout.

☐ The observed booster response rates to diphtheria and tetanus antigens were similarly low in both groups (the rates were below 41% for anti-D and below 60% for anti-T). This might be explained by high concentration values at pre-vaccination. Indeed, the alternative booster response adjusted for high concentration at pre-vaccination provided higher value (rate above 58% for anti-D, rate above 82% for anti-T).

☐ There was at least a 3-fold rise in the GMC value for anti-D and anti-T antibodies in both the groups indicating a good response to vaccination even though the booster response rates were low. This could be due to the high concentration values observed at the pre-vaccination.

☐ There was at least a 6-fold rise in the GMC value for anti-PT, anti-FHA and anti-PRN antibodies in both the groups. There was a good booster response rate observed.

☐ The percentage in booster response rates for PT, FHA and PRN antigens were similar in both groups (rate above 90% for PT and FHA, and rate above 68% for PRN).
8. SAFETY RESULTS

The analysis of safety was performed on the TVC.

8.1. Total vaccinated cohort analysis

8.1.1. Overall incidence of adverse events

The incidence and nature of symptoms (solicited and unsolicited) reported during the 4-day (Days 0-3) post-vaccination period for TVC are presented in Table 27, Table 28 and Table 29.

Table 27 Incidence and nature of symptoms (solicited and unsolicited) reported during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Td group</td>
<td>36</td>
<td>29</td>
<td>80.6</td>
<td>64.0</td>
<td>36</td>
<td>11</td>
<td>30.6</td>
<td>16.3</td>
<td>36</td>
<td>28</td>
<td>77.8</td>
<td>60.8</td>
</tr>
<tr>
<td>Tdap group</td>
<td>125</td>
<td>107</td>
<td>85.6</td>
<td>78.2</td>
<td>125</td>
<td>63</td>
<td>50.4</td>
<td>41.3</td>
<td>125</td>
<td>101</td>
<td>80.8</td>
<td>72.8</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
N = number of subjects with the documented dose
n/% = number/percentage of subjects presenting at least one type of symptom
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Table 28 Incidence and nature of Grade 3 symptoms (solicited and unsolicited) reported during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Td group</td>
<td>36</td>
<td>2</td>
<td>5.6</td>
<td>0.7</td>
<td>18.7</td>
<td>36</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>9.7</td>
<td>36</td>
<td>2</td>
</tr>
<tr>
<td>Tdap group</td>
<td>125</td>
<td>11</td>
<td>8.8</td>
<td>4.5</td>
<td>15.2</td>
<td>125</td>
<td>5</td>
<td>4.0</td>
<td>1.3</td>
<td>9.1</td>
<td>125</td>
<td>7</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
N = number of subjects with the documented dose
n/% = number/percentage of subjects presenting at least one type of symptom
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Table 29  Incidence and nature of symptoms (solicited and unsolicited) with causal relationship to vaccination, reported during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
<th>Group</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
<th>Group</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Td group</td>
<td>36</td>
<td>29</td>
<td>80.6</td>
<td>64.0</td>
<td>91.8</td>
<td>Tdap group</td>
<td>125</td>
<td>105</td>
<td>84.0</td>
<td>76.4</td>
<td>89.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tdap group</td>
<td>125</td>
<td>105</td>
<td>84.0</td>
<td>76.4</td>
<td>89.9</td>
<td>Td group</td>
<td>36</td>
<td>29</td>
<td>80.6</td>
<td>64.0</td>
<td>91.8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine

During the 4-day (Days 0-3) post-vaccination period:

- Any symptom (solicited and unsolicited) was reported for 80.6% of subjects in the Td group and 85.6% of subjects in the Tdap group.
- Any Grade 3 symptom (solicited and unsolicited) was reported for 5.6% of subjects in the Td group and 8.8% of subjects in the Tdap group.
- Any symptom (solicited and unsolicited) with causal relationship to vaccination, was reported for 80.6% of subjects in the Td group and 84.0% of subjects in the Tdap group.

8.1.2. Solicited local symptoms

The incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period for TVC is presented in Table 30.

Table 30  Incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Type</th>
<th>Td group</th>
<th>Tdap group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>95 % CI</td>
<td>95 % CI</td>
</tr>
<tr>
<td>Pain</td>
<td>All</td>
<td>36</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Grade 2 or 3</td>
<td>36</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>36</td>
<td>2</td>
</tr>
<tr>
<td>Redness (mm)</td>
<td>All</td>
<td>36</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>&gt;20</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;50</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>Swelling (mm)</td>
<td>All</td>
<td>36</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>&gt;20</td>
<td>36</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;50</td>
<td>36</td>
<td>0</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
N = number of subjects with the documented dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit
During the 4-day (Days 0-3) post-vaccination period:

- Pain was the most frequently reported solicited local symptom, reported for 58.3% of subjects in the Td group and 77.6% of subjects in the Tdap group.
- Pain was also the most frequently reported Grade 3 solicited local symptom, reported for 5.6% of subjects in the Td group and 4.8% of subjects in the Tdap group.

The difference between groups (Td group minus Tdap group) in percentage of subjects reporting solicited local symptom during the 4-day post-vaccination period for the TVC is presented in Table 31.

### Table 31  Difference between groups (Td group minus Tdap group) in percentage of subjects reporting solicited local symptom during the 4-day post vaccination period (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Type</th>
<th>Td group</th>
<th>Tdap group</th>
<th>Difference in percentage (Td group minus Tdap group)</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>n</td>
<td>%</td>
<td>N</td>
<td>n</td>
</tr>
<tr>
<td>Pain</td>
<td>All</td>
<td>37</td>
<td>21</td>
<td>56.8</td>
<td>128</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>37</td>
<td>2</td>
<td>5.4</td>
<td>128</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>37</td>
<td>2</td>
<td>5.4</td>
<td>128</td>
<td>6</td>
</tr>
<tr>
<td>Redness (mm)</td>
<td>All</td>
<td>37</td>
<td>15</td>
<td>40.5</td>
<td>128</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>&gt;50</td>
<td>37</td>
<td>0</td>
<td>0.0</td>
<td>128</td>
<td>1</td>
</tr>
<tr>
<td>Swelling (mm)</td>
<td>All</td>
<td>37</td>
<td>7</td>
<td>18.9</td>
<td>128</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>&gt;50</td>
<td>37</td>
<td>0</td>
<td>0.0</td>
<td>128</td>
<td>0</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine  
Tdap group = Subjects received a second dose of Tdap vaccine  
N = Number of subjects with the administered dose  
n/% = number/percentage of subjects reporting a specified symptom  
95% CI = Standardized asymptotic 95% confidence interval, LL = Lower Limit, UL = Upper Limit  
P-value = 2-sided Chi-square Test

During the 4-day (Days 0-3) post-vaccination period, no overall difference was observed between the groups (Td group minus Tdap group) in percentage of subjects reporting solicited local symptom.

#### 8.1.3. Solicited general symptoms

The incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period for TVC is presented in Table 32.
Table 32  Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Type</th>
<th>Td group</th>
<th></th>
<th></th>
<th>Tdap group</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/%</td>
<td>N</td>
<td>n</td>
<td>%</td>
<td>N</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>All</td>
<td>36</td>
<td>8</td>
<td>22.2%</td>
<td>125</td>
<td>38</td>
<td>30.4%</td>
</tr>
<tr>
<td></td>
<td>Grade 2 or 3</td>
<td>36</td>
<td>1</td>
<td>2.8%</td>
<td>125</td>
<td>17</td>
<td>13.6%</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>36</td>
<td>0</td>
<td>0.0%</td>
<td>125</td>
<td>3</td>
<td>2.4%</td>
</tr>
<tr>
<td></td>
<td>Related</td>
<td>36</td>
<td>7</td>
<td>19.4%</td>
<td>125</td>
<td>25</td>
<td>20.0%</td>
</tr>
<tr>
<td></td>
<td>Grade 2 or 3 Related</td>
<td>36</td>
<td>1</td>
<td>2.8%</td>
<td>125</td>
<td>1</td>
<td>0.8%</td>
</tr>
<tr>
<td></td>
<td>Grade 3 Related</td>
<td>36</td>
<td>0</td>
<td>0.0%</td>
<td>125</td>
<td>1</td>
<td>0.8%</td>
</tr>
<tr>
<td></td>
<td>Medical advice</td>
<td>36</td>
<td>0</td>
<td>0.0%</td>
<td>125</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>All</td>
<td>36</td>
<td>1</td>
<td>2.8%</td>
<td>125</td>
<td>17</td>
<td>13.6%</td>
</tr>
<tr>
<td></td>
<td>Grade 2 or 3</td>
<td>36</td>
<td>0</td>
<td>0.0%</td>
<td>125</td>
<td>2</td>
<td>1.6%</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>36</td>
<td>0</td>
<td>0.0%</td>
<td>125</td>
<td>7</td>
<td>5.6%</td>
</tr>
<tr>
<td></td>
<td>Related</td>
<td>36</td>
<td>0</td>
<td>0.0%</td>
<td>125</td>
<td>2</td>
<td>1.6%</td>
</tr>
<tr>
<td></td>
<td>Grade 2 or 3 Related</td>
<td>36</td>
<td>0</td>
<td>0.0%</td>
<td>125</td>
<td>1</td>
<td>0.8%</td>
</tr>
<tr>
<td></td>
<td>Grade 3 Related</td>
<td>36</td>
<td>0</td>
<td>0.0%</td>
<td>125</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td></td>
<td>Medical advice</td>
<td>36</td>
<td>0</td>
<td>0.0%</td>
<td>125</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Headache</td>
<td>All</td>
<td>36</td>
<td>8</td>
<td>22.2%</td>
<td>125</td>
<td>40</td>
<td>32.0%</td>
</tr>
<tr>
<td></td>
<td>Grade 2 or 3</td>
<td>36</td>
<td>1</td>
<td>2.8%</td>
<td>125</td>
<td>13</td>
<td>10.4%</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>36</td>
<td>0</td>
<td>0.0%</td>
<td>125</td>
<td>2</td>
<td>1.6%</td>
</tr>
<tr>
<td></td>
<td>Related</td>
<td>36</td>
<td>7</td>
<td>19.4%</td>
<td>125</td>
<td>22</td>
<td>17.6%</td>
</tr>
<tr>
<td></td>
<td>Grade 2 or 3 Related</td>
<td>36</td>
<td>1</td>
<td>2.8%</td>
<td>125</td>
<td>11</td>
<td>8.8%</td>
</tr>
<tr>
<td></td>
<td>Grade 3 Related</td>
<td>36</td>
<td>0</td>
<td>0.0%</td>
<td>125</td>
<td>2</td>
<td>1.6%</td>
</tr>
<tr>
<td></td>
<td>Medical advice</td>
<td>36</td>
<td>0</td>
<td>0.0%</td>
<td>125</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Temperature(Oral) (°C)</td>
<td>All</td>
<td>36</td>
<td>8</td>
<td>22.2%</td>
<td>125</td>
<td>40</td>
<td>32.0%</td>
</tr>
<tr>
<td></td>
<td>≥37.5</td>
<td>36</td>
<td>1</td>
<td>2.8%</td>
<td>125</td>
<td>13</td>
<td>10.4%</td>
</tr>
<tr>
<td></td>
<td>&gt;38.0</td>
<td>36</td>
<td>0</td>
<td>0.0%</td>
<td>125</td>
<td>3</td>
<td>2.4%</td>
</tr>
<tr>
<td></td>
<td>&gt;39.0</td>
<td>36</td>
<td>0</td>
<td>0.0%</td>
<td>125</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td></td>
<td>Related</td>
<td>36</td>
<td>7</td>
<td>19.4%</td>
<td>125</td>
<td>22</td>
<td>17.6%</td>
</tr>
<tr>
<td></td>
<td>≥37.5 Related</td>
<td>36</td>
<td>1</td>
<td>2.8%</td>
<td>125</td>
<td>11</td>
<td>8.8%</td>
</tr>
<tr>
<td></td>
<td>&gt;38.0 Related</td>
<td>36</td>
<td>0</td>
<td>0.0%</td>
<td>125</td>
<td>3</td>
<td>2.4%</td>
</tr>
<tr>
<td></td>
<td>&gt;39.0 Related</td>
<td>36</td>
<td>0</td>
<td>0.0%</td>
<td>125</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td></td>
<td>Medical advice</td>
<td>36</td>
<td>0</td>
<td>0.0%</td>
<td>125</td>
<td>0</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
N = number of subjects with the documented dose
n/% = number/percentage of subjects reporting the symptom at least once
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

During the 4-day (Days 0-3) post-vaccination period:

- Fatigue and headache were the most frequently reported solicited general symptom, reported for 22.2% of subjects in the Td group. Headache was the most frequently reported solicited general symptom, reported for 32.0% of subjects in the Tdap group.
- None of the subjects reported fatigue and headache of Grade 3 intensity in the Td group. Headache and fatigue were the most frequently reported Grade 3 solicited general symptom, reported for 2.4% of subjects in the Tdap group.
The difference between groups (Td group minus Tdap group) in percentage of subjects reporting solicited general symptom during the 4-day post-vaccination period for the TVC is presented in Table 33.

### Table 33 Difference between groups (Td group minus Tdap group) in percentage of subjects reporting solicited general symptom during the 4-day post-vaccination period (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Type</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>All</td>
<td>37</td>
<td>8</td>
<td>21.6</td>
<td>128</td>
<td>38</td>
<td>29.7</td>
<td>-8.07, -21.72</td>
<td>9.19</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>37</td>
<td>0</td>
<td>0.0</td>
<td>128</td>
<td>3</td>
<td>2.3</td>
<td>-2.34, -6.68</td>
<td>7.17</td>
</tr>
<tr>
<td></td>
<td>Related</td>
<td>37</td>
<td>7</td>
<td>18.9</td>
<td>128</td>
<td>25</td>
<td>19.5</td>
<td>-0.61, -13.10</td>
<td>15.91</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>All</td>
<td>37</td>
<td>1</td>
<td>2.7</td>
<td>128</td>
<td>11</td>
<td>8.6</td>
<td>-5.89, -12.76</td>
<td>5.72</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>37</td>
<td>0</td>
<td>0.0</td>
<td>128</td>
<td>2</td>
<td>1.6</td>
<td>-1.56, -5.54</td>
<td>7.93</td>
</tr>
<tr>
<td></td>
<td>Related</td>
<td>37</td>
<td>0</td>
<td>0.0</td>
<td>128</td>
<td>7</td>
<td>5.5</td>
<td>-5.47, -10.88</td>
<td>4.11</td>
</tr>
<tr>
<td>Headache</td>
<td>All</td>
<td>37</td>
<td>8</td>
<td>21.6</td>
<td>128</td>
<td>40</td>
<td>31.3</td>
<td>-9.63, -23.34</td>
<td>7.08</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>37</td>
<td>0</td>
<td>0.0</td>
<td>128</td>
<td>3</td>
<td>2.3</td>
<td>-2.34, -6.68</td>
<td>7.17</td>
</tr>
<tr>
<td></td>
<td>Related</td>
<td>37</td>
<td>7</td>
<td>18.9</td>
<td>128</td>
<td>33</td>
<td>25.8</td>
<td>-6.86, -19.77</td>
<td>9.94</td>
</tr>
<tr>
<td>Temperature (Oral) (°C)</td>
<td>All</td>
<td>37</td>
<td>1</td>
<td>2.7</td>
<td>128</td>
<td>3</td>
<td>2.3</td>
<td>0.36, -4.62</td>
<td>11.65</td>
</tr>
<tr>
<td></td>
<td>&gt;39.0</td>
<td>37</td>
<td>0</td>
<td>0.0</td>
<td>128</td>
<td>0</td>
<td>0.0</td>
<td>0.00, -2.93</td>
<td>9.46</td>
</tr>
<tr>
<td></td>
<td>Related</td>
<td>37</td>
<td>1</td>
<td>2.7</td>
<td>128</td>
<td>3</td>
<td>2.3</td>
<td>0.36, -4.62</td>
<td>11.65</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine  
Tdap group = Subjects received a second dose of Tdap vaccine  
N = Number of subjects with the administered dose  
n/% = number/percentage of subjects reporting a specified symptom  
95% CI = Standardized asymptotic 95% confidence interval, LL = Lower Limit, UL = Upper Limit  
P-value = 2-sided Chi-square Test

During the 4-day (Days 0-3) post-vaccination period, no overall difference was observed between the groups (Td group minus Tdap group) in percentage of subjects reporting a specified solicited general symptom.

The probability of false signal for solicited symptom for TVC is presented in Figure 1.
8.1.4. Unsolicited adverse events

The percentage of subjects reporting the occurrence of unsolicited symptoms and Grade 3 unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term occurring within the 31-day (Days 0-30) post-vaccination period and with causal relationship to vaccination, occurring within 31-day (Days 0-30) post-vaccination period for TVC is presented in Table 34, Table 35 and Table 36.

The percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term with medically attended visit, within the 31-day (Days 0-30) post-vaccination period for TVC is presented in Table 70.
### Table 34
Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MEDDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Primary System Organ Class (CODE)</th>
<th>Preferred Term (CODE)</th>
<th>Td group N = 37</th>
<th>Tdap group N = 128</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>LL</td>
</tr>
<tr>
<td>At least one symptom</td>
<td>10</td>
<td>27.0</td>
<td>13.8</td>
</tr>
<tr>
<td>Gastrointestinal disorders (10017947)</td>
<td>Constipation (10010774)</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia (10013948)</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Nausea (10028813)</td>
<td>1</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>Vomiting (10047700)</td>
<td>1</td>
<td>2.7</td>
</tr>
<tr>
<td>General disorders and administration site conditions (10018065)</td>
<td>Asthenia (10003549)</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Influenza like illness (10022004)</td>
<td>1</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>Injection site pruritus (10022093)</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Immune system disorders (10021428)</td>
<td>Pyrexia (10037660)</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Infections and infestations (10021881)</td>
<td>Seasonal allergy (10048908)</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Bronchitis (10006451)</td>
<td>1</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>Fungal infection (10017533)</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Influenza (10022000)</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Localised infection (10024774)</td>
<td>1</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>Lower respiratory tract infection (10024968)</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Nasopharyngitis (10028810)</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Tonsilitis (10044008)</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Upper respiratory tract infection (10046306)</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications (10022117)</td>
<td>Cartilage injury (10007710)</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Limb injury (10061225)</td>
<td>1</td>
<td>2.7</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders (10028395)</td>
<td>Back pain (10003988)</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Myalgia (10028411)</td>
<td>2</td>
<td>5.4</td>
</tr>
<tr>
<td>Nervous system disorders (10029205)</td>
<td>Pain in extremity (10033425)</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Headache (10019211)</td>
<td>5</td>
<td>13.5</td>
</tr>
<tr>
<td></td>
<td>Migraine (10027599)</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Paraesthesia (10033775)</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Syncope (10042772)</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Psychiatric disorders (10037175)</td>
<td>Insomnia (10022437)</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Reproductive system and breast disorders (10038604)</td>
<td>Dysmenorrhoea (10013935)</td>
<td>2</td>
<td>5.4</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders (10038738)</td>
<td>Cough (10011224)</td>
<td>1</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>Nasal congestion (10028735)</td>
<td>1</td>
<td>2.7</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders (10040785)</td>
<td>Pruritus (10037087)</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Rash (10037844)</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Rash maculo-papular (10037868)</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n/% = Number / percentage of subjects reporting at least once a specified symptom within 31 days after vaccination day 0 to day 30
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

### Table 35  
Percentage of subjects reporting the occurrence of Grade 3 unsolicited symptoms classified by MEDDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Primary System Organ Class (CODE)</th>
<th>Preferred Term (CODE)</th>
<th>Td group N = 37</th>
<th>Tdap group N = 128</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>At least one symptom</td>
<td></td>
<td>2</td>
<td>5.4</td>
</tr>
<tr>
<td>Gastrointestinal disorders (10017947)</td>
<td>Nausea (10028813)</td>
<td>1</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>Vomiting (10047700)</td>
<td>1</td>
<td>2.7</td>
</tr>
<tr>
<td>Infections and infestations (10021881)</td>
<td>Bronchitis (10006451)</td>
<td>1</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>Influenza (10022000)</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Nervous system disorders (10029205)</td>
<td>Headache (10019211)</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Migraine (10027599)</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine  
Tdap group = Subjects received a second dose of Tdap vaccine  
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)  
N = number of subjects with the administered dose  
n/% = Number / percentage of subjects reporting at least once a specified symptom within 31 days after vaccination day 0 to day 30  
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Table 36  Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MEDDRA Primary System Organ Class and Preferred Term with causal relationship to vaccination, within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Primary System Organ Class (CODE)</th>
<th>Preferred Term (CODE)</th>
<th>Td group N = 37</th>
<th>Tdap group N = 128</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>LL</td>
</tr>
<tr>
<td>At least one symptom</td>
<td>1</td>
<td>2.7</td>
<td>0.1</td>
</tr>
<tr>
<td>General disorders and administration site conditions (10018065)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza like illness (10022004)</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Injection site pruritus (10022093)</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders (10028395)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia (10028411)</td>
<td>1</td>
<td>2.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Pain in extremity (10033425)</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Nervous system disorders (10029205)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paraesthesia (10033775)</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders (10040785)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash (10037844)</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Rash maculo-papular (10037868)</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine  
Tdap group = Subjects received a second dose of Tdap vaccine  
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)  
N = number of subjects with the administered dose  
n/% = Number / percentage of subjects reporting at least once a specified symptom within 31 days after vaccination day 0 to day 30  
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

During the 31-day (Days 0-30) post-vaccination period:

- At least one unsolicited symptom was reported for 27.0% of subjects in the Td group and 25.8% of subjects in the Tdap group. Headache was the most frequently reported unsolicited symptom, reported for 13.5% of subjects in the Td group and 9.4% of subjects in the Tdap group.

- At least one Grade 3 unsolicited symptom was reported for 5.4% of subjects in the Td group and 2.3% of subjects in the Tdap group. Nausea, vomiting and bronchitis, reported for one subject each (2.7%) were the most frequently reported Grade 3 unsolicited symptom in the Td group while influenza, headache and migraine reported for one subject each (0.8%) were the most frequently reported Grade 3 unsolicited symptom in the Tdap group.

- At least one unsolicited symptom with causal relationship to vaccination was reported for one subject (2.7%) in the Td group and five subjects (3.9%) in the Tdap group. Myalgia, reported for one subject (2.7%) was the most frequently reported unsolicited symptom with causal relationship to vaccination in the Td group while influenza like illness, injection site pruritus, pain in extremity paraesthesia, rash and rash macula-papular, reported for one subject each (0.8%) were the most frequently reported unsolicited symptom with causal relationship to vaccination in the Tdap group.
The difference between the groups (Td minus Tdap) in percentage of subjects reporting unsolicited symptom, Grade 3 unsolicited symptoms and unsolicited symptom with causal relationship to vaccination within 31-day (Days 0-30) post-vaccination period for the TVC is presented in Table 37, Table 38 and Table 39.

### Table 37  Difference between groups (Td minus Tdap) in percentage of subjects reporting unsolicited symptom during the 31-day post vaccination period (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Primary System Organ Class (CODE)</th>
<th>Preferred Term (CODE)</th>
<th>Td group N = 37</th>
<th>Tdap group N = 128</th>
<th>Difference between Td group - Tdap group</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one symptom</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders (10017947)</td>
<td>Constipation (10010774)</td>
<td>10 27.0</td>
<td>13.8 9.5 44.1 33 25.8 18.5 34.3</td>
<td>1 0.8 0.0 4.3</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia (10013946)</td>
<td>0 0.0</td>
<td>0.0 9.5</td>
<td>1 0.8 0.0 4.3</td>
</tr>
<tr>
<td></td>
<td>Nausea (10028813)</td>
<td>1 2.7</td>
<td>0.1 14.2 0 0.0 0.0 2.8</td>
<td>2.70 -0.29</td>
</tr>
<tr>
<td></td>
<td>Vomiting (10047700)</td>
<td>1 2.7</td>
<td>0.1 14.2 0 0.0 0.0 2.8</td>
<td>2.70 -0.29</td>
</tr>
<tr>
<td>General disorders and administration site conditions (10018065)</td>
<td>Asthenia (10003549)</td>
<td>0 0.0</td>
<td>0.0 9.5</td>
<td>1 0.8 0.0 4.3</td>
</tr>
<tr>
<td></td>
<td>Influenza like illness (10022004)</td>
<td>1 2.7</td>
<td>0.1 14.2 0 0.8 0.0 4.3</td>
<td>1.92 -2.11</td>
</tr>
<tr>
<td></td>
<td>Injection site pruritus (10022093)</td>
<td>0 0.0</td>
<td>0.0 9.5</td>
<td>1 0.8 0.0 4.3</td>
</tr>
<tr>
<td></td>
<td>Pyrexia (10037660)</td>
<td>0 0.0</td>
<td>0.0 9.5</td>
<td>1 0.8 0.0 4.3</td>
</tr>
<tr>
<td>Immune system disorders (10021428)</td>
<td>Seasonal allergy (10048908)</td>
<td>0 0.0</td>
<td>0.0 9.5</td>
<td>2 1.6 0.2 5.5</td>
</tr>
<tr>
<td>Infections and infestations (10021881)</td>
<td>Bronchitis (10006451)</td>
<td>1 2.7</td>
<td>0.1 14.2 0 0.0 0.0 2.8</td>
<td>2.70 -0.29</td>
</tr>
<tr>
<td></td>
<td>Fungal infection (10017533)</td>
<td>0 0.0</td>
<td>0.0 9.5</td>
<td>1 0.8 0.0 4.3</td>
</tr>
<tr>
<td></td>
<td>Influenza (10022000)</td>
<td>0 0.0</td>
<td>0.0 9.5</td>
<td>2 1.6 0.2 5.5</td>
</tr>
<tr>
<td></td>
<td>Localised infection (10024774)</td>
<td>1 2.7</td>
<td>0.1 14.2 0 0.0 0.0 2.8</td>
<td>2.70 -0.29</td>
</tr>
<tr>
<td></td>
<td>Lower respiratory tract infection (10024968)</td>
<td>0 0.0</td>
<td>0.0 9.5</td>
<td>1 0.8 0.0 4.3</td>
</tr>
<tr>
<td></td>
<td>Nasopharyngitis (10028810)</td>
<td>0 0.0</td>
<td>0.0 9.5</td>
<td>2 1.6 0.2 5.5</td>
</tr>
<tr>
<td></td>
<td>Tonsillitis (10044008)</td>
<td>0 0.0</td>
<td>0.0 9.5</td>
<td>1 0.8 0.0 4.3</td>
</tr>
<tr>
<td></td>
<td>Upper respiratory tract infection (10046306)</td>
<td>0 0.0</td>
<td>0.0 9.5</td>
<td>2 1.6 0.2 5.5</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications (10022117)</td>
<td>Cartilage injury (10007710)</td>
<td>0 0.0</td>
<td>0.0 9.5</td>
<td>1 0.8 0.0 4.3</td>
</tr>
<tr>
<td></td>
<td>Limb injury (10061225)</td>
<td>1 2.7</td>
<td>0.1 14.2 0 0.0 0.0 2.8</td>
<td>2.70 -0.29</td>
</tr>
<tr>
<td>Primary System Organ Class (CODE)</td>
<td>Preferred Term (CODE)</td>
<td>Td group N = 37</td>
<td>Tdap group N = 128</td>
<td>Difference between Td group - Tdap group</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-----------------------</td>
<td>-----------------</td>
<td>-------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders (10028395)</td>
<td>Back pain (10003988)</td>
<td>0 0.0 0.0 9.5</td>
<td>2 1.6 0.2 5.5</td>
<td>-1.56 - 5.54</td>
</tr>
<tr>
<td></td>
<td>Myalgia (10029411)</td>
<td>2 5.4 0.7 18.2</td>
<td>1 0.8 0.0 4.3</td>
<td>4.62 - 0.25</td>
</tr>
<tr>
<td></td>
<td>Pain in extremity (10033425)</td>
<td>0 0.0 0.0 9.5</td>
<td>1 0.8 0.0 4.3</td>
<td>-0.78 - 4.31</td>
</tr>
<tr>
<td>Nervous system disorders (10029205)</td>
<td>Headache (10019211)</td>
<td>5 13.5 4.5 28.8</td>
<td>12 9.4 4.9 15.8</td>
<td>4.14 - 5.87</td>
</tr>
<tr>
<td></td>
<td>Migraine (10027599)</td>
<td>0 0.0 0.0 9.5</td>
<td>1 0.8 0.0 4.3</td>
<td>-0.78 - 4.31</td>
</tr>
<tr>
<td></td>
<td>Paraesthesia (10033775)</td>
<td>0 0.0 0.0 9.5</td>
<td>1 0.8 0.0 4.3</td>
<td>-0.78 - 4.31</td>
</tr>
<tr>
<td></td>
<td>Syncope (10042772)</td>
<td>0 0.0 0.0 9.5</td>
<td>1 0.8 0.0 4.3</td>
<td>-0.78 - 4.31</td>
</tr>
<tr>
<td>Psychiatric disorders (10037175)</td>
<td>Insomnia (10022437)</td>
<td>0 0.0 0.0 9.5</td>
<td>2 1.6 0.2 5.5</td>
<td>-1.56 - 5.54</td>
</tr>
<tr>
<td>Reproductive system and breast disorders (10038604)</td>
<td>Dysmenorrhoea (10013935)</td>
<td>2 5.4 0.7 18.2</td>
<td>2 1.6 0.2 5.5</td>
<td>3.84 - 1.54</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders (10038738)</td>
<td>Cough (10011224)</td>
<td>1 2.7 0.1 14.2</td>
<td>0 0.0 0.0 2.8</td>
<td>2.70 - 0.29</td>
</tr>
<tr>
<td></td>
<td>Nasal congestion (10028735)</td>
<td>1 2.7 0.1 14.2</td>
<td>0 0.0 0.0 2.8</td>
<td>2.70 - 0.29</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders (10040785)</td>
<td>Pruritus (10037087)</td>
<td>0 0.0 0.0 9.5</td>
<td>1 0.8 0.0 4.3</td>
<td>-0.78 - 4.31</td>
</tr>
<tr>
<td></td>
<td>Rash (10037844)</td>
<td>0 0.0 0.0 9.5</td>
<td>1 0.8 0.0 4.3</td>
<td>-0.78 - 4.31</td>
</tr>
<tr>
<td></td>
<td>Rash maculo-papular (10037868)</td>
<td>0 0.0 0.0 9.5</td>
<td>2 1.6 0.2 5.5</td>
<td>-1.56 - 5.54</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided Chi-square test
Table 38  Difference between groups (Td minus Tdap) in percentage of subjects reporting Grade 3 unsolicited symptom within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Primary System Organ Class (CODE)</th>
<th>Preferred Term (CODE)</th>
<th>Td group N = 37</th>
<th>Tdap group N = 128</th>
<th>Difference between Td group - Tdap group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/ %</td>
<td>95% CI</td>
<td>n/ %</td>
<td>95% CI</td>
</tr>
<tr>
<td>At least one symptom</td>
<td>2/ 5.4 %</td>
<td>0.7-18.2</td>
<td>3/ 2.3 %</td>
<td>0.5-6.7</td>
</tr>
<tr>
<td>Gastrointestinal disorders (10017947)</td>
<td>Nausea (10028813)</td>
<td>1/ 2.7 %</td>
<td>0.0-2.8</td>
<td>0.0-2.8</td>
</tr>
<tr>
<td></td>
<td>Vomiting (10047700)</td>
<td>1/ 2.7 %</td>
<td>0.0-2.8</td>
<td>0.0-2.8</td>
</tr>
<tr>
<td>Infections and infestations (10021881)</td>
<td>Bronchitis (10006451)</td>
<td>1/ 2.7 %</td>
<td>0.0-2.8</td>
<td>0.0-2.8</td>
</tr>
<tr>
<td></td>
<td>Influenza (10022000)</td>
<td>0/ 0.0 %</td>
<td>0.0-9.5</td>
<td>0.0-9.5</td>
</tr>
<tr>
<td>Nervous system disorders (10029205)</td>
<td>Headache (10019211)</td>
<td>0/ 0.0 %</td>
<td>0.0-9.5</td>
<td>0.0-9.5</td>
</tr>
<tr>
<td></td>
<td>Migraine (10027599)</td>
<td>0/ 0.0 %</td>
<td>0.0-9.5</td>
<td>0.0-9.5</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n/ % = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided Chi-square test
Table 39: Difference between groups (Td minus Tdap) in percentage of subjects reporting unsolicited symptom with causal relationship to vaccination within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Primary System Organ Class (CODE)</th>
<th>Preferred Term (CODE)</th>
<th>Td group N = 37</th>
<th>Tdap group N = 128</th>
<th>Difference between Td group - Tdap group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/%</td>
<td>95% CI</td>
<td>n/%</td>
<td>95% CI</td>
</tr>
<tr>
<td>At least one symptom</td>
<td>1 2.7 0.1 14.2</td>
<td>-6.81 10.17</td>
<td>5 3.9 3.1 8.9</td>
<td>-1.20</td>
</tr>
<tr>
<td>General disorders and administration site conditions (10018065)</td>
<td>Influenza like illness (10022004)</td>
<td>0 0.0 0.0 9.5</td>
<td>1 0.8 0.0 4.3</td>
<td>-4.31</td>
</tr>
<tr>
<td></td>
<td>Injection site pruritus (10022093)</td>
<td>0 0.0 0.0 9.5</td>
<td>1 0.8 0.0 4.3</td>
<td>-4.31</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders (10028395)</td>
<td>Myalgia (10028411)</td>
<td>1 2.7 0.1 14.2</td>
<td>0 0.0 0.0 2.8</td>
<td>-0.29</td>
</tr>
<tr>
<td></td>
<td>Pain in extremity (10033425)</td>
<td>0 0.0 0.0 9.5</td>
<td>1 0.8 0.0 4.3</td>
<td>-4.31</td>
</tr>
<tr>
<td>Nervous system disorders (10029205)</td>
<td>Paraesthesia (10033775)</td>
<td>0 0.0 0.0 9.5</td>
<td>1 0.8 0.0 4.3</td>
<td>-4.31</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders (10040785)</td>
<td>Rash (10037844)</td>
<td>0 0.0 0.0 9.5</td>
<td>1 0.8 0.0 4.3</td>
<td>-4.31</td>
</tr>
<tr>
<td></td>
<td>Rash maculo-papular (10037868)</td>
<td>0 0.0 0.0 9.5</td>
<td>1 0.8 0.0 4.3</td>
<td>-4.31</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided Chi-square test

During the 31-day (Days 0-30) post-vaccination period, no overall difference was observed between the groups (Td group minus Tdap group) in percentage of subjects reporting unsolicited symptom, Grade 3 unsolicited symptoms and unsolicited symptom with causal relationship to vaccination.

The probability of false signal for unsolicited symptom for TVC is presented in Figure 2.
8.2. Serious adverse events

No SAEs were reported in this study.

8.2.1. Fatal events

No fatal events were reported during the study period.

8.2.2. Non-fatal events

No non-fatal events were reported during the study period.

8.3. Adverse events leading to premature discontinuation of study vaccine and/or study

No AEs leading to premature discontinuation of study vaccine and/or study was reported.
8.4. Safety summary

☐ Any symptom (solicited and unsolicited): During the 4-day (Days 0-3) post-vaccination period, any symptom (solicited and unsolicited) was reported for 80.6% of subjects in the Td group and 85.6% of subjects in the Tdap group. Any Grade 3 symptom (solicited and unsolicited) was reported for 5.6% of subjects in the Td group and 8.8% of subjects in the Tdap group.

☐ Solicited local symptom: During the 4-day (Days 0-3) post-vaccination period, pain was the most frequently reported solicited local symptom, reported for 58.3% of subjects in the Td group and 77.6% of subjects in the Tdap group. Pain was also the most frequently reported Grade 3 solicited local symptom, reported for 5.6% of subjects in the Td group and 4.8% of subjects in the Tdap group.

☐ Solicited general symptom: During the 4-day (Days 0-3) post-vaccination period, fatigue and headache were the most frequently reported solicited general symptom, reported for 22.2% of subjects in the Td group. Headache was the most frequently reported solicited general symptom, reported for 32.0% of subjects in the Tdap group. None of the subjects reported fatigue and headache of Grade 3 intensity in the Td group. Headache and fatigue were the most frequently reported Grade 3 solicited general symptom, reported for 2.4% of subjects in the Tdap group.

☐ Unsolicited symptoms: During the 31-day (Days 0-30) post-vaccination period, at least one unsolicited symptom was reported for 27.0% of subjects in the Td group and 25.8% of subjects in the Tdap group. Headache was the most frequently reported unsolicited symptom, reported for 13.5% of subjects in the Td group and 9.4% of subjects in the Tdap group. At least one Grade 3 unsolicited symptom was reported for 5.4% of subjects in the Td group and 2.3% of subjects in the Tdap group. Nausea, vomiting and bronchitis, reported for one subject each (2.7%) were the most frequently reported Grade 3 unsolicited symptom in the Td group while influenza, headache and migraine reported for one subject each (0.8%) were the most frequently reported Grade 3 unsolicited symptom in the Tdap group. Myalgia, reported for one subject (2.7%) was the most frequently reported unsolicited symptom with causal relationship to vaccination in the Td group while influenza like illness, injection site pruritus, pain in extremity paraesthesia, rash and rash maculopapular reported for one subject each (0.8%) were the most frequently reported unsolicited symptom with causal relationship to vaccination in the Tdap group.

☐ There was no difference observed with respect to the safety profile (solicited [local and general] and unsolicited symptoms) between the two study groups.

☐ SAEs: No SAEs were reported in this study.

☐ Withdrawals due to AEs/SAEs: None of the subjects were withdrawn due to an AE or SAE, during the study period. There were also no large injection site reactions reported.

☐ Pregnancy: No pregnancies were reported in this study.
9. OVERALL CONCLUSIONS

All subjects were protected for anti-Diphtheria and anti-Tetanus ten years after previous booster vaccination of *Boostrix*. However, with respect to pertussis low GMTs were observed in both the groups.

*Boostrix* when administered in young adults, 10 years after previous booster vaccination was immunogenic and well tolerated. No safety concern was identified.

There were no SAEs reported in this study.
10. POST-TEXT TABLES AND FIGURES

10.1. Study population

Table 40  Number of subjects by center (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Center</th>
<th>Td group n</th>
<th>Tdap group n</th>
<th>Total n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>13</td>
<td>13</td>
<td>7.9</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>6</td>
<td>10</td>
<td>3.6</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>12</td>
<td>21</td>
<td>7.3</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>2.4</td>
</tr>
<tr>
<td>1</td>
<td>22</td>
<td>23</td>
<td>45</td>
<td>13.9</td>
</tr>
<tr>
<td>0</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>1.2</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1.2</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0.6</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1.2</td>
</tr>
<tr>
<td>0</td>
<td>5</td>
<td>5</td>
<td>10</td>
<td>3.0</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>5</td>
<td>8</td>
<td>3.0</td>
</tr>
<tr>
<td>7</td>
<td>18</td>
<td>25</td>
<td>43</td>
<td>15.2</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
<td>28</td>
<td>48</td>
<td>17.0</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0.6</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>13</td>
<td>24</td>
<td>7.9</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>17</td>
<td>28</td>
<td>10.3</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>5</td>
<td>9</td>
<td>3.0</td>
</tr>
<tr>
<td>All</td>
<td>37</td>
<td>128</td>
<td>165</td>
<td>100</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
n = number of subjects included in each group or in total for a given center or for all centers
All = sum of all subjects in each group or in total (sum of all groups)
% = n/All x 100
Center = GSK Biologicals assigned center number

Table 41  Deviation from specifications intervals between study visits (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Group</th>
<th>Protocol from 30 to 48 days</th>
<th>Adapted from 21 to 48 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Td group</td>
<td>N 36</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>n 4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>% 11.1</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>range 28 to 64</td>
<td>28 to 64</td>
</tr>
<tr>
<td>Tdap group</td>
<td>N 124</td>
<td>124</td>
</tr>
<tr>
<td></td>
<td>n 11</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>% 8.9</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td>range 24 to 96</td>
<td>24 to 96</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
Adapted = interval used for defining the ATP cohorts for immunogenicity
N = total number of subjects with available results
n/% = number / percentage of subjects with results outside of the interval
range = minimum-maximum for intervals
### Table 42 Demography: age (in years) at vaccination dose: 1 (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex</th>
<th>N</th>
<th>N with age</th>
<th>MEAN</th>
<th>SD</th>
<th>MIN</th>
<th>MAX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Td group</td>
<td>F</td>
<td>18</td>
<td>18</td>
<td>22.9</td>
<td>2.3</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>19</td>
<td>19</td>
<td>23.7</td>
<td>2.5</td>
<td>20</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>37</td>
<td>37</td>
<td>23.3</td>
<td>2.4</td>
<td>20</td>
<td>29</td>
</tr>
<tr>
<td>Tdap group</td>
<td>F</td>
<td>57</td>
<td>57</td>
<td>23.5</td>
<td>2.2</td>
<td>20</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>71</td>
<td>71</td>
<td>23.5</td>
<td>2.2</td>
<td>20</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>128</td>
<td>128</td>
<td>23.5</td>
<td>2.1</td>
<td>20</td>
<td>29</td>
</tr>
<tr>
<td>ALL</td>
<td>F</td>
<td>75</td>
<td>75</td>
<td>23.4</td>
<td>2.2</td>
<td>20</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>90</td>
<td>90</td>
<td>23.8</td>
<td>2.1</td>
<td>20</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>165</td>
<td>165</td>
<td>23.5</td>
<td>2.1</td>
<td>20</td>
<td>29</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine  
Tdap group = Subjects received a second dose of Tdap vaccine  
F = female; M = male  
N = number of subjects with documentation on gender  
N with age = number of subjects with documentation on gender and age  
SD = standard deviation  
Min, Max = minimum, maximum age

### Table 43 Demography: age (in years) at vaccination dose: 1 (ATP cohort for safety)

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex</th>
<th>N</th>
<th>N with age</th>
<th>MEAN</th>
<th>SD</th>
<th>MIN</th>
<th>MAX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Td group</td>
<td>F</td>
<td>18</td>
<td>18</td>
<td>22.9</td>
<td>2.3</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>19</td>
<td>19</td>
<td>23.7</td>
<td>2.5</td>
<td>20</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>37</td>
<td>37</td>
<td>23.3</td>
<td>2.4</td>
<td>20</td>
<td>29</td>
</tr>
<tr>
<td>Tdap group</td>
<td>F</td>
<td>57</td>
<td>57</td>
<td>23.5</td>
<td>2.2</td>
<td>20</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>71</td>
<td>71</td>
<td>23.5</td>
<td>2</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>128</td>
<td>128</td>
<td>23.5</td>
<td>2.1</td>
<td>20</td>
<td>29</td>
</tr>
<tr>
<td>ALL</td>
<td>F</td>
<td>75</td>
<td>75</td>
<td>23.4</td>
<td>2.2</td>
<td>20</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>90</td>
<td>90</td>
<td>23.6</td>
<td>2.1</td>
<td>20</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>165</td>
<td>165</td>
<td>23.5</td>
<td>2.1</td>
<td>20</td>
<td>29</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine  
Tdap group = Subjects received a second dose of Tdap vaccine  
F = female; M = male  
N = number of subjects with documentation on gender  
N with age = number of subjects with documentation on gender and age  
SD = standard deviation  
Min, Max = minimum, maximum age
### Table 44  Summary of demographic characteristics (ATP cohort for safety)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Parameters or Categories</th>
<th>Td group N = 37</th>
<th>Tdap group N = 128</th>
<th>Total N = 165</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) at vaccination dose: 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>23.3 (-)</td>
<td>23.5 (-)</td>
<td>23.5 (-)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>2.4 (-)</td>
<td>2.1 (-)</td>
<td>2.1 (-)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>23.0 (-)</td>
<td>23.0 (-)</td>
<td>23.0 (-)</td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>20 (-)</td>
<td>20 (-)</td>
<td>20 (-)</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>29 (-)</td>
<td>29 (-)</td>
<td>29 (-)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>18 (48.6 %)</td>
<td>57</td>
<td>44.5 %</td>
<td>75 (45.5 %)</td>
</tr>
<tr>
<td>Male</td>
<td>19 (51.4 %)</td>
<td>71</td>
<td>55.5 %</td>
<td>90 (54.5 %)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Hispanic or Latino</td>
<td>4 (10.8 %)</td>
<td>12</td>
<td>9.4 %</td>
<td>16 (9.7 %)</td>
</tr>
<tr>
<td>Not American Hispanic or Latino</td>
<td>33 (89.2 %)</td>
<td>116</td>
<td>90.6 %</td>
<td>149 (90.3 %)</td>
</tr>
<tr>
<td>Geographic Ancestry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1 (2.7 %)</td>
<td>6</td>
<td>4.7 %</td>
<td>7 (4.2 %)</td>
</tr>
<tr>
<td>White/caucasian</td>
<td>31 (83.8 %)</td>
<td>114</td>
<td>89.1 %</td>
<td>145 (87.9 %)</td>
</tr>
<tr>
<td>Oriental</td>
<td>0 (0.0 %)</td>
<td>1</td>
<td>0.8 %</td>
<td>1 (0.6 %)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (13.5 %)</td>
<td>14</td>
<td>8.5 %</td>
<td>12 (7.3 %)</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine  
Tdap group = Subjects received a second dose of Tdap vaccine  
N = total number of subjects  
n/% = number / percentage of subjects in a given category  
Value = value of the considered parameter  
SD = standard deviation

### Table 45  Number of subjects enrolled into the study as well as the number excluded from ATP analyses with reasons for exclusion

<table>
<thead>
<tr>
<th>Title</th>
<th>Total cohort</th>
<th>Td group</th>
<th>Tdap group</th>
<th>ATP cohort for safety</th>
<th>Protocol violation (inclusion/exclusion criteria) ( code 2010 )</th>
<th>Total</th>
<th>Td group</th>
<th>Tdap group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</td>
<td>n</td>
<td>s</td>
<td>%</td>
<td>n</td>
<td>s</td>
<td>n</td>
<td>s</td>
<td>n</td>
</tr>
<tr>
<td>Total cohort</td>
<td>165</td>
<td>37</td>
<td>100</td>
<td>165</td>
<td>37</td>
<td>128</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total vaccinated cohort</td>
<td>165</td>
<td>100</td>
<td>100</td>
<td>165</td>
<td>37</td>
<td>128</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATP cohort for safety</td>
<td>165</td>
<td>100</td>
<td>100</td>
<td>165</td>
<td>37</td>
<td>128</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol violation (inclusion/exclusion criteria) ( code 2010 )</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Non compliance with vaccination schedule ( including wrong and unknown dates ) ( code 2080 )</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Non compliance with blood sampling schedule ( including wrong and unknown dates ( code 2090 )</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Essential serological data missing ( code 2100 )</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>ATP cohort for analysis of immunogenicity</td>
<td>150</td>
<td>90.9</td>
<td>35</td>
<td>115</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine  
Tdap group = Subjects received a second dose of Tdap vaccine  
N = number of subjects with the elimination code assigned  
n/% = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number  
s = number of subjects with the elimination code assigned  
% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort
## Table 46
Summary of tracking log-sheets for all subjects initially enrolled in the primary study (Total cohort)

<table>
<thead>
<tr>
<th>Category</th>
<th>Td group N = 1034</th>
<th>Tdap group N = 3082</th>
<th>Total N = 4116</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Not participating to 116570</td>
<td>997</td>
<td>96.4</td>
<td>2954</td>
</tr>
<tr>
<td>SAE onset in the course or after previous study epoch</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>AE onset in the course or after previous study epoch</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Eligibility criteria not fulfilled (inclusion and exclusion criteria)</td>
<td>154</td>
<td>14.9</td>
<td>480</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Consent withdrawal/not willing to participate, not due to a (S)AE</td>
<td>40</td>
<td>3.9</td>
<td>94</td>
</tr>
<tr>
<td>Migrated / moved from the study area</td>
<td>38</td>
<td>3.7</td>
<td>129</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>231</td>
<td>22.3</td>
<td>658</td>
</tr>
<tr>
<td>Subject died</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Sponsor study termination</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>19</td>
<td>1.8</td>
<td>66</td>
</tr>
<tr>
<td>Missing</td>
<td>515</td>
<td>49.8</td>
<td>1521</td>
</tr>
<tr>
<td>Enrolled in 116570</td>
<td>37</td>
<td>3.6</td>
<td>128</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
N = number of subjects enrolled in the initial study
n/% = number/percentage of subjects in a given category
10.2. Immunogenicity

10.2.1. ATP cohort for immunogenicity

Figure 3 Reverse cumulative distribution curve for anti-Diphtheria antibody concentrations per group at pre and post booster vaccination time point (ATP cohort for analysis of immunogenicity)

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
Figure 4  Reverse cumulative distribution curve for anti-Tetanus antibody concentrations per group at pre and post booster vaccination time point (ATP cohort for analysis of immunogenicity)

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
Figure 5  Reverse cumulative distribution curve for anti-PT antibody concentrations per group at pre and post booster vaccination time point (ATP cohort for analysis of immunogenicity)

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
Figure 6  Reverse cumulative distribution curve for anti-FHA antibody concentrations per group at pre and post booster vaccination time point (ATP cohort for analysis of immunogenicity)

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine

Group:
- Td group at PRE
- Td group at P(1)
- Td group at PRE
- Td group at P(1)

Cut-off = 2.046 anti-FHA antibody antibody concentrations (IU/ml)
Figure 7  Reverse cumulative distribution curve for anti-PRN antibody concentrations per group at pre and post booster vaccination time point (ATP cohort for analysis of immunogenicity)

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
Table 47  Alternative booster response to anti-Diphtheria and anti-Tetanus antibodies one month after booster vaccination (ATP cohort for analysis of immunogenicity - excluding subjects with pre-vaccination concentration greater than or equal to 6 IU/mL)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group</th>
<th>Pre-vaccination status</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-D antibody (IU/mL)</td>
<td>Td group</td>
<td>S-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (&lt;1 IU/mL)</td>
<td>12</td>
<td>10</td>
<td>83.3</td>
<td>51.6</td>
<td>97.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (≥1 IU/mL)</td>
<td>18</td>
<td>11</td>
<td>61.1</td>
<td>35.7</td>
<td>82.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>30</td>
<td>21</td>
<td>70.0</td>
<td>50.6</td>
<td>85.3</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>S-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (&lt;1 IU/mL)</td>
<td>45</td>
<td>40</td>
<td>88.9</td>
<td>75.9</td>
<td>96.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (≥1 IU/mL)</td>
<td>53</td>
<td>18</td>
<td>34.0</td>
<td>21.5</td>
<td>48.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>98</td>
<td>58</td>
<td>59.2</td>
<td>48.8</td>
<td>69.0</td>
</tr>
<tr>
<td>anti-T antibody (IU/mL)</td>
<td>Td group</td>
<td>S-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (&lt;1 IU/mL)</td>
<td>8</td>
<td>8</td>
<td>100</td>
<td>63.1</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (≥1 IU/mL)</td>
<td>24</td>
<td>19</td>
<td>79.2</td>
<td>57.8</td>
<td>92.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>32</td>
<td>27</td>
<td>84.4</td>
<td>67.2</td>
<td>94.7</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>S-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (&lt;1 IU/mL)</td>
<td>29</td>
<td>28</td>
<td>96.6</td>
<td>82.2</td>
<td>99.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (≥1 IU/mL)</td>
<td>76</td>
<td>59</td>
<td>77.6</td>
<td>66.6</td>
<td>86.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>105</td>
<td>87</td>
<td>82.9</td>
<td>74.3</td>
<td>89.5</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine  
Tdap group = Subjects received a second dose of Tdap vaccine  
Total = subjects either seropositive or seronegative  
Alternative Booster response to Anti D and T antigens is defined as:  
- initially seronegative subjects (pre-vaccination concentration below the 0.1 IU/mL): antibody concentrations at least four times the 0.1 IU/mL one month after vaccination, and  
- initially seropositive subjects with pre-vaccination concentration < 1.0 IU/mL: antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.  
- initially seropositive subjects with pre-vaccination concentration in ≥ 1.0 IU/mL and < 6.0 IU/mL: antibody concentrations of at least two times the pre-vaccination concentration, one month after vaccination.  
- subjects with pre-vaccination concentration ≥6.0 IU/mL are not evaluable for vaccine response.  
N = number of subjects with both pre- and post-vaccination results available  
n/ % = number/percentage of responders  
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Table 48  Alternative booster responses to anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (ATP cohort for analysis of immunogenicity - excluding subjects with pre-vaccination concentration greater than or equal to 6 IU/mL)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group</th>
<th>Pre-vaccination status</th>
<th>N</th>
<th>n/%</th>
<th>95% CI</th>
<th>5% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>anti-PT antibody</td>
<td>Td group</td>
<td>S- ≥ assay cut-off and &lt; 60 IU/mL</td>
<td>14</td>
<td>14</td>
<td>100</td>
<td>76.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 60 IU/mL</td>
<td>1</td>
<td>1</td>
<td>100</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>35</td>
<td>32</td>
<td>91.4</td>
<td>76.9</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>S- ≥ assay cut-off and &lt; 60 IU/mL</td>
<td>14</td>
<td>14</td>
<td>100</td>
<td>92.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 60 IU/mL</td>
<td>1</td>
<td>1</td>
<td>100</td>
<td>66.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>15</td>
<td>15</td>
<td>100</td>
<td>92.9</td>
</tr>
<tr>
<td>anti-FHA antibody</td>
<td>Td group</td>
<td>S- ≥ assay cut-off and &lt; 60 IU/mL</td>
<td>25</td>
<td>25</td>
<td>100</td>
<td>96.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 60 IU/mL</td>
<td>9</td>
<td>9</td>
<td>100</td>
<td>88.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>34</td>
<td>34</td>
<td>100</td>
<td>94.3</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>S- ≥ assay cut-off and &lt; 60 IU/mL</td>
<td>82</td>
<td>82</td>
<td>100</td>
<td>95.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 60 IU/mL</td>
<td>33</td>
<td>33</td>
<td>100</td>
<td>84.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>115</td>
<td>115</td>
<td>100</td>
<td>95.7</td>
</tr>
<tr>
<td>anti-PRN antibody</td>
<td>Td group</td>
<td>S- ≥ assay cut-off and &lt; 60 IU/mL</td>
<td>24</td>
<td>24</td>
<td>100</td>
<td>95.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 60 IU/mL</td>
<td>9</td>
<td>9</td>
<td>100</td>
<td>44.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>33</td>
<td>33</td>
<td>100</td>
<td>82.9</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>S- ≥ assay cut-off and &lt; 60 IU/mL</td>
<td>43</td>
<td>43</td>
<td>100</td>
<td>97.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 60 IU/mL</td>
<td>72</td>
<td>72</td>
<td>100</td>
<td>72.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>115</td>
<td>115</td>
<td>100</td>
<td>81.7</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
Total = subjects either seropositive or seronegative
S- = seronegative subjects (antibody concentration < assay cut-off IU/mL for anti-PT antibody, anti-FHA antibody, anti-PRN anti) prior to vaccination
S+ = seropositive subjects (antibody concentration ≥ assay cut-off IU/mL for anti-PT antibody, anti-FHA antibody, anti-PRN anti) prior to vaccination

Alternative Booster response to pertussis antigens is defined as:
- initially seronegative subjects (pre-vaccination concentration below the assay cut-off): antibody concentrations at least four times the assay cut-off one month after vaccination
- initially seropositive subjects with pre-vaccination antibody concentration ≥ assay cut-off and < 60 IU/mL: antibody concentration increase of at least 30 IU/mL from the pre-vaccination concentration, one month after vaccination.
- initially seropositive subjects with pre-vaccination antibody concentration ≥ 60 IU/mL: at least 1.5-fold increase of antibody concentration from the pre-vaccination concentration, one month after vaccination.

N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of responders
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
### Table 49: Group difference in alternative booster response to the diphtheria and tetanus antigens [ATP cohort for analysis of immunogenicity - excluding subjects with pre-vaccination concentration greater than or equal to 6 IU/mL]

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Tdap group</th>
<th>Td group</th>
<th>Difference in booster response rate (Tdap group minus Td group)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>anti-D antibody (IU/mL)</td>
<td>98</td>
<td>58</td>
<td>59.2</td>
<td>30</td>
</tr>
<tr>
<td>anti-T antibody (IU/mL)</td>
<td>105</td>
<td>87</td>
<td>82.9</td>
<td>32</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine

Alternative Booster response to Anti D and T antigens is defined as:
- Initially seronegative subjects (pre-vaccination concentration below the 0.1 IU/mL): antibody concentrations at least four times the 0.1 IU/mL one month after vaccination, and
- Initially seropositive subjects with pre-vaccination concentration < 1.0 IU/mL: antibody concentrations at least four times the pre-vaccination concentration, one month after vaccination.
- Initially seropositive subjects with pre-vaccination concentration in ≥ 1.0 IU/mL and < 6.0 IU/mL: antibody concentrations of at least two times the pre-vaccination concentration, one month after vaccination.
- Subjects with pre-vaccination concentration ≥ 6.0 IU/mL are not evaluable for vaccine response.

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

### Table 50: Group difference in alternative booster response to anti-PT, anti-FHA and anti-PRN antigens [Tdap Group minus Td Group], one month after booster vaccination and their standardized asymptotic 95% CIs (ATP cohort for analysis of immunogenicity)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Tdap group</th>
<th>Td group</th>
<th>Difference in booster response rate (Tdap group minus Td group)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>anti-FHA antibody (IU/mL)</td>
<td>115</td>
<td>110</td>
<td>95.7</td>
<td>35</td>
</tr>
<tr>
<td>anti-PRN antibody (IU/mL)</td>
<td>115</td>
<td>94</td>
<td>81.7</td>
<td>35</td>
</tr>
<tr>
<td>anti-PT antibody (IU/mL)</td>
<td>115</td>
<td>104</td>
<td>90.4</td>
<td>35</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine

Total = subjects either seropositive or seronegative

Alternative Booster response to pertussis antigens is defined as:
- Initially seronegative subjects (pre-vaccination concentration below the assay cut-off): antibody concentrations at least four times the assay cut-off one month after vaccination
- Initially seropositive subjects with pre-vaccination antibody concentration ≥ assay cut-off and < 60 IU/mL: antibody concentration increase of at least 30 IU/mL from the pre-vaccination concentration, one month after vaccination.
- Initially seropositive subjects with pre-vaccination antibody concentration ≥ 60 IU/mL: at least 1.5-fold increase of antibody concentration from the pre-vaccination concentration, one month after vaccination.

N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with a booster response
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
Table 51  Number of years since the vaccination in primary study (ATP cohort for immunogenicity - adapted for each time point)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Characteristics</th>
<th>Parameters</th>
<th>Td group *N = 999</th>
<th>Tdap group *N = 2982</th>
<th>Total *N = 3981</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post_bst_001</td>
<td>years since vaccination</td>
<td>N</td>
<td>998</td>
<td>2977</td>
<td>3975</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>0.10</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median</td>
<td>0.10</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD</td>
<td>0.02</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minimum</td>
<td>0.08</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maximum</td>
<td>0.38</td>
<td>0.25</td>
<td>0.38</td>
</tr>
<tr>
<td>Pre_bst_012</td>
<td>years since vaccination</td>
<td>N</td>
<td>35</td>
<td>115</td>
<td>150</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>10.27</td>
<td>10.32</td>
<td>10.31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median</td>
<td>10.26</td>
<td>10.30</td>
<td>10.29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD</td>
<td>0.28</td>
<td>0.26</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minimum</td>
<td>9.73</td>
<td>9.81</td>
<td>9.73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maximum</td>
<td>10.77</td>
<td>10.82</td>
<td>10.82</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
Value = value of the considered parameter
SD = Standard deviation
*N= the total number of subjects corresponding to each activity
N= number of subjects
Post_bst_001= Post booster blood sampling time point after the booster dose dTpa0.3-001 study
Pre_bst_012= Pre booster blood sampling time point after the booster dose in dTpa0.3-001 study

Table 52  Observed number and percentage of subjects with an ANTI-D and T concentration equal to or above 0.1 and 1 IU/mL and GMCs in the 001 study (ATP cohort for immunogenicity - adapted for the time point)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group</th>
<th>Timing</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
<th>n</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
<th>value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-Diphtheria</td>
<td>Td group</td>
<td>Postbst001</td>
<td>998</td>
<td>997</td>
<td>99.9</td>
<td>99.4</td>
<td>100</td>
<td>991</td>
<td>99.3</td>
<td>98.8</td>
<td>99.7</td>
<td>14.1</td>
<td>13.4</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>Postbst001</td>
<td>2975</td>
<td>2972</td>
<td>99.9</td>
<td>99.7</td>
<td>100</td>
<td>2966</td>
<td>97.3</td>
<td>96.7</td>
<td>97.9</td>
<td>7.3</td>
<td>7.1</td>
</tr>
<tr>
<td>anti-Tetanus</td>
<td>Td group</td>
<td>Postbst001</td>
<td>998</td>
<td>998</td>
<td>100</td>
<td>99.6</td>
<td>100</td>
<td>996</td>
<td>99.8</td>
<td>99.3</td>
<td>100</td>
<td>20.7</td>
<td>19.7</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>Postbst001</td>
<td>2976</td>
<td>2975</td>
<td>100</td>
<td>99.8</td>
<td>100</td>
<td>2963</td>
<td>99.6</td>
<td>99.3</td>
<td>99.8</td>
<td>15.8</td>
<td>15.3</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine in 012 study
Tdap group = Subjects received a second dose of Tdap vaccine in 012 study
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Postbst001= Post booster blood sampling time point one month after the booster dose dTpa0.3-001 study
Table 53  Estimated antibody D and T GMCs, as predicted by modelling (ATP cohort for immunogenicity - adapted for each time point)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group</th>
<th>Timing</th>
<th>value</th>
<th>LL</th>
<th>UL</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-Diphtheria</td>
<td>Td group</td>
<td>Postbst001</td>
<td>14.1</td>
<td>13.3</td>
<td>14.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Td group</td>
<td>Prebst012</td>
<td>2.4</td>
<td>2.0</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>Postbst001</td>
<td>7.3</td>
<td>7.1</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>Prebst012</td>
<td>1.3</td>
<td>1.0</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>anti-Tetanus</td>
<td>Td group</td>
<td>Postbst001</td>
<td>20.6</td>
<td>19.6</td>
<td>21.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Td group</td>
<td>Prebst012</td>
<td>2.2</td>
<td>1.9</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>Postbst001</td>
<td>15.8</td>
<td>15.3</td>
<td>16.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>Prebst012</td>
<td>1.7</td>
<td>1.4</td>
<td>1.9</td>
<td></td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
GMC = predicted geometric mean antibody concentration
% = predicted percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Prediction and CI from linear regression on log-transformed concentration with random intercept and slope, where seronegative results are left censored
Postbst001= Post booster blood sampling time point one month after the booster dose dTpa0.3-001 study
Prebst012= Pre booster blood sampling time point one month after the booster dose in dTpa0.3-012 study

Table 54  Observed number and percentage of subjects with an ANTI-PT, ANTI-FHA and ANTI-PRN concentration equal to or above 5 EL.U/mL and GMCs in the 001 study (ATP cohort for immunogenicity - adapted for the time point)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group</th>
<th>Timing</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
<th>value</th>
<th>LL</th>
<th>UL</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-PT antibody</td>
<td>Td group</td>
<td>Postbst001</td>
<td>986</td>
<td>634</td>
<td>64.3</td>
<td>61.2</td>
<td>67.3</td>
<td>9.9</td>
<td>9.1</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>Postbst001</td>
<td>2939</td>
<td>2905</td>
<td>98.8</td>
<td>98.4</td>
<td>99.2</td>
<td>86.8</td>
<td>83.9</td>
<td>89.9</td>
<td></td>
</tr>
<tr>
<td>anti-FHA antibody</td>
<td>Td group</td>
<td>Postbst001</td>
<td>995</td>
<td>961</td>
<td>96.6</td>
<td>95.3</td>
<td>97.6</td>
<td>38.6</td>
<td>35.9</td>
<td>41.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>Postbst001</td>
<td>2977</td>
<td>2976</td>
<td>100</td>
<td>99.8</td>
<td>100</td>
<td>614.5</td>
<td>596.0</td>
<td>633.5</td>
<td></td>
</tr>
<tr>
<td>anti-PRN antibody</td>
<td>Td group</td>
<td>Postbst001</td>
<td>997</td>
<td>718</td>
<td>72.0</td>
<td>69.1</td>
<td>74.8</td>
<td>11.8</td>
<td>10.9</td>
<td>12.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>Postbst001</td>
<td>2976</td>
<td>2964</td>
<td>99.6</td>
<td>99.3</td>
<td>99.8</td>
<td>470.9</td>
<td>447.2</td>
<td>495.8</td>
<td></td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine in 012 study
Tdap group = Subjects received a second dose of Tdap vaccine in 012 study
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Postbst001= Post booster blood sampling time point one month after the booster dose dTpa0.3-001 study
## Table 55 Estimated antibody pertussis GMCs, as predicted by modelling (ATP cohort for immunogenicity - adapted for each time point)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group</th>
<th>Timing</th>
<th>value</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-PT antibody</td>
<td>Td group</td>
<td>Postbst001</td>
<td>9.1</td>
<td>6.2</td>
<td>13.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prebst012</td>
<td>5.3</td>
<td>3.6</td>
<td>7.7</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>Postbst001</td>
<td>98.4</td>
<td>80.7</td>
<td>120.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prebst012</td>
<td>10.2</td>
<td>8.4</td>
<td>12.4</td>
</tr>
<tr>
<td>anti-FHA antibody</td>
<td>Td group</td>
<td>Postbst001</td>
<td>46.3</td>
<td>33.4</td>
<td>64.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prebst012</td>
<td>21.8</td>
<td>15.8</td>
<td>30.0</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>Postbst001</td>
<td>610.6</td>
<td>510.3</td>
<td>730.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prebst012</td>
<td>37.0</td>
<td>31.0</td>
<td>44.1</td>
</tr>
<tr>
<td>anti-PRN antibody</td>
<td>Td group</td>
<td>Postbst001</td>
<td>15.0</td>
<td>9.0</td>
<td>24.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prebst012</td>
<td>27.8</td>
<td>17.1</td>
<td>45.4</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>Postbst001</td>
<td>547.6</td>
<td>417.5</td>
<td>718.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prebst012</td>
<td>71.8</td>
<td>54.9</td>
<td>94.0</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine  
Tdap group = Subjects received a second dose of Tdap vaccine  
GMC = predicted geometric mean antibody concentration  
% = predicted percentage of subjects with concentration within the specified range  
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit  
Prediction and CI from linear regression on log-transformed concentration with random intercept and interaction in slope, where seronegative results are left censored  
Postbst001= Post booster blood sampling time point one month after the booster dose dTpa0.3-001 study  
Prebst012= Pre booster blood sampling time point one month after the booster dose in dTpa0.3-012 study
### 10.2.2. TVC for immunogenicity

#### Table 56  
Number and percentage of subjects with anti-Diphtheria and anti-Tetanus antibody concentration ≥ 0.1 IU/mL, ≥ 1 IU/mL and GMCs at pre and post booster vaccination time points (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group</th>
<th>Timing</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
<th>95% CI</th>
<th>95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-D antibody</td>
<td>Tdap</td>
<td>PRE</td>
<td>37</td>
<td>37</td>
<td>100.0</td>
<td>90.5</td>
<td>100</td>
<td>67.6</td>
<td>50.2</td>
<td>82.0</td>
</tr>
<tr>
<td>(Assay cut-off = 0.057 IU/mL)</td>
<td></td>
<td>Post</td>
<td>36</td>
<td>36</td>
<td>100.0</td>
<td>90.3</td>
<td>100</td>
<td>97.2</td>
<td>85.5</td>
<td>99.9</td>
</tr>
<tr>
<td></td>
<td>Tdap</td>
<td>PRE</td>
<td>127</td>
<td>127</td>
<td>100.0</td>
<td>97.1</td>
<td>100</td>
<td>63.0</td>
<td>54.0</td>
<td>71.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post</td>
<td>124</td>
<td>124</td>
<td>100.0</td>
<td>97.1</td>
<td>100</td>
<td>100.0</td>
<td>97.1</td>
<td>100.0</td>
</tr>
<tr>
<td>anti-T antibody</td>
<td>Tdap</td>
<td>PRE</td>
<td>37</td>
<td>37</td>
<td>100.0</td>
<td>90.5</td>
<td>100</td>
<td>75.7</td>
<td>58.8</td>
<td>88.2</td>
</tr>
<tr>
<td>(Assay cut-off = 0.043 IU/mL)</td>
<td></td>
<td>Post</td>
<td>36</td>
<td>36</td>
<td>100.0</td>
<td>90.3</td>
<td>100</td>
<td>100.0</td>
<td>90.3</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>Tdap</td>
<td>PRE</td>
<td>128</td>
<td>128</td>
<td>100.0</td>
<td>97.2</td>
<td>100</td>
<td>94.2</td>
<td>65.7</td>
<td>81.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post</td>
<td>124</td>
<td>124</td>
<td>100.0</td>
<td>97.1</td>
<td>100</td>
<td>100.0</td>
<td>97.1</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine  
Tdap group = Subjects received a second dose of Tdap vaccine  
GMC = geometric mean antibody concentration calculated on all subjects  
N = number of subjects with available results  
n/% = number/percentage of subjects with concentration equal to or above specified value  
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit  
Pre = Pre booster vaccination blood sampling time-point  
Post = Post booster vaccination blood sampling time-point

#### Table 57  
Number and percentage of subjects with an anti-PT, anti-FHA, anti-PRN antibody concentration ≥ assay cut-off and GMCs at pre and post booster vaccination time points (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group</th>
<th>Timing</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
<th>95% CI</th>
<th>GMC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-PT antibody</td>
<td>Tdap</td>
<td>PRE</td>
<td>37</td>
<td>37</td>
<td>100.0</td>
<td>42.1</td>
<td>75.2</td>
<td>5.2</td>
<td>3.4</td>
<td>8.0</td>
</tr>
<tr>
<td>(Assay cut-off = 2.693 IU/mL)</td>
<td></td>
<td>Post</td>
<td>36</td>
<td>36</td>
<td>100.0</td>
<td>90.3</td>
<td>100</td>
<td>64.0</td>
<td>49.1</td>
<td>83.5</td>
</tr>
<tr>
<td></td>
<td>Tdap</td>
<td>PRE</td>
<td>128</td>
<td>128</td>
<td>100.0</td>
<td>97.3</td>
<td>100</td>
<td>85.8</td>
<td>99.9</td>
<td>22.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post</td>
<td>124</td>
<td>124</td>
<td>100.0</td>
<td>97.1</td>
<td>100</td>
<td>100.0</td>
<td>100.0</td>
<td>83.5</td>
</tr>
<tr>
<td>anti-FHA antibody</td>
<td>Tdap</td>
<td>PRE</td>
<td>37</td>
<td>37</td>
<td>100.0</td>
<td>85.8</td>
<td>99.9</td>
<td>22.1</td>
<td>13.9</td>
<td>34.9</td>
</tr>
<tr>
<td>(Assay cut-off = 2.046 IU/mL)</td>
<td></td>
<td>Post</td>
<td>36</td>
<td>36</td>
<td>100.0</td>
<td>90.3</td>
<td>100</td>
<td>323.2</td>
<td>249.0</td>
<td>443.5</td>
</tr>
<tr>
<td></td>
<td>Tdap</td>
<td>PRE</td>
<td>128</td>
<td>128</td>
<td>100.0</td>
<td>97.2</td>
<td>100</td>
<td>94.6</td>
<td>27.5</td>
<td>51.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post</td>
<td>124</td>
<td>124</td>
<td>100.0</td>
<td>97.1</td>
<td>100</td>
<td>100.0</td>
<td>100.0</td>
<td>85.5</td>
</tr>
<tr>
<td>anti-PRN antibody</td>
<td>Tdap</td>
<td>PRE</td>
<td>37</td>
<td>37</td>
<td>100.0</td>
<td>81.8</td>
<td>99.3</td>
<td>27.5</td>
<td>14.1</td>
<td>53.6</td>
</tr>
<tr>
<td>(Assay cut-off = 2.187 IU/mL)</td>
<td></td>
<td>Post</td>
<td>36</td>
<td>36</td>
<td>100.0</td>
<td>90.3</td>
<td>100</td>
<td>447.5</td>
<td>296.2</td>
<td>675.9</td>
</tr>
<tr>
<td></td>
<td>Tdap</td>
<td>PRE</td>
<td>128</td>
<td>128</td>
<td>100.0</td>
<td>97.2</td>
<td>100</td>
<td>94.6</td>
<td>27.5</td>
<td>51.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post</td>
<td>124</td>
<td>124</td>
<td>100.0</td>
<td>97.1</td>
<td>100</td>
<td>442.6</td>
<td>373.9</td>
<td>524.0</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine  
Tdap group = Subjects received a second dose of Tdap vaccine  
GMC = geometric mean antibody concentration calculated on all subjects  
N = number of subjects with available results  
n/% = number/percentage of subjects with concentration equal to or above specified value  
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit  
Pre = Pre booster vaccination blood sampling time-point  
Post = Post booster vaccination blood sampling time-point
Table 58  Seronegativity status for anti-Diphtheria antibody concentration by ELISA and VERO NEUTRALISATION at pre booster vaccination time points (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>n/N</th>
<th>%</th>
<th>n'/N'</th>
<th>%</th>
<th>n/N x n'/N'</th>
<th>%</th>
<th>SP</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Td group</td>
<td>37</td>
<td>0/37</td>
<td>0.0</td>
<td>0/0</td>
<td>0.0</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tdap group</td>
<td>127</td>
<td>1/127</td>
<td>0.8</td>
<td>0/1</td>
<td>0.0</td>
<td>1/127 x 0/1</td>
<td>0.0</td>
<td>100</td>
<td>97.1</td>
<td>100</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
N = number of subjects tested by ELISA
n/N = number of subjects with concentrations below the 0.1 IU/mL / number of subjects tested by ELISA
n'/N' = number of subjects with concentrations below the 0.01 IU/mL / number of subjects tested by NEU neutralisation test
% = proportion of subjects with concentrations below the considered cut-off (0.1 IU/mL for ELISA and 0.01 IU/mL for NEU)
n/N x n'/N' = the multiplication of the two proportions = overall seronegativity for anti-D antibody
Overall = based on both the ELISA and the NEU testing
95% CI = exact 95% confidence interval for group(s) Td group Tdap group ; LL = lower limit, UL = upper limit

Table 59  Group differences in the percentage of subjects with anti-Diphtheria and anti-Tetanus antibody concentrations ≥ 0.1 IU/mL [Tdap Group minus Td Group], one month after booster vaccination and their standardized asymptotic 95% CIs (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Antibody Type</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Td group</td>
<td></td>
<td></td>
<td></td>
<td>Tdap group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>anti-D antibody</td>
<td>0.1 IU/mL</td>
<td>36</td>
<td>36</td>
<td>100</td>
<td>124</td>
<td>124</td>
<td>100</td>
<td>-3.02</td>
</tr>
<tr>
<td>anti-T antibody</td>
<td>0.1 IU/mL</td>
<td>36</td>
<td>36</td>
<td>100</td>
<td>124</td>
<td>124</td>
<td>100</td>
<td>-3.02</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
N = number of subjects with available results
n/% = number/percentage of subjects with antibody concentrations above the specified cut-off (≥ 0.1IU/mL)
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
Table 60  Group difference in booster response to anti-diphtheria and anti-tetanus antigens [Tdap Group minus Td Group], one month after booster vaccination and their standardized asymptotic 95% CIs (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Tdap group</th>
<th>Td group</th>
<th>Difference in booster response rate (Tdap group minus Td group)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>anti-D antibody (IU/mL)</td>
<td>123</td>
<td>48</td>
<td>39.0</td>
<td>36</td>
</tr>
<tr>
<td>anti-T antibody (IU/mL)</td>
<td>124</td>
<td>66</td>
<td>53.2</td>
<td>36</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
Booster response to Anti D and T antigens is defined as:
- initially seronegative subjects with pre-booster antibody concentration below the 0.1 IU/mL, an increase of at least four times 0.1 IU/mL one month after vaccination,
- initially seropositive subjects with pre-booster antibody concentration≥ 0.1 IU/mL, an increase of at least four times the pre-booster antibody concentration one month after vaccination
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with a booster response
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit
Table 61  Group difference in booster response to anti-PT, anti-FHA and anti-PRN antigens [Tdap Group minus Td Group], one month after booster vaccination and their standardized asymptotic 95% CIs (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Tdap group</th>
<th>Td group</th>
<th>Difference in booster response rate (Tdap group minus Td group)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>anti-FHA antibody (IU/mL)</td>
<td>124</td>
<td>110</td>
<td>88.7</td>
<td>36</td>
</tr>
<tr>
<td>anti-PRN antibody (IU/mL)</td>
<td>124</td>
<td>84</td>
<td>67.7</td>
<td>36</td>
</tr>
<tr>
<td>anti-PT antibody (IU/mL)</td>
<td>124</td>
<td>114</td>
<td>91.9</td>
<td>36</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
Booster response to pertussis antigens is defined as:
- initially seronegative subjects (pre-booster antibody concentration below the assay cut-off) with an increase of at least four times the assay cut-off one month after vaccination,
- initially seropositive subjects with antibody concentration < four times the assay cut-off with an increase of at least four times the pre-booster antibody concentration one month after vaccination
- initially seropositive subjects with antibody concentration ≥ four times the assay cut-off with an increase of at least two times the pre-booster antibody concentration one month after vaccination

N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with a booster response
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit
Table 62 Group difference in alternative booster response to the diphtheria and tetanus antigens [Tdap Group minus Td Group], one month after booster vaccination and their standardized asymptotic 95% CIs (Total vaccinated cohort - excluding subjects with pre-vaccination concentration greater than or equal to 6 IU/mL)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Tdap group</th>
<th>Td group</th>
<th>Difference in booster response rate (Tdap group minus Td group)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>anti-D antibody (IU/mL)</td>
<td>103</td>
<td>60</td>
<td>58.3</td>
<td>31</td>
</tr>
<tr>
<td>anti-T antibody (IU/mL)</td>
<td>112</td>
<td>81</td>
<td>81.3</td>
<td>33</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine

Alternative Booster response to Anti D and T antigens is defined as:
- initially seronegative subjects (pre-vaccination concentration below the 0.1 IU/mL): antibody concentrations at least four times the 0.1 IU/mL one month after vaccination, and
- initially seropositive subjects with pre-vaccination concentration < 1.0 IU/mL: antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.
- initially seropositive subjects with pre-vaccination concentration ≥ 1.0 IU/mL and < 6.0 IU/mL: antibody concentrations of at least two times the pre-vaccination concentration, one month after vaccination.
- subjects with pre-vaccination concentration ≥ 6.0 IU/mL are not evaluable for vaccine response.

N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with a booster response
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
Table 63 Group difference in alternative booster response to anti-PT, anti-FHA and anti-PRN antigens [Tdap Group minus Td Group], one month after booster vaccination and their standardized asymptotic 95% CIs (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Tdap group</th>
<th>Td group</th>
<th>Difference in booster response rate (Tdap group minus Td group)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>anti-FHA antibody (IU/mL)</td>
<td>124</td>
<td>119</td>
<td>96.0</td>
<td>36</td>
</tr>
<tr>
<td>anti-PRN antibody (IU/mL)</td>
<td>124</td>
<td>99</td>
<td>79.8</td>
<td>36</td>
</tr>
<tr>
<td>anti-PT antibody (IU/mL)</td>
<td>124</td>
<td>111</td>
<td>89.5</td>
<td>36</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
Total = subjects either seropositive or seronegative

Alternative Booster response to pertussis antigens is defined as:
- initially seronegative subjects (pre-vaccination concentration below the assay cut-off): antibody concentrations at least four times the assay cut-off one month after vaccination
- initially seropositive subjects with pre-vaccination antibody concentration ≥ assay cut-off and < 60 IU/mL: antibody concentration increase of at least 30 IU/mL from the pre-vaccination concentration, one month after vaccination.
- initially seropositive subjects with pre-vaccination antibody concentration ≥ 60 IU/mL: at least 1.5-fold increase of antibody concentration from the pre-vaccination concentration, one month after vaccination.
- subjects with pre-vaccination concentration ≥6.0 IU/mL are not evaluable for vaccine response.

N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with a booster response
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
Table 64  Booster response to anti-diphtheria and anti-tetanus antigens one month after booster vaccination (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group</th>
<th>Pre-vaccination status</th>
<th>N</th>
<th>n/%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-D antibody (IU/mL)</td>
<td>Td group</td>
<td>S-</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+</td>
<td>36</td>
<td>14</td>
<td>38.9</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td>36</td>
<td>14</td>
<td>38.9</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>S-</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+</td>
<td>123</td>
<td>48</td>
<td>39.0</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td>123</td>
<td>48</td>
<td>39.0</td>
</tr>
<tr>
<td>anti-T antibody (IU/mL)</td>
<td>Td group</td>
<td>S-</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+</td>
<td>36</td>
<td>22</td>
<td>61.1</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td>36</td>
<td>22</td>
<td>61.1</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>S-</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+</td>
<td>124</td>
<td>66</td>
<td>53.2</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>124</td>
<td>66</td>
<td>53.2</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine  
Tdap group = Subjects received a second dose of Tdap vaccine  
S- = seronegative subjects (antibody concentration < 0.1 IU/mL for anti-Diphtheria and anti-Tetanus)  
S+ = seropositive subjects (antibody concentration ≥ 0.1 IU/mL for anti-Diphtheria and anti-Tetanus)  
Total = subjects either seropositive or seronegative at pre-vaccination  
Booster response to Anti D and T antigens is defined as:  
- initially seronegative subjects with pre-booster antibody concentration below the 0.1 IU/mL, an increase of at least four times 0.1 IU/mL one month after vaccination,  
- initially seropositive subjects with pre-booster antibody concentration ≥ 0.1 IU/mL, an increase of at least four times the pre-booster antibody concentration one month after vaccination  
N = number of subjects with both pre- and post-vaccination results available  
n/\% = number/percentage of responders  
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Table 65 Alternative booster response to anti-Diphtheria and anti-Tetanus antibodies one month after booster vaccination (Total vaccinated cohort - excluding subjects with pre-vaccination concentration greater than or equal to 6 IU/mL)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group</th>
<th>Pre-vaccination status</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-D antibody (IU/mL)</td>
<td>Td group</td>
<td>S-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (&lt;1 IU/mL)</td>
<td>12</td>
<td>10</td>
<td>83.3</td>
<td>51.6</td>
<td>97.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (≥1 IU/mL)</td>
<td>19</td>
<td>11</td>
<td>57.9</td>
<td>33.5</td>
<td>79.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>31</td>
<td>21</td>
<td>67.7</td>
<td>48.6</td>
<td>83.3</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>S-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (&lt;1 IU/mL)</td>
<td>46</td>
<td>41</td>
<td>89.1</td>
<td>76.4</td>
<td>96.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (≥1 IU/mL)</td>
<td>57</td>
<td>19</td>
<td>33.3</td>
<td>21.4</td>
<td>47.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>103</td>
<td>60</td>
<td>58.3</td>
<td>48.1</td>
<td>67.9</td>
</tr>
<tr>
<td>anti-T antibody (IU/mL)</td>
<td>Td group</td>
<td>S-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (&lt;1 IU/mL)</td>
<td>9</td>
<td>9</td>
<td>100</td>
<td>66.4</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (≥1 IU/mL)</td>
<td>24</td>
<td>19</td>
<td>79.2</td>
<td>57.8</td>
<td>92.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>33</td>
<td>28</td>
<td>84.8</td>
<td>68.1</td>
<td>94.9</td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>S-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (&lt;1 IU/mL)</td>
<td>32</td>
<td>30</td>
<td>93.8</td>
<td>79.2</td>
<td>99.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S+ (≥1 IU/mL)</td>
<td>80</td>
<td>61</td>
<td>76.3</td>
<td>65.4</td>
<td>85.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>112</td>
<td>91</td>
<td>81.3</td>
<td>72.8</td>
<td>88.0</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
Total = subjects either seropositive or seronegative
Alternative Booster response to Anti D and T antigens is defined as:
- initially seronegative subjects (pre-vaccination concentration below the 0.1 IU/mL): antibody concentrations at least four times the 0.1 IU/mL one month after vaccination, and
- initially seropositive subjects with pre-vaccination concentration < 1.0 IU/mL: antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.
- initially seropositive subjects with pre-vaccination concentration in ≥ 1.0 IU/mL and < 6.0 IU/mL: antibody concentrations of at least two times the pre-vaccination concentration, one month after vaccination.
- subjects with pre-vaccination concentration ≥6.0 IU/mL are not evaluable for vaccine response.
N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of responders
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
# Table 66  Alternative booster responses to anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group</th>
<th>Pre-vaccination status</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-PT antibody</td>
<td>Td group</td>
<td>S-</td>
<td>15</td>
<td>15</td>
<td>100</td>
<td>78.2 - 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ assay cut-off and &lt; 60 IU/mL</td>
<td>20</td>
<td>17</td>
<td>85.0</td>
<td>62.1 - 96.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 60 IU/mL</td>
<td>1</td>
<td>1</td>
<td>100</td>
<td>2.5 - 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>S-</td>
<td>36</td>
<td>33</td>
<td>91.7</td>
<td>77.5 - 98.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ assay cut-off and &lt; 60 IU/mL</td>
<td>101</td>
<td>90</td>
<td>89.1</td>
<td>81.3 - 94.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 60 IU/mL</td>
<td>6</td>
<td>5</td>
<td>83.3</td>
<td>35.9 - 99.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>anti-FHA antibody</td>
<td>Td group</td>
<td>S-</td>
<td>1</td>
<td>1</td>
<td>100</td>
<td>100 - 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ assay cut-off and &lt; 60 IU/mL</td>
<td>26</td>
<td>25</td>
<td>96.2</td>
<td>80.4 - 99.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 60 IU/mL</td>
<td>9</td>
<td>8</td>
<td>88.9</td>
<td>51.8 - 99.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>S-</td>
<td>36</td>
<td>34</td>
<td>94.4</td>
<td>81.3 - 99.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ assay cut-off and &lt; 60 IU/mL</td>
<td>88</td>
<td>88</td>
<td>100</td>
<td>95.9 - 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 60 IU/mL</td>
<td>36</td>
<td>31</td>
<td>86.1</td>
<td>70.5 - 95.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>anti-PRN antibody</td>
<td>Td group</td>
<td>S-</td>
<td>2</td>
<td>2</td>
<td>100</td>
<td>15.8 - 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ assay cut-off and &lt; 60 IU/mL</td>
<td>25</td>
<td>24</td>
<td>96.0</td>
<td>79.6 - 99.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 60 IU/mL</td>
<td>9</td>
<td>4</td>
<td>44.4</td>
<td>13.7 - 78.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tdap group</td>
<td>S-</td>
<td>36</td>
<td>30</td>
<td>83.3</td>
<td>67.2 - 93.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ assay cut-off and &lt; 60 IU/mL</td>
<td>47</td>
<td>46</td>
<td>97.9</td>
<td>88.7 - 99.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 60 IU/mL</td>
<td>77</td>
<td>53</td>
<td>68.8</td>
<td>57.3 - 78.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>124</td>
<td>99</td>
<td>79.8</td>
<td>71.7 - 86.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
Total = subjects either seropositive or seronegative

Alternative Booster response to pertussis antigens is defined as:
- initially seronegative subjects (pre-vaccination concentration below the assay cut-off): antibody concentrations at least four times the assay cut-off one month after vaccination
- initially seropositive subjects with pre-vaccination antibody concentration ≥ assay cut-off and < 60 IU/mL: antibody concentration increase of at least 30 IU/mL from the pre-vaccination concentration, one month after vaccination.
- initially seropositive subjects with pre-vaccination antibody concentration ≥ 60 IU/mL: at least 1.5-fold increase of antibody concentration from the pre-vaccination concentration, one month after vaccination.

For initially seropositive subjects with pre-vaccination antibody concentration < 60 IU/mL: antibody concentration at Post ≥ 4 fold the pre-vaccination antibody concentration
For initially seropositive subjects with pre-vaccination antibody concentration ≥ 60 IU/mL: antibody concentration at Post ≥ 1.5 fold the pre-vaccination antibody concentration

N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of responders
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
### Table 67  Adjusted GMC ratio between groups [Tdap group divided by Td group] and their 95% CIs for anti-diphtheria and anti-tetanus antigens one month after booster vaccination (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group description</th>
<th>N</th>
<th>Adjusted GMC</th>
<th>Group description</th>
<th>N</th>
<th>Adjusted GMC</th>
<th>Ratio order</th>
<th>Value</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-D antibody (IU/mL)</td>
<td>Tdap group</td>
<td>122</td>
<td>6.0</td>
<td>Td group</td>
<td>35</td>
<td>6.5</td>
<td>Tdap group /Td group</td>
<td>0.92</td>
<td>0.72</td>
<td>1.18</td>
</tr>
<tr>
<td>anti-T antibody (IU/mL)</td>
<td>Tdap group</td>
<td>122</td>
<td>9.5</td>
<td>Td group</td>
<td>35</td>
<td>10.0</td>
<td>Tdap group /Td group</td>
<td>0.95</td>
<td>0.73</td>
<td>1.24</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
Adjusted GMC = geometric mean antibody concentration adjusted for baseline of 001 study
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for baseline concentration - pooled variance); LL = lower limit, UL = upper limit

### Table 68  Adjusted GMC ratio between groups [Tdap group divided by Td group] and their 95% CIs for anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group description</th>
<th>N</th>
<th>Adjusted GMC</th>
<th>Group description</th>
<th>N</th>
<th>Adjusted GMC</th>
<th>Ratio order</th>
<th>Value</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-PT antibody (IU/mL)</td>
<td>Tdap group</td>
<td>119</td>
<td>82.6</td>
<td>Td group</td>
<td>34</td>
<td>66.3</td>
<td>Tdap group /Td group</td>
<td>1.25</td>
<td>0.92</td>
<td>1.68</td>
</tr>
<tr>
<td>anti-FHA antibody (IU/mL)</td>
<td>Tdap group</td>
<td>122</td>
<td>286.8</td>
<td>Td group</td>
<td>35</td>
<td>345.2</td>
<td>Tdap group /Td group</td>
<td>0.83</td>
<td>0.63</td>
<td>1.10</td>
</tr>
<tr>
<td>anti-PRN antibody (IU/mL)</td>
<td>Tdap group</td>
<td>122</td>
<td>443.1</td>
<td>Td group</td>
<td>35</td>
<td>457.1</td>
<td>Tdap group /Td group</td>
<td>0.97</td>
<td>0.68</td>
<td>1.39</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
Adjusted GMC = geometric mean antibody concentration adjusted for baseline of 001 study
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for baseline concentration - pooled variance); LL = lower limit, UL = upper limit
Figure 8 Reverse cumulative distribution curve for anti-Diphtheria antibody concentrations per group at pre and post booster vaccination time point (Total vaccinated cohort)

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
Figure 9  Reverse cumulative distribution curve for anti-Tetanus antibody concentrations per group at pre and post booster vaccination time point (Total vaccinated cohort)

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
Figure 10  Reverse cumulative distribution curve for anti-PT antibody concentrations per group at pre and post booster vaccination time point (Total vaccinated cohort)

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
Figure 11  Reverse cumulative distribution curve for anti-FHA antibody concentrations per group at pre and post booster vaccination time point (Total vaccinated cohort)

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
Figure 12  Reverse cumulative distribution curve for anti-PRN antibody concentrations per group at pre and post booster vaccination time point (Total vaccinated cohort)

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
10.3. Safety

Table 69 Compliance in returning symptom sheets (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of doses</th>
<th>Doses NOT according to protocol</th>
<th>Number of general SS</th>
<th>Compliance % general SS</th>
<th>Number of local SS</th>
<th>Compliance % local SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Td group</td>
<td>37</td>
<td>0</td>
<td>36</td>
<td>97.3</td>
<td>36</td>
<td>97.3</td>
</tr>
<tr>
<td>Tdap group</td>
<td>128</td>
<td>0</td>
<td>125</td>
<td>97.7</td>
<td>125</td>
<td>97.7</td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
SS = Symptom screens/sheets used for the collection of local and general solicited AEs
Compliance % = (number of doses with symptom screen/sheet return / number of administered doses) X 100

Table 70 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MEDDRA Primary System Organ Class and Preferred Term with medically attended visit, within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Primary System Organ Class (CODE)</th>
<th>Preferred Term (CODE)</th>
<th>Td group N = 37</th>
<th>Tdap group N = 128</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one symptom</td>
<td></td>
<td>n % 95% CI</td>
<td>n % 95% CI</td>
</tr>
<tr>
<td>Infections and infestations (10021881)</td>
<td>Bronchitis (10006451)</td>
<td>1 2.7 0.1 14.2 0.0 0.0 2.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Influenza (10022000)</td>
<td>0 0.0 0.0 9.5 1 0.8 0.0 4.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Localised infection (10024774)</td>
<td>1 2.7 0.1 14.2 0 0.0 0.0 2.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tonsillitis (10044008)</td>
<td>0 0.0 0.0 9.5 1 0.8 0.0 4.3</td>
<td></td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Cartilage injury (10007710)</td>
<td>0 0.0 0.0 9.5 1 0.8 0.0 4.3</td>
<td></td>
</tr>
<tr>
<td>(10022117)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders (10029205)</td>
<td>Migraine (10027599)</td>
<td>0 0.0 0.0 9.5 1 0.8 0.0 4.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paraesthesia (10033775)</td>
<td>0 0.0 0.0 9.5 1 0.8 0.0 4.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Syncope (10042772)</td>
<td>0 0.0 0.0 9.5 1 0.8 0.0 4.3</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders (10040785)</td>
<td>Rash maculo-papular (10037868)</td>
<td>0 0.0 0.0 9.5 1 0.8 0.0 4.3</td>
<td></td>
</tr>
</tbody>
</table>

Td group = Subjects received the first dose of Tdap vaccine
Tdap group = Subjects received a second dose of Tdap vaccine
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
11. REFERENCES


CDC, Pertussis outbreaks - United States, 2011


Centers for Disease Control and Prevention Metropolitan Atlanta Congenital Defects Program (CDC MACDP) guidelines. Birth defects and genetic diseases branch 6-digit code for reportable congenital anomalies;

EMA Guideline on the exposure to medicinal products during pregnancy: need for post-authorization data (Doc. Ref. EMEA/CHMP/313666/2005 ) ‘adopted at Community level in May 2006);

Frampton JE, Keating GM. Reduced-antigen, combined diphtheria, tetanus and acellular pertussis vaccine (*Boostrix*). *BioDrugs* 2006; 20: 371-89.


GlaxoSmithKline Biologicals Annex Report 208355 (APV) 022. Double-blind, randomised comparative assessment of the immunogenicity and reactogenicity of three different lots of GSK Biologicals’combined diphtheria, tetanus, acellular pertussis vaccine (PT 25mcg + FHA 25mcg + 69kDa 8mcg). The vaccines were administered to
healthy infants as a primary vaccination course of three consecutive doses at 3, 4 and 5 months of age. GSK Biologicals’ data on file.


12. STUDY REPORT AUTHORS /CONTRIBUTING AUTHORS

Scientific Writer: PPD

Statisticians: PPD and PPD

Study Delivery Lead: PPD

Central Safety Contacts: PPD and PPD

Clinical Research and Development Lead: PPD

Regulatory Affairs representative: PPD

Clinical and Epidemiology Project Lead: PPD
13. SERIOUS ADVERSE EVENTS

There were no SAEs reported in the study.
MODULAR APPENDICES

List of modular appendices available for the study report and ICH-specific appendices - Study Information equivalent numbering

<table>
<thead>
<tr>
<th>Modular appendices</th>
<th>ICH numbering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol and protocol amendments.</td>
<td>16.1.1</td>
</tr>
<tr>
<td>Sample Case Report form (unique pages only).</td>
<td>16.1.2</td>
</tr>
<tr>
<td>List of IECs or IRBs &amp; List of Investigators and other important participants in the study</td>
<td>16.1.3 &amp; 16.1.4</td>
</tr>
<tr>
<td>Representative written information for patient and sample consent forms.</td>
<td>16.1.3</td>
</tr>
<tr>
<td>Investigator CVs or equivalent summaries of training and experience relevant to the performance of the clinical study</td>
<td>16.1.4</td>
</tr>
<tr>
<td>Signatures of principal or coordinating investigator(s) or sponsor’s responsible medical officer, depending on the regulatory authority’s requirement</td>
<td>16.1.5</td>
</tr>
<tr>
<td>Listings of patients receiving test drug(s) /investigational product(s) from specific batches, where more than one batch was used</td>
<td>16.1.6</td>
</tr>
<tr>
<td>Randomization list (patient identification and treatment assigned).</td>
<td>16.1.7</td>
</tr>
<tr>
<td>Audit certificates</td>
<td>16.1.8</td>
</tr>
<tr>
<td>Documentation of statistical methods</td>
<td>16.1.9</td>
</tr>
<tr>
<td>Documentation of inter-laboratory standardization methods and quality assurance procedures</td>
<td>16.1.10</td>
</tr>
<tr>
<td>Publications based on the study.</td>
<td>16.1.11</td>
</tr>
<tr>
<td>Important publications referenced in the report</td>
<td>16.1.12</td>
</tr>
<tr>
<td>Individual listings</td>
<td>16.2</td>
</tr>
<tr>
<td>Case report forms (CRFs /eCRFs) CRFs /eCRFs for deaths, other SAEs and withdrawals due to adverse events</td>
<td>16.3, 16.3.1</td>
</tr>
</tbody>
</table>
Protocol and Protocol Amendments
CONFIDENTIAL
116570 (DTPA 0.3 (BOOSTRIX)-012 EXT:001)
Report Final

CONFIDENTIAL
116570 [DTPA 0.3 (BOOSTRIX)-012 EXT:001]
Protocol Amendment 2 Final

Clinical Study Protocol
Sponsor: GlaxoSmithKline Biologicals
Rue de l’Institut, 89
1330 Rixensart, Belgium

Primary Study vaccine and number
GlaxoSmithKline (GSK) Biologicals’ combined reduced antigen content diphtheria-tetanus toxoids and acellular pertussis vaccine (Tdap), Boostrix™ [776423 BIO DTPA 0.3 (BOOSTRIX)]

eTrack study number and Abbreviated Title
116570 [DTPA 0.3 (BOOSTRIX)-012 EXT:001]

Investigational New Drug (IND) number
BB-IND 8461

Date of protocol
Final: 24 May 2012

Date of protocol amendment
Amendment 1 Final: 12 October 2012
Amendment 2 Final: 03 October 2013

Title
Evaluation of immunogenicity and safety of GSK Biologicals' Tdap booster vaccine (Boostrix™) in young adults, administered 10 years after previous Tdap boosting.

Detailed Title
An open, phase III, non-randomized, multi-center study to assess the immunogenicity and safety of a booster dose of GlaxoSmithKline (GSK) Biologicals’ combined reduced antigen content diphtheria-tetanus toxoids and acellular pertussis vaccine (Boostrix™), when administered in young adults, 10 years after previous booster vaccination in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001]

Co-ordinating author
PPD Scientific Writer
eTrack study number and
Abbreviated Title
IND number
Date of protocol
Date of protocol amendment
Detailed Title
Contributing authors
(Amendment 2: 03 October 2013)

116570 [DTPA 0.3 (BOOSTRIX)-012 EXT:001]
BB-IND 8461
Final: 24 May 2012
Amendment 1 Final: 12 October 2012
Amendment 2 Final: 03 October 2013
An open, phase III, non-randomized, multi-center study to assess the immunogenicity and safety of a booster dose of GlaxoSmithKline (GSK) Biologica’s combined reduced antigen content diphtheria-tetanus toxoids and acellular pertussis vaccine (Boostrix™), when administered in young adults, 10 years after previous booster vaccination in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001]

• PPD Senior Manager, Global Vaccine Development, Combination Vaccines
• PPD Clinical Development Manager, Combination Vaccines, Global Vaccine Development
• PPD Lead, Clinical Development, Combination Vaccines-Infanrix, Boostrix, Hepatitis and Rotavirus Vaccines
• PPD Project Statistician
• PPD Global Study Manager, Harrison Clinical Research Benelux for GSK Biologica

• PPD Study Delivery Lead
• PPD Global Vaccines Clinical Laboratories Project Manager
• PPD Scientist, Biologica Clinical Safety & Pharmacovigilance
eTrack study number and Abbreviated Title
IND number
Date of protocol
Date of protocol amendment
Detailed Title
Contributing authors (Amendment 2: 03 October 2013)

An open, phase III, non-randomized, multi-center study to assess the immunogenicity and safety of a booster dose of GlaxoSmithKline (GSK) Biologicals’ combined reduced antigen content diphtheria-tetanus toxoids and acellular pertussis vaccine (Boostrix™), when administered in young adults, 10 years after previous booster vaccination in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001]

PPD Safety Physician, Biologicals Clinical Safety & Pharmacovigilance
PPD Safety Physician, Vaccines Clinical Safety & Pharmacovigilance
PPD Global Patents
PPD and Study Data Managers
PPD Global Clinical Regulatory Affairs Representative.
PPD Director, Global Regulatory Affairs
PPD US Vaccines Medical Affairs
PPD US Clinical and Medical Affairs
PPD Study Manager, Vaccines, GSK US
PPD Local Delivery Lead, Vaccines, GSK US

GSK Biologicals’ Protocol DS v 14.0

Copyright 2012-2013 the GlaxoSmithKline group of companies. All rights reserved. Unauthorized copying or use of this information is prohibited.
Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and Abbreviated Title
116570 [DTPA 0.3 (BOOSTRIX)-012 EXT:001]

IND number
BB-IND 8461

Date of protocol amendment
Amendment 2 Final: 03 October 2013

Detailed Title
An open, phase III, non-randomized, multi-center study to assess the immunogenicity and safety of a booster dose of GlaxoSmithKline (GSK) Biologicals’ combined reduced antigen content diphtheria-tetanus toxoids and acellular pertussis vaccine (Boostrix™), when administered in young adults, 10 years after previous booster vaccination in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001]

Sponsor signatory
Htay Htay Han, Director
Lead, Clinical Development, DTP Combination Vaccines and Rotavirus Vaccines

Signature

Date

For internal use only
Protocol Amendment 2 Rationale

<table>
<thead>
<tr>
<th>Amendment number:</th>
<th>Amendment 2</th>
</tr>
</thead>
</table>

**Rationale/background for changes:**
Due to slow enrollment of subjects into the study, the protocol is being amended to facilitate enrollment by:

- Extending the window period for re-vaccination from ± 6 months to ± 300 days from the Year 10 timepoint.
- Extending the recruitment period from 6 months to 14 months.

The format of non-inferiority criterion of the first co-primary objective has been updated to keep it aligned with the format of non-inferiority criterion of the second co-primary objective.

The list of contributing authors was updated for this amendment. Typographical errors have been corrected throughout the document.
Protocol Amendment 2 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals.

- To assume responsibility for the proper conduct of the study at this site.

- That I am aware of, and will comply with, ‘Good Clinical Practice’ (GCP) and all applicable regulatory requirements.

- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals’ investigational vaccine and other study-related duties and functions as described in the protocol.

- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory’s current certification or Quality Assurance procedure manual.

- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject’s legally acceptable representative.

- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).

- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.

- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator’s ownership interest in the sponsor or the investigational vaccine, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).

- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.

- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.
An open, phase III, non-randomized, multi-center study to assess the immunogenicity and safety of a booster dose of GlaxoSmithKline (GSK) Biologics’ combined reduced antigen content diphtheria-tetanus toxoids and acellular pertussis vaccine (Boostrix™), when administered in young adults, 10 years after previous booster vaccination in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001]
Sponsor Information

1. Sponsor
GlaxoSmithKline Biologicals
Rue de l’Institut, 89
1330 Rixensart, Belgium

2. Sponsor Medical Expert for the Study
Refer to the local study contact information document.

3. Sponsor Study Monitor
Refer to the local study contact information document.

4. Sponsor Study Contact for Reporting of a Serious Adverse Event
GSK Biologicals Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 8.4.2.
SYNOPSIS

Detailed Title
An open, phase III, non-randomized, multi-center study to assess the immunogenicity and safety of a booster dose of GlaxoSmithKline (GSK) Biologicals’ combined reduced antigen content diphtheria-tetanus toxoids and acellular pertussis vaccine (Boostrix™), when administered in young adults, 10 years after previous booster vaccination in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001]

Indication
Booster vaccination against diphtheria, tetanus and pertussis diseases in adults.

Rationale for the study and study design
- Rationale for the study
Currently the Advisory Committee on Immunization Practices (ACIP) of the US Centers for Disease Control and Prevention (CDC) recommends a single dose of Tdap vaccine for persons 11 years of age and older in the US. (ACIP, 2011b). Immunity to pertussis, provided by acellular pertussis vaccines is known to wane over time. Hence, it is likely that additional booster vaccinations will be needed to maintain adequate immunity. However, Tdap vaccines are only approved for use by the US Food and Drug Administration (FDA) as a single dose in adolescents and adults.

Currently in the US, no data is available on the immunogenicity and safety of Boostrix given as a second dose. This study is planned to fill the acknowledged information gap.

- Rationale for the study design
This study is a follow-up of Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001], in which children and adolescents aged 10-18 years received vaccination with either Boostrix or a control Td (reduced-antigen-content diphtheria-tetanus) vaccine (Pichichero, 2006).

The purpose of this follow-up study is to evaluate 10 years later, the persistence of antibodies against all the vaccine antigens, and to evaluate the immunogenicity and safety of a second Boostrix dose. This study will be conducted in an open-label manner since all the subjects will receive a booster dose of the study vaccine. The study is non-randomized since both the study groups will receive a single dose of Boostrix.

Subjects who were vaccinated in the 776423/001 [DTPA 0.3 (BOOSTRIX)-001] study will be invited to participate in this study.

03-OCT-2013
Objectives

(Amendment 2: 03 October 2013)

Co-Primary

- To demonstrate that a second dose of Tdap vaccine (administered to the Tdap Group) is non-inferior to a first dose of Tdap vaccine (administered to the Td Group), with respect to immune response to diphtheria and tetanus antigens.

  The criteria for meeting the above objective are defined as:

  - One month after vaccination, the lower limits of the 95% CI on the difference of the seroprotection rates [second dose of Tdap (Tdap Group) minus first dose of Tdap (Td Group)] for anti-diphtheria, anti-tetanus antibody concentrations are greater than or equal to -10% (clinical limit for non-inferiority).

- To demonstrate that a second dose of Tdap vaccine, (administered to the Tdap group) is non-inferior to a three dose series ofInfanrix vaccine in infants who received this vaccine in German household contact efficacy study APV-039, with respect to antibodies against pertussis toxoid (anti-PT), antibodies against filamentous hemagglutinin (anti-FHA) and antibodies against pertactin (anti-PRN) antibody concentrations.

  The criteria for meeting the above objective are defined as:

  - One month after vaccination, the lower limits of the 95% CI on the anti-PT, anti-FHA and anti-PRN GMC ratios (Tdap Group divided by Infanrix Group in APV-039) are greater than or equal to 0.67.

Secondary

- To assess the persistence of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 10 years after the previous booster dose of the Tdap vaccine in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].

- To assess the immunogenicity of the Tdap vaccine in terms of seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies, one month after vaccination.

- To explore the potential difference in terms of booster response* to anti-D, anti-T, anti-PT, anti-FHA and anti-PRN between the second dose of Tdap vaccine (administered to the Tdap Group) and the first dose of Tdap vaccine (administered to the Td Group).

- To explore the potential difference in terms of anti-D,
anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations between a second dose of Tdap vaccine (administered to the Tdap Group) and a first dose of Tdap vaccine (administered to the Td Group).

- To evaluate and compare the safety of a second dose of Tdap vaccine (administered to the Tdap Group) and a first dose of Tdap vaccine (administered to the Td Group), with respect to solicited symptoms (local and general), unsolicited symptoms and serious adverse events (SAEs).

Study design

(Amendment 2: 03 October 2013)

- Experimental design: A phase III, open-label, non-randomized, multi-centric, single-country study with two parallel groups.

- Duration of the study: The intended duration of the study, for each subject will be approximately one month:
  - Booster Epoch: Starting at Visit 1 (Day 0) and ending at Visit 2 (Day 30).

- Study groups:
  - Tdap Group: Subjects randomized to the Lot A, Lot B or Lot C groups in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001] will be pooled and will receive a second dose of the Tdap vaccine in this study.
  - Td Group: Subjects who had received Td vaccine in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001] will receive first dose of the Tdap vaccine in this study.

Synopsis Table 1  Study groups and epoch foreseen in the study

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>Number of subjects</th>
<th>Age (Min - Max) (age unit)</th>
<th>Epoch</th>
<th>Booster epoch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tdap Group*</td>
<td>Approximately 375</td>
<td>19 years – 30 years</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Td Group</td>
<td>Approximately 125</td>
<td>19 years – 30 years</td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

* Tdap Group (Second Tdap dose group): The subjects will receive a second dose of Tdap vaccine.
**Td Group (First Tdap dose group): The subjects will receive the first dose of Tdap vaccine.

Synopsis Table 2  Study groups and treatment foreseen in the study

<table>
<thead>
<tr>
<th>Treatment name</th>
<th>Vaccine/Product name</th>
<th>Study Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boostrix</td>
<td>Tdap</td>
<td>Tdap Group</td>
</tr>
<tr>
<td></td>
<td>Tdap</td>
<td>Td Group</td>
</tr>
</tbody>
</table>

- Control: active control.
- Vaccination schedule: A single dose of Tdap vaccine will be administered to all subjects, 10 years (± 300 days) after the previous booster vaccination in
Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].

- Treatment allocation: Non-randomized.
- Blinding: Open-label (Refer Synopsis Table 3)

### Synopsis Table 3  Blinding of study epoch

<table>
<thead>
<tr>
<th>Study Epoch</th>
<th>Blinding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Booster Epoch</td>
<td>open</td>
</tr>
</tbody>
</table>

- Sampling schedule: A blood sample of approximately 5 mL will be collected from all subjects before vaccination (Pre-Bst) and one month after vaccination (Post-Bst).
- Type of study: extension of other protocol(s) (Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].
- Data collection: electronic Case Report Form (eCRF).

### Number of subjects

Approximately 500 subjects are expected to be enrolled in this follow-up study (approximately 375 subjects in the Tdap Group and approximately 125 subjects in the Td Group).

### Endpoints

**Primary**

- Immunogenicity with respect to components of the study vaccine.
  - Anti-D and anti-T antibody concentrations \( \geq 0.1 \) IU/mL by ELISA, one month after vaccination.
  - Anti-pertussis (PT, FHA and PRN) antibodies GMCs one month after vaccination.
  - Anti-pertussis (PT, FHA and PRN) antibodies GMCs one month after the third dose of Infanrix in Study APV-039 Total Vaccinated cohort.

**Secondary**

- Immunogenicity with respect to components of the study vaccine.
  - Anti-D* and anti-T antibody concentrations \( \geq 0.1 \) IU and \( \geq 1.0 \) IU/mL by ELISA or \( \geq 0.01 \) IU/mL by Vero cell testing for subjects with post-vaccination ELISA anti-diphtheria toxoid antibody concentration < 0.1 IU/mL, prior to and one month after vaccination.
  - Anti-PT, anti-FHA and anti-PRN antibody concentrations \( \geq 5 \) EL.U/mL, anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations prior
to and one month after vaccination.

- Booster response to the diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens one month after vaccination

* Sera with ELISA concentrations < 0.1 IU/mL will be tested for neutralizing antibodies using a Vero-cell neutralization assay.

- Solicited local and general symptoms.
  - Occurrence of each solicited local and general symptoms (any and Grade 3) within 4 days (Day 0 – 3) after vaccination.
  - Occurrence of large injection site reactions (defined as swelling with a diameter > 100 mm, noticeable diffuse swelling or noticeable increase of limb circumference) within 4 days (Day 0 – 3) after vaccination.

- Unsolicited adverse events.
  - Occurrence of unsolicited AEs within 31 days (Day 0 – 30) after vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.

- Serious adverse events.
  - Occurrence of serious adverse events from the administration of the vaccine dose up to 31 days following vaccination.
TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPONSOR INFORMATION</td>
<td>8</td>
</tr>
<tr>
<td>SYNOPSIS</td>
<td>9</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>20</td>
</tr>
<tr>
<td>GLOSSARY OF TERMS</td>
<td>22</td>
</tr>
<tr>
<td>TRADEMARKS</td>
<td>26</td>
</tr>
<tr>
<td>1. INTRODUCTION</td>
<td>27</td>
</tr>
<tr>
<td>1.1. Background</td>
<td>27</td>
</tr>
<tr>
<td>1.2. Rationale for the study and study design</td>
<td>28</td>
</tr>
<tr>
<td>1.2.1. Rationale for the study</td>
<td>28</td>
</tr>
<tr>
<td>1.2.2. Rationale for the study design</td>
<td>28</td>
</tr>
<tr>
<td>2. OBJECTIVES</td>
<td>28</td>
</tr>
<tr>
<td>2.1. Co-Primary objectives</td>
<td>28</td>
</tr>
<tr>
<td>2.2. Secondary objectives</td>
<td>29</td>
</tr>
<tr>
<td>3. STUDY DESIGN OVERVIEW</td>
<td>30</td>
</tr>
<tr>
<td>4. STUDY COHORT</td>
<td>31</td>
</tr>
<tr>
<td>4.1. Number of subjects/centers</td>
<td>31</td>
</tr>
<tr>
<td>4.2. Inclusion criteria for enrolment</td>
<td>32</td>
</tr>
<tr>
<td>4.3. Exclusion criteria for enrolment</td>
<td>33</td>
</tr>
<tr>
<td>5. CONDUCT OF THE STUDY</td>
<td>34</td>
</tr>
<tr>
<td>5.1. Regulatory and ethical considerations, including the informed consent process</td>
<td>34</td>
</tr>
<tr>
<td>5.2. Subject identification and randomization of treatment</td>
<td>35</td>
</tr>
<tr>
<td>5.2.1. Subject identification</td>
<td>35</td>
</tr>
<tr>
<td>5.2.1.1. Randomization of supplies</td>
<td>35</td>
</tr>
<tr>
<td>5.2.1.2. Treatment allocation to the subject</td>
<td>35</td>
</tr>
<tr>
<td>5.2.1.2.1. Study group and treatment number allocation</td>
<td>35</td>
</tr>
<tr>
<td>5.3. Method of blinding</td>
<td>36</td>
</tr>
<tr>
<td>5.4. General study aspects</td>
<td>36</td>
</tr>
<tr>
<td>5.5. Outline of study procedures</td>
<td>37</td>
</tr>
<tr>
<td>5.6. Detailed description of study procedures</td>
<td>38</td>
</tr>
<tr>
<td>5.6.1. Informed consent</td>
<td>38</td>
</tr>
<tr>
<td>5.6.2. Check inclusion and exclusion criteria</td>
<td>38</td>
</tr>
<tr>
<td>5.6.3. Medical history</td>
<td>38</td>
</tr>
<tr>
<td>5.6.4. Vaccination history</td>
<td>38</td>
</tr>
<tr>
<td>5.6.5. Collect demographic data</td>
<td>38</td>
</tr>
<tr>
<td>5.6.6. History directed physical examination</td>
<td>38</td>
</tr>
<tr>
<td>5.6.7. Urine pregnancy test</td>
<td>39</td>
</tr>
<tr>
<td>5.6.8. Assess pre-vaccination body temperature</td>
<td>39</td>
</tr>
</tbody>
</table>
CONFIDENTIAL
116570 (DTPA 0.3 (BOOSTRIX)-012 EXT:001)
Protocol Amendment 2 Final

5.6.9. Sampling....................................................................................... 39
5.6.9.1. Blood sampling for immune response assessments ....................... 39
5.6.10. Check contraindications, warnings and precautions to vaccination .............. 39
5.6.11. Study group and treatment number allocation ........................................ 39
5.6.12. Study Vaccine administration .......................................................... 39
5.6.13. Check and record concomitant medication/vaccination and intercurrent medical conditions ........................................................................ 40
5.6.14. Recording of AEs, SAEs, pregnancies .................................................. 40
5.6.15. Study conclusion ............................................................................... 41

5.7. Biological sample handling and analysis .................................................. 41
5.7.1. Use of specified study materials .......................................................... 41
5.7.2. Biological sample .............................................................................. 42
5.7.3. Laboratory assays .............................................................................. 42
5.7.4. Biological samples evaluation .............................................................. 43
5.7.4.1. Immunological read-outs ............................................................. 43
5.7.5. Immunological correlates of protection ................................................ 43

6. STUDY VACCINE ADMINISTRATION ......................................................... 44
6.1. Description of study vaccine ..................................................................... 44
6.2. Storage and handling of study vaccine ..................................................... 44
6.3. Dosage and administration of study vaccine ............................................. 45
6.4. Replacement of unusable vaccine doses .................................................... 45
6.5. Contraindications to vaccination ............................................................. 46
6.6. Warnings and precautions ........................................................................ 46
6.7. Concomitant medication/product and concomitant vaccination ..................... 46
6.7.1. Recording of concomitant medications/products and concomitant vaccination .................................................................................. 46
6.7.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from ATP analyses .............................................. 47
6.8. Intercurrent medical conditions that may lead to elimination of a subject from ATP analyses .................................................................................. 47

7. HEALTH ECONOMICS.............................................................................. 48

8. SAFETY ....................................................................................................... 48
8.1. Safety definitions .................................................................................... 48
8.1.1. Definition of an adverse event ............................................................ 48
8.1.2. Definition of a serious adverse event ................................................... 49
8.1.3. Solicited adverse events ....................................................................... 50
8.1.3.1. Solicited local (injection-site) adverse events ..................................... 50
8.1.3.2. Solicited general adverse events ....................................................... 50
8.1.4. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events .......................................................... 50
8.2. Events or outcomes not qualifying as adverse events or serious adverse events ........................................................................................................ 51
8.2.1. Pregnancy ........................................................................................... 51
8.3. Detecting and recording adverse events, serious adverse events and pregnancies .................................................................................................. 52
8.3.1. Time period for detecting and recording adverse events, serious adverse events and pregnancies ........................................ 52
8.3.2. Post-Study adverse events and serious adverse events .......... 53
8.3.3. Evaluation of adverse events and serious adverse events ........ 54
  8.3.3.1. Active questioning to detect adverse events and serious adverse events ........................................ 54
  8.3.3.2. Assessment of adverse events ........................................ 55
     8.3.3.2.1. Assessment of intensity .................................... 55
     8.3.3.2.2. Assessment of causality ............................ 56
  8.3.3.3. Assessment of outcomes ........................................ 58
  8.3.3.4. Medically attended visits ....................................... 58

8.4. Reporting of serious adverse events, pregnancies, and other events ........................................ 58
  8.4.1. Prompt reporting of serious adverse events, pregnancies, and other events to GSK Biologicals ........................................ 58
  8.4.2. Contact information for reporting serious adverse events and other events to GSK Biologicals ........................................ 59
  8.4.3. Completion and transmission of SAE reports to GSK Biologicals ....................................................... 59
     8.4.3.1. Back-up system in case the electronic SAE reporting system does not work ........................................ 59
  8.4.4. Completion and transmission of pregnancy reports to GSK Biologicals ....................................................... 59
  8.4.5. Updating of SAE, pregnancy information after freezing of the subject’s eCRF ....................................................... 60
  8.4.6. Regulatory reporting requirements for serious adverse events ....................................................... 60

8.5. Follow-up of adverse events, serious adverse events, and pregnancies ....................................................... 60
  8.5.1. Follow-up of adverse events and serious adverse events ....................................................... 60
     8.5.1.1. Follow-up during the study .................................... 60
     8.5.1.2. Follow-up after the subject is discharged from the study ....................................................... 61
  8.5.2. Follow-up of pregnancies ........................................ 61

8.6. Treatment of adverse events ........................................ 61

8.7. Subject card ....................................................... 61

9. SUBJECT COMPLETION AND WITHDRAWAL ....................................................... 62
  9.1. Subject completion ....................................................... 62
  9.2. Subject withdrawal ....................................................... 62
     9.2.1. Subject withdrawal from the study ....................................................... 62
     9.2.2. Subject withdrawal from investigational vaccine ....................................................... 63

10. STATISTICAL METHODS ....................................................... 63
  10.1. Primary endpoint ....................................................... 63
  10.2. Secondary endpoints ....................................................... 63
  10.3. Determination of sample size ....................................................... 64
  10.4. Study cohorts/ data sets to be analyzed ....................................................... 65
     10.4.1. Total vaccinated cohort ....................................................... 65
     10.4.2. According-to-protocol cohort for analysis of safety ....................................................... 65
     10.4.3. According-to-protocol cohort for analysis of immunogenicity ....................................................... 66
  10.5. Derived and transformed data ....................................................... 66
10.6. Analysis of demographics ................................................................. 68
10.7. Analysis of immunogenicity ................................................................. 68
10.7.1. Within groups assessment .............................................................. 68
10.7.2. Between groups assessment .............................................................. 69
10.7.3. Interpretation of analyses ................................................................. 69
10.7.4. Sensitivity analysis ....................................................................... 70
10.8. Analysis of safety ........................................................................... 70
10.8.1. Within groups assessment .............................................................. 70
10.8.2. Between groups assessment .............................................................. 71
10.9. Statistical methods ........................................................................ 71
10.10. Conduct of analyses ...................................................................... 71
10.10.1. Sequence of analyses ................................................................. 71
10.10.2. Statistical considerations for interim analyses ......................... 72

11. ADMINISTRATIVE MATTERS ................................................................. 72
11.1. Remote Data Entry instructions ......................................................... 72
11.2. Study Monitoring by GSK Biologicals ............................................... 72
11.3. Record retention ............................................................................... 73
11.4. Quality assurance ......................................................................... 73
11.5. Posting of information on publicly available clinical trial registers and publication policy ......................................................... 74
11.6. Provision of study results to investigators ....................................... 74

12. COUNTRY SPECIFIC REQUIREMENTS ............................................... 74

13. REFERENCES ................................................................................... 75
<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 1</td>
<td>Study groups and epoch foreseen in the study</td>
<td>31</td>
</tr>
<tr>
<td>Table 2</td>
<td>Study groups and treatment foreseen in the study</td>
<td>31</td>
</tr>
<tr>
<td>Table 3</td>
<td>Blinding of study epoch</td>
<td>31</td>
</tr>
<tr>
<td>Table 4</td>
<td>List of study procedures</td>
<td>37</td>
</tr>
<tr>
<td>Table 5</td>
<td>Intervals between study visits</td>
<td>38</td>
</tr>
<tr>
<td>Table 6</td>
<td>Biological sample</td>
<td>42</td>
</tr>
<tr>
<td>Table 7</td>
<td>Humoral Immunity (Antibody determination)</td>
<td>42</td>
</tr>
<tr>
<td>Table 8</td>
<td>Immunological read-outs</td>
<td>43</td>
</tr>
<tr>
<td>Table 9</td>
<td>Study vaccine</td>
<td>44</td>
</tr>
<tr>
<td>Table 10</td>
<td>Dosage and administration</td>
<td>45</td>
</tr>
<tr>
<td>Table 11</td>
<td>Solicited local adverse events</td>
<td>50</td>
</tr>
<tr>
<td>Table 12</td>
<td>Solicited general adverse events</td>
<td>50</td>
</tr>
<tr>
<td>Table 13</td>
<td>Reporting periods for adverse events, serious adverse events and pregnancies</td>
<td>53</td>
</tr>
<tr>
<td>Table 14</td>
<td>Intensity scales for solicited symptoms in adults</td>
<td>55</td>
</tr>
<tr>
<td>Table 15</td>
<td>Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK Biologicals</td>
<td>58</td>
</tr>
<tr>
<td>Table 16</td>
<td>Power to demonstrate non-inferiority of second dose of Tdap vaccine to first dose of Tdap vaccine with respect to anti-D and anti-T seroprotection rate</td>
<td>64</td>
</tr>
<tr>
<td>Table 17</td>
<td>Power to demonstrate non-inferiority of second dose of Tdap vaccine to Infanrix vaccine in APV-039 with respect to anti-PT, anti-FHA and anti-PRN GMCs</td>
<td>65</td>
</tr>
<tr>
<td>Table 18</td>
<td>GSK Biologicals' laboratories</td>
<td>79</td>
</tr>
</tbody>
</table>
## LIST OF APPENDICES

<table>
<thead>
<tr>
<th>Appendix</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendix A</td>
<td>LABORATORY ASSAYS</td>
<td>78</td>
</tr>
<tr>
<td>Appendix B</td>
<td>CLINICAL LABORATORIES</td>
<td>79</td>
</tr>
<tr>
<td>Appendix C</td>
<td>AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL</td>
<td>80</td>
</tr>
</tbody>
</table>
LIST OF ABBREVIATIONS

AE: Adverse Event
ACIP: Advisory Committee on Immunization Practices
ANOVA: Analysis Of Variance
ATP: According-To-Protocol
CDC: Centers for Disease Control and Prevention
eCRF: electronic Case Report Form
EDD: Estimated Date of Delivery
EGA: Estimated Gestational Age
eTDF: electronic Temperature excursion Decision Form
ELISA: Enzyme-Linked Immunosorbent Assay
EL.U: ELISA Unit(s)
FHA: Filamentous Hemagglutinin
GMC: Geometric Mean Concentration
GCP: Good Clinical Practice
GSK: GlaxoSmithKline
IB: Investigator Brochure
ICF: Informed Consent Form
ICH: International Conference on Harmonization
IEC: Independent Ethics Committee
IMP: Investigational Medicinal Product
IDMC: Independent Data Monitoring Committee
IND: Investigational New Drug
IRB: Institutional Review Board
IU: International Unit(s)
CONFIDENTIAL
116570 (DTPA 0.3 (BOOSTRIX)-012 EXT: 001)
Protocol Amendment 2 Final

LMP: Last Menstrual Period
LSLV: Last Subject Last Visit
MedDRA: Medical Dictionary for Regulatory Activities
PRN: Pertactin
PT: Pertussis Toxoid
RCC: Reverse Cumulative Curve
RDE: Remote Data Entry
SAE: Serious Adverse Event
SBIR: Randomization System on Internet
SPC: Summary of Product Characteristics
SPM: Study Procedures Manual
Td: Reduced-antigen-content diphtheria–tetanus vaccine
Tdap: Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis
GLOSSARY OF TERMS

Adequate contraception: Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label for example:

- abstinence from penile-vaginal intercourse, when this is their preferred and usual lifestyle,
- oral contraceptives, either combined or progestogen alone,
- injectable progestogen,
- implants of etenogestrel or levonorgestrel,
- estrogenic vaginal ring,
- percutaneous contraceptive patches,
- intrauterine device or intrauterine system,
- male partner sterilization prior to the female subject’s entry into the study, and this male is the sole partner for that subject,
- The information on the male sterility can come from the site personnel’s review of the subject’s medical records; or interview with the subject on her medical history.
- male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository),
- male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository).

Adequate contraception does not apply to subjects of child bearing potential with same sex partners, when this is their preferred and usual lifestyle.

Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Blinding: A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an open-label study, no blind is used. Both the investigator and the subject know the identity of the treatment assigned.

Eligible: Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.

Epoch: An epoch is a self-contained set of consecutive timepoints or a single timepoint from a single protocol. Self-contained means that data collected for all subjects at all timepoints within that epoch allows to draw a complete conclusion to define or precise the targeted label of the product. Typical examples of epochs are primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.

eTrack: GSK’s tracking tool for clinical trials.

Evaluable: Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis (see Sections 6.7.2 and 10.4 for details on criteria for evaluable).

Immunological correlate of protection: The defined humoral antibody response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.

Investigational vaccine/product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Menarche: Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, thelarche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).

Menopause: Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile at the appropriate age e.g. > 45 years.

Primary completion date: The date that the final subject was examined or received an intervention for the purpose of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

Randomization: Process of random attribution of treatment to subjects in order to reduce bias of selection.

Seronegative subject: A seronegative subject is a subject whose antibody concentration/titer is below the assay cut-off.

Seropositive subject: A seropositive subject is a subject whose antibody concentration/titer is greater than or equal to the assay cut-off.

Site Monitor: An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.

Solicited adverse event: AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Subject: Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the vaccine(s)/product(s) or as a control.

Subject number: A unique number identifying a subject, assigned to each subject consenting to participate in the study.

Treatment: Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomization or treatment allocation.

Treatment number: A number identifying a treatment to a subject, according to the study randomization or treatment allocation.

Unsolicited adverse event: Any AE reported in addition to those solicited during the clinical study. Also any ‘solicited’ symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.
TRADEMARKS

The following trademarks are used in the present protocol.

Note: In the body of the protocol (including the synopsis), the names of the vaccines will be written without the superscript symbol ™ and in *italics*.

<table>
<thead>
<tr>
<th>Trademarks of the GlaxoSmithKline group of companies</th>
<th>Generic description</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Boostrix™</em></td>
<td>Reduced antigen content Diphtheria and Tetanus toxoids and acellular Pertussis (Tdap) vaccine</td>
</tr>
<tr>
<td><em>Infanrix™</em></td>
<td>Combined diphtheria, tetanus and acellular pertussis vaccine</td>
</tr>
</tbody>
</table>
1. INTRODUCTION

1.1. Background

Pertussis (whooping cough) is a highly contagious respiratory tract infection caused by *Bordetella pertussis*, the etiologic bacterial agent. The disease is characterized by severe coughing and spreads via respiratory droplets. WHO estimates that in 2008 about 16 million cases of pertussis were reported worldwide, 95% of which occurred in developing countries and about 195,000 children died from the disease (Black, 2010). Since the 1980s, there has been an increase in the number of reported cases of pertussis in the US, especially among 10-19 year olds and infants younger than 6 months of age. In 2010, about 27,550 cases of pertussis were reported in the US (CDC, 2011).

Waning immunity over time and the benefit of the ‘cocooning’ strategy warrants a vaccination against pertussis beyond childhood (adolescence and adulthood) (ACIP, 2011a; ACIP, 2006). Reduced antigen content diphtheria, tetanus and acellular pertussis (Tdap) vaccines have been developed predominantly for boosting adolescents and adults (Wendelboe, 2005; ACIP, 2006). According to the recent General Recommendations on Immunization, adolescents and adults ≥ 11 years of age are recommended to receive a single Tdap dose by the Advisory Committee on Immunization Practices (ACIP). It is also recommended for all adults who have or anticipate having close contact with an infant aged < 12 months, pregnant women and postpartum mothers who have not received Tdap previously (ACIP, 2011b; CDC, 2012).

GSK Biologicals’ Boostrix has been evaluated as a booster dose in adults, adolescents and children with a variety of previous vaccination and/or natural infection histories. Results obtained after immunization with the Tdap vaccine demonstrated that regardless of vaccination or natural infection history and age, local and general reactions were all within clinically acceptable ranges. In addition, the vaccine was shown to be immunogenic, since most subjects developed protective antibody concentrations against diphtheria and tetanus as well as a vaccine response against pertussis after vaccination, (Zepp, 2007; Blatter , 2009) and are comparable to other booster vaccines such as reduced-antigen-content diphtheria–tetanus vaccine (Td) vaccine (Frampton, 2006; Pichichero, 2006).

Research suggests that immunity to pertussis wanes approximately 5-10 years after childhood vaccination (Olin, 2003; Tan, 2005; Wendelboe, 2005). Decennial studies with Boostrix formulation containing 0.5 mg aluminum (Al) per dose have been conducted in Australia and Finland and these studies evaluated the persistence of antibody concentrations against diphtheria, tetanus and pertussis after a previous dose of Tdap. In these studies geometric mean concentrations (GMC) to all antigens had returned to pre-vaccination levels 10 years after the first booster dose. Following a decennial booster dose, robust increase in antibody titers against all antigens were observed irrespective of vaccination history (Booy, 2010; Mertsola, 2010). These studies were conducted in subjects who received a second dose of Boostrix as decennial booster vaccination (dTpa-039 and dTpa-040) and showed adequate immunogenicity and acceptable safety profile of the vaccine (Booy, 2010; Mertsola, 2010).
Please refer to the Prescribing Information for information regarding the potential risks and benefits of *Boostrix*.

1.2. **Rationale for the study and study design**

1.2.1. **Rationale for the study**

Currently the Advisory Committee on Immunization Practices (ACIP) of the US Center for Disease Control and Prevention (CDC) recommends a single dose of Tdap vaccine for persons 11 years of age and older in the US. (ACIP, 2011b). Immunity to pertussis, provided by acellular pertussis vaccines is known to wane over time. Hence, it is likely that additional booster vaccinations will be needed to maintain adequate immunity. However, Tdap vaccines are only approved for use as a single dose in adolescents and adults by the US Food and Drug Administration (FDA).

Currently in the US, no data is available on the immunogenicity and safety of *Boostrix* given as a second dose. This study is planned to fill the acknowledged information gap.

1.2.2. **Rationale for the study design**

This study is a follow-up of Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001], in which children and adolescents aged 10-18 years received vaccination with either *Boostrix* or a control Td vaccine (Pichichero, 2006).

The purpose of this follow-up study is to evaluate 10 years later, the persistence of antibodies against all the vaccine antigens, and to evaluate the immunogenicity and safety of a second dose of *Boostrix*. This study will be conducted in an open-label manner since all the subjects will receive a booster dose of the study vaccine. The study is non-randomized since both the study groups will receive a single dose of *Boostrix*.

Subjects who were vaccinated in the 776423/001 [DTPA 0.3 (BOOSTRIX)-001] study will be invited to participate in this study.

2. **OBJECTIVES**

2.1. **Co-Primary objectives**

*(Amendment 2: 03 October 2013)*

- To demonstrate that a second dose of Tdap vaccine (administered to the Tdap Group) is non-inferior to a first dose of Tdap vaccine (administered to the Td Group), with respect to immune response to diphtheria and tetanus antigens.

  *The criteria for meeting the above objective are defined as:*

  - One month after vaccination, **the lower limits of the 95% CI on the difference of the seroprotection rates** [second dose of Tdap (Tdap Group) minus first dose of Tdap (Td Group)] for anti-diphtheria, anti-tetanus antibody concentrations are **greater** than or equal to -10% (clinical limit for non-inferiority).
• To demonstrate that a second dose of Tdap vaccine, (administered to the Tdap group) is non-inferior to a three dose series of Infanrix vaccine in infants who received this vaccine in German household contact efficacy study APV-039, with respect to antibodies against pertussis toxoid (anti-PT), antibodies against filamentous hemagglutinin (anti-FHA) and antibodies against pertactin (anti-PRN) antibody concentrations.

The criteria for meeting the above objective are defined as:

− One month after vaccination, the lower limits of the 95%CI on the anti-PT, anti-FHA and anti-PRN GMC ratios (Tdap Group divided by Infanrix Group in APV-039) are greater than or equal to 0.67.

Refer to Section 10.1 for the definition of the co-primary endpoints.

2.2. Secondary objectives

• To assess the persistence of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 10 years after the previous booster dose of the Tdap vaccine in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].

• To assess the immunogenicity of the Tdap vaccine in terms of seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies, one month after vaccination.

• To explore the potential difference in terms of booster response* to anti-D, anti-T, anti-PT, anti-FHA and anti-PRN between the second dose of Tdap vaccine (administered to the Tdap Group) and the first dose of Tdap vaccine (administered to the Td Group).

• To explore the potential difference in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations between a second dose of Tdap vaccine (administered to the Tdap Group) and a first dose of Tdap vaccine (administered to the Td Group).

• To evaluate and compare the safety of a second dose of Tdap vaccine (administered to the Tdap group) and a first dose of Tdap vaccine (administered to the Td group), with respect to solicited symptoms (local and general), unsolicited symptoms and serious adverse events (SAEs).

Refer to Section 10.2 for the definition of the secondary endpoints.

*Refer to Section 10.5 for the definition of booster response.
3. **STUDY DESIGN OVERVIEW**

(Amendment 2: 03 October 2013)

![Diagram of study design]

N = Number of subjects planned to be enrolled; Pre-BS = Pre-vaccination blood sampling; Post-BS = Post-vaccination blood sampling.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 5.5), are essential and required for study conduct.

- **Experimental design:** A phase III, open-label, non-randomized, multi-centric, single-country study with two parallel groups.

- **Duration of the study:** The intended duration of the study, for each subject will be approximately one month;
  - Booster epoch: Starting at Visit 1 (Day 0) and ending at Visit 2 (Day 30).

- **Study groups:**
  - Tdap Group: Subjects randomized to the Lot A, Lot B or Lot C groups in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001] will be pooled and will receive a second dose of the Tdap vaccine in this study.
  - Td Group: Subjects who had received Td vaccine in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001] and will receive the first dose of Tdap vaccine in this study.
Table 1  Study groups and epoch foreseen in the study

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>Number of subjects</th>
<th>Age (Min - Max) (age unit)</th>
<th>Epoch</th>
<th>Booster epoch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tdap Group *</td>
<td>Approximately 375</td>
<td>19 years - 30 years</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Td Group**</td>
<td>Approximately 125</td>
<td>19 years - 30 years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Tdap Group (Second Tdap dose group): The subjects will receive a second dose of Tdap vaccine.
**Td Group (First Tdap dose group): The subjects will receive the first dose of Tdap vaccine.

Table 2  Study groups and treatment foreseen in the study

<table>
<thead>
<tr>
<th>Treatment name</th>
<th>Vaccine/Product name</th>
<th>Study Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boostrix</td>
<td>Tdap</td>
<td>Tdap Group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Td Group</td>
</tr>
<tr>
<td></td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

- Control: active control.
- Vaccination schedule: A single dose of Tdap vaccine will be administered to all subjects, 10 years (± 300 days) after the previous booster vaccination in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].
- Treatment allocation: Non-randomized.
- Blinding: Open-label (Refer to Table 3)

Table 3  Blinding of study epoch

<table>
<thead>
<tr>
<th>Study Epoch</th>
<th>Blinding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Booster epoch</td>
<td>open</td>
</tr>
</tbody>
</table>

- Sampling schedule: A blood sample of approximately 5 mL will be collected from all subjects before vaccination (Pre-Bst) and one month after vaccination (Post-Bst).
- Type of study: extension of other protocol(s) (Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].
- Data collection: electronic Case Report Form (eCRF).

4. STUDY COHORT

4.1. Number of subjects/centers

All centers that participated in the 776423/001 [DTPA 0.3 (BOOSTRIX)-001] study will be contacted to participate in this follow-up booster study. Approximately 500 subjects are expected to be enrolled in this follow-up study (approximately 375 subjects in the Tdap Group and approximately 125 subjects in the Td Group). Recruitment will be terminated when approximately 500 subjects have been enrolled.

At the time of initiation of the booster study, the investigators accepting to participate in the study, will contact ALL subjects who completed the primary study. The reason for non-participation in the booster study will be recorded in the study continuation screen in the eCRF. No demography data will be collected for non-participating subjects.
Overview of the recruitment plan: (Amendment 2: 03 October 2013)

− The study will take place at multiple centers in the United States of America.
− Enrolment is expected to be completed within a period of approximately 14 months.
− The study duration per subject will be approximately one month.
− The follow-up of recruitment of subjects into the study will be performed using GSK Biologicals’ central randomization system on Internet (SBIR).
− Recruitment will be monitored by the site monitor.

4.2. Inclusion criteria for enrolment

(Amendment 2: 03 October 2013)

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

All subjects must satisfy ALL the following criteria at study entry:

• Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visit).
• Subjects who have received a dose of Tdap or Td vaccines 10 years (± 300 days) back, in study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].
• Written informed consent obtained from the subject.
• Healthy subjects as established by medical history and clinical examination before entering into the study.
• Female subjects of non-childbearing potential may be enrolled in the study.
  − Non-childbearing potential is defined as pre-menarche, current tubal ligation, hysterectomy, ovariectomy or post-menopause.

Please refer to the glossary of terms for the definition of menarche and menopause.

• Female subjects of childbearing potential may be enrolled in the study, if the subject
  − has practiced adequate contraception for 30 days prior to vaccination, and
  − has a negative pregnancy test on the day of vaccination, and
  − has agreed to continue adequate contraception during the entire treatment period and for 1 month after completion of the vaccine dose.

Please refer to the glossary of terms for the definition of adequate contraception.
4.3. Exclusion criteria for enrolment

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criteria should be checked at the time of study entry. If ANY exclusion criterion applies, the subject must not be included in the study:

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the dose of study vaccine, or planned use during the study period.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs within six months prior to the booster vaccine dose. For corticosteroids, this will mean prednisone (≥ 20 mg/day for adult subjects), or equivalent. Inhaled and topical steroids are allowed.
- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before and ending 31 days after the dose of vaccine, with the exception of Influenza vaccine which is allowed throughout the study period.
- Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
- Previous vaccination against diphtheria, tetanus or pertussis since the last dose received in the Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].
- History of diphtheria, tetanus or pertussis diseases following the receipt of booster dose in the Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].
- Severe allergic reaction (e.g. anaphylaxis) after previous administration of any tetanus toxoid, diphtheria toxoid, or pertussis-antigen containing vaccines, or any component of Boostrix.
- Hypersensitivity to latex.
- Encephalopathy (e.g. coma, decreased level of consciousness, prolonged seizures) of unknown etiology occurring within 7 days following previous vaccination with pertussis-containing vaccine.
- History of any neurological disorders or seizures.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature ≥ 99.5°F for oral, axillary or tympanic route, or ≥ 100.4°F for rectal route. The preferred route for recording temperature in this study will be oral.
Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may, be enrolled at the discretion of the investigator.

- Administration of immunoglobulins and/or any blood products within the 3 months preceding the booster dose of study vaccine or planned administration during the study period.

- Pregnant or lactating female.

- Female planning to become pregnant or planning to discontinue contraceptive precautions up to 1 month post-vaccination.

5. CONDUCT OF THE STUDY

5.1. Regulatory and ethical considerations, including the informed consent process

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with the ICH Guideline for Good Clinical Practice (GCP), all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

GSK will obtain favorable opinion/approval to conduct the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a site initiating the study in that country.

Conduct of the study includes, but is not limited to, the following:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favorable opinion/approval of study protocol and any subsequent amendments.

- Subject informed consent as appropriate.

- Investigator reporting requirements as stated in the protocol.

GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.

Freely given and written informed consent must be obtained from each subject, as appropriate, prior to participation in the study.

GSK Biologicals will prepare a model Informed Consent Form (ICF) which will embody the ICH GCP and GSK Biologicals required elements. While it is strongly recommended that this model ICF is to be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgment, local regulations and requirements should guide the final structure and content of the local version of the ICF.

The investigator has the final responsibility for the final presentation of the ICF, respecting the mandatory requirements of local regulations. The ICF generated by the
investigator with the assistance of the sponsor’s representative must be acceptable to GSK Biologicals and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

5.2. **Subject identification and randomization of treatment**

5.2.1. **Subject identification**

Subjects will keep their subject number from Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001]. These subject numbers will also be used to identify blood samples collected in the study. New treatment numbers will be allocated which will be recorded in the eCRF at the vaccination visit.

5.2.1.1. **Randomization of supplies**

The randomization of supplies within blocks will be performed at GSK Biologicals, using MATerial EXcellence (MATEX), a program developed for use in Statistical Analysis System (SAS®) (Cary, NC, USA) by GSK Biologicals. Entire blocks will be shipped to the study centers/warehouse(s).

To allow GSK Biologicals to take advantage of greater rates of recruitment than anticipated at individual centers in this multi-center study and to thus reduce the overall study recruitment period, an over-randomization of supplies will be prepared.

5.2.1.2. **Treatment allocation to the subject**

The treatment numbers will be allocated by dose.

5.2.1.2.1. **Study group and treatment number allocation**

The target will be to enroll approximately 500 eligible subjects who will be assigned to two study groups- Tdap Group (subjects who received Tdap vaccine) and Td Group (subjects who received Td vaccine) according to the vaccine they received in the previous Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001]. The study group allocation is expected to be similar to previous group allocation ratio 3:1 and the enrolment will be monitored using SBIR.

After obtaining the signed and dated ICF from the subject and having checked the eligibility of the subject, the site staff in charge of the vaccine administration will access SBIR. Upon providing the subject identification number, the randomization system will provide the treatment number to be used for the vaccine dose.

The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

When SBIR is not available, please refer to the SBIR user guide or the Study Procedures Manual (SPM) for specific instructions.
5.3. **Method of blinding**

This study will be conducted in an open-label manner, where all subjects in the Tdap group and Td group will receive a dose of the same study vaccine.

The laboratory in charge of the laboratory testing will be blinded to the treatment, and codes will be used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

5.4. **General study aspects**

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SPM. The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the subjects.
### 5.5. Outline of study procedures

<table>
<thead>
<tr>
<th>Table 4</th>
<th>List of study procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Booster epoch</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Type of contact</strong></td>
<td>Visit 1</td>
</tr>
<tr>
<td><strong>Time point</strong></td>
<td>Day 0</td>
</tr>
<tr>
<td><strong>Sampling time point</strong></td>
<td>Pre-Bst#</td>
</tr>
<tr>
<td>Informed consent</td>
<td>●</td>
</tr>
<tr>
<td>Check inclusion/exclusion criteria</td>
<td>●</td>
</tr>
<tr>
<td>Medical history</td>
<td>●</td>
</tr>
<tr>
<td>Vaccination history</td>
<td>●</td>
</tr>
<tr>
<td>Record demography data *</td>
<td>●</td>
</tr>
<tr>
<td>History directed physical examination</td>
<td>●</td>
</tr>
<tr>
<td>Urine pregnancy test **</td>
<td>●</td>
</tr>
<tr>
<td>Pre-vaccination body temperature</td>
<td>●</td>
</tr>
<tr>
<td>Blood sampling</td>
<td>●</td>
</tr>
<tr>
<td>Check warnings and precautions</td>
<td>●</td>
</tr>
<tr>
<td>Study group and treatment number allocation</td>
<td>●</td>
</tr>
<tr>
<td>Recording of administered treatment number</td>
<td>●</td>
</tr>
<tr>
<td>Vaccination</td>
<td>●</td>
</tr>
<tr>
<td>Distribution of diary cards</td>
<td>O</td>
</tr>
<tr>
<td>Daily recording of solicited adverse events during the 4-day (Day 0-3) follow-up period post-vaccination, by subject</td>
<td>●</td>
</tr>
<tr>
<td>Recording of non-serious adverse events within 31 days post-vaccination, by subject</td>
<td>●</td>
</tr>
<tr>
<td>Return of diary cards</td>
<td>O</td>
</tr>
<tr>
<td>Transcription of diary cards by the investigator</td>
<td>●</td>
</tr>
<tr>
<td>Recording of any large injection site reactions in the eCRF by the investigator *</td>
<td>●</td>
</tr>
<tr>
<td>Record any concomitant medication and vaccination</td>
<td>●</td>
</tr>
<tr>
<td>Record any intercurrent medical conditions</td>
<td>●</td>
</tr>
<tr>
<td>Recording of SAEs related to study participation or to a concurrent GSK medication/vaccine</td>
<td>●</td>
</tr>
<tr>
<td>Recording of serious adverse events</td>
<td>●</td>
</tr>
<tr>
<td>Recording of pregnancies</td>
<td>●</td>
</tr>
<tr>
<td>Investigator sign-off on data</td>
<td>●</td>
</tr>
<tr>
<td>Study conclusion</td>
<td>●</td>
</tr>
</tbody>
</table>

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
# Pre-Bst: before the administration of study vaccine; Post-Bst: one month after the administration of study vaccine.
\* Only for subjects participating in the study.
\** Refer to Section 8.1.3.1 for detailed explanation on the reporting of large injection site reactions
\*Applicable to female subjects only.

It is the investigator’s responsibility to ensure that the interval between the two visits is strictly followed.
Table 5 presents the intervals between study visits.

### Table 5  Intervals between study visits

<table>
<thead>
<tr>
<th>Interval</th>
<th>Optimal length of interval ¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1 → Visit 2</td>
<td>30-48 days (at least 30 days*)</td>
</tr>
</tbody>
</table>

¹ Whenever possible the investigator should arrange study visits within this interval. An interval of 21-48 days between Visit 1 and Visit 2 will be considered for the ATP cohort of immunogenicity. Refer to Section 10.4 for the definition of the cohorts for analysis.

* If subjects return for the visits prior to 30 days, they should take home the diary card and continue to record unsolicited safety information until 30 days post-vaccination and mail/send it upon completion. Investigators will make an attempt to retrieve diary cards from subjects who have not mailed/sent them in.

#### 5.6. Detailed description of study procedures

##### 5.6.1. Informed consent

The signed informed consent of the subject must be obtained before study participation. Refer to Section 5.1 for the requirements on how to obtain informed consent, as appropriate.

##### 5.6.2. Check inclusion and exclusion criteria

Check all inclusion and exclusion criteria as described in Sections 4.2 and 4.3 before enrolment.

##### 5.6.3. Medical history

Obtain the subject’s medical history by interview and/or review of the subject’s medical records and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the study vaccination in the eCRF.

##### 5.6.4. Vaccination history

Obtain the subject’s vaccination history by interview and/or review of the subject’s medical records and record any vaccine administration within 30 days prior to the study vaccination in the eCRF.

##### 5.6.5. Collect demographic data

Record demographic data such as age at vaccination visit in years, gender, geographical ancestry and ethnicity in the subject’s eCRF only for subjects agreeing to participate in this study.

##### 5.6.6. History directed physical examination

Perform a history directed physical examination. If the investigator determines that the subject’s health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled. Collected information needs to be recorded in the eCRF.
Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

5.6.7. Urine pregnancy test

Female subjects of childbearing potential are to have a urine pregnancy test prior to any study vaccine administration. The study vaccine may only be administered if the pregnancy test is negative. Note: The urine pregnancy test must be performed even if the subject is menstruating at the time of the study visit.

5.6.8. Assess pre-vaccination body temperature

The axillary, rectal, oral or tympanic body temperature of all subjects needs to be measured prior to any study vaccine administration. The preferred route for recording temperature in this study will be oral. If the subject has fever [fever is defined as temperature ≥ 99.5°F for oral, axillary or tympanic route, or ≥ 100.4°F for rectal route] on the day of vaccination, the vaccination visit will be rescheduled within the optimal interval for this visit (see Table 5).

5.6.9. Sampling

Refer to the Module on Biospecimen Management in the SPM for detailed instructions for the collection, handling and processing of the samples.

5.6.9.1. Blood sampling for immune response assessments

Blood samples will be taken during certain study visits as specified in Section 5.5 List of Study Procedures.

- A volume of at least 5 mL of whole blood should be drawn from all subjects for each analysis of humoral immune response at each pre-defined time point. After centrifugation, serum samples should be kept at –4°F or below until shipment. Refer to the SPM for more details on sample storage conditions.

5.6.10. Check contraindications, warnings and precautions to vaccination

Contraindications, warnings and precautions to vaccination must be checked at the beginning of the vaccination visit. Refer to Sections 6.5 and 6.6 for more details.

5.6.11. Study group and treatment number allocation

Study group and treatment number allocation will be performed as described in Section 5.2.1.2. The number of each administered treatment must be recorded in the eCRF.

5.6.12. Study Vaccine administration

After completing all prerequisite procedures prior to vaccination, one dose of study vaccine will be administered intramuscularly (IM), preferably in the deltoid of the non-
dominant arm (refer to Section 6.3 for detailed description of the vaccine administration procedure). If the investigator or delegate determines that the subject’s health on the day of administration temporarily precludes vaccine administration, the visit will be rescheduled within the optimal interval for this visit (refer to Table 5).

The subjects will be observed closely for at least 30 minutes following the administration of the vaccine, with appropriate medical treatment readily available in case of anaphylaxis.

5.6.13. Check and record concomitant medication/vaccination and intercurrent medical conditions

Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 6.7.

Intercurrent medical conditions must be checked and recorded in the eCRF as described in Section 6.8.

5.6.14. Recording of AEs, SAEs, pregnancies

- Refer to Section 8.3 for procedures for the investigator to record AEs, SAEs, pregnancies. Refer to Section 8.4 for guidelines on how to submit SAE, pregnancy reports to GSK Biologicals.
- The subjects will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.
- Management of diary cards:
  After the vaccination visit, diary cards will be provided to the subject. The subjects will be instructed to record the following information in appropriate sections of the diary card:
  - Record body (oral) temperature and any solicited local/general AEs on the day of vaccination and during the next 3 days, i.e. Day (0 - 3)
  - any unsolicited AEs on the day of vaccination and during the next 30 days, i.e. Day (0 - 30)
  - any concomitant medication/vaccination given after the administration of the study vaccine.
- The subject will be instructed to return the completed diary card to the investigator at the next study visit. The completed diary card will be collected and verified during discussion with the subject at Visit 2. Any unreturned diary cards will be sought from the holder through telephone call(s) or any other convenient procedure.
5.6.15. Study conclusion

The investigator will:

- review data collected to ensure accuracy and completeness.
- complete the Study Conclusion screen in the eCRF.

At study completion, no post-trial commercial vaccines will be provided in this study.

5.7. Biological sample handling and analysis

Please refer to the SPM for details on biospecimen management (handling, storage and shipment).

Samples will not be labeled with information that directly identifies the subject but will be coded with the identification number for the subject (subject number).

Under the following circumstances, additional testing on the samples may be performed by GSK Biologicals outside the scope of this protocol:

- Collected samples may be used in other assays, for test improvement or development of analytical methods related to the study vaccine and its constituents or the disease under study.
- Collected samples may be used for purposes related to the quality assurance of data generated linked to the study vaccine or the disease under study, such as for maintenance of assays described in this protocol and comparison between analytical methods and/or laboratories.

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing will be done in line with the consent of the individual subject. Refer also to the Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

If additional testing is performed, the marker priority ranking given in Section 5.7.4 may be changed.

Collected samples will be stored for a maximum of 20 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

5.7.1. Use of specified study materials

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the
exclusion of the subject from the according to protocol (ATP) analysis (See Section 10.4 for the definition of study cohorts/ data sets to be analyzed). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, appropriate materials from the investigator’s site must be used. Refer to the Module on Clinical Trial Supplies in the SPM.

5.7.2. Biological sample

Table 6 presents the biological sample planned to be collected in the study and collection timepoints.

Table 6 Biological sample

<table>
<thead>
<tr>
<th>Sample type</th>
<th>Quantity</th>
<th>Unit</th>
<th>Timepoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>At least 5 mL</td>
<td></td>
<td>Visit 1 and Visit 2</td>
</tr>
</tbody>
</table>

5.7.3. Laboratory assays

Please refer to Appendix A for laboratory assays and Appendix B the addresses of the clinical laboratories used for sample analysis.

Refer to Table 7 for the assays used for antibody determination.

Table 7 Humoral Immunity (Antibody determination)

<table>
<thead>
<tr>
<th>System</th>
<th>Component</th>
<th>Method</th>
<th>Kit / Manufacturer</th>
<th>Unit</th>
<th>Cut-off</th>
<th>Laboratory*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>Corynebacterium diphtheriae. Diphtheria Toxoid Ab lgG</td>
<td>ELISA</td>
<td>In-house</td>
<td>IU/mL</td>
<td>.1</td>
<td>GSK Biologicals**</td>
</tr>
<tr>
<td>Serum</td>
<td>Corynebacterium diphtheriae. Diphtheria Toxoid Ab lgG</td>
<td>Neutralization assay on Vero cells***</td>
<td>In house</td>
<td>IU/mL</td>
<td>.004</td>
<td>GSK Biologicals**</td>
</tr>
<tr>
<td>Serum</td>
<td>Clostridium tetani. Tetanus Toxoid Ab lgG</td>
<td>ELISA</td>
<td>In-house</td>
<td>IU/mL</td>
<td>.1</td>
<td>GSK Biologicals**</td>
</tr>
<tr>
<td>Serum</td>
<td>Bordetella pertussis. Pertussis Toxin Ab lgG</td>
<td>ELISA</td>
<td>In-house</td>
<td>EL.U/mL</td>
<td>5</td>
<td>GSK Biologicals**</td>
</tr>
<tr>
<td>Serum</td>
<td>Bordetella pertussis. Filamentous Hemagglutinin Ab lgG</td>
<td>ELISA</td>
<td>In-house</td>
<td>EL.U/mL</td>
<td>5</td>
<td>GSK Biologicals**</td>
</tr>
<tr>
<td>Serum</td>
<td>Bordetella pertussis. Pertactin Ab lgG</td>
<td>ELISA</td>
<td>In-house</td>
<td>EL.U/mL</td>
<td>5</td>
<td>GSK Biologicals**</td>
</tr>
</tbody>
</table>

*Refer to Appendix B for the laboratory addresses.

**GSK Biologicals laboratory refers to the Global Vaccines Clinical Laboratories (GVCL) in Rixensart, Belgium; Wavre, Belgium; Laval, Canada.

***Test on Vero cells will be performed on pre-vaccination samples with concentrations < 0.1IU/mL by ELISA.
The GSK Biologicals’ clinical laboratories have established a Quality System supported by procedures. The activities of GSK Biologicals’ clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

5.7.4. Biological samples evaluation

5.7.4.1. Immunological read-outs

Table 8 Immunological read-outs

<table>
<thead>
<tr>
<th>Blood sampling timepoint</th>
<th>No. of subjects</th>
<th>Components priority rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of contact and timepoint</td>
<td>Sampling timepoint</td>
<td></td>
</tr>
<tr>
<td>Visit 1 (Day 0)</td>
<td>Pre-Bst*</td>
<td>All</td>
</tr>
<tr>
<td>Visit 2 (Month 1)</td>
<td>Post-Bst*</td>
<td>All</td>
</tr>
</tbody>
</table>

*Bst: Booster.

* Test on Vero cells will be performed on pre-vaccination samples with concentrations < 0.1 IU/mL by ELISA.

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analyzed according to priority ranking provided in Table 8.

5.7.5. Immunological correlates of protection

The following cut-offs are accepted as immunological correlates of protection:

Seroprotection for diphtheria and tetanus antigens:

- Specific antibodies against diphtheria toxoid (anti-diphtheria) and tetanus toxoid (anti-tetanus) will be measured by an ELISA developed in-house. The assay cut-offs for antibodies against diphtheria and tetanus toxoids is set at 0.1 IU/mL (ELISA), which provides a conservative estimate of the percentage of subjects deemed to be protected (Camargo, 1984; Melville-Smith, 1983).

- The cut-off of the Vero-cell assay (performed for pre-vaccination serum samples when ELISA anti-diphtheria antibody concentrations is < 0.1 IU/mL) is 0.004 IU/mL. Antibody concentrations ≥ 0.01 IU/mL are considered as protective (Camargo, 1984). The ELISA test will define the seroprotection status for the primary endpoint.

No correlate of protection is defined for the immune response to pertussis antigens. Antibodies against the pertussis components PT, FHA and PRN will be measured by an ELISA technique developed in-house. The cut-off for all three pertussis antibodies is 5 ELISA Units per mL (EL.U/mL). Subjects with antibody concentration below this cut-off will be considered seronegative (Granström, 1987; Karpinsky, 1987).

The immunological assay results will be communicated to the investigator as soon as they become available and in any case no later than 12 months after the visit date at which sampling allows the assessment of protection.
The investigator is encouraged to share the immunological assay results for non-responders with the study subjects.

For the study subjects identified as non-responders, it remains the responsibility of the study investigator in charge of the subject’s clinical management to determine the medical need for re-vaccination and to re-vaccinate the subjects as per local/regional practices.

6. STUDY VACCINE ADMINISTRATION

6.1. Description of study vaccine

The candidate vaccine to be used has been developed and manufactured by GSK Biologicals.

The Quality Control Standards and Requirements for the candidate vaccine are described in separate Quality Assurance documents (e.g. release protocols, certificate of analysis) and the required approvals have been obtained.

The vaccine is labeled and packed according to applicable regulatory requirements.

Commercial vaccine is assumed to comply with the specifications given in the manufacturer’s Summary of Product Characteristics.

Table 9 presents the composition of the study vaccine.

Table 9 Study vaccine

<table>
<thead>
<tr>
<th>Treatment name</th>
<th>Vaccine/product name</th>
<th>Formulation</th>
<th>Presentation</th>
<th>Volume</th>
<th>Number of doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boostrix</td>
<td>Tdap</td>
<td>Diphtheria toxoid: 2.5Lf, Tetanus toxoid: 5Lf, Pertussis toxoid: 8µg, Filamentous hemagglutinin: 8µg, Pertactin: 2.5µg, Aluminum as Al(OH):≤0.39 mg, Sodium chloride</td>
<td>Pre-fill syringes, Homogeneous turbid white suspension</td>
<td>0.5mL</td>
<td>1</td>
</tr>
</tbody>
</table>

6.2. Storage and handling of study vaccine

The study vaccine must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorized study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccine.
Temperature excursions must be reported in degree Celsius.

Any temperature excursion outside the range of 0.0 to +8.0°C (for +2 to +8°C/+36 to +46°F label storage condition) impacting investigational medicinal products (IMPs) must be reported in the appropriate (electronic) temperature excursion decision form (eTDF). The impacted IMPs must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the sponsor.

In case of temperature excursion below +2.0°C down to 0.0°C impacting IMP(s) there is no need to report in (e)TDF, but adequate actions must be taken to restore the +2 to +8°C/+36 to +46°F label storage temperature conditions. The impacted IMP(s) may still be administered, but the site should avoid re-occurrence of such temperature excursion. Refer to the Module on Clinical Trial Supplies in the SPM for more details on actions to take.

Refer to the Module on Clinical Trial Supplies in the SPM for details and instructions on the temperature excursion reporting and usage decision process, packaging and accountability of the study vaccine.

6.3. Dosage and administration of study vaccine

The vaccines will be administered as detailed in Table 10.

The vaccine is to be administered as a deep intramuscular injection into the deltoid muscle of the non-dominant arm*, i.e. in the left arm if the subject is right-handed or in the right arm if the subject is left-handed. Boostrix should in no circumstances be administered intravascularly.

In order to ensure proper intramuscular injection of the vaccine, a needle of 1 - 1 1/2 inch length, 25 gauge will be used (ACIP, 2011b; Zuckerman, 2000).

* Vaccination can be performed in dominant arm in case of medical indication preventing vaccination in the non-dominant arm, as judged by the investigator.

Table 10 Dosage and administration

<table>
<thead>
<tr>
<th>Type of contact and timepoint</th>
<th>Dose</th>
<th>Treatment group</th>
<th>Vaccine/product</th>
<th>Route 1</th>
<th>Site</th>
<th>Side</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1 (Day 0)</td>
<td>1</td>
<td>Tdap Group and Td Group</td>
<td>Tdap</td>
<td>IM</td>
<td>Deltoid</td>
<td>Non-dominant*</td>
</tr>
</tbody>
</table>

* Intramuscular (IM)

* Vaccination can be performed in dominant arm in case of medical indication preventing vaccination in the non-dominant arm, as judged by the investigator.

6.4. Replacement of unusable vaccine doses

In addition to the vaccine doses provided for the planned number of subjects (including over-randomization when applicable), at least 10% additional vaccine doses will be supplied to replace those that are unusable.
6.5. Contraindications to vaccination

Since this is a single dose study, contraindications to vaccination are included in the exclusion criteria. Refer to 4.3.

The following events constitute contraindications to administration of Boostrix at that point in time; if any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (see Section 5.5), or the subject may be withdrawn at the discretion of the investigator (see Section 8.5).

- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as temperature $\geq 99.5$ F for oral, axillary or tympanic route, or $\geq 100.4$ F for rectal route. The preferred route for recording temperature in this study will be oral.
  - Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever can be administered the vaccine dose.

6.6. Warnings and precautions

Refer to the approved product label/package insert of Boostrix.

6.7. Concomitant medication/product and concomitant vaccination

At each study visit/contact, the investigator should question the subject about any medication/product taken and vaccination received by the subject.

6.7.1. Recording of concomitant medications/products and concomitant vaccination

The following concomitant medications/products/vaccines must be recorded in the eCRF if administered during the indicated recording period:

- All concomitant medications/products, except vitamins and dietary supplements, administered within 30 days following the dose of study vaccine.
- Any concomitant vaccination administered in the period starting at Visit 1 (Day 0) and ending at Visit 2 (Day 30).
• Prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).
  – E.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring [fever is defined as temperature ≥ 99.5°F for oral, axillary or tympanic route, or ≥ 100.4°F for rectal route. The preferred route for recording temperature in this study will be oral.].

• Any concomitant medications/products/vaccines listed in Section 6.7.2.

• Any concomitant medication/product/vaccine relevant to a SAE* or administered at any time during the study period for the treatment of a SAE*.
  *SAEs that are required to be reported per protocol.

6.7.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from ATP analyses

The use of the following concomitant medications/products/vaccines will not require withdrawal of the subject from the study but may determine a subject’s evaluability in the ATP analysis. See Section 10.4 for study cohorts/data sets to be analyzed.

• Any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) used during the study period.

• Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days in total) during the study period up to Visit 2. For corticosteroids, this will mean prednisone ≥ 20 mg/day, or equivalent. Inhaled and topical steroids are allowed.

• A vaccine not foreseen by the study protocol administered during the period starting 30 days before the study vaccination and ending at Visit 2 (Day 30), with the exception of influenza vaccine which is allowed throughout the study period.

In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organized by the public health authorities, outside the routine immunization program, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its SPC or PI and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.

• Immunoglobulins and/or any blood products administered within 3 months preceding the dose of study vaccine or planned administration during the study period.

6.8. Intercurrent medical conditions that may lead to elimination of a subject from ATP analyses

At each study visit subsequent to the vaccination visit, it must be verified if the subject has experienced or is experiencing any intercurrent medical condition. If it is the case, the condition(s) must be recorded in the eCRF.
Subjects may be eliminated from the ATP cohort for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response or are confirmed to have an alteration of their initial immune status.

7. HEALTH ECONOMICS

Not Applicable.

8. SAFETY

The investigator or site staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE) as provided in this protocol.

Each subject will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

8.1. Safety definitions

8.1.1. Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational vaccine administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational vaccine or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with vaccine administration.
- Significant failure of expected pharmacological or biological action.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject’s previous therapeutic regimen).
AEs to be recorded as endpoints (solicited AEs) are described in Section 8.1.3. All other AEs will be recorded as UNSOLICITED AEs.

Examples of an AE DO NOT include:

- Medical or surgical procedures (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE/SAE.
- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Pre-existing conditions or signs and/or symptoms present in a subject prior to the first study vaccination. These events will be recorded in the medical history section of the eCRF.

8.1.2. Definition of a serious adverse event

A serious adverse event is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

Note: The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c. Requires hospitalization or prolongation of existing hospitalization,

Note: In general, hospitalization signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or in an out-patient setting. Complications that occur during hospitalization are also considered AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event will also be considered serious. When in doubt as to whether ‘hospitalization’ occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

d. Results in disability/incapacity, OR

Note: The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect in the offspring of a study subject.
Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

8.1.3. Solicited adverse events

8.1.3.1. Solicited local (injection-site) adverse events

The following local (injection-site) AEs will be solicited:

<table>
<thead>
<tr>
<th>Table 11  Solicited local adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain at injection site</td>
</tr>
<tr>
<td>Redness at injection site</td>
</tr>
<tr>
<td>Swelling at injection site</td>
</tr>
</tbody>
</table>

N.B. If subjects observe any large injection site reaction (defined as swelling with a diameter > 100 mm, noticeable diffuse swelling or noticeable increase of limb circumference), they will be asked to contact study personnel and to visit the investigator's office and/or home visit for evaluation as soon as possible. The investigator will record detailed information describing the adverse event on a specific large injection site reaction in the eCRF.

8.1.3.2. Solicited general adverse events

The following general AEs will be solicited:

<table>
<thead>
<tr>
<th>Table 12  Solicited general adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Gastrointestinal symptoms †</td>
</tr>
<tr>
<td>Headache</td>
</tr>
</tbody>
</table>

†Gastrointestinal symptoms include nausea, vomiting, diarrhea and/or abdominal pain.

Note: Temperature will be recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature will be recorded in the eCRF.

8.1.4. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

In absence of diagnosis, abnormal laboratory findings (e.g. clinical chemistry, hematology, urinalysis, serology, cultures) or other abnormal assessments (e.g. vital signs electrocardiograms, X-rays, MRI, CT scans, etc) that are judged by the investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE
or SAE (refer to Sections 8.1.1 and 8.1.2). Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject’s condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8.2. Events or outcomes not qualifying as adverse events or serious adverse events

8.2.1. Pregnancy

Female subjects who become pregnant after the vaccination may continue the study at the discretion of the investigator.

While pregnancy itself is not considered an AE or SAE, any adverse pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an AE or a SAE.

Note: The pregnancy itself should always be recorded on an electronic pregnancy report.

The following should always be considered as SAE and will be reported as described in Sections 8.4.1 and 8.4.3:

- Spontaneous pregnancy loss, including:
  - spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation)
  - ectopic and molar pregnancy
  - stillbirth (intrauterine death of fetus after 22 weeks of gestation).

Note: the 22 weeks cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure (EMA, 2006). It is recognized that national regulations might be different.

- Any early neonatal death (i.e. death of a live born infant occurring within the first 7 days of life).

- Any congenital anomaly or birth defect [as per (CDC MACDP) guidelines] identified in the offspring of a study subject (either during pregnancy, at birth or later) regardless of whether the fetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related to the investigational vaccine will be reported
to GSK Biologicals as described in Section 8.4.3. While the investigator is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

8.3. **Detecting and recording adverse events, serious adverse events and pregnancies**

8.3.1. **Time period for detecting and recording adverse events, serious adverse events and pregnancies**

All AEs starting within 30 days following administration of the dose of study vaccine must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The time period for collecting and recording SAEs will begin at the receipt of study vaccine and will end on Day 30 following administration of the dose of study vaccine for each subject. See Section 8.4 for instructions on reporting of SAEs.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the receipt of study vaccine.

In addition to the above-mentioned reporting requirements and in order to fulfill international reporting obligations, SAEs that are related to study participation (i.e. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged from the study.

The time period for collecting and recording pregnancies will begin at the receipt of study vaccine and will end on Day 30 following administration of the dose of study vaccine. See section 8.4 for instructions on reporting of pregnancies.
An overview of the protocol-required reporting periods for AEs, SAEs, and pregnancies is given in Table 13.

### Table 13 Reporting periods for adverse events, serious adverse events and pregnancies

<table>
<thead>
<tr>
<th>Event</th>
<th>Pre-vacc (consent obtained)</th>
<th>Vaccination (Day 0)</th>
<th>4 days (Day 0-3) post vacc</th>
<th>31 days (Day 0-30) post vacc</th>
<th>Study conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solicited local and general AEs including large injection site reactions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unsolicited AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEs/SAEs leading to withdrawal from the study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAEs related to study participation or concurrent GSK medication/vaccination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

vacc: vaccination

### 8.3.2. Post-Study adverse events and serious adverse events

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 13. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational vaccine/product, the investigator will promptly notify the Study Contact for Reporting SAEs.
8.3.3. Evaluation of adverse events and serious adverse events

8.3.3.1. Active questioning to detect adverse events and serious adverse events

As a consistent method of collecting AEs, the subject should be asked a non-leading question such as:

‘Have you felt different in any way since receiving the vaccine or since the previous visit?’

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the eCRF. The investigator is not allowed to send photocopies of the subject’s medical records to GSK Biologicals instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.
8.3.3.2. Assessment of adverse events

8.3.3.2.1. Assessment of intensity

The intensity of the following solicited AEs will be assessed as described:

**Table 14 Intensity scales for solicited symptoms in adults**

<table>
<thead>
<tr>
<th>Adults</th>
<th>Adverse Event</th>
<th>Intensity grade</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pain at injection site</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Pain at injection site</td>
<td>1</td>
<td>Mild: Any pain neither interfering with nor preventing normal every day activities.</td>
</tr>
<tr>
<td></td>
<td>Pain at injection site</td>
<td>2</td>
<td>Moderate: Painful when limb is moved and interferes with every day activities.</td>
</tr>
<tr>
<td></td>
<td>Pain at injection site</td>
<td>3</td>
<td>Severe: Significant pain at rest. Prevents normal every day activities.</td>
</tr>
<tr>
<td></td>
<td>Redness at injection site</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Redness at injection site</td>
<td>1</td>
<td>Mild: Redness that is easily tolerated</td>
</tr>
<tr>
<td></td>
<td>Redness at injection site</td>
<td>2</td>
<td>Moderate: Redness that interferes with normal activity</td>
</tr>
<tr>
<td></td>
<td>Redness at injection site</td>
<td>3</td>
<td>Severe: Redness that prevents normal activity</td>
</tr>
<tr>
<td></td>
<td>Swelling at injection site</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Swelling at injection site</td>
<td>1</td>
<td>Mild: Swelling that is easily tolerated</td>
</tr>
<tr>
<td></td>
<td>Swelling at injection site</td>
<td>2</td>
<td>Moderate: Swelling that interferes with normal activity</td>
</tr>
<tr>
<td></td>
<td>Swelling at injection site</td>
<td>3</td>
<td>Severe: Swelling that prevents normal activity</td>
</tr>
<tr>
<td></td>
<td>Fever*</td>
<td>0</td>
<td>Record temperature in °C/F</td>
</tr>
<tr>
<td></td>
<td>Fever*</td>
<td>1</td>
<td>Record greatest surface diameter in mm</td>
</tr>
<tr>
<td></td>
<td>Fever*</td>
<td>2</td>
<td>Record greatest surface diameter in mm</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal symptoms (nausea, vomiting, diarrhea and/or abdominal pain)</td>
<td>0</td>
<td>Gastrointestinal symptoms normal</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal symptoms (nausea, vomiting, diarrhea and/or abdominal pain)</td>
<td>1</td>
<td>Mild: Gastrointestinal symptoms that are easily tolerated</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal symptoms (nausea, vomiting, diarrhea and/or abdominal pain)</td>
<td>2</td>
<td>Moderate: Gastrointestinal symptoms that interfere with normal activity</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal symptoms (nausea, vomiting, diarrhea and/or abdominal pain)</td>
<td>3</td>
<td>Severe: Gastrointestinal symptoms that prevent normal activity</td>
</tr>
</tbody>
</table>

*Fever is defined as temperature ≥ 99.5°F for oral, axillary or tympanic route, or ≥ 100.4°F for rectal route. The preferred route for recording temperature in this study will be oral.

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals as follows:

<table>
<thead>
<tr>
<th>0</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≤ 20 mm</td>
</tr>
<tr>
<td>2</td>
<td>&gt; 20 mm and ≤ 50 mm</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 50 mm</td>
</tr>
</tbody>
</table>
The maximum intensity of fever will be scored at GSK Biologicals as follows:

<table>
<thead>
<tr>
<th>Oral/Axillary</th>
<th>0 : &lt; 99.5°F</th>
<th>1 : ≥ 99.5°F and ≤ 100.4°F</th>
<th>2 : &gt; 100.4°F and ≤ 102.2°F</th>
<th>3 : &gt; 102.2°F</th>
</tr>
</thead>
</table>

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the investigator’s clinical judgment.

The intensity should be assigned to one of the following categories:

1 (mild) = An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

2 (moderate) = An AE which is sufficiently discomforting to interfere with normal everyday activities.

3 (severe) = An AE which prevents normal, everyday activities. 
(In adults such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy.)

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as ‘serious’ when it meets one of the pre-defined outcomes as described in Section 8.1.2.

8.3.3.2. Assessment of causality

The definitions for ‘NO’ and ‘YES’ have been written in such a way that all events that have been attributed a ‘NO’ can be pooled with events which in the primary vaccination study were determined to be ‘not related’ or ‘unlikely to be related’ to vaccination. Those events that are attributed a ‘YES’ can be pooled with those events that in the past were determined to have a ‘suspected’ or ‘probable’ relationship to vaccination in the primary vaccination study.

The investigator is obligated to assess the relationship between investigational vaccine/product and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational vaccine/product will be considered and investigated. The investigator will also consult the IB and PI for marketed products to determine his/her assessment.
There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the SAE report to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information and update the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

In case of concomitant administration of multiple vaccines/products, it may not be possible to determine the causal relationship of general AEs to the individual vaccines/products administered. The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines/products.

All solicited local (injection site) reactions will be considered causally related to vaccination. Causality of all other AEs should be assessed by the investigator using the following question:

*Is there a reasonable possibility that the AE may have been caused by the investigational vaccine/product?*

**YES** : There is a reasonable possibility that the vaccine(s) contributed to the AE.

**NO** : There is no reasonable possibility that the AE is causally related to the administration of the study vaccine(s). There are other, more likely causes and administration of the study vaccine(s) is not suspected to have contributed to the AE.

If an event meets the criteria to be determined as ‘serious’ (see Section 8.1.2), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the vaccine, if applicable.
- Erroneous administration.
- Other cause (specify).
8.3.3.3. **Assessment of outcomes**

The investigator will assess the outcome of all unsolicited AEs (including SAEs) recorded during the study as:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

8.3.3.4. **Medically attended visits**

For each solicited and unsolicited symptom the subject experiences, will be asked if the subject received medical attention defined as hospitalization, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the eCRF.

8.4. **Reporting of serious adverse events, pregnancies, and other events**

8.4.1. **Prompt reporting of serious adverse events, pregnancies, and other events to GSK Biologicals**

SAEs that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 15, once the investigator determines that the event meets the protocol definition of a SAE.

Pregnancies that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 15, once the investigator becomes aware of the pregnancy.

**Table 15  Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK Biologicals**

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Initial Reports</th>
<th>Follow-up of Relevant Information on a Previous Report</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Timeframe</td>
<td>Documents</td>
</tr>
<tr>
<td>SAEs</td>
<td>24 hours*</td>
<td>Electronic SAE report</td>
</tr>
<tr>
<td>Pregnancies</td>
<td>2 weeks*</td>
<td>Electronic pregnancy report</td>
</tr>
</tbody>
</table>

* Timeframe allowed after receipt or awareness of the information.
8.4.2. Contact information for reporting serious adverse events and other events to GSK Biologicals

<table>
<thead>
<tr>
<th>Back-up Study Contact for Reporting SAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>24/24 hour and 7/7 day availability:</td>
</tr>
<tr>
<td>GSK Biologicals Clinical Safety &amp; Pharmacovigilance</td>
</tr>
<tr>
<td>Fax: PPD or PPD Back-up</td>
</tr>
<tr>
<td>Study Contact for USA for Reporting SAEs US Safety CSA</td>
</tr>
<tr>
<td>Fax: PPD Tel: PPD</td>
</tr>
</tbody>
</table>

8.4.3. Completion and transmission of SAE reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator (or designate) must complete the information in the electronic SAE report WITHIN 24 HOURS. The SAE report will always be completed as thoroughly as possible with all available details of the event. Even if the investigator does not have all information regarding a SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report.

8.4.3.1. Back-up system in case the electronic SAE reporting system does not work

If the electronic SAE reporting system does not work, the investigator (or designate) must complete, then date and sign a paper SAE report and fax it to the GSK Biologicals Clinical Safety and Pharmacovigilance department within 24 hours.

This back-up system should only be used if the electronic SAE reporting system is not working and NOT if the system is slow. As soon as the electronic SAE reporting system is working again, the investigator (or designate) must complete the electronic SAE report within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic SAE reporting system.

8.4.4. Completion and transmission of pregnancy reports to GSK Biologicals

Once the investigator becomes aware that a subject is pregnant, the investigator (or designate) must complete the required information onto the electronic pregnancy report WITHIN 2 WEEKS.

Note: Conventionally, the estimated gestational age (EGA) of a pregnancy is dated from the first day of the last menstrual period (LMP) of the cycle in which a woman conceives. If the LMP is uncertain or unknown, dating of EGA and the estimated date of delivery
(EDD) should be estimated by ultrasound examination and recorded in the pregnancy report.

8.4.5. Updating of SAE, pregnancy information after freezing of the subject’s eCRF

When additional SAE, pregnancy, information is received after freezing of the subject’s eCRF, new or updated information should be recorded on a paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the GSK Biologics Clinical Safety and Pharmacovigilance department or to the Study Contact for Reporting SAEs (refer to the Sponsor Information Sheet) within the designated reporting time frames specified in Table 15.

8.4.6. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.4.1. GSK Biologics has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

Investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to the investigational vaccine/product and unexpected. The purpose of the report is to fulfill specific regulatory and GCP requirements, regarding the product under investigation.

8.5. Follow-up of adverse events, serious adverse events, and pregnancies

8.5.1. Follow-up of adverse events and serious adverse events

8.5.1.1. Follow-up during the study

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide additional relevant information on the subject’s condition to GSK Biologics (within 24 hours for SAEs; refer to Table 15).

All SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the end of the study.

All AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 30 days after the vaccination.
8.5.1.2. Follow-up after the subject is discharged from the study

The investigator will follow subjects:

- with SAEs, or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilized, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.

If the investigator receives additional relevant information on a previously reported SAE, he/she will provide this information to GSK Biologicals using a paper SAE and/or pregnancy report as applicable.

GSK Biologicals may request that the investigator performs or arranges the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognized follow-up period, GSK Biologicals will be provided with any available post-mortem findings, including histopathology.

8.5.2. Follow-up of pregnancies

Pregnant subjects will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK Biologicals using the electronic pregnancy report and the SAE report if applicable. Generally, the follow-up period doesn’t need to be longer than six to eight weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs for this study, if the pregnancy outcome is a SAE, it should always be reported as SAE.

8.6. Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the subject’s eCRF (refer to Section 6.7).

8.7. Subject card

Study subjects must be provided with the address and telephone number of the main contact for information about the clinical study.

The investigator (or designate) must therefore provide a “subject card” to each subject. In an emergency situation this card serves to inform the responsible attending physician that the subject is in a clinical study and that relevant information may be obtained by contacting the investigator.

Subjects must be instructed to keep subject cards in their possession at all times.
9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

A subject who returns for the concluding visit/is available for the concluding contact foreseen in the protocol is considered to have completed the study.

9.2. Subject withdrawal

Withdrawals will not be replaced.

9.2.1. Subject withdrawal from the study

From an analysis perspective, a ‘withdrawal’ from the study refers to any subject who did not come back for the concluding visit/was not available for the concluding contact foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject is considered a ‘withdrawal’ from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Investigators will make an attempt to contact those subjects who do not return for scheduled visits or follow-up.

Information relative to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a subject from the study was made by the subject himself/herself, or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Non-serious adverse event.
- Protocol violation (specify).
- Consent withdrawal, not due to an adverse event*.
- Moved from the study area.
- Lost to follow-up.
- Other (specify).

*In case a subject is withdrawn from the study because he/she has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject, in the CRF.

Subjects who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will
9.2.2. **Subject withdrawal from investigational vaccine**

Not applicable, since this is a single dose study.

**10. STATISTICAL METHODS**

**10.1. Primary endpoint**

- Immunogenicity with respect to components of the study vaccine.
  - Anti-D and anti-T antibody concentrations \( \geq 0.1 \text{ IU/mL} \) by ELISA, one month after vaccination.
  - Anti-pertussis (PT, FHA and PRN) antibodies GMCs one month after vaccination.
  - Anti-pertussis (PT, FHA and PRN) antibodies GMCs one month after the third dose of *Infanrix* in Study APV-039 Total Vaccinated cohort.

**10.2. Secondary endpoints**

- Immunogenicity with respect to components of the study vaccine.
  - Anti-D* and anti-T antibody concentrations \( \geq 0.1 \text{ IU} \) and \( \geq 1.0 \text{ IU/mL} \) by ELISA or \( \geq 0.01 \text{ IU/ml} \) by Vero cell testing for subjects with post-vaccination ELISA anti-diphtheria toxoid antibody concentration \( < 0.1 \text{ IU/mL} \), prior to and one month after vaccination.
  - Anti-PT, anti-FHA and anti-PRN antibody concentrations \( \geq 5 \text{ EL.U/mL} \), anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations prior to and one month after vaccination.
  - Booster response to the diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens one month after vaccination

* Sera with ELISA concentrations \( < 0.1 \text{ IU/mL} \) will be tested for neutralizing antibodies using a Vero-cell neutralization assay.

- Solicited local and general symptoms.
  - Occurrence of each solicited local and general symptoms (any and Grade 3) within 4 days (Day 0 – 3) after vaccination.
  - Occurrence of large injection site reactions (defined as swelling with a diameter > 100 mm, noticeable diffuse swelling or noticeable increase of limb circumference) within 4 days (Day 0 - 3) after vaccination.

- Unsolicited adverse events.
  - Occurrence of unsolicited AEs within 31 days (Day 0 – 30) after vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
• Serious adverse events.
  – Occurrence of serious adverse events from the administration of the vaccine dose up to 31 days following vaccination.

10.3. **Determination of sample size**

The sample size estimation for the immunogenicity cohort is based on the co-primary objectives below:

• Non-inferiority of the second dose of Tdap vaccine, administered to young adults 10 years after the previous booster dose of the same vaccine, to the first booster dose of Tdap vaccine administered to young adults 10 years after a previous booster dose of Td vaccine, with respect to anti-D and anti-T seroprotection rates (antibody concentration ≥ 0.1 IU/mL by ELISA);

• Non-inferiority of the second dose of Tdap vaccine to the primary *Infanrix* vaccination series in the Study APV-039, with respect to anti-pertussis (PT, FHA and PRN) antibody response.

*Table 16* and *Table 17* show the power to demonstrate non-inferiority between second Tdap and first Tdap/*Infanrix* with respect to each of the five antibodies. With 100 evaluable subjects in the Td Group and 300 evaluable subjects in the Tdap Group, the study would have an overall power of 97% to meet both co-primary objectives simultaneously.

Assuming 20% subjects who give blood samples may be non-evaluable, the study will need to take blood samples from at least 500 young adults, i.e. 125 subjects in Td Group and 375 subjects in Tdap Group assuming group allocation ratio would be similar to that of the primary study.

*Table 16* **Power to demonstrate non-inferiority of second dose of Tdap vaccine to first dose of Tdap vaccine with respect to anti-D and anti-T seroprotection rate**

<table>
<thead>
<tr>
<th>Endpoint (antibody concentration &gt;0.1 IU/mL)</th>
<th>DTPA 0.3 (BOOSTRIX)-007 (Boostrix sub-group 19-29)</th>
<th>Non-inferiority criterion Difference(2nd dose- 1st dose)</th>
<th>Power* to reject H0: LL of 95%CI of difference &lt; -10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-D</td>
<td>99.4%</td>
<td>LL of 95% CI ≥ -10%</td>
<td>&gt;99.99%</td>
</tr>
<tr>
<td>Anti-T</td>
<td>99.8%</td>
<td>LL of 95% CI ≥ -10%</td>
<td>&gt;99.99%</td>
</tr>
<tr>
<td>Overall power**</td>
<td></td>
<td></td>
<td>99.99%</td>
</tr>
</tbody>
</table>

*Pass 2005, non-inferiority test on 2 independent proportions (Miettinen & Nurminen), alpha=2.5%; non-inferiority margin=10% power under alternative of equal proportions in both groups; LL= lower limit.

**Overall power is the probability to reject all null hypotheses simultaneously, computed by subtracting the sum of individual type-II errors (beta) from 1.
Table 17  Power to demonstrate non-inferiority of second dose of Tdap vaccine to *Infanrix* vaccine in APV-039 with respect to anti-PT, anti-FHA and anti-PRN GMCs

<table>
<thead>
<tr>
<th>Endpoint (GMCs)</th>
<th>Reference values (Standard Deviation of log10 transformed concentration)</th>
<th>Power* to reject H0: LL of 95%CI of GMC ratio (Tdap/Infanrix) &lt; 0.67</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTPA 0.3 (BOOSTRIX)-007 (Boostrix sub-group 19-29)</td>
<td>APV-039 <em>Infanrix</em></td>
</tr>
<tr>
<td>Anti-PT</td>
<td>0.464</td>
<td>0.306</td>
</tr>
<tr>
<td>Anti-FHA</td>
<td>0.374</td>
<td>0.370</td>
</tr>
<tr>
<td>Anti-PRN</td>
<td>0.645</td>
<td>0.413</td>
</tr>
<tr>
<td>Overall power**</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Pass 2005, non-inferiority test on 2 independent means, alpha=2.5%; equivalence margin=\(\log_{10}(0.67)\), variance from DTPA 0.3 (BOOSTRIX)-007 was considered as common variance for both groups, power under alternative of equal means in both groups; LL= lower limit.

**Overall power is the probability to reject the primary objective and all three null hypotheses simultaneously, computed by subtracting the sum of the three type-II errors (beta) from 1.

10.4. Study cohorts/ data sets to be analyzed

Three cohorts are defined for the purpose of analysis:

- The Total vaccinated cohort (TVC).
- ATP cohort for analysis of safety.
- ATP cohort for analysis of immunogenicity.

10.4.1. Total vaccinated cohort

The TVC will include all subjects with a study vaccine administration dose documented:

- A safety analysis based on the TVC will include all vaccinated subjects.
- An immunogenicity analysis based on the TVC will include all vaccinated subjects for whom immunogenicity results are available.

10.4.2. According-to-protocol cohort for analysis of safety

The ATP cohort for analysis of safety will include all eligible and vaccinated subjects

- Who have received the dose of study vaccine.
- For whom administration site of study vaccine is known.
- Who did not receive a vaccine leading to elimination from an ATP analysis as listed in Section 6.7.2.
10.4.3. **According-to-protocol cohort for analysis of immunogenicity**

The ATP cohort for analysis of immunogenicity will include all evaluable subjects from the ATP cohort for analysis of safety:

- Who meet all eligibility criteria.
- Who comply with the procedures and intervals defined in the protocol (refer to Table 5).
- Who do not meet any of the criteria for elimination from an ATP analysis (refer to Section 6.7.2) during the study.
- Who did not receive a product leading to elimination from an ATP analysis as listed in Section 6.7.2.
- Who did not present with a medical condition leading to elimination from an ATP analysis, before the visit 2 blood sample as listed in Section 6.8.
- For whom data concerning immunogenicity endpoint measures are available. This will include subjects for whom assay results are available for antibodies against at least one study vaccine antigen component after vaccination.

10.5. **Derived and transformed data**

- **Immunogenicity**
  - The cut-off value is defined by the laboratory before the analysis and is described in Section 5.7.3.
  - A seronegative subject is a subject whose titer is below the cut-off value.
  - A seropositive subject is a subject whose titer is greater than or equal to the cut-off value.
  - Seropositivity for anti-PT, anti-FHA or anti-PRN is defined as $\geq 5$ El.U/mL.
- A seroprotected subject is a subject whose antibody concentration/titer is greater than or equal to the level defining clinical protection. The following seroprotection thresholds are applicable:
  - Anti-D antibody concentrations $\geq 0.1$ IU/mL.
  - Anti-T antibody concentrations $\geq 0.1$ IU/mL.
- Other cut-offs to be considered:
  - Anti-D antibody concentrations $\geq 1.0$ IU/mL.
  - Anti-T antibody concentrations $\geq 1.0$ IU/mL.
- Booster response to D and T antigens is defined as:
  - for initially seronegative subjects (pre-vaccination concentration below cut-off: $< 0.1$ IU/mL): antibody concentrations at least four times the cut-off (post-vaccination concentration $\geq 0.4$ IU/mL) one month after vaccination, and...
– for initially seropositive subjects (pre-vaccination concentration ≥ 0.1 IU/mL): an increase in antibody concentrations of at least four times the pre-vaccination concentration one month after vaccination.

• Booster response to PT, FHA and PRN antigens is defined as:
  – for subjects with pre-vaccination antibody concentration < 5 EL.U/mL: antibody concentration ≥ 20 EL.U/mL one month after vaccination;
  – for subjects with pre-vaccination antibody concentration ≥ 5 EL.U/mL and < 20 EL.U/mL: antibody concentration at least four times the pre-vaccination concentration one month after vaccination; and
  – for subjects with pre-vaccination antibody concentration ≥ 20 EL.U/mL: antibody concentration at least two times the pre-vaccination concentration, one month after vaccination.

• Alternative Booster response to D and T antigens is defined as:
  – for subjects with pre-vaccination antibody concentration < 5 EL.U/mL: antibody concentration ≥ 20 EL.U/mL one month after vaccination;
  – for subjects with pre-vaccination antibody concentration ≥ 5 EL.U/mL and < 20 EL.U/mL: antibody concentration at least four times the pre-vaccination concentration one month after vaccination; and
  – for subjects with pre-vaccination antibody concentration ≥ 20 EL.U/mL: antibody concentration at least two times the pre-vaccination concentration, one month after vaccination.

• Alternative Booster response to PT, FHA and PRN antigens is defined as:
  – for subjects with pre-vaccination antibody concentration in Boostrix-001 study < 5 EL.U/mL: antibody concentration ≥ 20 EL.U/mL one month after vaccination;
  – for subjects with pre-vaccination antibody concentration in Boostrix-001 study ≥ 5 EL.U/mL and < 20 EL.U/mL: antibody concentration at least four times the pre-vaccination concentration one month after vaccination; and
  – for subjects with pre-vaccination antibody concentration in Boostrix-001 study ≥ 20 EL.U/mL: antibody concentration at least two times the pre-vaccination concentration, one month after vaccination.

• The Geometric Mean Concentrations (GMC) calculations are performed by taking the anti-log of the mean of the log concentration/titer transformations. Antibody concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC calculation.

Handling of missing data:

Immunogenicity:

• For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.
Reactogenicity and Safety:

- For a given subject and the analysis of solicited symptom within 4 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the TVC will include only vaccinated subjects and doses with documented safety data (i.e. symptom screen completed).

- For analysis of unsolicited adverse events, such as serious adverse events or adverse events by primary MedDRA term, and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.

- For summaries reporting both solicited and unsolicited adverse events, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.

10.6. Analysis of demographics

Demographic characteristics (age at vaccination visit in years, gender, geographical ancestry and ethnicity) will be summarized by group using descriptive statistics:

- Frequency tables will be generated for categorical variable such as center.
- Mean, median, standard deviation will be provided for continuous data such as age.

In addition, a summary of the tracking log-sheet documenting outcomes of the contacts made with subjects for enrolment will be provided.

10.7. Analysis of immunogenicity

The primary analysis will be based on the ATP cohort for analysis of immunogenicity. If, in any vaccine group, the percentage of vaccinated subjects with serological results excluded from the ATP cohort for analysis of immunogenicity is 5% or more, a second analysis based on the TVC will be performed to complement the ATP analysis.

10.7.1. Within groups assessment

For each group and each antigen:

- Seropositivity-seroprotection rate at pre-vaccination, one month post-vaccination will be calculated with exact 95% confidence intervals (CIs).
- GMCs or at pre-vaccination, one month post-vaccination will be tabulated with 95% CIs.
- Booster response rate one month post-vaccination will be calculated with exact 95% CIs.
• Antibody concentrations distribution at pre-vaccination and one month post-vaccination will be displayed using reverse cumulative curves (RCC).

10.7.2. Between groups assessment

• For anti-D, anti-T seroprotection rates, the two-sided standardized asymptotic 95% CI for the group differences (Tdap Group – Td Group) will be calculated.

• For anti-D, anti-T antibody response, the two-sided 95% CIs of the GMC ratios between subjects in the Tdap Group and (divided by) the Td Group one month after vaccination will be computed using an analysis of variance (ANOVA) model on the logarithm_{10} transformation of the concentrations adjusted to pre-vaccination titer in Boostrix-001.

• For anti-PT, anti-FHA and anti-PRN antibody response, the two-sided 95% CIs of the GMC ratios between subjects in the Tdap Group and (divided by) the Infanrix Group in APV-039 one month after vaccination (one month after vaccination for Tdap Group, one month after the third dose of Infanrix for Infanrix group in APV-039) will be computed using an ANOVA model on the logarithm_{10} transformation of the concentrations.

• For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN booster response, the two-sided standardized asymptotic 95% CI for the group differences (Td Group - Td Group) will be calculated.

• For anti-PT, anti-FHA and anti-PRN antibody response, the two-sided 95% CI of the GMC ratios between subjects in the Tdap Group and Td Group one month after vaccination will be computed using an ANOVA model on the logarithm_{10} transformation of the concentrations adjusted to pre-vaccination titer in Boostrix-001.

• For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN alternative booster response, the two-sided standardized asymptotic 95% CI for the group differences (Tdap Group - Td Group) will be calculated.

10.7.3. Interpretation of analyses

Except for analyses addressing criteria specified in the objectives, comparative analyses will be exploratory with the aim to characterize the difference between groups in immunogenicity. These exploratory analyses should not be used to conclude since there is no adjustment for multiplicity of endpoints.

With respect to the two co-primary objectives, the interpretation must be done according to a hierarchical procedure. More specifically, the second primary objective can only be reached if all the associated criteria are met and the first primary objectives has been reached.
10.7.4. Sensitivity analysis

- A complementary analysis will be carried out in order to evaluate the robustness of GMC results with respect to drop-out from previous study. More specifically, multiple imputation techniques will be used to estimate the seropositivity and seroprotection rates and GMC that would have been observed if all subjects had been enrolled in this study. The imputation of missing data will account for the correlation between results from previous study and this study.

10.8. Analysis of safety

10.8.1. Within groups assessment

The primary analysis will be based on the TVC. If the percentage of vaccinated subjects excluded from the ATP cohort for analysis of safety is more than 5%, a second analysis based on this ATP cohort will be performed to complement the analysis of the TVC.

Safety data will be analyzed by subject incidence rates of solicited and unsolicited adverse events in the vaccine schedules treatment groups by solicited local and general symptom terms, and, for unsolicited AEs, by MedDRA preferred term and system organ class. Safety data will be summarized for all subjects by treatment group.

The incidence of solicited local and general symptoms occurring during 4 days after vaccination will be tabulated with exact 95% CI for each treatment group. The same calculations will be performed for symptoms of any intensity, those with intensity grade ≥ 2, and those with intensity of grade 3 (occurrence of fever will be reported per 32.9°F cumulative increments), as well as for solicited general events with relationship to vaccination and events requiring medical attention, respectively. Note that all solicited local adverse events will be considered to be causally related.

The percentage of subjects with at least one report of an unsolicited adverse event classified by MedDRA up to 31 days after vaccine will be tabulated with exact 95% CI for each treatment group. The same tabulation will be performed for grade 3 unsolicited adverse events, AEs resulting in a medically attended visit and for unsolicited adverse events that are considered by the investigator to be possibly related to vaccination.

Serious adverse events will be summarized from Day 0 to 31 days post-vaccination. Serious adverse events, large injection site reaction (defined as swelling with a diameter >100 mm, noticeable diffuse swelling or noticeable increase of limb circumference) and withdrawals due to adverse event(s) will be described in detail.
10.8.2. **Between groups assessment**

The standardized asymptotic 95% CI for the difference between the two groups and the associated 2-sided p-value to detect group difference (Newcombe, 1998) will be computed for the following endpoints:

- For each solicited symptom, the percentage of subjects reporting the symptom within 4 days after vaccination (any grade, grade 3, causally related, respectively).
- The percentage of subjects reporting adverse events within 31 days post vaccination (any, grade 3, causally related, requiring medical attention).
- The percentage of subjects reporting serious adverse events (any, causally related) during the study period.

P-value below 5% will be used to identify events that are recognised as worthy of further investigation. It is to be noted that the use of such analyses has the potential to identify a large number of events which may or may not have a causal relationship to treatment due to unadjustment for multiplicity. In order to put these in perspective, the analysis will be complemented by a permutation test that will quantify the probability of identifying erroneously an event according to the threshold p-value. In addition, clinical judgment and biological plausibility should be taken into account when performing overall assessment.

10.9. **Statistical methods**

- The exact 95% CIs for a proportion within a group will be calculated from Proc StatXact, (Clopper, 1934).
- Proc StatXact 7.0 will be used to derive the standardized asymptotic 95% CI for the group difference in proportion and the p-value associated to non-inferiority (Newcombe, 1998) the standardized asymptotic method used within GSK Biologicals is Method 6.
- The 95% CI for GMCs will be obtained within each group separately. The 95% CI for the mean of log-transformed titer/concentration will be first obtained assuming that log-transformed values were normally distributed with unknown variance. The 95% CI for the GMCs will then be obtained by exponential-transformation of the 95% CI for the mean of log-transformed titer/concentration.

10.10. **Conduct of analyses**

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

10.10.1. **Sequence of analyses**

The immunogenicity analyses of antibody persistence and immune response to the booster dose and safety analysis of the booster dose will be performed as soon as all immunogenicity and safety data up to Visit 2 have been cleaned. These analyses will be
10.10.2. Statistical considerations for interim analyses

All analyses will be conducted on final data and therefore no statistical adjustment for interim analyses is required.

11. ADMINISTRATIVE MATTERS

To comply with ICH GCP administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality and publications must be fulfilled.

11.1. Remote Data Entry instructions

Remote Data Entry (RDE), a validated computer application, will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologics’ Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

11.2. Study Monitoring by GSK Biologics

GSK will monitor the study to verify that, amongst others, the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.
Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform a RDE review and a Source Document Verification (SDV). By SDV we understand verifying RDE entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the RDE. This document should be completed and signed by the site monitor and investigator and should be filed in the monitor’s and investigator’s study file. Any data item for which the RDE will serve as the source must be identified, agreed and documented in the source documentation agreement form.

For RDE, the monitor will mark completed and approved screens at each visit.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

11.3. Record retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible, when needed (e.g. audit or inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g. microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for making these reproductions.

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP, any institutional requirements, applicable laws or regulations, or GSK standards/procedures; otherwise, the minimum retention period will default to 15 years.

The investigator/institution must notify GSK of any changes in the archival arrangements, including, but not limited to archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

11.4. Quality assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after the study.
completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

11.5. Posting of information on publicly available clinical trial registers and publication policy

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

Summaries of the results of GSK interventional studies (phase I-IV) are posted on publicly available results registers within 12 months of the primary completion date for studies of authorized vaccines and 18 months for studies of non-authorized vaccines.

GSK also aims to publish the results of these studies in the searchable, peer reviewed scientific literature. Manuscripts are submitted for publication within 24 months of the last subject’s last visit.

11.6. Provision of study results to investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK Biologicals will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

12. COUNTRY SPECIFIC REQUIREMENTS

Not Applicable.
13. REFERENCES


Booy R, Van der Meeren O, Ng S et al. A decennial booster dose of reduced antigen content diphtheria, tetanus, acellular pertussis vaccine (Boostrix™) is immunogenic and well tolerated in adults. Vaccine 2010; 29: 45–50.


Frampton JE, Keating GM. Reduced-antigen, combined diphtheria, tetanus and acellular pertussis vaccine (Boostrix™). BioDrugs 2006; 20: 371-89.


Appendix A   LABORATORY ASSAYS

Serological assays for the determination of antibodies against diphtheria, tetanus and pertussis (PT, FHA and PRN) will be performed by ELISA and/or Neutralization assay (test on Vero cells will be performed on pre-vaccination samples with concentrations < 0.1IU/mL by ELISA) at a GSK Biologicals’ laboratory or in a laboratory designated by GSK Biologicals using standardized and validated procedures.
## Appendix B  CLINICAL LABORATORIES

### Table 18  GSK Biologicals’ laboratories

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK Biologicals Global Vaccine Clinical Laboratory, Rixensart</td>
<td>Biospecimen Reception - B7/44 Rue de l'Institut, 89 - B-1330 Rixensart - Belgium</td>
</tr>
<tr>
<td>GSK Biologicals Global Vaccine Clinical Laboratory, North America- Laval</td>
<td>Biospecimen Reception - Clinical Serology 525 Cartier blvd West - Laval - Quebec - Canada - H7V 3S8</td>
</tr>
<tr>
<td>GSK Biologicals Global Vaccine Clinical Laboratory, Wavre-Nord Noir Épine</td>
<td>Avenue Fleming, 20 - B-1300 Wavre - Belgium</td>
</tr>
</tbody>
</table>
Appendix C  AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment 1

<table>
<thead>
<tr>
<th>eTrack study number and Abbreviated Title(s)</th>
<th>116570 [DTPA 0.3 (BOOSTRIX)-012 EXT:001]</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND number</td>
<td>BB-IND 8461</td>
</tr>
<tr>
<td>Amendment number:</td>
<td>Amendment 1</td>
</tr>
<tr>
<td>Amendment date:</td>
<td>12 October 2012</td>
</tr>
<tr>
<td>Co-ordinating authors:</td>
<td>PPD and PPD Scientific Writers</td>
</tr>
</tbody>
</table>

Rationale/background for changes:
Following consultation with Center for Biologics Evaluation and Research (CBER), the objectives have been updated and the endpoints have been aligned accordingly. Additionally extended safety follow-up was removed as it is not applicable to the study.

Amended text has been included in bold italics and deleted text in strikethrough in the following sections:

Contributing authors:
- PPD Clinical Development Manager, Combination Vaccines, Global Vaccine Development
- PPD Safety Physicians, Biologicals Clinical Safety & Pharmacovigilance
- PPD and PPD Study Data Managers
- PPD Director, Global Regulatory Affairs
- PPD US Clinical and Medical Affairs

List of Abbreviations:
- ESFU Extended Safety Follow-Up
Glossary of terms

**Menarche:** Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, thelarche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).

**Menopause:** Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile at the appropriate age e.g. > 45 years.

Section 1.2.1 Rationale for the study

Currently the Advisory Committee on Immunization Practices (ACIP) of the US Centers for Disease Control and Prevention (CDC) recommends a single dose of Tdap vaccine for persons 11 years of age and older in the US. (ACIP, 2011b). Immunity to pertussis, provided by acellular pertussis vaccines is known to wane over time. Hence, it is likely that additional booster vaccinations will be needed to maintain adequate immunity. However, Tdap vaccines are only approved for use as a single dose in adolescents and adults by the US Food and Drug Administration (FDA).

The ACIP recommends booster vaccination against diphtheria and tetanus every 10 years in adults (ACIP, 2011b). However, Tdap vaccine is only recommended as a single dose in adolescents and adults with no suggestion of further booster doses.

Currently in the US, no data is available on the immunogenicity and safety of Boostrix given as a second dose. This study is planned to fill the acknowledged information gap. For long-term persistence of the Tdap vaccine, though, a three year antibody persistence following Tdap vaccination supports the immunogenicity of this vaccine in US adolescents and adults and demonstrates the persistence of antibodies against vaccine antigens through the first three years after vaccination (Weston, 2011).
Section 1.2.2 Rationale for the study design

The purpose of this follow-up study is to evaluate 10 years later, the persistence of antibodies against all the vaccine antigens, and to evaluate the immunogenicity and safety of a second dose of Boostrix dose. This study will be conducted in an open-label manner since all the subjects will receive a booster dose of the study vaccine. The study is non-randomized since both the study groups will receive a single dose of Boostrix.

Subjects who were vaccinated in the 776423/001 [DTPA 0.3 (BOOSTRIX)-001] study will be invited to participate in this decennial booster study.

Section 2 Objectives

Section 2.1 Co-Primary objectives

- To demonstrate that a second dose of Tdap vaccine (administered to the Tdap Group) administered 10 years after a previous dose of Tdap vaccine is non-inferior to a first dose of Tdap vaccine (administered to the Td Group), 10 years after a previous dose of Td vaccine with respect to immune response to diphtheria and tetanus antigens.

  The criteria for meeting the above objective are defined as:
  - One month after vaccination, the upper limit of the 95% CI on the difference of the seroprotection rate [second dose of Tdap (Tdap Group) minus first dose of Tdap (Td Group)] for anti-diphtheria, anti-tetanus antibody concentrations is lesser than or equal to 10 % (clinical limit for non-inferiority)

- To demonstrate that a second dose of Tdap vaccine (administered to the Tdap Group) 10 years after a previous dose of Tdap vaccine, is non-inferior to a three dose series of Infanrix vaccine in infants who received this vaccine in German household contact efficacy study APV-039, with respect to antibodies against pertussis toxoid (anti-PT), antibodies against filamentous hemagglutinin (anti-FHA) and antibodies against pertactin (anti-PRN) antibody concentrations.
Section 2.2 Secondary objectives

- To assess the immunogenicity of the Tdap vaccine in terms of seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies, one month after vaccination.

- To explore the potential difference in terms of booster response* to anti-D, anti-T, anti-PT, anti-FHA and anti-PRN between the second dose of Tdap vaccine, (administered to the Tdap Group) and the first dose of Tdap vaccine (administered to the Td Group).

- To explore the potential difference in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations between a second dose of Tdap vaccine (administered 10 years after a previous dose to the Tdap Group) and a first dose of Tdap vaccine (administered to the Td Group) 10 years after a previous dose of Td vaccine.

- To evaluate the safety and reactogenicity of the study vaccine in terms of solicited symptoms (local and general), unsolicited symptoms and serious adverse events (SAEs).

- To evaluate and compare the safety of a second dose of Tdap vaccine (administered to the Tdap Group) and a first dose of Tdap vaccine (administered to the Td Group), with respect to solicited symptoms (local and general), unsolicited symptoms and serious adverse events (SAEs).

*Refer to Section 10.5 for the definition of booster response.
Section 3 Study Design Overview:

Number of subjects planned to be enrolled; Pre-BS = Pre-vaccination blood sampling; Post-BS = Post-vaccination blood sampling; ESFU = Extended safety follow-up.

- Duration of the study: The intended duration of the study, for each subject will be approximately **one month six months**;
- Booster epoch: Starting at Visit 1 (Day 0) and ending at **Visit 2 (Day 30)**.
- Safety follow-up contact (i.e. six months following vaccination).

Overview of the recruitment plan:

- The study duration per subject will be approximately **one month six months**.
- Control: **uncontrolled active control**.
Section 4.2 Inclusion criteria for enrolment

- Subjects who have received a dose of Tdap or Td vaccines *10 years (+/-180 days) back*, in study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].

- Female subjects of non-childbearing potential may be enrolled in the study.
  - Non-childbearing potential is defined as pre-menarche, current tubal ligation, hysterectomy, ovariectomy or post-menopause.

*Please refer to the glossary of terms for the definition of menarche and menopause.*

Section 5.5 Outline of study procedures

Table 4 List of study procedures

<table>
<thead>
<tr>
<th>Booster epoch</th>
<th>Time point</th>
<th>Sampling time point</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit 1</td>
<td>Visit 2</td>
</tr>
<tr>
<td></td>
<td>Day 0</td>
<td>Month 1</td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td></td>
</tr>
<tr>
<td><strong>Type of contact</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed consent</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Check inclusion/exclusion criteria</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Vaccination history</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Record demography data †</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>History directed physical examination</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Urine pregnancy test **</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Pre-vaccination body temperature</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Blood sampling</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td><strong>Check warnings and precautions</strong></td>
<td>▲ ●</td>
<td></td>
</tr>
<tr>
<td><strong>Study group and treatment number allocation</strong></td>
<td>▲ ●</td>
<td></td>
</tr>
<tr>
<td>Recording of administered treatment number</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Vaccination</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td><strong>Distribution of diary cards</strong></td>
<td>▲ ◊</td>
<td></td>
</tr>
<tr>
<td>Daily recording of solicited adverse events during the 4-day (Day 0-3) follow-up period post-vaccination , by subject</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Recording of non-serious adverse events within 31 days post-vaccination, by subject</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td><strong>Return of diary cards and transcription by the investigator</strong></td>
<td>▲ ○</td>
<td></td>
</tr>
<tr>
<td>Transcription of diary cards by the investigator</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Recording of any large injection site reactions in the eCRF by the investigator *</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Record any concomitant medication and vaccination</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Record any intercurrent medical conditions</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Recording of SAEs related to study participation or to a concurrent GSK medication/Vaccine</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Recording of serious adverse events</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Recording of pregnancies</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Investigator sign-off on data</td>
<td>●</td>
<td>▲</td>
</tr>
<tr>
<td><strong>Study conclusion</strong></td>
<td>●</td>
<td></td>
</tr>
</tbody>
</table>

*At the end of the safety follow-up following vaccination, the subject will be called by the investigator or study staff to collect information on SAEs.*
Table 5 Intervals between study visits

<table>
<thead>
<tr>
<th>Interval</th>
<th>Optimal length of interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1 → Visit 2</td>
<td>30 -48 days (at least 30 days*)</td>
</tr>
<tr>
<td>Visit 1 → ESFU</td>
<td>180 days</td>
</tr>
</tbody>
</table>

Section 5.7.3 Laboratory assays

Please refer to Appendix A for Laboratory assays and Appendix B the address of the clinical laboratories used for sample analysis.

Please refer to Appendix A for the address of the clinical laboratories used for sample analysis.

Sero logical assays for the determination of antibodies against diphtheria, tetanus and pertussis (PT, FHA and PRN) will be performed by ELISA and/or Neutralization assay (test on Vero cells will be performed on pre-vaccination samples with concentrations < 0.1 IU/mL by ELISA) at a GSK Biologicals’ laboratory or in a laboratory designated by GSK Biologicals using standardized and validated procedures.

Section 5.7.5 Immunological correlates of protection

- The cut-off of the Vero-cell assay (performed for pre-vaccination primary serum samples when ELISA anti-diphtheria antibody concentrations is < 0.1 IU/mL) is 0.004 IU/mL. Antibody concentrations ≥ 0.01 IU/mL are considered as protective (Camargo, 1984). The ELISA test will define the seroprotection status for the primary endpoint.

Section 8.3.1 Time period for detecting and recording adverse events, serious adverse events and pregnancies

The time period for collecting and recording SAEs will begin at the receipt of study vaccine and will end on Day 30 6 months following administration of the dose of study vaccine for each subject.

<table>
<thead>
<tr>
<th>Event</th>
<th>Pre-vacc (consent obtained)</th>
<th>Vaccination (Day 0)</th>
<th>4 days (Day 0-3) post vacc</th>
<th>31 days (Day 0-30) post vacc</th>
<th>ESFU Phone call 6 months after vacc</th>
<th>Study conclusion</th>
<th>Study conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solicited local and general AEs including large injection site reactions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unsolicited AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEs/SAEs leading to withdrawal from the study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Section 10.1 Primary endpoint

- Immunogenicity with respect to components of the study vaccine.
  - Anti-D and anti-T antibody concentrations ≥ 0.1 IU/mL by ELISA, one month after vaccination.

### Section 10.2 Secondary endpoints

- Immunogenicity with respect to components of the study vaccine.
  - Anti-D* and anti-T antibody concentrations ≥ 0.1 IU and ≥ 1.0 IU/mL by ELISA or ≥ 0.01 IU/mL by Vero cell testing for subjects with post-vaccination ELISA anti-diphtheria toxoid antibody concentration < 0.1 IU/mL, prior to and one month after vaccination.
  - Anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ 5 EL.U/mL, anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations prior to and one month after vaccination. (Refer to Section 10.5 for the definition of booster response).
  - Booster response to the diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens one month after vaccination

* Sera with ELISA concentrations < 0.1 IU/mL will be tested for neutralizing antibodies using a Vero-cell neutralization assay.

-Serious adverse events.
  - Occurrence of serious adverse events from the administration of the vaccine dose up to **31 days after vacc** following vaccination.
Section 10.3 Determination of sample size

- Non-inferiority of the second dose of Tdap vaccine, administered to young adults 10 years after the previous booster dose of the same vaccine, to the first booster dose of Tdap vaccine administered to young adults 10 years after a previous booster dose of Td vaccine, with respect to anti-D and anti-T antibody response seroprotection rates (antibody concentration) ≥ 0.1 IU/mL by ELISA;

Table 16 and Table 17 show the power to demonstrate non-inferiority between second Tdap and first Tdap/Infanrix with respect to each of the five antibodies. With 100 evaluable subjects in the Td Group and 300 evaluable subjects in the Tdap Group, the study would have an overall power of 89% to 97% to meet both co-primary objectives simultaneously.

Table 16 Power to demonstrate non-inferiority of 2nd dose of Tdap to first booster dose of Tdap with respect to anti-D, anti-T antibody GMCs

<table>
<thead>
<tr>
<th>Endpoint (GMCs)</th>
<th>Reference values (Standard Deviation of log10 transformed concentration)</th>
<th>Power* to reject H0: LL of 95%CI of GMC ratio (Tdap/Td) &lt; 0.67</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-D</td>
<td>0.437</td>
<td>93.04%</td>
</tr>
<tr>
<td>Anti-T</td>
<td>0.354</td>
<td>98.88%</td>
</tr>
<tr>
<td>Overall power**</td>
<td></td>
<td>91.92%</td>
</tr>
</tbody>
</table>

*Pass 2005, non-inferiority test on means, alpha=2.5%; equivalence margin= log10 (0.67), power under alternative of equal means in both groups; LL= lower limit.
**Overall power is the probability to reject both null hypotheses simultaneously, computed by subtracting both type II errors (beta) from 1.

Table 16 Power to demonstrate non-inferiority of second dose of Tdap vaccine to first dose of Tdap vaccine with respect to anti-D and anti-T seroprotection rate

<table>
<thead>
<tr>
<th>Endpoint (antibody concentration &gt;0.1 IU/mL)</th>
<th>Reference values</th>
<th>Power* to reject H0: LL of 95%CI of difference &lt;0.10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-D</td>
<td>99.4%</td>
<td>LL of 95% CI ≥-10% &gt;99.99%</td>
</tr>
<tr>
<td>Anti-T</td>
<td>99.8%</td>
<td>LL of 95% CI ≥-10% &gt;99.99%</td>
</tr>
<tr>
<td>Overall power**</td>
<td></td>
<td>99.99%</td>
</tr>
</tbody>
</table>

*Pass 2005, non-inferiority test on 2 independent proportions (Miettinen & Nurminen), alpha=2.5%; non-inferiority margin=10% power under alternative of equal proportions in both groups; LL= lower limit.
**Overall power is the probability to reject all null hypotheses simultaneously, computed by subtracting the sum of individual type-II errors (beta) from 1.
Table 17  Power to demonstrate non-inferiority of second dose of Tdap vaccine to Infanrix vaccine in APV-039 with respect to anti-PT, anti-FHA and anti-PRN GMCs

<table>
<thead>
<tr>
<th>Endpoint (GMCS)</th>
<th>DTPA 0.3 (BOOSTRIX)-007 (Boostrix sub-group 19-29)</th>
<th>APV-039 Infantrix</th>
<th>N in APV-039 (TVC)</th>
<th>N =300 in Tdap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-PT</td>
<td>0.464</td>
<td>0.306</td>
<td>2884</td>
<td>&gt; 99.99%</td>
</tr>
<tr>
<td>Anti-FHA</td>
<td>0.374</td>
<td>0.370</td>
<td>685</td>
<td>&gt; 99.99%</td>
</tr>
<tr>
<td>Anti-PRN</td>
<td>0.645</td>
<td>0.413</td>
<td>631</td>
<td>97.02%</td>
</tr>
</tbody>
</table>

Overall power** 97.02%

*Pass 2005, non-inferiority test on 2 independent means, alpha=2.5%; equivalence margin=\log_{10}(0.67), variance from DTPA 0.3 (BOOSTRIX)-007 was considered as common variance for both groups, power under alternative of equal means in both groups; LL= lower limit. Overall power is the probability to reject the primary objective and all three null hypotheses simultaneously, computed by subtracting the sum of the three type-II errors (beta) from 1.

Section 10.5 Derived and transformed data

The Geometric Mean Concentrations/Titers (GMC/GMTs) calculations are performed by taking the anti-log of the mean of the log concentration/titer transformations. Antibody concentrations/titers below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC/GMT calculation.

- **Alternative Booster response to D and T antigens is defined as:**
  - for initially seronegative subjects (pre-vaccination concentration in Boostrix-001 study below cut-off: < 0.1 IU/mL): antibody concentrations at least four times the cut-off (post-vaccination concentration ≥ 0.4 IU/mL) one month after vaccination, and
  - for initially seropositive subjects (pre-vaccination concentration in Boostrix-001 study ≥ 0.1 IU/mL): an increase in antibody concentrations of at least four times the pre-vaccination concentration one month after vaccination.

- **Alternative Booster response to PT, FHA and PRN antigens is defined as:**
  - for subjects with pre-vaccination antibody concentration in Boostrix-001 study < 5 EL.U/mL: antibody concentration ≥ 20 EL.U/mL one month after vaccination;
  - for subjects with pre-vaccination antibody concentration in Boostrix-001 study ≥ 5 EL.U/mL and < 20 EL.U/mL: antibody concentration at least four times the pre-vaccination concentration one month after vaccination; and
  - for subjects with pre-vaccination antibody concentration in Boostrix-001 study ≥ 20 EL.U/mL: antibody concentration at least two times the pre-vaccination concentration, one month after vaccination.
### Section 10.7.1 Within groups assessment

- GMCs or GMTs at pre-vaccination, one month post-vaccination will be tabulated with 95% CIs.
- Antibody concentrations/titers distribution at pre-vaccination and one month post-vaccination will be displayed using reverse cumulative curves (RCC).

### Section 10.7.2 Between groups analysis

- **For anti-D, anti-T seroprotection rates, the two-sided standardized asymptotic 95% CI for the group differences (Tdap Group – Td Group) will be calculated.**
- For anti-D, anti-T antibody response, the two-sided 95% CIs of the GMC ratios between subjects in the Tdap Group and (divided by) the Td Group one month after vaccination will be computed using an analysis of variance (ANOVA) model on the logarithm transformation of the concentrations adjusted to pre-vaccination titer in Boostrix-001.
- For anti-PT, anti-FHA and anti-PRN antibody response, the two-sided 95% CI of the GMC ratios between subjects in the Tdap Group and Td Group one month after vaccination will be computed using an ANOVA model on the logarithm transformation of the concentrations adjusted to pre-vaccination titer in Boostrix-001.
- **For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN alternative booster response, the two-sided standardized asymptotic 95% CI for the group differences (Tdap Group - Td Group) will be calculated.**

### Section 10.7.4 Sensitivity analysis

A complementary analysis will be carried out in order to evaluate the robustness of GMT/GMC results with respect to drop-out from previous study. More specifically multiple imputation techniques will be used to estimate the seropositivity and seroprotection rates and GMC/GMT that would have been observed if all subjects had been enrolled in this study. The imputation of missing data will account for the correlation between results from previous study and this study.

### Section 10.8 Analysis of safety

#### Section 10.8.1 Within groups assessment

The incidence of solicited local and general symptoms occurring during 4 days after vaccination will be tabulated with exact 95% CI for each treatment group. The same calculations will be performed for symptoms of any intensity, those with intensity grade ≥ 2, and those with intensity of grade 3 (occurrence of fever will be reported per 32.9°F cumulative increments), as well as for solicited general events with relationship to vaccination and events requiring medical attention, respectively. Note that all solicited local adverse events will be considered to be causally related.

Serious adverse events will be summarized from Day 0 to 31 days post-vaccination.
### Section 10.8.2 Between groups assessment

The standardized asymptotic 95% CI for the difference between the two groups and the associated 2-sided p-value to detect group difference (Newcombe, 1998) will be computed for the following endpoints:

- For each solicited symptom, the percentage of subjects with the symptom within 4 days after vaccination (any grade, grade 3, causally related, respectively).
- The percentage of subjects with adverse events within 31 days post vaccination (any, grade 3, causally related, requiring medical attention).
- The percentage of subjects with serious adverse events within the study (any, causally related).

P-value below 5% will be used to identify events that are recognised as worthy of further investigation. It is to be noted that the use of such analyses has the potential to identify a large number of events which may or may not have a causal relationship to treatment due to unadjustment for multiplicity. In order to put these in perspective, the analysis will be complemented by a permutation test that will quantify the probability of identifying erroneously an event according to the threshold p-value. In addition, clinical judgment and biological plausibility should be taken into account when performing overall assessment.

### Section 10.9 Statistical methods

- The 95% CI for GMTs/GMCs will be obtained within each group separately. The 95% CI for the mean of log-transformed titer/concentration will be first obtained assuming that log-transformed values were normally distributed with unknown variance. The 95% CI for the GMTs/GMCs will then be obtained by exponential-transformation of the 95% CI for the mean of log-transformed titer/concentration.

The GMC group ratio will be obtained using an ANOVA model on the logarithm-transformed concentrations. The ANOVA model will include the vaccine group as fixed effects.

### Section 10.10.1 Sequence of analyses

The immunogenicity analyses of antibody persistence and immune response to the booster dose and safety analysis of the booster dose will be performed as soon as all immunogenicity and safety data up to Visit 2 have been cleaned. These analyses will be the basis for the study report of the booster phase. The clinical report will be updated as soon as data of the ESFU phone contact are available. Results will not be shared with the investigator before study conclusion.
## Appendix A Laboratory assays

Text moved from section 5.7.3 to Appendix A as per the instruction in the document standard template.

*Serological assays for the determination of antibodies against diphtheria, tetanus and pertussis (PT, FHA and PRN) will be performed by ELISA and/or Neutralization assay (test on Vero cells will be performed on pre-vaccination samples with concentrations < 0.1IU/mL by ELISA) at a GSK Biologicals’ laboratory or in a laboratory designated by GSK Biologicals using standardized and validated procedures.*
GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment 2

| eTrack study number and Abbreviated Title(s) | 116570 [DTPA 0.3 (BOOSTRIX)-012 EXT:001] |
| IND number | BB-IND 8461 |
| Amendment number: | Amendment 2 |
| Amendment date: | Final: 03 October 2013 |
| Co-ordinating authors: | PPD Scientific Writer |

Rationale/background for changes:
Due to slow enrollment of subjects into the study, the protocol is being amended to facilitate enrollment by:

- Extending the window period for re-vaccination from ± 6 months to ± 300 days from the Year 10 timepoint.
- Extending the recruitment period from 6 months to 14 months.

The non-inferiority criterion of the first co-primary objective has been updated to keep it aligned with the non-inferiority criterion of the second co-primary objective.

The list of contributing authors was updated for this amendment. Typographical errors have been corrected throughout the document.
Contributing authors:

- PPD Study Delivery Lead
- PPD Safety Physician, Vaccines Clinical Safety & Pharmacovigilance
- PPD and PPD Study Data Managers
- PPD US Vaccines Medical Affairs
- PPD Local Delivery Lead, Vaccines, GSK US

Glossary of terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seronegative subject</td>
<td>A seronegative subject was a subject whose antibody concentration/titer was below the assay cut-off.</td>
</tr>
<tr>
<td>Seropositive subject</td>
<td>A seropositive subject was a subject whose antibody concentration/titer was greater than or equal to the assay cut-off.</td>
</tr>
</tbody>
</table>
Synopsis Page 10 and Section 2.1 Co-primary objectives

- One month after vaccination, upper the lower limits of the 95% CI on the difference of the seroprotection rates [second dose of Tdap (Tdap Group) minus first dose of Tdap (Td Group)] for anti-diphtheria, anti-tetanus antibody concentrations is lesser are greater than or equal to -10% (clinical limit for non-inferiority).

Synopsis Page 11 and Section 3 Study design overview

Table 1

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>Number of subjects</th>
<th>Age (Min - Max) (age unit)</th>
<th>Epoch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tdap Group*</td>
<td>Approximately 375</td>
<td>20–19 years – 28–30 years</td>
<td>x</td>
</tr>
<tr>
<td>Td Group</td>
<td>Approximately 125</td>
<td>20–19 years – 28–30 years</td>
<td>x</td>
</tr>
</tbody>
</table>

- Vaccination schedule: A single dose of Tdap vaccine will be administered to all subjects, 10 years (± 180-300 days) after the previous booster vaccination in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].

Section 4.1 Number of subjects/centers

Overview of the recruitment plan:
- Enrolment is expected to be completed within a period of approximately six 14 months.

Section 4.2 Inclusion criteria for enrolment

- Subjects who have received a dose of Tdap or Td vaccines 10 years (± 180-300 days) back, in study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].
Sample Case Report Form
Protocol 116570
(DTPA 0.3 (BOOSTRIX)-012
EXT:001)

An open, phase III, non-randomized, multi-center study to assess the immunogenicity and safety of a booster dose of GlaxoSmithKline (GSK) Biologicals' combined reduced antigen content diphtheria-tetanus toxoids and acellular pertussis vaccine (Boostrix™), when administered in young adults, 10 years after previous booster vaccination in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001]
GENERAL INSTRUCTIONS

ABBREVIATIONS

Abbreviations for medical conditions, clinical events or drug names are to be avoided.

DATES

Use the following 3-letter abbreviations to indicate months:

January = JAN
February = FEB
March = MAR
April = APR
May = MAY
June = JUN
July = JUL
August = AUG
September = SEP
October = OCT
November = NOV
December = DEC

Example: 01 JAN 2011 = 1st January 2011
GENERAL INSTRUCTIONS (continued)

GUIDANCE FOR INITIATING / STARTING A CRF

All subjects who have been approached for a study have to be recorded in the site Screening / Enrolment Log.

For those whom informed consent (IC) was obtained, a unique subject number has to be assigned: an eTrack subject number is to be taken from the range of numbers provided for the centre.

In case of interventional studies (with administration of a medicinal product as described in a research protocol):

- For those who signed an informed consent form (ICF) and who had a GSK treatment (vaccination or medication) and/or an invasive study procedure* to document in the CRF, a CRF must be initiated.

- For those who signed an informed consent form (ICF) but did not have any GSK treatment (vaccination or medication) and/or an invasive study procedure* to document in the CRF, a CRF must not be initiated, unless a SAE must be reported according to protocol requirement.

In case of observational studies and interventional studies without administration of a medicinal product as described in a research protocol, a CRF must be initiated for all subjects who have signed an ICF. For database studies initiation of a CRF is not required.

Subject number must be entered on the CRF cover page and in the header of all CRF pages. Number must be right-aligned.

* Are considered here as invasive study procedures: protocol defined biological samplings, such as blood samplings or biopsies, protocol defined vaccination or other treatment administration;

Are not considered here as invasive study procedures: physical examination, X-ray, collection of medical records such as medical history.

For all subjects participating in the study, the Study Conclusion and the Medication, Concomitant Vaccination, (S)AE sections, Pregnancy Information and other sections, if applicable must be completed.

If a subject doesn't participate in the study, neither the Study Conclusion nor the Medication, Concomitant Vaccination, (S)AE sections, Pregnancy Information and other sections if applicable have to be completed.
### DEMOGRAPHY

**PREVIOUS STUDY**

776423/001 [DTPA 0.3 (BOOSTRIX)-001]

Subject number will be the same as in the previous study

**Date of Birth:**

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Gender:**

- [M] Male
- [F] Female

**Ethnicity:**

- [1] American Hispanic or Latino
- [2] Not American Hispanic or Latino
Informed Consent has to be obtained prior to any study procedure
<table>
<thead>
<tr>
<th>Book</th>
<th>Visit</th>
<th>Subject Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>VISIT 1</td>
<td></td>
</tr>
</tbody>
</table>

**CHECK FOR STUDY CONTINUATION**

Did the subject return for this new study epoch?

[ ] Yes → Date of visit: [ ]

→ Go to next page
INFORMED CONSENT

I certify that Informed Consent has been obtained prior to any study procedure.

Informed Consent Date: __________

Did the subject agree that her/his biological sample(s) may be used by GSK Biologicals for future research?

[ ] No
[ ] Yes
[ ] Not applicable

[type 4 tests]
<table>
<thead>
<tr>
<th>Book</th>
<th>Visit</th>
<th>Subject Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>VISIT 1</td>
<td></td>
</tr>
</tbody>
</table>

**DISEASE HISTORY**

**DIPHTHERIA DISEASE HISTORY**

- [N] ☐ No
- [N] ☑ Yes ➔ Date(s) of diagnosis
- [U] ☐ Unknown

**TETANUS DISEASE HISTORY**

- [N] ☐ No
- [N] ☑ Yes ➔ Date(s) of diagnosis
- [U] ☐ Unknown

**PERTUSSIS DISEASE HISTORY**

- [N] ☐ No
- [N] ☑ Yes ➔ Date(s) of diagnosis
- [U] ☐ Unknown
ELIGIBILITY CHECK
Did the subject meet all the entry criteria?

[ ] Yes
[ ] No  → If No, tick all boxes corresponding to violations of any inclusion/exclusion criteria.
Do not enter the subject into the study if he/she failed any of the inclusion or exclusion criteria below.

INCLUSION CRITERIA
Tick the boxes corresponding to any of the inclusion criteria the subject failed.

[1] Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visit).

[2] Subjects who have received a dose of Tdap or Td vaccines 10 years (± 300 days) back, in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].


[4] Healthy subjects as established by medical history and clinical examination before entering into the study.

[5] Female subjects of childbearing potential may be enrolled in the study, if the subject
   - has practiced adequate contraception for 30 days prior to vaccination, and
   - has a negative pregnancy test on the day of vaccination, and
   - has agreed to continue adequate contraception during the entire treatment period and for 1 month after completion of the vaccine dose.

EXCLUSION CRITERIA
Tick the boxes corresponding to any of the exclusion criteria that disqualified the subject from entry.

[6] Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the dose of study vaccine, or planned use during the study period.

[7] Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs within six months prior to the booster vaccine dose. For corticosteroids, this will mean prednisone (≥ 20 mg/day (for adult subjects), or equivalent. Inhaled and topical steroids are allowed.

[8] Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before and ending 31 days after the dose of vaccine, with the exception of Influenza vaccine which is allowed throughout the study period.
ELIGIBILITY CHECK (continued)

EXCLUSION CRITERIA

Tick the boxes corresponding to any of the exclusion criteria that disqualified the subject from entry.

[ 9 ] Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).

[ 10 ] Previous vaccination against diphtheria, tetanus or pertussis since the last dose received in the Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].

[ 11 ] History of diphtheria, tetanus or pertussis diseases following the receipt of booster dose in the Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].

[ 12 ] Severe allergic reaction (e.g. anaphylaxis) after previous administration of any tetanus toxoid, diphtheria toxoid, or pertussis-antigen containing vaccines, or any component of Boostrix.


[ 14 ] Encephalopathy (e.g. coma, decreased level of consciousness, prolonged seizures) of unknown etiology occurring within 7 days following previous vaccination with pertussis-containing vaccine.


[ 16 ] Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).

[ 17 ] Acute disease and/or fever at the time of enrolment.
   - Fever is defined as temperature ≥ 99.5°F for oral, axillary or tympanic route, or ≥ 100.4°F for rectal route. The preferred route for recording temperature in this study will be oral.
   - Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may, be enrolled at the discretion of the investigator.

[ 18 ] Administration of immunoglobulins and/or any blood products within the 3 months preceding the booster dose of study vaccine or planned administration during the study period.

[ 19 ] Pregnant or lactating female.

[ 20 ] Female planning to become pregnant or planning to discontinue contraceptive precautions up to 1 month post-vaccination.
GENERAL MEDICAL HISTORY / EXAMINATION

Are you aware of any pre-existing conditions, signs or symptoms having started before the study vaccination?

[ ] No  [ ] Yes  → Please give diagnosis and tick appropriate Past/Current box

Please report medication(s) as specified in the protocol and fill in the medication section.

<table>
<thead>
<tr>
<th>MedDRA SYSTEM ORGAN CLASS</th>
<th>DIAGNOSIS</th>
<th>PAST</th>
<th>CURRENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>[1] Skin and subcutaneous tissue</td>
<td>____________________________</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>[2] Musculoskeletal and connective tissue</td>
<td>____________________________</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>[3] Cardiac</td>
<td>____________________________</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>[4] Vascular</td>
<td>____________________________</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>[5] Respiratory, thoracic and mediastinal</td>
<td>____________________________</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>[7] Hepatobiliary</td>
<td>____________________________</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>[8] Renal and urinary</td>
<td>____________________________</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>[9] Nervous system</td>
<td>____________________________</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>[10] Eye</td>
<td>____________________________</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>[12] Endocrine</td>
<td>____________________________</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>[13] Metabolism and nutrition</td>
<td>____________________________</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>[14] Blood and lymphatic system</td>
<td>____________________________</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>[15] Immune system (incl allergies, autoimmune disorders)</td>
<td>____________________________</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>[16] Infections and infestations</td>
<td>____________________________</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>[17] Neoplasms benign, malignant and unspecified (incl cysts, polyps)</td>
<td>____________________________</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>[18] Surgical and medical procedures</td>
<td>____________________________</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>[19] Reproductive system and breast</td>
<td>____________________________</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>[20] Psychiatric</td>
<td>____________________________</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>[99] Other</td>
<td>____________________________</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
### VACCINATION HISTORY

Has the subject received any vaccine within 30 days prior to the study vaccination?

- [ ] N Yes
- [U] Unknown
- [Y] No

→ Please complete the following table

<table>
<thead>
<tr>
<th>Vaccine name Trade name is preferred</th>
<th>Route Use codes given below</th>
<th>Dose number</th>
<th>Date of vaccination*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For GSK</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For GSK</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For GSK</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Enter approximate date in case the exact date is unknown.

**Route codes:**

- Inhalation [IH]
- Intradermal [ID]
- Intramuscular [IM]
- Intranasal [IN]
- Intravenous [IV]
- Oral [PO]
- Parenteral [PE]
- Subcutaneous [SC]
- Sublingual [SL]
- Transdermal [TD]
- Other [OTH]
- Unknown [UNK]
CONFIDENTIAL
116570 (DTPA 0.3 (BOOSTRIX)-012 EXT:001)
Report Final

<table>
<thead>
<tr>
<th>Book</th>
<th>Visit</th>
<th>Subject Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>VISIT 1</td>
<td></td>
</tr>
</tbody>
</table>

LABORATORY TESTS
SERUM SAMPLE
Has a serum sample been taken? [SER]

[N] No

[Y] Yes → Date if different from visit date: [ ] [ ] [ ] [ ] [ ] [ ]

HCG URINE PREGNANCY TEST
Has a urine sample been taken? [PRG]

[N] No

[Y] Yes → Date if different from visit date: [ ] [ ] [ ] [ ] [ ] [ ]

Pregnancy test result: [N] Negative
[P] Positive

[NA] Not applicable (female of non childbearing potential or male)

CRF template version 14 – October 22, 2013 - System page 13
### VACCINE ADMINISTRATION

Pre-vaccination temperature: [ ] Fahrenheit Route: [ ] Axillary [ ] Oral (preferred) [ ] Rectal [ ] Tympanic (not recommended)

Has Boostrix Vaccine been administered? [ ] No → Please give reason hereafter. [ ] Yes → Date of administration: ____________________________ (if different from visit date)

→ Administered treatment number: ____________________

→ Injection Site/Side/Route:

   According to protocol: Deltoid - [ ] Dominant/ [ ] Non dominant - IM

   Not according to protocol:

   Specify Site: [ ] Deltoid [ ] Thigh [ ] Buttock
   Side: [ ] Dominant [ ] Non dominant
   Route: [ ] Intramuscular [ ] Subcutaneous

→ If relevant, comment on administration: ____________________________

If no vaccination, → Please tick the major reason for non administration

   [ ] Serious Adverse Event: → Please complete a SAE Report
   → Please specify SAE Report No. ________

   [ ] Non-Serious Adverse Event: → Please complete Non-Serious Adverse Event section
   → Please specify AE No. ________

   [ ] Other, please specify: ____________________________

   (e.g.: consent withdrawal, Protocol violation, ...)

→ Please select who made the decision: [ ] Investigator [ ] Subject
**SOLICITED ADVERSE EVENTS - LOCAL SIGNS/SYMPTOMS**

**Study vaccine injection site**

Has the subject experienced any of the following signs/symptoms between Day 0 and Day 3?

- [X] No
- [Y] Yes, please tick No/Yes for each sign/symptom and complete further as necessary
- [U] Unknown, no information available
- [NA] Not applicable, no vaccine administered

<table>
<thead>
<tr>
<th>Local sign/symptom</th>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Max intensity</th>
<th>After Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redness [RE]</td>
<td>[N] No</td>
<td>[Y] Yes</td>
<td>[N] No</td>
<td>[Y] Yes</td>
<td>_____</td>
<td>_____</td>
</tr>
<tr>
<td>Swelling [SW]</td>
<td>[N] No</td>
<td>[Y] Yes</td>
<td>[N] No</td>
<td>[Y] Yes</td>
<td>_____</td>
<td>_____</td>
</tr>
<tr>
<td>Pain [PA]</td>
<td>[N] No</td>
<td>[Y] Yes</td>
<td>[N] No</td>
<td>[Y] Yes</td>
<td>_____</td>
<td>_____</td>
</tr>
</tbody>
</table>

**Intensity:** 0 / 1 / 2 / 3

**Medically attended visit:**

- NO: None
- HO: Hospitalisation
- ER: Emergency Room
- MD: Medical Personnel

* In case of large swelling reaction at the injected limb, please fill in ALSO the Large Swelling Reaction form.

If any of these adverse events meets the definition of **serious**, complete a Serious Adverse Event Report to GSK Biologicals Study Contact for SAE reporting within 24 hours.
### SOLICITED ADVERSE EVENTS - GENERAL SIGNS/SYMPTOMS

Has the subject experienced any of the following signs/symptoms between Day 0 and Day 3?

- [N] No
- [Y] Yes, please tick No/Yes for each sign/symptom and complete further as necessary
- [U] Unknown, no information available
- [NA] Not applicable, no vaccine administered

Record temperatures if during the solicited period at least one oral/axillary/tympanic measure is above or equal to 99.5 °F or at least one rectal measure is above or equal to 100.4 °F.

<table>
<thead>
<tr>
<th>Temperature [TE] ≥99.5 °F [A/O/T] ≥100.4 °F [R]</th>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>After Day 3</th>
<th>Rel. to inv. product</th>
<th>Medically attended visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>[N] No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Y] Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[N] Not Taken</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Route:
- [A] Axillary
- [O] Oral (preferred)
- [R] Rectal
- [T] Tympanic (not recommended)

### General sign/symptom

- **Headache [HE]**
  - [N] No
  - [Y] Yes → intensity: 0 / 1 / 2 / 3

- **Fatigue [FA]**
  - [N] No
  - [Y] Yes → intensity: 0 / 1 / 2 / 3

- **Gastrointestinal symptoms [GI]**
  - [N] No
  - [Y] Yes → intensity: 0 / 1 / 2 / 3

*Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain

- **Intensity:** 0 / 1 / 2 / 3

- **Relationship to investigational product:** Is there a reasonable possibility that the AE may have been caused by the investigational product?

- **Medically attended visit:**
  - NO: None
  - HO: Hospitalisation
  - ER: Emergency Room
  - MD: Medical Personnel

If any of these adverse events meets the definition of serious, complete a Serious Adverse Event Report to GSK Biologicals Study Contact for SAE reporting within 24 hours.
## CHECK FOR STUDY CONTINUATION

Did the subject return for this visit?

- [Y] Yes → Date of visit: __________
  
  → Go to next page

- [N] No → Please tick only one major reason:
  
  - [SAE] Serious Adverse Event
    
    → Please complete a SAE Report
  
    → Please specify SAE Report No. __________
  
    → Tick box if SAE is fatal: [ ]

  - [AEX] Non-Serious Adverse Event
    
    → Please complete Non-Serious Adverse Event section
  
    → Please specify AE No. __________ or solicited AE code __________

  - [PTV] Protocol violation, please specify: ___________________________________

  - [CWS] Consent withdrawal, not due to an adverse event
    
    → Please specify the reason (only if the Subject has spontaneously explained it):
    
    ___________________________________

  - [MIG] Migrated / moved from the study area

  - [LFU] Lost to follow-up

  - [SST] Sponsor study termination

  - [OTH] Other, please specify: ___________________________________

  → For serious (except death), non-serious adverse events and Other reasons only:

  Please tick who made the decision: [ ] Investigator

  [ ] Subject
## LABORATORY TESTS

**SERUM SAMPLE**

Has a serum sample been taken? [SER]

- [ ] No
- [Y] Yes → Date if different from visit date: __________

---

CRF template version 14 – October 22, 2013 - System page 19
Diary Cards

Protocol 116570

(DTPA 0.3 (BOOSTRIX)-012 EXT:001)

<table>
<thead>
<tr>
<th>Subject number</th>
</tr>
</thead>
<tbody>
<tr>
<td>To be completed by the Investigator or delegate</td>
</tr>
</tbody>
</table>

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON NEXT VISIT

CONFIDENTIAL
Thank you for your participation in this clinical trial. During your study visit, you received a "Diary Card" to fill in every day for a defined period, so that your study doctor or the study staff will know your general health status after the vaccination.

Here below you will find general instructions on how to complete the "Diary Card". There are also other specific instructions relative to each part of the "Diary Card" that you will need to fill in.

INSTRUCTIONS TO COMPLETE THE "DIARY CARD"

- Write in clearly, use a pen (never pencil).
- The grey areas are dedicated to the investigator or delegate only. Do not write in these areas.

<table>
<thead>
<tr>
<th>Illness/Sign/Symptom</th>
<th>Worst Intensity</th>
<th>Start Date</th>
<th>End Date</th>
<th>Did you receive medical attention?</th>
<th>Type of medical attention</th>
<th>Relationship to inv. Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tendinitis</td>
<td>2</td>
<td>01-01-2023</td>
<td>31-01-2023</td>
<td>No</td>
<td>Aspirin</td>
<td>No</td>
</tr>
</tbody>
</table>
Please contact your study doctor or the study staff immediately if you have any symptoms you think are serious.
Instructions to complete:
Local and general symptoms

- Symptoms to record on this page:
  - If you experience any other symptoms than those listed in the local symptoms or general symptoms pages, please write these symptoms down in the Adverse Event section.
  - If a symptom appears only after day 3, please write this symptom down in the Adverse Event section.

- How to complete “After day 3”?
  - In the columns “After day 3”, if the symptom is still ongoing after day 3, tick “Yes”. Otherwise, tick “No”.
    - Ongoing means:
      - Intensity is ≥ 1 or higher
      - Oral (in the mouth), higher or equal 99.5°F
    - If Yes,
      - Please write the worst intensity, the highest temperature or the greatest measure recorded during this follow-up period, after day 3.
      - And note the date when the symptom has disappeared or tick the box “still ongoing”.
    - If No, then leave empty the columns “Worst intensity/ greatest size/ highest temperature” and “End Date”.

- Box “Still ongoing” in column “End date” – When to tick it?
  - Tick the box “Still ongoing” if the illness /sign /symptom is still present at the time you return the diary card to the site.
**DID YOU RECEIVE ANY MEDICAL ATTENTION? HOW TO COMPLETE THIS QUESTION?**

- Medical attention means hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor).
- Tick the box “No” if you did not visit a doctor or go to the hospital or an emergency room for the symptom.
- Tick the box “Yes” if you went to the hospital, an emergency room or if you visited a doctor for the symptom. Keep the type of medical attention (grey column) empty. It will be completed by the study doctor or study staff.
Instructions to complete:
Local symptoms

- **HOW TO COMPLETE THE DAILY VALUE?**
  - Write down a value for each symptom and each day (measure or intensity). **Don't leave any field empty.**
  - If there is no symptom, please write "0".

<table>
<thead>
<tr>
<th>Injection site</th>
<th>2</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>No</th>
<th>Yes →</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swelling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In case of large injection site reactions (defined as swelling with a diameter greater than 100 mm, noticeable diffuse swelling or noticeable increase of limb circumference), please contact the study doctor or study staff and go as soon as possible to the study doctor or study staff’s office for evaluation.

Redness and swelling: Measure and record the greatest surface diameter in millimetres (mm).

Pain: Intensity:
0: None
1: Any pain neither interfering with nor preventing normal everyday activities
2: Painful when limb is moved and interferes with everyday activities
3: Significant pain at rest. Prevents normal everyday activities

Redness, swelling and pain may appear around the area where you received the vaccine as shown in this drawing. These are called LOCAL symptoms.

If similar symptoms appear on another part of your body than this/those shown in the drawing, please report them in the Adverse Event section.

Write down the size of the redness and swelling in millimetres (mm) only. Use the ruler given to you by the site staff.

Redness, swelling, and pain may appear around the area where you received the vaccine as shown in this drawing. These are called LOCAL symptoms.
## LOCAL SYMPTOMS

**Study vaccine**

To be completed by the investigator or delegate:

**Date of vaccination = Day 0:**

<table>
<thead>
<tr>
<th>Injection Site</th>
<th>Side</th>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Ongoing</th>
<th>Worst Intensity/</th>
<th>End Date</th>
<th>Did you receive any medical attention?</th>
<th>Type of medical attention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Greatest size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site</td>
<td>Redness</td>
<td>→</td>
<td>size (mm)</td>
<td>No</td>
<td>Yes</td>
<td>mm</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site</td>
<td>Swelling</td>
<td>→</td>
<td>size (mm)</td>
<td>No</td>
<td>Yes</td>
<td>mm</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site</td>
<td>Pain</td>
<td>→</td>
<td>intensity (0/1/2/3)</td>
<td>No</td>
<td>Yes</td>
<td>1/2/3</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

To be completed by the investigator or delegate:

**Injection Site:**

**Side:**

**Date of vaccination:**

**Day 0:**

**Day 1:**

**Day 2:**

**Day 3:**

**Ongoing:**

**Worst Intensity/Greatest size:**

**End Date:**

**Did you receive any medical attention?**

**Type of medical attention:**

**Tick box if still ongoing ↓**

Clarification(s) for Investigator or delegate only:

---

*Diary Cards template version 14 – June 28, 2012 – System page 8*
Instructions to complete: General symptoms

**How to complete the Daily Value?**

- Write down a value for each symptom and each day (measure or intensity). **Don't leave any field empty.**
- Write "0" if there is no increase compared to normal

**General symptoms: Temperature**

- Please use the provided thermometer.
- Take your temperature each day from day of vaccination (day 0) until day 3, and write down the values.
- If you took more than once a day your temperature, then write down the highest one.

Example: if on Day 0
- At 8 am: 99.1
- At 1 pm: 99.4
- At 7 pm: 99.6

99.6 is to be recorded in for Day 0

- Please write down NT (Not Taken) if you did not take the temperature.
<table>
<thead>
<tr>
<th>Subject Number</th>
<th>DIARY CARDS</th>
<th>Vaccine Booster Dose</th>
<th>To be completed by the investigator or delegate</th>
</tr>
</thead>
</table>

### GENERAL SYMPTOMS

<table>
<thead>
<tr>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>After Day 3</th>
<th>Did you receive any medical attention?</th>
<th>Type of medical attention</th>
<th>Relationship to inv. Product</th>
</tr>
</thead>
</table>

#### Temperature
- [☐] No
- [☐] Yes

#### Ongoing
- [☐] 99.5°F or higher Oral
- [☐] Highest Temp.

#### End Date

#### Route of measurement:
- [☐] Oral (in the mouth) (preferred)

- [☐] No
- [☐] Yes

---

**Clarification(s) for Investigator or delegate only:**

---

Diary Cards template version 14 – June 28, 2012 – System page: 11
INTENSITY DEFINITIONS

- Headache: Intensity: 0 Normal 1: Headache that is easily tolerated 2: Headache that interferes with normal activity 3: Headache that prevents normal activity
- Fatigue: Intensity: 0 Normal 1: Fatigue that is easily tolerated 2: Fatigue that interferes with normal activity 3: Fatigue that prevents normal activity
- Gastrointestinal symptoms: Intensity: 0 Gastrointestinal symptoms normal 1: Gastrointestinal symptoms that interfere with normal activity 2: Gastrointestinal symptoms that prevent normal activity
<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Headache</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensity (0/1/2/3)</td>
<td>0/1/2/3</td>
<td>0/1/2/3</td>
<td>0/1/2/3</td>
<td>0/1/2/3</td>
</tr>
<tr>
<td>Did you receive medical attention?</td>
<td>No</td>
<td>Yes</td>
<td>1/2/3</td>
<td>No</td>
</tr>
<tr>
<td>HO/ER/MD</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Relationship to inv.</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

| **Fatigue**            |       |       |       |       |
|                        |       |       |       |       |
| Intensity (0/1/2/3)    | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 |
| Did you receive medical attention? | No | Yes | 1/2/3 | No |
| HO/ER/MD               | No   | No   | No   | Yes |
| Relationship to inv.   | No   | No   | No   | Yes |

| **Gastrointestinal symptoms** |       |       |       |       |
| Intensity (0/1/2/3)         | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 |
| Did you receive medical attention? | No | Yes | 1/2/3 | No |
| HO/ER/MD                   | No   | No   | No   | Yes |
| Relationship to inv.       | No   | No   | No   | Yes |

Clarification(s) for Investigator or delegate only:

Diary Cards template version 14 – June 28, 2012 – Sysems page 13
Instructions to complete:

Adverse Events

- If you experience(s) any other symptoms than those listed in the local symptoms or general symptoms pages, please write these symptoms down in this section.
- If a symptom appears only after day 3, please write this symptom down in this section.
- If redness, swelling or pain appears on another area than area where you received the vaccine, please report these symptoms in this section.

➢ INTENSITY DEFINITIONS

- 1: Mild. An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- 2: Moderate. An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
- 3: Severe. An adverse event which prevents normal, everyday activities.

➢ Box “Still ongoing” in the column “End date” – When to tick it?

- Tick the box “Still ongoing” if the illness / sign / symptom is still present at the time you return the diary card to the site.

➢ Did you receive any medical attention? How to complete this question?

- Medical attention means hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor).
- Tick the box “No” if you did not visit a doctor or go to the hospital or an emergency room for the symptom.
- Tick the box “Yes” if you went to the hospital, an emergency room or if you visited a doctor for the symptom. Keep the type of medical attention (grey column) empty. It will be completed by the study doctor or study staff.
ADVERSE EVENTS

Record any adverse event (= any illness, sign, symptom) other than the local and general symptoms listed on the previous pages, which may have started or any medical condition which may have worsened since the study vaccination.

<table>
<thead>
<tr>
<th>Illness/Sign/Symptom</th>
<th>Worst Intensity 1/3</th>
<th>Start Date</th>
<th>End Date</th>
<th>Did you receive medical attention?</th>
<th>Type of medical attention</th>
<th>Relationship to inv. Product</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tick box if still ongoing ☐

Did you receive medical attention?

☐ No ☐ Yes

Type of medical attention

☐ HO/ER/MD

Relationship to inv. Product

☐ No ☐ Yes

Clarification(s) for Investigator or delegate only:
VACCINATION

Record any vaccination received since the study vaccination

<table>
<thead>
<tr>
<th>Vaccination</th>
<th>Date of administration</th>
<th>Route*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Route codes: inhalation [IH], intraarticular [IR], intradermal [ID], intramuscular [IM], intranasal [IN], intravenous [IV], oral [PO], parenteral [PE], rectal [PR], subcutaneous [SC], sublingual [SL], topical [TO], transdermal [TD], vaginal [VA], other [OTH], unknown [UNK]

Clarification(s) for Investigator or delegate only:
Instructions to complete: Medication

- **Dose, unit and frequency**
  - Write the amount of the medication you took.

<table>
<thead>
<tr>
<th>Dose, unit and frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>200mg pill 3 times a day</td>
</tr>
<tr>
<td>2 coffee spoon 100mg 50ct per day</td>
</tr>
<tr>
<td>3 suppositories per day</td>
</tr>
<tr>
<td>Nasal drops 4 times per day</td>
</tr>
</tbody>
</table>

- Most of this information can be found on the label of the medication. You may want to bring the medication to your next visit with the study doctor or study staff. Then they can help you to fill in the required information.

- **Box “Still ongoing” in the column “End date” – When to tick it?**
  - Tick the box “Still ongoing” if the medication is still taken at the time you return the diary card to the site.
### MEDICATION

Record any medication taken since the study vaccination.

| Medication | Reason | Dose, unit and frequency | Start Date | End Date | Route*
|-------------|--------|--------------------------|------------|----------|---------
|             |        |                          |            |          |         
|             |        |                          |            |          |         
|             |        |                          |            |          |         
|             |        |                          |            |          |         
|             |        |                          |            |          |         
|             |        |                          |            |          |         
|             |        |                          |            |          |         
|             |        |                          |            |          |         

*Route codes = inhalation [IH], intraarticular [IR], intradermal [ID], intramuscular [IM], intranasal [IN], intravenous [IV], oral [PO], parenteral [PR], rectal [PR], subcutaneous [SC], sublingual [SL], topical [TO], transdermal [TD], vaginal [VA], other [OTH], unknown [UNK]]
<table>
<thead>
<tr>
<th>Subject Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot; &quot; &quot; &quot; &quot; &quot;</td>
</tr>
</tbody>
</table>

To be completed by the investigator or delegate

### NOTES

### INVESTIGATOR’S OR DELEGATE’S SIGNATURE

Investigator's or delegate's signature: _____________________ Date: __________

Printed Investigator's or delegate's name: _____________________
List of investigators, IEC/IRB and distribution of subjects

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Sub-Investigator</th>
<th>Center no.</th>
<th>Description of Research Facility, Hospital/Institution, and Address</th>
<th>Name of IEC/IRB Committee, Address</th>
<th>Number of Subjects</th>
<th>% of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohen, Kenneth</td>
<td>Baumgartner, Betty Bretz, Amber Carangi, Gwen Pavol, Bristol Wise, Roxanna</td>
<td>PPD</td>
<td>New West Physicians, 1687 Cole Blvd, Colorado, Golden, 80401, United States.</td>
<td>PPD</td>
<td>13</td>
<td>7.9</td>
</tr>
<tr>
<td>Fiel, Thomas</td>
<td>Anthony, Claire Cadwell, Kristina DiTullio-Merrill, Nicole Kellin, Christy Lopez, Jessica Lytle, Emily Taghavi, Sogol</td>
<td></td>
<td>Clinical Research Advantage, Inc, 1840 E. Baseline Road, Arizona, Tempe, 85283, United States.</td>
<td></td>
<td>6</td>
<td>3.6</td>
</tr>
<tr>
<td>Gilbert Jr., John</td>
<td></td>
<td></td>
<td>St. Jude Heritage Medical Group, 100 East Valencia Mesa Drive, California, Fullerton, 92835, United States.</td>
<td></td>
<td>4</td>
<td>2.4</td>
</tr>
<tr>
<td>Hedrick, James</td>
<td>Block, Stanley Cardin, Diane Denton, Christal Findlay, Rebecca Finn, Daniel Lewis, Kali Smith, Robert</td>
<td></td>
<td>Kentucky Pediatric/Adult Research, 201 South 5th Street, Kentucky, Bardstown, 40004, United States.</td>
<td></td>
<td>23</td>
<td>13.9</td>
</tr>
<tr>
<td>Investigator</td>
<td>Sub-Investigator</td>
<td>Center no.</td>
<td>Description of Research Facility, Hospital/Institution, and Address</td>
<td>Name of IEC/IRB Committee, Address</td>
<td>Number of Subjects</td>
<td>% of Subjects</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------------------------------------------</td>
<td>------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------</td>
<td>--------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Tyler, Ronald</td>
<td>Henry, Dan</td>
<td>PPD</td>
<td>J. Lewis Research, Inc., Foothill Family Clinic, 2295 Foothill Drive, Salt Lake City, 84109, United States.</td>
<td>PPD</td>
<td>13</td>
<td>7.9</td>
</tr>
<tr>
<td></td>
<td>Julian, Katie</td>
<td></td>
<td>J. Lewis Research, Inc., Jordan River Family Medicine Suite 100, 1868 West 9800 South, South Jordan, Utah, 84095, United States.</td>
<td></td>
<td>17</td>
<td>10.3</td>
</tr>
<tr>
<td></td>
<td>LaBarbera, Anthony</td>
<td></td>
<td>PEAK Research LLC, 2589 Washington Rd, Pennsylvania, Upper St. Clair, 15241, United States.</td>
<td></td>
<td>5</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>Leader, Joseph</td>
<td></td>
<td>Woburn Pediatric Associates, 7 Alfred Street, Massachusetts, Woburn, 01801, United States.</td>
<td></td>
<td>2</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>Munoz, Flor</td>
<td></td>
<td>Baylor College of Medicine, Texas Children's Hospital, One Baylor Plaza, Texas, Houston, 77030 United States.</td>
<td></td>
<td>2</td>
<td>1.2</td>
</tr>
<tr>
<td>Investigator</td>
<td>Sub-Investigator</td>
<td>Description of Research Facility, Hospital/Institution, and Address</td>
<td>Name of IEC/IRB Committee, Address</td>
<td>Number of Subjects</td>
<td>% of Subjects</td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------------------------------</td>
<td>--------------------</td>
<td>---------------</td>
<td></td>
</tr>
<tr>
<td>Nachman, Sharon</td>
<td>Beneri, Christy Ferraro, Denise Hymes, Saul Kelly, Michele</td>
<td>Stony Brook Clinical Trials Research Center, 33 Research Way East Setauket New York, 11733, United States.</td>
<td>PPD</td>
<td>1</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Rathore, Mbeen</td>
<td>Alarcon, Andres Alvarez, Ana Armas-Kolostroubis, Laura Bragg, Leigh Fulton, Carol Mahmoudi, Saniyyah Maraq, Nizar Mirza, Ayesha Ravi, Maleswari Wells, Saran</td>
<td>University of Florida Health Sciences Center, 653-1 West 8th Street, Florida, Jacksonville, 32209, United States.</td>
<td></td>
<td>1</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Rouse, Kevin</td>
<td>Buxton, Gregory Edwards, Angela George, Stacey Johnson, Roehl Matthews, David Skaug, Phyllis Sloan, Amber Sneed, Jane</td>
<td>The Children's Clinic of Jonesboro, 800 South Church Street, Arkansas, Jonesboro, 72401, United States.</td>
<td></td>
<td>2</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Senders, Shelly</td>
<td>Bowen, Dawn Bucchieri, Elizabeth Caschera, Julia</td>
<td>Senders Pediatrics, 2054 South Green Road, Ohio, Cleveland, 44121, United States.</td>
<td></td>
<td>5</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Investigator</td>
<td>Sub-Investigator</td>
<td>Center no.</td>
<td>Description of Research Facility, Hospital/ Institution, and Address</td>
<td>Name of IEC/IRB Committee, Address</td>
<td>Number of Subjects</td>
<td>% of Subjects</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------------------</td>
<td>------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------------------------------</td>
<td>--------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Childress, Brandie Kelmes, Kelly Mann, Andrea Rybak, Tiffany Sangree, Jill Witt, Ann</td>
<td></td>
<td>PPD</td>
<td>Peninsula Research Associates, 550 Deep Valley Drive, Suite 317, California, Rolling Hills Estates, 90274, United States.</td>
<td>PPD</td>
<td>5</td>
<td>3.0</td>
</tr>
<tr>
<td>Sher, Lawrence</td>
<td>Saad, Nadra</td>
<td>PPD</td>
<td>Desert Clinical Research, LLC, Clinical Research Advantage, 2310 East Brown Road, Arizona, Mesa, 85213, United States.</td>
<td></td>
<td>25</td>
<td>15.2</td>
</tr>
<tr>
<td>Shockey, Gerald</td>
<td>Bruce, David Gardner, Mara Grucky, Marian Hawking, Nicole Kocour, Jennifer Laufer, Robert Munson, Leslie Naholowaa, Callie Osesky, Kimberly Raban, Trisha Shea, Lisa Wheeler, Brittany</td>
<td>PPD</td>
<td>Creighton University Medical Center, 601 North 30th Street, Dept. of Pediatrics Suite 6820, Nebraska, Omaha, 68131, United States.</td>
<td></td>
<td>28</td>
<td>17.0</td>
</tr>
<tr>
<td>Investigator</td>
<td>Sub-Investigator</td>
<td>Center no.</td>
<td>Description of Research Facility, Hospital/ Institution, and Address</td>
<td>Name of IEC/IRB Committee, Address</td>
<td>Number of Subjects</td>
<td>% of Subjects</td>
</tr>
<tr>
<td>-------------------</td>
<td>------------------</td>
<td>------------</td>
<td>---------------------------------------------------------------------</td>
<td>-----------------------------------</td>
<td>-------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Synowiecki, Barbara Vasudevan, Jayan Wilderman, Patricia Yager, Amy Yaghmour, Anthony</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yogev, Ram</td>
<td>Stamos, Julie</td>
<td>PPD</td>
<td>Lurie Outpatient Center in Lincoln Park, 2515 North Clark Street, Illinois, Chicago, 60614, United States.</td>
<td>PPD</td>
<td>1</td>
<td>0.6</td>
</tr>
</tbody>
</table>
Representative written information for patient and sample consent forms
Instructions for Local ICF development

The LOC should ensure that all local legal regulatory requirements are satisfied before finalizing the Local ICF. It is strongly recommended to align the content of the Local ICF with the content of the Model ICF and this template.

When developing a Local ICF, all changes to the content that affect the meaning of the Model ICF should be justified and documented locally. Any black bold text in the final Model ICF is GSK Biologicals’ mandatory wording and should be retained; any alterations or additions to this text must be communicated to the central team prior to the finalization of the local ICF.

Refer to Appendix A Best Practices document for the development of the Local ICF.

Note: In the final Local ICF all text should be in the same format i.e. any bold text must be in normal font and red hidden text must not be retained.

Refer to SOP_54823, GUI_51905 and GUI-BIO-CLIN-0014 for more information.

(Delete the instructions above from the Final Local ICF).
INFORMED CONSENT FORM

Study Identification: 116570 [DTPA 0.3 (BOOSTRIX)-012 Ext: 001]

Study Title: Evaluation of GSK Biologicals’ Tdap booster vaccine (Boostrix™) in young adults, administered 10 years after previous Tdap boosting.

Model ICF Version Number: 1 (replace with Version of Local ICF)

Date: 24/May/2012 (replace with Date of Local ICF)

Company Name: GlaxoSmithKline (GSK) Biologicals S.A.

Subject Identification: ________________

What is consent?

Consent means agreeing to take part in this research study. You can decide if you want to take part in this study or not. Please take time to read the following information and ask the study doctor or study staff if you have any questions. They will explain the study fully to you. You can talk in confidence with your family, friends and your doctor to help you make a decision. You must sign the Consent pages at the end of this form if you decide to join this study. You will receive a copy of this form.

Why is this study being done?

You have been contacted because you have shown interest to participate in this follow-up study. This is a follow-up of a previous study- 776423/001 [DTPA 0.3 (BOOSTRIX)-001] in which you took part, 10 years ago.

The vaccine (Tdap) is approved in the USA under the trade name Boostrix for protecting against 3 severe diseases:

- Diphtheria is an infection of the throat. Children with diphtheria may stop breathing, have permanent damage to the heart and brain, or even die.
- Tetanus is an infection of the blood. It causes strong cramps that prevent breathing and can lead to death.
- Pertussis is a highly infectious disease characterized by severe coughing during which children are unable to breath. The disease can lead to death.

It is recommended that a booster dose for diphtheria and tetanus should be administered every ten years. But the optimal time for booster dose of pertussis vaccine is not yet known.

Booster dose against pertussis protects against the disease and prevents transmission to infants and adolescents.
Informed Consent Form

CONFIDENTIAL
Study Identification 116570 [DTPA 0.3 (BOOSTRIX)-012 Ext: 001]

This study is being done to test the amount of antibodies produced by your body by Boostrix vaccine. This study will tell us how your immunity is 10 years after your previous vaccination, and how it can be strengthened by a booster vaccination.

Vaccination is the best way to protect against these diseases and Boostrix vaccine provides protection in only one injection.

How is GSK involved?

GSK is a company that studies and makes vaccines, medicines and other health products. GSK planned and organized this study. GSK pays the study doctor and the institution to run this study.

GSK will be the owner of the study results. GSK plans to use these to get patents, sell the vaccine in the future or make profits in other ways. You will not be paid for any part of this.

The information and materials we give you about this study are confidential and belong to GSK. We ask that you keep it private. You can share this information with your doctor, family or friends when discussing about your participation in this study and your healthcare.

Who can join this study?

You can participate in this study if:

- You have taken part in the previous trial 776423/001 [DTPA 0.3 (BOOSTRIX)-001] conducted by GSK Biologicals, 10 years ago.
- You have not had a booster vaccination against diphtheria, tetanus, pertussis since the last dose received in the study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].
- You do not have a history of diphtheria, tetanus or pertussis diseases since the previous vaccination.
- You are not pregnant or breast-feeding your baby (if applicable).
- You are healthy.
- You have not had any serious side effects after previous administration of diphtheria, tetanus or pertussis vaccines.

The study doctor will also explain and check some other aspects before you can join this study. You can ask your study doctor for more details.

What does this study involve?

About 500 people who participated in the previous study 776423/001 [DTPA 0.3 (BOOSTRIX)-001] will be invited to participate in this follow-up study. When we have enough people taking part in this study, we will not include or invite any more. There will be two groups in this study- Tdap Group, and Td Group and all people in both the groups...
Informed Consent Form

CONFIDENTIAL
Study Identification 116570 [DTPA 0.3 (BOOSTRIX)-012 Ext: 001]

will receive a single dose of *Boostrix* vaccine. Depending on the vaccine you received in
the previous study 10 years back, you will be assigned to a group:

- **Tdap Group**: You received Tdap vaccine previously and will receive the second dose
  of Tdap vaccine in this study.
- **Td Group**: You received the Td vaccine previously and will receive the first dose of
  Tdap vaccine in this study.

The study will last for approximately 6 months. You will need to visit the study site 2
times and will receive 1 phone call by the study staff. Information about the effect of the
vaccine on your body and on your health will be collected by taking a blood sample and
asking you questions. You will get 1 vaccine shot in upper part of your arm. You will
have 2 blood draws, one before vaccination and the second one, a month after
vaccination. You will have to complete a diary card during the 30 days after the
vaccination.

If you take part in this study then it is important that you follow all study activities as
described here below:

<table>
<thead>
<tr>
<th>Visit</th>
<th>What will happen at this visit</th>
</tr>
</thead>
</table>
| **Visit 1 (Day 0)** | You will be explained the study procedures and you will be asked to sign the present “informed consent” document.  
The doctor will ask you about your medical and vaccination history.  
You will undergo:  
  • Physical examination including measurement of body temperature  
  • Urine pregnancy test (if applicable)  
  • You will undergo blood sampling  
  • Administration of *Boostrix* vaccine  
You will receive a diary card and will be asked to use it to record any symptom you experience in the coming month until the next visit. |
| **Visit 2 (Day 30)** | You will return the diary card.  
The doctor will ask you whether you have received any medication or vaccination since the last visit.  
You will undergo:  
  • Blood sampling |
| **Phone Contact (Month 6)** | You will have to report if you experienced any serious side effects or symptoms during the 5 months after your last visit to the study site.  
End of the study. |

In addition, you should call the doctor if at any time during the study:

- you are hospitalized
- you have symptoms that interfere greatly with your ability to carry out your normal daily activities

Note: You should contact the health care provider immediately should you have any signs or symptoms you think may be serious.

Local (USA) ICF Version Number **NN**, Dated: **DD/MMM/YYYY**, based on Model ICF Version Number 01,  
Dated: **24-MAY-2012**

(Page 3 of 11)
What about pregnancy and breastfeeding?

It is not known whether the vaccine used in this study may have an effect on the unborn baby. You should not join this study if you are pregnant. Mothers should not breastfeed a baby while in this study.

If you are a woman who can get pregnant, you will need to use birth control while in this study. You will have a urine pregnancy test before receiving the booster dose of the vaccine. Check with the study doctor about what kind of birth control methods to use and how long to use them. Some methods may not be allowed to use during this study.

Tell the study doctor if you are pregnant. If you get pregnant during the study, you will need to remain in the study for follow-up. We will follow-up until the delivery of the baby.

What will happen to samples taken in this study?

The content of this section needs to be aligned with the Use of Human Samples form. Any request to changes in this section must be discussed with the central study team and the GSK Biologicals' ICF taskforce prior to finalization of the ICF.

As part of the study, you will be asked to give samples of your blood. Your blood samples may be sent to GSK or other laboratories working with GSK including those outside [insert name of country] to:

- Measure how your body reacts to the study vaccine.

Your samples will be given a code so that it does not directly identify you.

Your samples will be kept for a maximum of 20 years from the end of the study. Any sample remaining at that time will be destroyed.

Optional tests on your samples:

If you agree, your sample(s) may also be used for future research. GSK will always ask approval for this research to an independent ethics committee or independent review board.

You can choose not to allow these optional tests and still be in the study.

What side effects or risks can you expect in this study?

The potential risks associated with receiving the study vaccine is similar to those seen with routine vaccination:
Informed Consent Form

CONFIDENTIAL
Study Identification 116570 [DTPA 0.3 (BOOSTRIX)-012 Ext: 001]

Side effects observed within 4 days of vaccine administration:

- Injection site reactions: Pain, redness and swelling.
- General side effects: Tiredness, fever, headache, vomiting, diarrhea and abdominal pain.

Expected risks for adults are detailed below according to the following frequency of occurrence:

- Very common: Injection-site pain, injection-site reactions (such as redness and/or swelling), tiredness and headache.
- Common: Fever (greater than or equal to 99.5°F), hard lump and pus at injection site, nausea and dizziness.
- Uncommon: Fever (greater than 102.2°F), vomiting, sore throat, cough, fainting, skin rash, flu like symptoms like fever, sore throat, runny nose, cough and chills, muscle tension, muscle pain, joint stiffness, excessive sweating, severe itching all over the body, swelling of glands in neck, groin and arm pits.
- Rare: Water retention with swelling of the injected limb, allergic reaction, (characterized by swelling of lips, tongue, or other parts of the body, shortness of breath, rashes across body and difficulty swallowing), unusual weakness, seizures and hives.
- Very rare: As with all injectable vaccines, severe allergic reactions (anaphylactic and anaphylactoid reactions) may very rarely occur. They are characterized by, itchy rash of the hands and feet, swelling of the eyes and face, difficulty in breathing or swallowing, sudden drop in blood pressure and loss of consciousness.

BOOSTRIX can cause side effects that may be mild or more severe. We will follow-up everyone in the study for any side effects.

There may be other side effects that are not known now.

The following side effects related to the study procedures may occur:

When you give blood, you may feel faint, or locally experience mild pain, bruising, irritation or redness.

The vaccines in this study may not protect all people who get them. Your response to the vaccine in this study will be tested. In some cases, the test results may show your response to the vaccination was not optimal. If the study doctor believes you would benefit from another vaccination, he or she will contact you.

**What benefits can you expect in this study?**

This study may be beneficial to you. In this case benefits include:

- The opportunity to protect yourself against 3 major diseases- diphtheria, tetanus and pertussis.
Informed Consent Form

Study Identification 116570 [DTPA 0.3 (BOOSTRIX)-012 Ext: 001]

- A detailed assessment of your response to the vaccination through analysis of blood samples, a procedure not usually performed outside a study situation.
- Information from this study helps to learn more about the vaccine or disease.
- The vaccine and study tests will be free for you.

**Are there other products or treatment?**

*This section should be completed locally using the most current information regarding the treatments/vaccines/products that are available in the country and their important potential benefits and risks. State if there are no alternate treatments.*

You may choose another booster vaccine for diphtheria, tetanus and pertussis. Talk with your doctor about your options, before you decide if you will take part in this study. The study doctor can advise you if you need more information.

**Do you have to stay in the study?**

You may choose to leave the study at any time, without giving a reason. If you do give a reason, then it may be recorded. Your choice will not change the medical care or other benefits you receive outside of this study.

We will share with you as soon as possible any new information that may change your choice to stay in the study.

Tell the study doctor if you no longer want to take part.

GSK may choose to stop the study or the study doctor may choose to stop your participation in the study at any time. We will then tell you why. We may ask you to leave the study if:

- Test results show that this study is not right for you
- You do not follow study instructions
- The study doctor thinks it is in your best interest to stop, e.g. if you have specific health problems.

**What happens if you leave the study?**

*Check local regulations and seek local legal advice for the use of data after subject/patient withdrawal. If any changes are made to this section in the Local ICF compared to the Model ICF, in response to a request from any source, these should be discussed with the central study team and GSK Biologicals ICF taskforce for alignment prior to the finalization of the local ICF, so that the impact for database collection can be taken into account.*
Informed Consent Form

CONFIDENTIAL
Study Identification 116570 [DTPA 0.3 (BOOSTRIX)-012 Ext: 001]

No more information about you will be collected after you leave the study. All the information and samples collected before you left the study will still be used.

If the doctor becomes aware of any relevant safety information about you after you left the study, this will be collected.

We may also contact you later for information. This is to help us better understand the safety profile of the vaccine.

What about your personal and medical information?

If changes are made to this text it needs to be checked with the local Legal team that this is aligned with local rules and regulations.

It is very important that your personal and medical information stay confidential and secure. Your personal and medical information will be protected in accordance with current law.

When you sign this consent form you agree that your personal and medical information can be used as described here.

- Your personal and medical information may be checked by GSK and others (like agencies that approve and monitor studies for example, Food and Drug Administration (FDA)). This is to make sure that the study is being run properly.
- Besides that, only the researchers at this study site can use information that identifies you (such as name and address) and only for the purpose of the study.
- Your information collected during the study will be labeled with a code number (for example, PPD). It will not include your name or address. The study doctor will have the link between your name and the code number.
- The link between your name and the code number will not be shared. Only the code number and coded information will be sent to GSK.
- GSK will use your coded information for research only, including research looking at improving the quality and efficiency in conducting clinical research trials in general.
- GSK may:
  - Keep it electronically, and analyze it by computer to find out what the study is telling us. This may be done by GSK or a third party, in which case GSK will ensure that the third party is required to keep your data secure.
  - Share it with regulatory agencies that approve new vaccines and medicines,
  - Share it with people who check that the study is done properly (like the independent ethics committee or review boards),
  - Combine it with results from other studies to learn more about the vaccine, other vaccines and this disease and related diseases. This may help us to assess the risks

Local (USA) ICF Version Number NN, Dated: DD/MMM/YYYY, based on Model ICF Version Number 01, Dated: 24-MAY-2012

(Page 7 of 11) [Template Edition 6.1]
Informed Consent Form

Study Identification 116570 [DTPA 0.3 (BOOSTRIX)-012 Ext: 001]

and benefits of GSK (or other) vaccines or medicines, or to improve disease understanding,

- Publish study results in medical journals, for meetings and on the internet for other researchers to use. Your name will not appear in any publication.

Share coded information with other companies, organizations or universities to carry out research, including research looking at improving the quality and efficiency in conducting clinical research trials in general.

Personal and medical data collected during the trial may be moved to, stored and used in the country where you live or another country where GSK or those working with GSK work.

Use of this information may take place in countries with lower data protection rules than the country where you live. GSK will make sure that if your data are moved to another country, it will still be treated as stated in this Informed Consent Form.

A description of this clinical trial will be available on the GSK Clinical Study Register http://www.gsk-clinicalstudyregister.com/ and may also appear in clinical trial registries in countries in which the clinical study is conducted.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

If you withdraw your consent for us to use your personal information you will no longer be able to continue in the study.

At any time, you may ask to see your personal information and correct it if necessary.

In some circumstances you may not be able to access your study information while the study is ongoing. However the study doctor will share any important medical information if it is relevant to your health during the course of the study.

You should know that once identifiable medical information about you is given to someone that is not a health care provider, it is not protected by the US federal privacy rules called the HIPAA Privacy Regulations.

What happens if you get hurt while taking part in this study?

GSK will help pay for your care if you are hurt by the study vaccine or a procedure done to you as part of the study. GSK will pay for reasonable and necessary care for the injury that is not covered by the National Vaccine Injury Compensation Fund. GSK will not pay for any other expenses. To pay these medical expenses, GSK will need to know some information about you like your name, date of birth, and social security number or Medicare Health Insurance Claim Number. This is because GSK has to check to see if
Informed Consent Form

Study Identification 116570 [DTPA 0.3 (BOOSTRIX)-012 Ext: 001]
you receive Medicare and if you do, report the payment it makes to Medicare. GSK will not use this information for any other purpose.

Signing this consent form does not change any legal rights you may have.

**Will you be paid for being in the study?**

This section should be completed locally.

We will reimburse you for the cost of travelling to your study visits. You may receive up to [amount] for travel / per visit.

**Do you have to pay anything to be in the study?**

Authors note that this section is optional. This section should be completed locally.

You will get all the study tests and procedures for free [or indicate if there is a cost].

**Who should you contact if you have questions?**

Identify who the subject/ legally acceptable representative should contact for information about the study, the subject's rights or study-related injuries. This section may be completed at Country Level.

Person to contact for any questions: name, address, telephone number.

Person to contact about your rights: name, address, telephone number.

Person to contact in case of injury: name, address, telephone number.
CONFIDENTIAL
Study Identification 116570 [DTPA 0.3 (BOOSTRIX)-012 Ext: 001]

Consent statement

I, ____________________________________________

Printed name of Subject

• confirm that I have read the written information (or have had the information read to me) for study 116570 [DTPA 0.3 (BOOSTRIX)-012 Ext: 001], Version 1, 24/May/2012, 11 pages (to be updated locally), and the study procedures have been explained to me by study staff during the consent process for this study.

• confirm that I have had the chance to ask questions about this study and I am satisfied with the answers and explanations that have been given.

• understand that I give access to data about me to authorized persons described in this information sheet.

• I know what will happen to my blood samples

• understand that by signing this form any of my identifiable medical information given to someone that is not a health care provider is not protected by the US federal privacy rules called the HIPAA Privacy Regulations.

• have been given time and opportunity to consider taking part in this study.

Tick as appropriate (this decision will not affect your ability to enter the study):

I agree that my family doctor will be told about my participation in the study.

☐ Yes ☐ No

Tick as appropriate

I agree that my biological sample(s) may be used for future research. GSK will always ask approval for this research to an independent ethics committee or independent review board. I understand that if I select “No”, I can still take part in the study.

☐ Yes ☐ No

I agree to take part in this study.

Signature of subject ________________________________ Date: day/ month/ year

Local (USA) ICF Version Number NN, Dated: DD/MMM/YYYY, based on Model ICF Version Number 01, Dated: 24-MAY-2012

(Please sign and date above)

(Page 10 of 11) [Template Edition 6.1]
Informed Consent Form

Subject ID ________________

Study Identification 116570 [DTPA 0.3 (BOOSTRIX)-012 Ext: 001] I confirm that I have conducted the consent process according to applicable regulations.

Printed name of person conducting consent __________________________

Signature of person conducting consent __________________________ Date: day/ month/ year

Local (USA) ICF Version Number NN, Dated: DD/MMM/YYYY, based on Model ICF Version Number 01, Dated: 24-MAY-2012

(Page 11 of 11) [Template Edition 6.1]
Delete the following Appendix in the Final local ICF.

Appendix A  GlaxoSmithKline Biologics Best Practices Document for the Development of the Local ICF

Introduction

The local informed consent form (ICF) is created based on the GSK Biologics internally approved model ICF and is adapted according to country or local requirements.

The model ICF is the recommended content and structure which contains all ICH and GSK required elements and is aligned with the study protocol.

The content of the local ICF should be aligned with the Model ICF and any local specifications and regulations included.

The local GSK approved version should be submitted for ethical/regulatory approval and should be presented to the subject/patient and/or their legally acceptable representative.

It is essential that the version of the local ICF is accurately tracked, with a unique version number, date and reference to the model ICF on which it is based, to ensure that the correct version of the ICF is used and can be identified if needed.

It is strongly recommended to have a final local ICF, back-translated in English, available in the Investigator’s study file to ensure site readiness in case of audits and/or inspections.

Objective

These best practices are intended to give adequate support and to ensure consistency while developing the local ICF from the model ICF.

It is a tool to know what changes are not permitted and what changes can be justified and/or are required per local regulations and site specific information.

The development of the accurate and complete local ICF is a local responsibility and alignment with the model ICF is essential to study conduct.

Any changes made to the local ICF from the model ICF must be documented at local level.

Human Sample Management

The collection of human tissue samples, the intended use, and secondary use, if retained, and how the subject’s confidentiality would be maintained for the retained samples, must be reported in the ICF.

The content of this section must be fully aligned with the Use of Human Samples form. This form allows the central project team to track the actual testing at GSK (or laboratories used for GSK-sponsored studies) with the individual subject’s consent and
Best Practices Document for the Development of the Local ICF

local regulations. To avoid ethical and legal implications and invalidating the study data, any changes made to this section must be discussed with the central project team and GSK Biologicals’ central ICF taskforce for alignment prior to the finalization of the local ICF.

Subject/patient data after withdrawal

The retention of samples collected and data recorded before withdrawal and the continued collection of safety information after withdrawal must be reported in the ICF. Check local regulations and seek local legal advice for the use of data after subject/patient withdrawal. If any changes are made to this section in response to a request from any source, these changes must be discussed with the central project team and GSK Biologicals’ central ICF taskforce for alignment prior to the finalization of the local ICF, so that the impact for database collection and sample destruction can be taken into account

Type of changes

Changes to the local ICF can be classified into 3 categories:

‘Not permitted’ changes

BOLD BLACK mandatory text in the model ICF should not be changed.

‘Required’ changes

Required changes must be made in the local ICF to add country-specific or center-specific information. (Indicated as BOLD RED text in the model ICF e.g. investigator details).

‘Justified’ changes

Justified changes may be necessary in some countries to comply with local requirements / regulations or to comply with a specific template e.g. country specific compensation guidance text.

In addition, some text can be clarified / simplified, provided the meaning remains the same as in the model ICF and does not contradict or change the intended meaning of the model ICF.

Changes that require a specific rationale or justification, that may be necessary in specific situations e.g. storage duration of samples, or changes required by the relevant Ethics Committees, can also be justified.

Best Practices per ICF Section

This table describes the type of changes (not permitted, required or justified) for each ICF section of the local ICF compared to the model ICF.
## ICF section

<table>
<thead>
<tr>
<th>Study Identification</th>
<th>Type of changes</th>
<th>Rationale/Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Check if study identification is identical to Model ICF.</td>
<td>Not permitted</td>
<td>The study identification and study number allows us to link the document to the study protocol, the corresponding IRB/IEC approvals, all relevant study documentation and ensures that the subject/patient is linked to the correct study.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Title</th>
<th>Type of changes</th>
<th>Rationale/Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Check if study title is identical to Model ICF.</td>
<td>Not permitted</td>
<td>The study title allows us to link the document to the study protocol, the corresponding IRB/IEC approvals, all relevant study documentation and ensures that the subject/patient is linked to the correct study.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICF Version Number and Date</th>
<th>Type of changes</th>
<th>Rationale/Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Update with version and date of Local ICF and check if reference to the Model ICF version and date is included. Specify country and subset if applicable.</td>
<td>Required</td>
<td>It is mandatory to include an ICF version number, the date of the final version, the page number and the total number of pages (for the Local and Model ICF). Each ICF type has to be uniquely identified and must include a reference to the source. The version of the local ICF allows us to link the ICF to the corresponding approval documents. If the version is omitted in the local ICF, the subject may not receive the most up to date ICF and thus may not receive the complete information required to make an informed consent.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Type of changes</th>
<th>Rationale/Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Check if company name is GlaxoSmithKline (GSK) Biologicals S.A. or the local GSK affiliate if this is required by local regulations.</td>
<td>Justified</td>
<td>A change to this section is permitted if it is justified by local regulations. For some countries, the local GSK affiliate should be indicated as Company Name.</td>
</tr>
</tbody>
</table>
# Best Practices Document for the Development of the Local ICF

## ICF section

<table>
<thead>
<tr>
<th>Subject/Patient Identification</th>
<th>Type of changes</th>
<th>Rationale/Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Check whether there is space foreseen to insert the subject ID.</td>
<td>Required</td>
<td>The subject/patient ID should be mentioned on the ICF to be able to link the subject/patient ID with the corresponding source documents and RDE entries.</td>
</tr>
</tbody>
</table>

## Header

| Check if study identification in header is identical to Model ICF. | Not permitted | The study identification and study number allows us to link the document to the study protocol, the corresponding IRB/IEC approvals, all relevant study documentation and ensures that the subject/patient is linked to the correct study. |

## Footer

| Indicate version of Local ICF and check if reference to the Model ICF version is included. Specify country and subset if applicable. | Required | It is mandatory to include an ICF version number, the date of the final version, the page number and the total number of pages (for the Local and Model ICF). Each ICF type has to be uniquely identified and must include a reference to the source. The version of the local ICF allows us to link the ICF to the corresponding approval documents. If the version is omitted in the local ICF, the subject/patient may not receive the most up to date ICF and thus may not receive the complete information required to make an informed consent. |

## What is consent?

<p>| Explain the consent process and check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary). | Justified | Freely given and written informed consent must be obtained from each subject/patient/LAR prior to study participation. Informed consent involves an education and information exchange that takes place between the researcher and the potential subject/patient. How the process of consenting looks like, needs to be explained in the |</p>
<table>
<thead>
<tr>
<th>ICF section</th>
<th>Type of changes</th>
<th>Rationale/Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Why is this study being done?</td>
<td></td>
<td>ICF. The text can be simplified, if necessary.</td>
</tr>
<tr>
<td>Describe the study aim and check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).</td>
<td>Justified</td>
<td>The content of this section is required by ICH-GCP. If any of this information is omitted in the local ICF, the subject/patient may not receive the complete information required to make an informed consent. Text can be simplified if necessary.</td>
</tr>
<tr>
<td>How is GSK involved?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).</td>
<td>Justified</td>
<td>The role of the sponsor should be explained in this section. The text can be simplified if necessary.</td>
</tr>
<tr>
<td>Who can join this study?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summarize the main inclusion and exclusion criteria. Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).</td>
<td>Justified</td>
<td>If any of this information is omitted in the local ICF, the subject/patient may not receive the complete information required to make an informed consent. Text can be simplified if necessary.</td>
</tr>
<tr>
<td>What does this study involve?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Explain the approximate number of subjects/patients involved in the study, the study design and groups, the study procedures and check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).</td>
<td>Justified</td>
<td>The content of this section is required by ICH-GCP. If any of this information is omitted in the local ICF, the subject/patient may not receive the complete information required to make an informed consent. Text can be simplified if necessary.</td>
</tr>
<tr>
<td>If subject cards are used, check if the text is identical to the Model ICF.</td>
<td>Not permitted</td>
<td>Subject cards provide information about the study which can be used in the event of a medical emergency. Provision of this information in the ICF ensures that the subject/patient is aware of the use of the subject card. This</td>
</tr>
</tbody>
</table>
### Best Practices Document for the Development of the Local ICF

<table>
<thead>
<tr>
<th>ICF section</th>
<th>Type of changes</th>
<th>Rationale/Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>What about pregnancy and breastfeeding?</td>
<td></td>
<td>Information will also indicate to the ethics committee that it is provided to the subject/patient.</td>
</tr>
<tr>
<td>Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).</td>
<td>Justified</td>
<td>If any of this information is omitted in the local ICF, the subject/patient may not receive the complete information required to make an informed consent. Text can be simplified if necessary.</td>
</tr>
<tr>
<td>What will happen to samples taken in this study?</td>
<td></td>
<td>Justified</td>
</tr>
<tr>
<td>Check if all mandatory wording from the Model ICF is present in the Local ICF.</td>
<td>Not permitted</td>
<td>If this text is changed, there is a risk to use human samples outside the subject's/patient’s consent. This has major ethical implications and can lead to a loss of company reputation, lack of confidence, invalid study data etc….</td>
</tr>
<tr>
<td>Check if the content of this section is aligned with the Use of Human samples form (UHSF).</td>
<td>Not permitted</td>
<td>The text in the ICF should match 100% with the information documented in the UHSF. This form allows the central project team to track the actual testing at GSK (or laboratories used for GSK-sponsored studies) with the individual subject’s/patient’s consent and local regulations. If this text is changed, there is a risk to use human samples outside the subject’s/patient’s consent. This has major ethical and legal implications and can lead to a loss of company reputation, lack of confidence, invalid study data, etc….</td>
</tr>
</tbody>
</table>
### Best Practices Document for the Development of the Local ICF

<table>
<thead>
<tr>
<th>ICF section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Check if the QA (Quality Assurance) on tests related to the study vaccine/disease (type 2 testing) is reported in the Local ICF.</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>QA testing will be done at all times, assuming it is allowed as per individual subject's/patient’s consent. If QA testing is not mentioned in the ICF, there is a risk that GSK will be unable to perform the protocol tests and therefore this type of testing cannot be omitted.</td>
</tr>
</tbody>
</table>

<p>| Check local regulations regarding tests related to the product/disease under study (type 3a and 3b testing). [If there are concerns regarding this text then this should be discussed with the central team and GSK Biologicals’ central ICF taskforce for alignment prior to the finalization of the local ICF] | Justified | A change to this section is justified, since type 3a or 3b should be chosen according to local regulations. However, the wording of the text itself, should not be changed! We capture this info in the CRF/eCRF by the mean of the UHSF, which contains standard wording. So if the wording in the ICF is changed, this will not be matching with the UHSF. This form allows the central project team to track the actual testing at GSK (or laboratories used for GSK-sponsored studies) with the individual subject’s consent and local regulations. If this text is changed, there is a risk to use human samples outside the subject’s consent. This has major ethical and legal implications and can lead to a loss of company reputation, lack of confidence, invalid study data, etc….. |</p>
<table>
<thead>
<tr>
<th>ICF section</th>
<th>Type of changes</th>
<th>Rationale/Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Check Local regulations regarding storage duration. Check if the wording “for a maximum of 20 years” is not changed into “for 20 years”. [If there are concerns regarding this text then this should be discussed with the central project team and GSK Biologics’ central ICF taskforce for alignment prior to the finalization of the local ICF]</td>
<td>Justified</td>
<td>It is necessary to put a defined storage period in the ICF. As a standard, GSK proposes to store samples for “for a maximum of” 20 years. Attention should be paid to the used wording “for a maximum of” 20 years. This wording allows GSK to cover different situations (e.g. to keep samples for maximum 20 years, to destroy samples when GSK no longer wants to store them or no longer is interested in testing, when physical integrity of some type of samples does not permit such long storage, etc). Any changes to this section should be captured in the UHSF. This will allow the laboratory to take the appropriate measures for sample storage, “for a maximum of 20” years or as defined in the ICF and documented in the UHSF section called “other”.</td>
</tr>
<tr>
<td>Check local regulations regarding future research. [If there are concerns regarding this text then this should be discussed with the central project team and GSK Biologics’ central ICF taskforce for alignment prior to the finalization of the local ICF]</td>
<td>Justified</td>
<td>A change to this section is justified, since depending on local regulations, this type of testing is allowed or not. However, the wording of the text itself, should not be changed and nothing should be added! We capture this info in the CRF/eCRF by the mean of the UHSF, which contains standard wording so if the wording in the ICF is changed, this will not be matching with the UHSF. This form allows the central project team to track the actual testing at GSK (or laboratories used for GSK-sponsored studies) with the individual subject’s/patient’s consent and local regulations. If this text is changed, there is a risk to use human samples outside the</td>
</tr>
<tr>
<td>ICF section</td>
<td>Type of changes</td>
<td>Rationale/Impact</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>-----------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>subject’s consent. This has major ethical and legal implications and can lead to a loss of company reputation, lack of confidence, invalid study data, etc….</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What side effects or risks can you expect in the study?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).</td>
<td>Justified</td>
<td>The content of this section is required by ICH-GCP. The reasonably foreseeable risks or inconveniences to the subject should be mentioned in the ICF. If any of this information is omitted in the local ICF, the subject may not receive the complete information required to make an informed consent. Text can be simplified if necessary. Refer to the GSK Position Paper on ‘Communication of Individual Immunological Assay Results to Study Sites’ for additional information.</td>
</tr>
<tr>
<td>Check if the text on autoimmune diseases (applicable if product/vaccine contains an adjuvant) is identical to the Model ICF.</td>
<td>Not permitted</td>
<td>The text on autoimmune diseases has been approved by GSK upper management following feedback from Authorities. The AID wording should remain consistent in all projects and countries. There is a reputational risk associated to the fact that GSK might seem to be sharing different information with Subjects/Patients/Externally on AID.</td>
</tr>
<tr>
<td>Check if the text on Rotarix, if applicable, is identical to the Model ICF.</td>
<td>Not permitted</td>
<td>This text has been approved by GSK upper management following feedback from Authorities.</td>
</tr>
</tbody>
</table>

Best Practices Document for the Development of the Local ICF
# Best Practices Document for the Development of the Local ICF

## ICF section | Type of changes | Rationale/Impact
--- | --- | ---
**What benefits can you expect in the study?** | Justified | The content of this section is required by ICH-GCP. The reasonably expected benefits or indirect benefits or if there is no direct clinical benefit for the subjects/patients must be included in the local ICF. Text can be simplified if necessary.

Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary). | Justified | The content of this section is required by ICH-GCP. The reasonably expected benefits or indirect benefits or if there is no direct clinical benefit for the subjects/patients must be included in the local ICF. Text can be simplified if necessary.

**Are there other products or treatment?** | Justified | It is an ICH-GCP requirement to provide to the subject information on alternative procedures or treatment that may be available and their important potential benefits and risks. Omitting any of this information would be violating the rights of the subject/patient to freely participate to the study and would be putting the company reputation at risk. Text can be simplified if necessary.

Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary). | Required | This information must be added locally to the ICF using the most current information regarding the treatments that are available in the country.

Add currently available local alternatives, if applicable. | | |

**Do you have to stay in the study?** | Justified | The content of this section is required by ICH-GCP. Omitting any of this information would be violating the rights of the subject/patient to freely participate to the study and would be putting the company reputation at risk. Text can be simplified if necessary.

Explain voluntary participation and check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary). | | |

**What happens if you leave the study?** | Justified | The bold text in this section has been approved by Medical Governance. Changes to this

Check if the text on the use of data after subject/patient withdrawal is identical to the | | |
# Best Practices Document for the Development of the Local ICF

<table>
<thead>
<tr>
<th>ICF section</th>
<th>Type of changes</th>
<th>Rationale/Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model ICF.</td>
<td></td>
<td>section in response to a request from any source, can have an impact for database collection and sample handling and should therefore be discussed with the central teams for alignment. Also refer to GSK’s Clarification Paper on ‘Handling Data after Subject withdrawal’ for additional information.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>What about your personal and medical information?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary). [If the text needs to be changed, it should be reviewed by the local legal team]</td>
<td>Justified</td>
<td>The content of this section is required by ICH-GCP and must be included in the ICF so that the subject is well informed before consenting to participation. Omitting this information would be violating the confidentiality and the data privacy of the subject/patient and could have legal implications. Text can be simplified if necessary.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>What happens if you get hurt while taking part in this study?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- For UK, US and countries without special local regulations, check if compensation section is not changed compared to the section in the Model ICF. [If changes are made, the CMD (Country Medical Department) should ensure that all local legal regulatory requirements are satisfied.]</td>
<td>Justified</td>
<td>The content of this section is required by ICH-GCP. In the UK and in countries where there is no local scheme, GSK will apply the Clinical Trial Compensation guidelines set down by the UK Association of British Pharmaceutical Industry (ABPI) to compensate subjects/patients for GSK sponsored clinical study related injury.</td>
</tr>
<tr>
<td>- For other countries where there is compensation for injury, the CMD (Country Medical Department) should ensure that the rules and conventions required locally are applied.</td>
<td>Justified</td>
<td>The content of this section is required by ICH-GCP and must be completed so that the subject/patient is well informed before consenting to participation.</td>
</tr>
<tr>
<td>ICF section</td>
<td>Type of changes</td>
<td>Rationale/Impact</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Will you be paid for being in the study?</td>
<td>Information related to this section is added at a regional or country level.</td>
<td>Required</td>
</tr>
<tr>
<td>Do you have to pay anything to be in the study?</td>
<td>This section is optional. Information related to this section is added at a regional or country level when it is appropriate for a study and/or is required by local practice.</td>
<td>Justified</td>
</tr>
<tr>
<td>Who should you contact if you have questions?</td>
<td>Add local contact details.</td>
<td>Required</td>
</tr>
<tr>
<td>Consent statement</td>
<td>Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).</td>
<td>Justified</td>
</tr>
</tbody>
</table>
## References

SOP_54823, Development and implementation of Informed Consent for clinical studies.

GUI_51905, Guidance for Informed Consent documents.


GSK’s Position Paper on Communication of Individual Immunological Assay Results To Study Sites.

GSK’s Clarification Paper on Handling Data after Subject withdrawal.

GSK’s Clarification Paper on Future Use of Biospecimens
Instructions for Local ICF development

The LOC should ensure that all local legal regulatory requirements are satisfied before finalizing the Local ICF. It is strongly recommended to align the content of the Local ICF with the content of the Model ICF and this template.

When developing a Local ICF, all changes to the content that affect the meaning of the Model ICF should be justified and documented locally. Any black bold text in the final Model ICF is GSK Biologicals’ mandatory wording and should be retained; any alterations or additions to this text must be communicated to the central team prior to the finalization of the local ICF.

Refer to Appendix A Best Practices document for the development of the Local ICF.

Note: In the final Local ICF all text should be in the same format i.e. any bold text must be in normal font and red hidden text must not be retained.

Refer to SOP_54823, GUI_51905 and GUI-BIO-CLIN-0014 for more information.

(Delete the instructions above from the Final Local ICF).
Informed Consent Form

CONFIDENTIAL
Study Identification 116570 [DTPA 0.3 (BOOSTRIX)-012 EXT: 001]

INFORMED CONSENT FORM

Study Identification: 116570 [DTPA 0.3 (BOOSTRIX)-012 EXT:001]

Study Title: Evaluation of immunogenicity and safety of GSK Biologicals' Tdap booster vaccine (Boostrix™) in young adults, administered 10 years after previous Tdap boosting.

Model ICF Version Number: 02 (replace with Version of Local ICF)

Date: 17/October/2012 (replace with Date of Local ICF)

Company Name: GlaxoSmithKline (GSK) Biologicals S.A.

Subject Identification: __________________________ (Insert subject ID here)

What is consent?

Consent means agreeing to take part in this research study. You can decide if you want to take part in this study or not. Please take time to read the following information and ask the study doctor or study staff if you have any questions. They will explain the study fully to you. You can talk in confidence with your family, friends and your doctor to help you make a decision. You must sign the consent pages at the end of this form if you decide to join this study. You will receive a copy of this form.

Why is this study being done?

You have been contacted because you had shown interest to participate in this follow-up study. This is a follow-up of a previous study- 776423/001 [DTPA 0.3 (BOOSTRIX)-001] in which you took part, 10 years ago.

The vaccine (Tdap) is approved in the USA under the trade name Boostrix for protecting against 3 severe diseases:

- Diphtheria is an infection of the throat. Children with diphtheria may stop breathing, have permanent damage to the heart and brain, or even die.
- Tetanus is an infection of the blood. It causes strong cramps that prevent breathing and can lead to death.
- Pertussis is a highly infectious disease characterized by severe coughing during which children are unable to breath. The disease can lead to death.

It is recommended that a booster dose for diphtheria and tetanus should be administered every ten years. But the optimal time for booster dose of pertussis vaccine is not yet known.

Booster dose against pertussis protects against the disease and prevents transmission to infants and adolescents.
Informed Consent Form

This study is being done to test the amount of antibodies produced by your body by Boostrix vaccine. This study will tell us how your immunity is 10 years after your previous vaccination, and how it can be strengthened by a booster vaccination.

Vaccination is the best way to protect against these diseases and Boostrix vaccine provides protection in only one injection.

How is GSK involved?

GSK is a company that studies and makes vaccines, medicines and other health products. GSK planned and organized this study. GSK pays the study doctor and the institution to run this study.

GSK will be the owner of the study results. GSK plans to use these to get patents, sell the vaccine in the future or make profits in other ways. You will not be paid for any part of this.

The information and materials we give you about this study are confidential and belong to GSK. We ask that you keep it private. You can share this information with your doctor, family or friends when discussing about your participation in this study and your healthcare.

Who can join this study?

You can participate in this study if:

- You have taken part in the previous trial 776423/001 [DTPA 0.3 (BOOSTRIX)-001] conducted by GSK Biologicals, 10 years ago.
- You have not had a booster vaccination against diphtheria, tetanus, pertussis since the last dose received in the study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].
- You do not have a history of diphtheria, tetanus or pertussis diseases since the previous vaccination.
- You are not pregnant or breast-feeding your baby (if applicable).
- You are healthy.
- You have not had any serious side effects after previous administration of diphtheria, tetanus or pertussis vaccines.

The study doctor will also explain and check some other aspects before you can join this study. You can ask your study doctor for more details.

What does this study involve?

About 500 people who participated in the previous study 776423/001 [DTPA 0.3 (BOOSTRIX)-001] will be invited to participate in this follow-up study. When we have enough people taking part in this study, we will not include or invite any more. There will be two groups in this study- Tdap Group, and Td Group and all people in both the groups...
Informed Consent Form

CONFIDENTIAL
Study Identification 116570 [DTPA 0.3 (BOOSTRIX)-012 EXT: 001]

will receive a single dose of Boostrix vaccine. Depending on the vaccine you received in the previous study 10 years back, you will be assigned to a group:

- Tdap Group: You received Tdap vaccine previously and will receive the second dose of Tdap vaccine in this study.
- Td Group: You received the Td vaccine previously and will receive the first dose of Tdap vaccine in this study.

The study will last for approximately 30 days. You will need to visit the study site twice, on the day of the vaccination and one month after receiving vaccination. Information about the effect of the vaccine on your body and on your health will be collected by taking a blood sample and asking you questions. You will get 1 vaccine shot in upper part of your arm. You will have 2 blood draws, one before vaccination and the second one, a month after vaccination. You will have to complete a diary card during the 30 days after the vaccination.

If you take part in this study then it is important that you follow all study activities as described here below:

<table>
<thead>
<tr>
<th>Visit</th>
<th>What will happen at this visit</th>
</tr>
</thead>
</table>
| Visit 1 (Day 0)     | You will be explained the study procedures and you will be asked to sign the present “informed consent” document. The doctor will ask you about your medical and vaccination history. You will undergo:  
  - Physical examination including measurement of body temperature  
  - Urine pregnancy test (if applicable)  
  - You will undergo blood sampling  
  - Administration of Boostrix vaccine  
  You will receive a diary card and will be asked to use it to record any symptom you experience in the coming month until the next visit. |
| Visit 2 (Day 30)    | You will return the diary card.  
  The doctor will ask you whether you have received any medication or vaccination since the last visit.  
  You will undergo:  
  Blood sampling  
  End of study |

In addition, you should call the doctor if at any time during the study:

- you are hospitalized
- you have symptoms that interfere greatly with your ability to carry out your normal daily activities

Note: You should contact the health care provider immediately should you have any signs or symptoms you think may be serious.

Local (USA) ICF Version Number NN, Dated: DD/MMM/YYYY, based on Model ICF Version Number 02, Dated: 17-OCT-2012

(Page 3 of 11) [Template Edition 6.1]
Informed Consent Form

CONFIDENTIAL
Study Identification 116570 [DTPA 0.3 (BOOSTRIX)-012 EXT: 001]

You will receive a card with study contact information. Keep this card with you at all times during the study. Show this card to the medical staff if you need emergency care during the study. The medical staff can then contact your study doctor if needed to ask about the vaccine or product you received.

What about pregnancy and breastfeeding?

It is not known whether the vaccine used in this study may have an effect on the unborn baby. You should not join this study if you are pregnant. Mothers should not breastfeed a baby while in this study.

If you are a woman who can get pregnant, you will need to use birth control while in this study. You will have a urine pregnancy test before receiving the booster dose of the vaccine. Check with the study doctor about what kind of birth control methods to use and how long to use them. Some methods may not be allowed to use during this study.

Tell the study doctor if you are pregnant. If you get pregnant during the study, you will need to remain in the study for follow-up. We will follow-up until the delivery of the baby.

What will happen to samples taken in this study?

The content of this section needs to be aligned with the Use of Human Samples form. Any request to changes in this section must be discussed with the central study team and the GSK Biologicals’ ICF taskforce prior to finalization of the ICF.

As part of the study, you will be asked to give samples of your blood. Your blood samples may be sent to GSK or other laboratories working with GSK including those outside [insert name of country] to:

- Measure how your body reacts to the study vaccine.
- Ensure the quality of the tests we use for the study vaccine and/or diseases,
- Improve tests and develop new tests linked to the study vaccine and/or diseases. These tests will never include testing related to your genes’ hereditary characteristics.

Your samples will be given a code so that it does not directly identify you.

Your samples will be kept for a maximum of 20 years from the end of the study. Any sample remaining at that time will be destroyed.

Optional tests on your samples:

If you agree, your sample(s) may also be used for future research. GSK will always ask approval for this research to an independent ethics committee or independent review board.

You can choose not to allow these optional tests and still be in the study.
What side effects or risks can you expect in this study?

The potential risks associated with receiving the study vaccine is similar to those seen with routine vaccination:

Side effects observed within 4 days of vaccine administration:

- Injection site reactions: Pain, redness and swelling.
- General side effects: Tiredness, fever, headache, vomiting, diarrhea and abdominal pain.

Expected risks for adults are detailed below according to the following frequency of occurrence:

- Very common: Injection-site pain, injection-site reactions (such as redness and/or swelling), tiredness and headache.
- Common: Fever (greater than or equal to 99.5°F), hard lump and pus at injection site, nausea and dizziness.
- Uncommon: Fever (greater than 102.2°F), vomiting, sore throat, cough, fainting, skin rash, flu like symptoms like fever, sore throat, runny nose, cough and chills, muscle tension, muscle pain, joint stiffness, excessive sweating, severe itching all over the body, swelling of glands in neck, groin and arm pits.
- Rare: Water retention with swelling of the injected limb, allergic reaction, (characterized by swelling of lips, tongue, or other parts of the body, shortness of breath, rashes across body and difficulty swallowing), unusual weakness, seizures and hives.
- Very rare: As with all injectable vaccines, severe allergic reactions (anaphylactic and anaphylactoid reactions) may very rarely occur. They are characterized by, itchy rash of the hands and feet, swelling of the eyes and face, difficulty in breathing or swallowing, sudden drop in blood pressure and loss of consciousness.

Boostrix can cause side effects that may be mild or more severe. We will follow-up everyone in the study for any side effects.

There may be other side effects that are not known now.

The following side effects related to the study procedures may occur:

When you give blood, you may feel faint, or locally experience mild pain, bruising, irritation or redness.

The vaccines in this study may not protect all people who get them. Your response to the vaccine in this study will be tested. In some cases, the test results may show your response to the vaccination was not optimal. If the study doctor believes you would benefit from another vaccination, he or she will contact you.
Informed Consent Form

What benefits can you expect in this study?

This study may be beneficial to you. In this case benefits include:

- The opportunity to protect yourself against 3 major diseases- diphtheria, tetanus and pertussis.
- A detailed assessment of your response to the vaccination through analysis of blood samples, a procedure not usually performed outside a study situation.
- Information from this study helps to learn more about the vaccine or disease.
- The vaccine and study tests will be free for you.

Are there other products or treatment?

This section should be completed locally using the most current information regarding the treatments/ vaccines/ products that are available in the country and their important potential benefits and risks. State if there are no alternate treatments.

You may choose another booster vaccine for diphtheria, tetanus and pertussis. Talk with your doctor about your options, before you decide if you will take part in this study. The study doctor can advise you if you need more information.

Do you have to stay in the study?

You may choose to leave the study at any time, without giving a reason. If you do give a reason, then it may be recorded. Your choice will not change the medical care or other benefits you receive outside of this study.

We will share with you as soon as possible any new information that may change your choice to stay in the study.

Tell the study doctor if you no longer want to take part.

GSK may choose to stop the study or the study doctor may choose to stop your participation in the study at any time. We will then tell you why. We may ask you to leave the study if:

- Test results show that this study is not right for you
- You do not follow study instructions
- The study doctor thinks it is in your best interest to stop, e.g. if you have specific health problems.

What happens if you leave the study?

Check local regulations and seek local legal advice for the use of data after subject/patient withdrawal. If any changes are made to this section in the Local ICF
Informed Consent Form

Study Identification 116570 [DTPA 0.3 (BOOSTRIX)-012 EXT: 001]

Compared to the Model ICF, in response to a request from any source, these should be discussed with the central study team and GSK Biologicals ICF taskforce for alignment prior to the finalization of the local ICF, so that the impact for database collection can be taken into account.

No more information about you will be collected after you leave the study. All the information and samples collected before you left the study will still be used.

If the doctor becomes aware of any relevant safety information about you after you left the study, this will be collected.

We may also contact you later for information. This is to help us better understand the safety profile of the vaccine.

What about your personal and medical information?

If changes are made to this text it needs to be checked with the local Legal team that this is aligned with local rules and regulations.

It is very important that your personal and medical information stay confidential and secure. Your personal and medical information will be protected in accordance with current law.

When you sign this consent form you agree that your personal and medical information can be used as described here.

- Your personal and medical information may be checked by GSK and others (like agencies that approve and monitor studies for example, Food and Drug administration (FDA)). This is to make sure that the study is being run properly.
- Besides that, only the researchers at this study site can use information that identifies you (such as name and address) and only for the purpose of the study.
- Your information collected during the study will be labeled with a code number (for example, PPD). It will not include your name or address. The study doctor will have the link between your name and the code number.
- The link between your name and the code number will not be shared. Only the code number and coded information will be sent to GSK.
- GSK will use your coded information for research only, including research looking at improving the quality and efficiency in conducting clinical research trials in general.
- GSK may:
  - Keep it electronically, and analyze it by computer to find out what the study is telling us. This may be done by GSK or a third party, in which case GSK will ensure that the third party is required to keep your data secure.
  - Share it with regulatory agencies that approve new vaccines and medicines.
Informed Consent Form

CONFIDENTIAL
Study Identification 116570 [DTPA 0.3 (BOOSTRIX)-012 EXT: 001]

- Share it with people who check that the study is done properly (like the independent ethics committee or review boards),
- Combine it with results from other studies to learn more about the vaccine, other vaccines and these diseases and related diseases. This may help us to assess the risks and benefits of GSK (or other) vaccines or medicines, or to improve disease understanding,
- Publish study results in medical journals, for meetings and on the internet for other researchers to use. Your name will not appear in any publication.

Share coded information with other companies, organizations or universities to carry out research, including research looking at improving the quality and efficiency in conducting clinical research trials in general.

Personal and medical data collected during the trial may be moved to, stored and used in the country where you live or another country where GSK or those working with GSK work.

Use of this information may take place in countries with lower data protection rules than the country where you live. GSK will make sure that if your data are moved to another country, it will still be treated as stated in this Informed Consent Form.

A description of this clinical trial will be available on the GSK Clinical Study Register http://www.gsk-clinicalstudyregister.com/ and may also appear in clinical trial registries in countries in which the clinical study is conducted.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

If you withdraw your consent for us to use your personal information you will no longer be able to continue in the study.

At any time, you may ask to see your personal information and correct it if necessary.

In some circumstances you may not be able to access your study information while the study is ongoing. However the study doctor will share any important medical information if it is relevant to your health during the course of the study.

You should know that once identifiable medical information about you is given to someone that is not a health care provider, it is not protected by the US federal privacy rules called the HIPAA Privacy Regulations.

What happens if you get hurt while taking part in this study?

GSK will help pay for your care if you are hurt by the study vaccine or a procedure done to you as part of the study. GSK will pay for reasonable and necessary care for the injury that is not covered by the National Vaccine Injury Compensation Fund. GSK will not pay...
Informed Consent Form

CONFIDENTIAL
Study Identification 116570 [DTPA 0.3 (BOOSTRIX)-012 EXT: 001]

for any other expenses. To pay these medical expenses, GSK will need to know some information about you like your name, date of birth, and social security number or Medicare Health Insurance Claim Number. This is because GSK has to check to see if you receive Medicare and if you do, report the payment it makes to Medicare. GSK will not use this information for any other purpose.

Signing this consent form does not change any legal rights you may have.

Will you be paid for being in the study?

This section should be completed locally.

We will reimburse you for the cost of travelling to your study visits. You may receive up to [amount] for travel / per visit.

Do you have to pay anything to be in the study?

Authors note that this section is optional. This section should be completed locally.

You will get all the study tests and procedures for free [or indicate if there is a cost].

Who should you contact if you have questions?

Identify who the subject/legally acceptable representative should contact for information about the study, the subject's rights or study-related injuries. This section may be completed at Country Level.

Person to contact for any questions: name, address, telephone number.

Person to contact about your rights: name, address, telephone number.

Person to contact in case of injury: name, address, telephone number.
I, ________________________________________________________________

Printed name of Subject

- confirm that I have read the written information (or have had the information read to me) for study 116570 [DTPA 0.3 (BOOSTRIX) -012 EXT: 001], Version 02, 17/October/2012, 11 pages (to be updated locally), and the study procedures have been explained to me by study staff during the consent process for this study.

- confirm that I have had the chance to ask questions about this study and I am satisfied with the answers and explanations that have been given.

- understand that I give access to data about me to authorized persons described in this information sheet.

- I know what will happen to my blood samples.

- understand that by signing this form any of my identifiable medical information given to someone that is not a health care provider is not protected by the US federal privacy rules called the HIPAA Privacy Regulations.

- have been given time and opportunity to consider taking part in this study.

Tick as appropriate (this decision will not affect your ability to enter the study):

I agree that my family doctor will be told about my participation in the study.

☐ Yes    ☐ No

Tick as appropriate

I agree that my biological sample(s) may be used for future research. GSK will always ask approval for this research to an independent ethics committee or independent review board. I understand that if I select “No”, I can still take part in the study.

☐ Yes    ☐ No

I agree to take part in this study.

Signature of subject _______________________________ Date: day/ month/ year

Local (USA) ICF Version Number NN, Dated: DD/MMM/YYYY, based on Model ICF Version Number 02, Dated: 17-OCT-2012

(Page 10 of 11) [Template Edition 6.1]
I confirm that I have conducted the consent process according to applicable regulations.

<table>
<thead>
<tr>
<th>Printed name of person conducting consent</th>
<th>Signature of person conducting consent</th>
<th>Date: day/month/year</th>
</tr>
</thead>
</table>

(Updated fields are placeholders for actual information)
Delete the following Appendix in the Final local ICF.

Appendix A  GlaxoSmithKline Biologicals Best Practices Document for the Development of the Local ICF

Introduction

The local informed consent form (ICF) is created based on the GSK Biologicals internally approved model ICF and is adapted according to country or local requirements.

The model ICF is the recommended content and structure which contains all ICH and GSK required elements and is aligned with the study protocol.

The content of the local ICF should be aligned with the Model ICF and any local specifications and regulations included.

The local GSK approved version should be submitted for ethical/regulatory approval and should be presented to the subject/patient and/or their legally acceptable representative.

It is essential that the version of the local ICF is accurately tracked, with a unique version number, date and reference to the model ICF on which it is based, to ensure that the correct version of the ICF is used and can be identified if needed.

It is strongly recommended to have a final local ICF, back-translated in English, available in the Investigator’s study file to ensure site readiness in case of audits and/or inspections.

Objective

These best practices are intended to give adequate support and to ensure consistency while developing the local ICF from the model ICF.

It is a tool to know what changes are not permitted and what changes can be justified and/or are required per local regulations and site specific information.

The development of the accurate and complete local ICF is a local responsibility and alignment with the model ICF is essential to study conduct.

Any changes made to the local ICF from the model ICF must be documented at local level.

Human Sample Management

The collection of human tissue samples, the intended use, and secondary use, if retained, and how the subject’s confidentiality would be maintained for the retained samples, must be reported in the ICF.

The content of this section must be fully aligned with the Use of Human Samples form. This form allows the central project team to track the actual testing at GSK (or laboratories used for GSK-sponsored studies) with the individual subject’s consent and
Best Practices Document for the Development of the Local ICF

local regulations. To avoid ethical and legal implications and invalidating the study data, any changes made to this section must be discussed with the central project team and GSK Biologicals’ central ICF taskforce for alignment prior to the finalization of the local ICF.

Subject/patient data after withdrawal

The retention of samples collected and data recorded before withdrawal and the continued collection of safety information after withdrawal must be reported in the ICF. Check local regulations and seek local legal advice for the use of data after subject/patient withdrawal. If any changes are made to this section in response to a request from any source, these changes must be discussed with the central project team and GSK Biologicals’ central ICF taskforce for alignment prior to the finalization of the local ICF, so that the impact for database collection and sample destruction can be taken into account.

Type of changes

Changes to the local ICF can be classified into 3 categories:

‘Not permitted’ changes

BOLD BLACK mandatory text in the model ICF should not be changed.

‘Required’ changes

Required changes must be made in the local ICF to add country-specific or center-specific information. (Indicated as BOLD RED text in the model ICF e.g. investigator details).

‘Justified’ changes

Justified changes may be necessary in some countries to comply with local requirements / regulations or to comply with a specific template e.g. country specific compensation guidance text.

In addition, some text can be clarified / simplified, provided the meaning remains the same as in the model ICF and does not contradict or change the intended meaning of the model ICF.

Changes that require a specific rationale or justification, that may be necessary in specific situations e.g. storage duration of samples, or changes required by the relevant Ethics Committees, can also be justified.

Best Practices per ICF Section

This table describes the type of changes (not permitted, required or justified) for each ICF section of the local ICF compared to the model ICF.
<table>
<thead>
<tr>
<th>ICF section</th>
<th>Type of changes</th>
<th>Rationale/Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Identification</td>
<td></td>
<td>The study identification and study number allows us to link the document to the study protocol, the corresponding IRB/IEC approvals, all relevant study documentation and ensures that the subject/patient is linked to the correct study.</td>
</tr>
<tr>
<td>Study Title</td>
<td></td>
<td>The study title allows us to link the document to the study protocol, the corresponding IRB/IEC approvals, all relevant study documentation and ensures that the subject/patient is linked to the correct study.</td>
</tr>
<tr>
<td>ICF Version Number and Date</td>
<td>Required</td>
<td>It is mandatory to include an ICF version number, the date of the final version, the page number and the total number of pages (for the Local and Model ICF). Each ICF type has to be uniquely identified and must include a reference to the source. The version of the local ICF allows us to link the ICF to the corresponding approval documents. If the version is omitted in the local ICF, the subject may not receive the most up to date ICF and thus may not receive the complete information required to make an informed consent.</td>
</tr>
<tr>
<td>Company Name</td>
<td></td>
<td>A change to this section is permitted if it is justified by local regulations. For some countries, the local GSK affiliate should be indicated as Company Name.</td>
</tr>
</tbody>
</table>

Best Practices Document for the Development of the Local ICF

Study Identification
Check if study identification is identical to Model ICF. Not permitted

Study Title
Check if study title is identical to Model ICF. Not permitted

ICF Version Number and Date
Update with version and date of Local ICF and check if reference to the Model ICF version and date is included. Specify country and subset if applicable. Required

Company Name
Check if company name is GlaxoSmithKline (GSK) Biologicals S.A. or the local GSK affiliate if this is required by local regulations. Justified
<table>
<thead>
<tr>
<th>ICF section</th>
<th>Type of changes</th>
<th>Rationale/Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subject/Patient Identification</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Check whether there is space</td>
<td>Required</td>
<td>The subject/patient ID should be mentioned on the ICF to be able to link the</td>
</tr>
<tr>
<td>foreseen to insert the subject</td>
<td></td>
<td>subject/patient ID with the corresponding source documents and RDE entries.</td>
</tr>
<tr>
<td>ID.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Header</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Check if study identification in</td>
<td>Not permitted</td>
<td>The study identification and study number allows us to link the document to the</td>
</tr>
<tr>
<td>header is identical to Model ICF.</td>
<td></td>
<td>study protocol, the corresponding IRB/IEC approvals, all relevant study</td>
</tr>
<tr>
<td></td>
<td></td>
<td>documentation and ensures that the subject/patient is linked to the correct</td>
</tr>
<tr>
<td></td>
<td></td>
<td>study.</td>
</tr>
<tr>
<td><strong>Footer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indicate version of Local ICF and</td>
<td>Required</td>
<td>It is mandatory to include an ICF version number, the date of the final version,</td>
</tr>
<tr>
<td>check if reference to the Model</td>
<td></td>
<td>the page number and the total number of pages (for the Local and Model ICF).</td>
</tr>
<tr>
<td>ICF version is included. Specify</td>
<td></td>
<td>Each ICF type has to be uniquely identified and must include a reference to the</td>
</tr>
<tr>
<td>country and subset if applicable.</td>
<td></td>
<td>source. The version of the local ICF allows us to link the ICF to the</td>
</tr>
<tr>
<td></td>
<td></td>
<td>corresponding approval documents.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If the version is omitted in the local ICF, the subject/patient may not receive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>the most up to date ICF and thus may not receive the complete information</td>
</tr>
<tr>
<td></td>
<td></td>
<td>required to make an informed consent.</td>
</tr>
<tr>
<td><strong>What is consent?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Explain the consent process and</td>
<td>Justified</td>
<td>Freely given and written informed consent must be obtained from each subject/</td>
</tr>
<tr>
<td>check if the meaning of the text is</td>
<td></td>
<td>patient/LAR prior to study participation. Informed consent involves an</td>
</tr>
<tr>
<td>not changed compared to the Model</td>
<td></td>
<td>education and information exchange that takes place between the researcher and</td>
</tr>
<tr>
<td>ICF (Text can be simplified if</td>
<td></td>
<td>the potential subject/patient. How the process of consenting looks like, needs</td>
</tr>
<tr>
<td>necessary).</td>
<td></td>
<td>to be explained in the</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Best Practices Document for the Development of the Local ICF

<table>
<thead>
<tr>
<th>ICF section</th>
<th>Type of changes</th>
<th>Rationale/Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Why is this study being done?</strong></td>
<td></td>
<td>ICF. The text can be simplified, if necessary.</td>
</tr>
<tr>
<td>Describe the study aim and check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).</td>
<td>Justified</td>
<td>The content of this section is required by ICH-GCP. If any of this information is omitted in the local ICF, the subject/patient may not receive the complete information required to make an informed consent. Text can be simplified if necessary.</td>
</tr>
<tr>
<td><strong>How is GSK involved?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).</td>
<td>Justified</td>
<td>The role of the sponsor should be explained in this section. The text can be simplified if necessary.</td>
</tr>
<tr>
<td><strong>Who can join this study?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summarize the main inclusion and exclusion criteria. Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).</td>
<td>Justified</td>
<td>If any of this information is omitted in the local ICF, the subject/patient may not receive the complete information required to make an informed consent. Text can be simplified if necessary.</td>
</tr>
<tr>
<td><strong>What does this study involve?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Explain the approximate number of subjects/patients involved in the study, the study design and groups, the study procedures and check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).</td>
<td>Justified</td>
<td>The content of this section is required by ICH-GCP. If any of this information is omitted in the local ICF, the subject/patient may not receive the complete information required to make an informed consent. Text can be simplified if necessary.</td>
</tr>
<tr>
<td>If subject cards are used, check if the text is identical to the Model ICF.</td>
<td>Not permitted</td>
<td>Subject cards provide information about the study which can be used in the event of a medical emergency. Provision of this information in the ICF ensures that the subject/patient is aware of the use of the subject card. This</td>
</tr>
</tbody>
</table>
### ICF section

<table>
<thead>
<tr>
<th>ICF section</th>
<th>Type of changes</th>
<th>Rationale/Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>What about pregnancy and breastfeeding?</td>
<td></td>
<td>information will also indicate to the ethics committee that it is provided to the subject/patient.</td>
</tr>
<tr>
<td>Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).</td>
<td>Justified</td>
<td>If any of this information is omitted in the local ICF, the subject/patient may not receive the complete information required to make an informed consent. Text can be simplified if necessary.</td>
</tr>
<tr>
<td>What will happen to samples taken in this study?</td>
<td></td>
<td>If this text is changed, there is a risk to use human samples outside the subject's/patient’s consent. This has major ethical implications and can lead to a loss of company reputation, lack of confidence, invalid study data etc….</td>
</tr>
<tr>
<td>Check if all mandatory wording from the Model ICF is present in the Local ICF.</td>
<td>Not permitted</td>
<td>The text in the ICF should match 100% with the information documented in the UHSF. This form allows the central project team to track the actual testing at GSK (or laboratories used for GSK-sponsored studies) with the individual subject’s/patient’s consent and local regulations. If this text is changed, there is a risk to use human samples outside the subject’s/patient’s consent. This has major ethical and legal implications and can lead to a loss of company reputation, lack of confidence, invalid study data, etc….</td>
</tr>
<tr>
<td>Check if the content of this section is aligned with the Use of Human samples form (UHSF).</td>
<td>Not permitted</td>
<td></td>
</tr>
<tr>
<td>ICF section</td>
<td>Type of changes</td>
<td>Rationale/Impact</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------</td>
<td>-----------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Check if the QA (Quality Assurance) on tests related to the study vaccine/disease (type 2 testing) is reported in the Local ICF.</td>
<td>Not permitted</td>
<td>QA testing will be done at all times, assuming it is allowed as per individual subject’s/patient’s consent. If QA testing is not mentioned in the ICF, there is a risk that GSK will be unable to perform the protocol tests and therefore this type of testing cannot be omitted.</td>
</tr>
<tr>
<td>Check local regulations regarding tests related to the product/disease under study (type 3a and 3b testing). [If there are concerns regarding this text then this should be discussed with the central team and GSK Biologics’ central ICF taskforce for alignment prior to the finalization of the local ICF]</td>
<td>Justified</td>
<td>A change to this section is justified, since type 3a or 3b should be chosen according to local regulations. However, the wording of the text itself, should not be changed! We capture this info in the CRF/eCRF by the mean of the UHSF, which contains standard wording. So if the wording in the ICF is changed, this will not be matching with the UHSF. This form allows the central project team to track the actual testing at GSK (or laboratories used for GSK-sponsored studies) with the individual subject’s consent and local regulations. If this text is changed, there is a risk to use human samples outside the subject’s consent. This has major ethical and legal implications and can lead to a loss of company reputation, lack of confidence, invalid study data, etc….</td>
</tr>
<tr>
<td>ICF section</td>
<td>Type of changes</td>
<td>Rationale/Impact</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Check Local regulations regarding storage duration. Check if the wording “for a maximum of 20 years” is not changed into “for 20 years”. [If there are concerns regarding this text then this should be discussed with the central project team and GSK Biologics’ central ICF taskforce for alignment prior to the finalization of the local ICF]</td>
<td>Justified</td>
<td>It is necessary to put a defined storage period in the ICF. As a standard, GSK proposes to store samples for “for a maximum of” 20 years. Attention should be paid to the used wording “for a maximum of” 20 years. This wording allows GSK to cover different situations (e.g. to keep samples for maximum 20 years, to destroy samples when GSK no longer wants to store them or no longer is interested in testing, when physical integrity of some type of samples does not permit such long storage, etc). Any changes to this section should be captured in the UHSF. This will allow the laboratory to take the appropriate measures for sample storage, “for a maximum of 20” years or as defined in the ICF and documented in the UHSF section called “other”.</td>
</tr>
<tr>
<td>Check local regulations regarding future research. [If there are concerns regarding this text then this should be discussed with the central project team and GSK Biologics’ central ICF taskforce for alignment prior to the finalization of the local ICF]</td>
<td>Justified</td>
<td>A change to this section is justified, since depending on local regulations, this type of testing is allowed or not. However, the wording of the text itself should not be changed and nothing should be added! We capture this info in the CRF/eCRF by the mean of the UHSF, which contains standard wording so if the wording in the ICF is changed, this will not be matching with the UHSF. This form allows the central project team to track the actual testing at GSK (or laboratories used for GSK-sponsored studies) with the individual subject’s/patient’s consent and local regulations. If this text is changed, there is a risk to use human samples outside the</td>
</tr>
<tr>
<td>ICF section</td>
<td>Type of changes</td>
<td>Rationale/Impact</td>
</tr>
<tr>
<td>-----------------------------------------------------------------------------</td>
<td>-----------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>subject’s consent. This has major ethical and legal implications and can lead to a loss of company reputation, lack of confidence, invalid study data, etc…..</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What side effects or risks can you expect in the study?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).</td>
<td>Justified</td>
<td>The content of this section is required by ICH-GCP. The reasonably foreseeable risks or inconveniences to the subject should be mentioned in the ICF. If any of this information is omitted in the local ICF, the subject may not receive the complete information required to make an informed consent. Text can be simplified if necessary. Refer to the GSK Position Paper on ‘Communication of Individual Immunological Assay Results to Study Sites’ for additional information.</td>
</tr>
<tr>
<td>Check if the text on autoimmune diseases (applicable if product/vaccine contains an adjuvant) is identical to the Model ICF.</td>
<td>Not permitted</td>
<td>The text on autoimmune diseases has been approved by GSK upper management following feedback from Authorities. The AID wording should remain consistent in all projects and countries. There is a reputational risk associated to the fact that GSK might seem to be sharing different information with Subjects/Patients/Externally on AID.</td>
</tr>
<tr>
<td>Check if the text on Rotarix, if applicable, is identical to the Model ICF.</td>
<td>Not permitted</td>
<td>This text has been approved by GSK upper management following feedback from Authorities.</td>
</tr>
<tr>
<td>ICF section</td>
<td>Type of changes</td>
<td>Rationale/Impact</td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>-----------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>What benefits can you expect in the study?</td>
<td></td>
<td>Justified The content of this section is required by ICH-GCP. The reasonably expected benefits or indirect benefits or if there is no direct clinical benefit for the subjects/patients must be included in the local ICF. Text can be simplified if necessary.</td>
</tr>
<tr>
<td>Are there other products or treatment?</td>
<td></td>
<td>Justified It is an ICH-GCP requirement to provide to the subject information on alternative procedures or treatment that may be available and their important potential benefits and risks. Omitting any of this information would be violating the rights of the subject/patient to freely participate to the study and would be putting the company reputation at risk. Text can be simplified if necessary.</td>
</tr>
<tr>
<td>Add currently available local alternatives, if applicable.</td>
<td>Required</td>
<td>This information must be added locally to the ICF using the most current information regarding the treatments that are available in the country.</td>
</tr>
<tr>
<td>Do you have to stay in the study?</td>
<td></td>
<td>Justified The content of this section is required by ICH-GCP. Omitting any of this information would be violating the rights of the subject/patient to freely participate to the study and would be putting the company reputation at risk. Text can be simplified if necessary.</td>
</tr>
<tr>
<td>What happens if you leave the study?</td>
<td></td>
<td>Justified The bold text in this section has been approved by Medical Governance. Changes to this</td>
</tr>
<tr>
<td>ICF section</td>
<td>Type of changes</td>
<td>Rationale/Impact</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Model ICF. [Check local regulations and seek local legal advice]</td>
<td>section in response to a request from any source, can have an impact for database collection and sample handling and should therefore be discussed with the central teams for alignment. Also refer to GSK’s Clarification Paper on ‘Handling Data after Subject withdrawal’ for additional information.</td>
<td></td>
</tr>
<tr>
<td>[If the text needs to be changed it should be discussed with the central project team and GSK Biologicals’ central ICF taskforce for alignment prior to the finalization of the local ICF.]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What about your personal and medical information?</td>
<td>Justified</td>
<td>The content of this section is required by ICH-GCP and must be included in the ICF so that the subject is well informed before consenting to participation. Omitting this information would be violating the confidentiality and the data privacy of the subject/patient and could have legal implications. Text can be simplified if necessary.</td>
</tr>
<tr>
<td>Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary). [If the text needs to be changed, it should be reviewed by the local legal team]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What happens if you get hurt while taking part in this study?</td>
<td>Justified</td>
<td>The content of this section is required by ICH-GCP. In the UK and in countries where there is no local scheme, GSK will apply the Clinical Trial Compensation guidelines set down by the UK Association of British Pharmaceutical Industry (ABPI) to compensate subjects/patients for GSK sponsored clinical study related injury.</td>
</tr>
<tr>
<td>- For UK, US and countries without special local regulations, check if compensation section is not changed compared to the section in the Model ICF. [If changes are made, the CMD (Country Medical Department) should ensure that all local legal regulatory requirements are satisfied.]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- For other countries where there is compensation for injury, the CMD (Country Medical Department) should ensure that the rules and conventions required locally are applied.</td>
<td>Justified</td>
<td>The content of this section is required by ICH-GCP and must be completed so that the subject/patient is well informed before consenting to participation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICF section</td>
<td>Type of changes</td>
<td>Rationale/Impact</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Will you be paid for being in the study?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information related to this section is added at a regional or country level.</td>
<td>Required</td>
<td>The content of this section is required by ICH-GCP and must be included in the ICF so that the subject/patient is well informed before consenting to participation. The anticipated prorated payment or other financial benefit, if any, to the subject for participating in the study should be mentioned in the ICF. Explain if expenses incurred by subjects for clinical visits made because of their participation in the study will be reimbursed or not.</td>
</tr>
<tr>
<td>Do you have to pay anything to be in the study?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>This section is optional. Information related to this section is added at a regional or country level when it is appropriate for a study and/or is required by local practice.</td>
<td>Justified</td>
<td>If appropriate for a study, include here information on cost/expenses that subject/patient will have to bear for taking part in the study i.e., whether the subject/patient or the subject's/patient’s insurance will be charged for any study item or procedure. According to ICH-GCP, the anticipated expenses, if any, to the subject/patient for participating in the study should be mentioned.</td>
</tr>
<tr>
<td>Who should you contact if you have questions?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Add local contact details.</td>
<td>Required</td>
<td>The content of this section is required by ICH-GCP. The subject/patient must have a contact person for further information regarding the study, his rights and who to contact in the event of trial-related injury.</td>
</tr>
<tr>
<td>Consent statement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).</td>
<td>Justified</td>
<td>The consent statement should be aligned with ICH-GCP requirements. Omitting any of the information can have legal...</td>
</tr>
<tr>
<td>ICF section</td>
<td>Type of changes</td>
<td>Rationale/Impact</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>-----------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Check local regulations regarding future research (type 4 testing).</td>
<td>Justified</td>
<td>A change to this section is justified, since depending on local regulations, this type of testing is allowed or not. This type of testing is optional for the subject/patient, meaning that if this testing is mentioned in the body of the ICF, a tick box should be available in the consent statement. The wording of the text itself, should not be changed and nothing should be added! We capture this info in the CRF/eCRF by using the UHSF, which contains standard wording so if the wording in the ICF is changed, this will not be matching with the UHSF.</td>
</tr>
<tr>
<td>Check if the wording is identical to the wording in the body of the ICF.</td>
<td></td>
<td>[If there are concerns regarding this text then this should be discussed with the central project team and GSK Biologicals' central ICF taskforce for alignment prior to the finalization of the local ICF]</td>
</tr>
</tbody>
</table>

**References**

SOP_54823, Development and implementation of Informed Consent for clinical studies.

GUI_51905, Guidance for Informed Consent documents.


GSK’s Position Paper on Communication of Individual Immunological Assay Results To Study Sites.

GSK’s Clarification Paper on Handling Data after Subject withdrawal.

GSK’s Clarification Paper on Future Use of Biospecimens.
Investigator CVs or equivalent summaries of training and experience relevant to the performance of the clinical study
PPD - This section contained Curriculum Vitae(s) and has been excluded to protect personal privacy.
STUDY TITLE: An open, phase III, non-randomized, multi-center study to assess the immunogenicity and safety of a booster dose of GlaxoSmithKline (GSK) Biologicals' combined reduced antigen content diphtheria-tetanus toxoids and acellular pertussis vaccine (Boostrix), when administered in young adults, 10 years after previous booster vaccination in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].

Study: 116570 (DTPA 0.3 (BOOSTRIX)-012 EXT 001) Development Phase: III

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Investigator: Dr Meera Varman

Affiliation /investigational centre: 2412 Cummings Street, Suite 100, Room 1022, Department of Pediatrics, Creighton University School of Medicine, Omaha, Nebraska 68131, United States

Signature of Investigator: ____________________________

Date: ____________________________

For internal use only
GlaxoSmithKline Biologicals

Vaccines R&D

Sponsor Signatory Approval Page

Please note that by signing this page, you take responsibility for the content of the Study Report including appendices

STUDY TITLE: An open, phase III, non-randomized, multi-center study to assess the immunogenicity and safety of a booster dose of GlaxoSmithKline (GSK) Biologicals’ combined reduced antigen content diphtheria-tetanus toxoids and acellular pertussis vaccine (Boostrix), when administered in young adults, 10 years after previous booster vaccination in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].

Study: 116570 (DTPA 0.3 (BOOSTRIX)-012 EXT 001) Development Phase: III

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory: Narcisa Mesaros

Title of Sponsor Signatory: Clinical and Epidemiology R&D Project Leader, DTP, Polio and Hib containing vaccines
R&D Centre Belgium
GlaxoSmithKline Biologicals

Signature: ______________________________________

Date: ____________________________

For internal use only

- Checksum----------------Ver.:Created On - -
0aa4a5f282809a50d46fa3b779a50c6978c3 2.0 9/22/2017 12:15:24 PM - -
df92c9dc63ef118a356c73dd60d53a9f405f6655 2.0 9/21/2017 3:55:00 PM - -
a525cb9464bf10db23a120fcaabdb0caadd1f702a9 2.0 9/21/2017 4:01:31 PM - -
764a03df08dec196935911bc76942a9c86650b00 2.0 9/21/2017 4:04:09 PM - -
dd49129d8502902e982768ca5ae82f2809d9c9e 2.0 9/21/2017 4:01:02 PM - -
a811d47bef331bd241ac21a2537ebf628435797 2.0 9/21/2017 4:00:11 PM - -
8220e9ec19e78dd11d6bd022bec63c7e211440ae 2.0 9/21/2017 3:59:37 PM - -
cadd41d8c05d6749843746df8995f71ca1adb 2.0 9/21/2017 3:54:24 PM - -
26b73a1551a4bd7e2b6da9c9bad6f344691459 2.0 9/21/2017 3:59:05 PM - -
5381adc1d7dbb5e55ea3572c126f3c64788be 2.0 9/21/2017 4:03:25 PM - -
3b904c7ca4e7e8cc806cf7d312c7311e417a0424ef4 2.0 9/21/2017 3:56:00 PM - -
d6bc135f4553b921e69d4f821a12dd8a221a18 2.0 9/21/2017 3:57:49 PM - -
293d45de56d35ec87f0109h3870707b2d691096707 2.0 9/21/2017 3:57:15 PM - -
79836700a02dd4d9be57a4a451c303e263cd7a 2.0 9/21/2017 4:02:48 PM - -
54ac1622874acbe10f1e667e662a212955e51cedb4b 2.0 9/21/2017 4:02:10 PM - -
2054a5f38ec58f70b0c49c7f88a46ba073cf09a 2.0 9/21/2017 3:56:41 PM - -
Listings of patients receiving test drug(s) /investigational product(s) from specific batches, where more than one batch was used

Not Applicable.
Randomization list

Not Applicable
Audit Certificates
Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

Clinical studies are conducted by or on behalf of GlaxoSmithKline in accordance with Standard Operating Procedures, which conform to the requirements of international GCP guidelines (ICH Harmonised Tripartite Guidelines E6 for Good Clinical Practice, FDA 21CFR parts 50, 56 and 312).

During the conduct and reporting of this/these study(s), the following independent audits were performed by or on behalf of GlaxoSmithKline.

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Type</th>
<th>Conducted by</th>
<th>Centre number</th>
<th>Country</th>
<th>Audit Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>116570</td>
<td>Investigator Site</td>
<td>CDQA</td>
<td>PPD</td>
<td>USA</td>
<td>11-13 Mar 2014</td>
</tr>
<tr>
<td>116570</td>
<td>Investigator Site</td>
<td>CDQA</td>
<td>PPD</td>
<td>USA</td>
<td>17-19 Feb 2014</td>
</tr>
</tbody>
</table>

Clinical Development Quality Assurance hereby confirm that the audits detailed above were carried out in accordance with appropriate regulatory requirements and guidelines in order to assess compliance with the study protocol, ICH GCP, FDA 21CFR parts 314.50 and 601.2, appropriate standard operating procedures and policies.

Name: PPD
Date: 07 Mar 2017
Role: Senior Manager CDQA
Clinical Development Quality Assurance
GlaxoSmithKline Research and Development
Documentation of statistical methods
**Statistical Analysis Plan**

Study alias & e-track number(s): DTPA 0.3 (BOOSTRIX)-012 EXT:001 (116570)

| Detailed Title: | An open, phase III, non-randomized, multi-center study to assess the immunogenicity and safety of a booster dose of GlaxoSmithKline (GSK) Biologicals’ combined reduced antigen content diphtheria-tetanus toxoids and acellular pertussis vaccine (Boostrix™), when administered in young adults, 10 years after previous booster vaccination in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001]. |
| SAP version | Amendment 1 |
| SAP date | 20-Apr-2017 |
| Scope: | All data pertaining to the above study |
| Co-ordinating author: | PPD | PPD |
| Other author(s): | PPD and PPD for previous versions |

This version is approved by:

- Clinical Research and Development Lead: PPD
- Project Statistician: PPD
- Lead Statistician: PPD
Statistical Analysis Plan

Study alias & e-track number(s): DTPA 0.3 (BOOSTRIX)-012 EXT:001 (116570)

TABLE OF CONTENTS

1. DOCUMENT HISTORY ................................................................. 5
2. STUDY DESIGN ................................................................. 6
   2.1. Design Overview ......................................................... 6
   2.2. Duration of the study .................................................. 7
   2.3. Groups description ..................................................... 7
   2.4. Sub-Groups description .............................................. 7
3. OBJECTIVES ................................................................. 8
   3.1. Primary Objectives ..................................................... 8
   3.2. Secondary Objectives .................................................. 8
4. ENDPOINTS ................................................................. 10
   4.1. Primary endpoints ..................................................... 10
   4.2. Secondary endpoints .................................................. 10
5. STUDY POPULATION .......................................................... 12
   5.1. Total vaccinated cohort ............................................. 12
   5.2. According-to-protocol cohort for analysis of safety .......... 12
   5.3. According-to-protocol cohort for analysis of immunogenicity 12
6. STATISTICAL METHODS .................................................. 13
   6.1. Analysis of demographics/baseline characteristics .......... 13
   6.2. Analysis of immunogenicity ......................................... 13
      6.2.1. Within groups assessment ................................... 13
      6.2.2. Between groups assessment .................................. 13
      6.2.3. Sensitivity analysis of persistence ......................... 14
   6.3. Analysis of safety ...................................................... 16
      6.3.1. Within groups assessment ................................... 16
      6.3.2. Between groups assessment .................................. 16
7. STATISTICAL CALCULATIONS ........................................... 19
   7.1. Derived and transformed data ..................................... 19
   7.2. Number of decimals ................................................ 21
   7.3. Handling of missing data ........................................... 22
      7.3.1. Handling of missing immunogenicity data ............. 22
      7.3.2. Handling of missing safety data ........................... 22
8. CONDUCT OF ANALYSES .................................................. 23
   8.1. Sequence of analyses ................................................ 23
   8.2. Statistical considerations for interim analyses .............. 23
9. CHANGES FROM PLANNED ANALYSES .................................. 24
Statistical Analysis Plan

Study alias & e-track number(s): DTPA 0.3 (BOOSTRIX)-012 EXT:001 (116570)

10. REFERENCES ........................................................................................................ 25

11. ABBREVIATIONS .................................................................................................... 26
Statistical Analysis Plan

Study alias & e-track number(s): DTPA 0.3 (BOOSTRIX)-012 EXT:001 (116570)

LIST OF TABLES

<table>
<thead>
<tr>
<th>TABLE</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 1</td>
<td>7</td>
</tr>
</tbody>
</table>

Study groups in the study
Statistical Analysis Plan

Study alias & e-track number(s): DTPA 0.3 (BOOSTRIX)-012 EXT:001 (116570)

The SAP is divided into 2 parts: the first part detailing the analyses to be performed (current document) and a second part, annexes (called TFL) describing the flow and format of tables, figures and listings to be annexed to the SR.

1. DOCUMENT HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Version</th>
<th>Description</th>
<th>Protocol Version</th>
</tr>
</thead>
<tbody>
<tr>
<td>02-JUL-2014</td>
<td>Final Version</td>
<td></td>
<td>DTPA 0.3 (BOOSTRIX)-012 EXT 001 (116570) Protocol Amendment 2 (03-Oct-2013).docx</td>
</tr>
<tr>
<td>20-Apr-2017</td>
<td>Amendment 1</td>
<td>The definition of booster response was adapted to the new assay cut-off (see section 7.1) The sensitivity analysis was clarified: this will be based on a repeated mixed model.</td>
<td>DTPA 0.3 (BOOSTRIX)-012 EXT 001 (116570) Protocol Amendment 2 (03-Oct-2013).docx</td>
</tr>
</tbody>
</table>
2. STUDY DESIGN

2.1. Design Overview

Experimental design: A phase III, open-label, non-randomized, multi-centric, single-country study with two parallel groups.

N = Number of subjects planned to be enrolled; Pre-BS = Pre-vaccination blood sampling; Post-BS = Post-vaccination blood sampling.
2.2. Duration of the study

Duration of the study: The intended duration of the study, for each subject will be approximately one month;
- Booster epoch: Starting at Visit 1 (Day 0) and ending at Visit 2 (Day 30).

2.3. Groups description

The following group names will be used for the statistical analyses:

Table 1  Study groups in the study

<table>
<thead>
<tr>
<th>Group order in tables</th>
<th>Group label in tables</th>
<th>Group definition for footnote</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Td</td>
<td>Subjects receiving the first dose of Tdap vaccine</td>
</tr>
<tr>
<td>2</td>
<td>Tdap</td>
<td>Subjects receiving a second dose of Tdap vaccine</td>
</tr>
</tbody>
</table>

2.4. Sub-Groups description

No sub-groups analysis
3. OBJECTIVES

3.1. Primary Objectives

**Immunogenicity**

- To demonstrate that a second dose of Tdap vaccine (administered to the Tdap Group) is non-inferior to a first dose of Tdap vaccine (administered to the Td Group), with respect to immune response to diphtheria and tetanus antigens.

  The criteria for meeting the above objective are defined as:

  - One month after vaccination, the lower limits of the 95% CI on the difference of the seroprotection rates (second dose of Tdap (Tdap Group) minus first dose of Tdap (Td Group)) for anti-diphtheria, anti-tetanus antibody concentrations are greater than or equal to -10% (clinical limit for non-inferiority).

- To demonstrate that a second dose of Tdap vaccine, (administered to the Tdap group) is non-inferior to a three dose series of Infanrix vaccine in infants who received this vaccine in German household contact efficacy study APV-039, with respect to antibodies against pertussis toxoid (anti-PT), antibodies against filamentous hemagglutinin (anti-FHA) and antibodies against pertactin (anti-PRN) antibody concentrations.

  The criteria for meeting the above objective are defined as:

  - One month after vaccination, the lower limits of the 95% CI on the anti-PT, anti-FHA and anti-PRN GMC ratios (Tdap Group divided by Infanrix Group in APV-039) are greater than or equal to 0.67.

3.2. Secondary Objectives

- To assess the persistence of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 10 years after the previous booster dose of the Tdap vaccine in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].

- To assess the immunogenicity of the Tdap vaccine in terms of seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies, one month after vaccination.

- To explore the potential difference in terms of booster response* to anti-D, anti-T, anti-PT, anti-FHA and anti-PRN between the second dose of Tdap vaccine (administered to the Tdap Group) and the first dose of Td vaccine (administered to the Td Group).

- To explore the potential difference in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations between a second dose of Tdap vaccine
Statistical Analysis Plan

 Study alias & e-track number(s): DTPA 0.3 (BOOSTRIX)-012 EXT:001 (116570)

(administered to the Tdap Group) and a first dose of Tdap vaccine (administered to
the Td Group).

- To evaluate and compare the safety of a second dose of Tdap vaccine (administered
to the Tdap group) and a first dose of Tdap vaccine (administered to the Td group),
with respect to solicited symptoms (local and general), unsolicited symptoms and
serious adverse events (SAEs).
4. ENDPOINTS

4.1. Primary endpoints

Immunogenicity
- Anti-D and anti-T antibody concentrations ≥ 0.1 IU/mL by ELISA, one month after vaccination.
- Anti-pertussis (PT, FHA and PRN) antibodies GMCs one month after vaccination.
- Anti-pertussis (PT, FHA and PRN) antibodies GMCs one month after the third dose of *Infanrix* in Study APV-039 Total Vaccinated cohort.

4.2. Secondary endpoints

Immunogenicity
- Anti-D* and anti-T antibody concentrations ≥ 0.1 IU and ≥ 1.0 IU/mL by ELISA or ≥ 0.01 IU/ml by Vero cell testing for subjects with post-vaccination ELISA anti-diphtheria toxoid antibody concentration < 0.1 IU/ml, prior to and one month after vaccination.
- Anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ 5 EL.U/mL, anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations prior to and one month after vaccination.
- Booster response to the diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens one month after vaccination.

* Sera with ELISA concentrations < 0.1 IU/mL will be tested for neutralizing antibodies using a Vero-cell neutralization assay.

Reactogenicity
Solicited local and general symptoms
- Occurrence of each solicited local and general symptoms (any and Grade 3) within 4 days (Day 0 – 3) after vaccination.
- Occurrence of large injection site reactions (defined as swelling with a diameter > 100 mm, noticeable diffuse swelling or noticeable increase of limb circumference) within 4 days (Day 0 - 3) after vaccination.
**Statistical Analysis Plan**

| gsk GlaxoSmithKline

---

**Study alias & e-track number(s):** DTPA 0.3 (BOOSTRIX)-012 EXT:001 (116570)

Unsolicited adverse events
- Occurrence of unsolicited AEs within 31 days (Day 0 – 30) after vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.

Serious adverse events
- Occurrence of serious adverse events from the administration of the vaccine dose up to 31 days following vaccination.
5. **STUDY POPULATION**

5.1. **Total vaccinated cohort**

The TVC will include all subjects with a study vaccine administration dose documented:

- A safety analysis based on the TVC will include all vaccinated subjects.
- An immunogenicity analysis based on the TVC will include all vaccinated subjects for whom immunogenicity results are available.

5.2. **According-to-protocol cohort for analysis of safety**

The ATP cohort for analysis of safety will include all eligible and vaccinated subjects:

- Who have received the dose of study vaccine.
- For whom administration site of study vaccine is known.
- Who did not receive a vaccine leading to elimination from an ATP analysis.

5.3. **According-to-protocol cohort for analysis of immunogenicity**

The ATP cohort for analysis of immunogenicity will include all evaluable subjects from the ATP cohort for analysis of safety:

- Who meet all eligibility criteria.
- Who comply with the procedures and intervals defined in the protocol.
- Who do not meet any of the criteria for elimination from an ATP analysis during the study.
- Who did not receive a product leading to elimination from an ATP analysis.
- Who did not present with a medical condition leading to elimination from an ATP analysis, before the visit 2 blood sample.
- For whom data concerning immunogenicity endpoint measures are available. This will include subjects for whom assay results are available for antibodies against at least one study vaccine antigen component after vaccination.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Elimination codes</th>
<th>Eli Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP cohort for analysis of immunogenicity</td>
<td>1010-2500</td>
<td>MA</td>
</tr>
<tr>
<td>ATP cohort for analysis of safety</td>
<td>1010-1500</td>
<td>MA</td>
</tr>
</tbody>
</table>
6. STATISTICAL METHODS

6.1. Analysis of demographics/baseline characteristics

Demographic characteristics (age at vaccination visit in years, gender, geographical ancestry and ethnicity) will be summarized by group using descriptive statistics:

- Frequency tables will be generated for categorical variable such as center.
- Mean, median, standard deviation will be provided for continuous data such as age.

In addition, a summary of the tracking log-sheet documenting outcomes of the contacts made with subjects for enrolment will be provided.

6.2. Analysis of immunogenicity

The primary analysis will be based on the ATP cohort for analysis of immunogenicity. If, in any vaccine group, the percentage of vaccinated subjects with serological results excluded from the ATP cohort for analysis of immunogenicity is 5% or more, a second analysis based on the TVC will be performed to complement the ATP analysis.

6.2.1. Within groups assessment

For each group and each antigen:

- Seropositivity/seroprotection rate at pre-vaccination, one month post-vaccination will be calculated with exact 95% confidence intervals (CIs).
- GMCs at pre-vaccination, one month post-vaccination will be tabulated with 95% CIs.
- Booster response rate one month post-vaccination will be calculated with exact 95% CIs.
- Alternative response rate one month post-vaccination will be calculated with exact 95% CIs.
- Antibody concentrations distribution at pre-vaccination and one month post-vaccination will be displayed using reverse cumulative curves (RCC).

6.2.2. Between groups assessment

- For anti-D, anti-T seroprotection rates, the two-sided standardized asymptotic 95% CI for the group differences (Tdap Group – Td Group) will be calculated.
**Statistical Analysis Plan**

<table>
<thead>
<tr>
<th>Study alias &amp; e-track number(s): DTPA 0.3 (BOOSTRIX)-012 EXT:001 (116570)</th>
</tr>
</thead>
</table>

- For anti-D, anti-T antibody response, the two-sided 95% CIs of the GMC ratios between subjects in the Tdap Group and (divided by) the Td Group one month after vaccination will be computed using an analysis of covariance (ANCOVA) model on the logarithm_{10} transformation of the concentrations adjusted to pre-vaccination titer in 776423/001 [DTPA 0.3 (BOOSTRIX)-001] study.

- For the assessment of anti-PT, anti-FHA and anti-PRN antibody concentrations, the two-sided 95% CIs of the GMC ratios between subjects in the Tdap group (divided by) the Infanrix Group in APV-039 one month after vaccination (one month after vaccination for Tdap group, one month after the third dose of Infanrix for Infanrix group in APV-039) will be computed using the method proposed by G.Y. Zou and A. Donner [Zou, 2008] in order to account heterogeneity of variance between this study and APV-039.

- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN booster response, the two-sided standardized asymptotic 95% CI for the group differences (Tdap Group - Td Group) will be calculated.

- For anti-PT, anti-FHA and anti-PRN antibody response, the two-sided 95% CI of the GMC ratios between subjects in the Tdap Group and Td Group one month after vaccination will be computed using an ANCOVA model on the logarithm_{10} transformation of the concentrations adjusted to pre-vaccination titer in Boostrix-001.

- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN alternative booster response, the two-sided standardized asymptotic 95% CI for the group differences (Tdap Group - Td Group) will be calculated.

### 6.2.3. Sensitivity analysis of persistence

An analysis of persistence will be carried out by using a repeated generalised linear model. This model will use all results from 776423/001 [DTPA 0.3 (BOOSTRIX)-001]. post vaccination visit and pre booster results of the current study. Analyses will be based on the ATP cohort of 776423/001 [DTPA 0.3 (BOOSTRIX)-001] and 116570 studies respectively.

Serology results below cut-off will be considered as left censored at the assay cut-off.

The model will include the fixed group effect, the fixed effect of time since last vaccination, the random intercept effect and, if data allows, the random slope effect [Reference: Thiébaut R. and Jacqmin-Gadda H]. It should be noted that since the assay changed between studies 776423/001 and 116570, the slope estimate will combine both the decrease in concentration and the effect in assay change.
The following SAS-code will be applied to obtain prediction in term of log10-transformed GMC and to estimate log10-transformed group GMC ratio for antigen D, T, PT, FHA, PRN:

*** start value derived from a simple ANCOVA;
*** duration is the time since vaccination in study 776423/001;
*** assay indicator (1 when same assay used as in study 776423/001, 0 otherwise);

Model 1 – random intercept & slope
PROC NLMIXED data=sero QTOL=1E-5 itdetails /* maxiter=20 tech=newraph*/;
PARMS sig1=&sig1. sig12=0 sig2=&sig2. sige=&sige. alpha1=&alpha1.
alpha2=&alpha2. beta=&beta. ;
pi=2*arcsin(1);
if group_nb=1 then grp1=1; else grp1=0;
if group_nb=2 then grp2=1; else grp2=0;
mu=alpha1*grp1+alpha2*grp2+beta*duration+a*duration + gamma*assay;
IF s=1 THEN ll=(1/(sqrt(2*pi*sige*sige)))*exp(-(yc-mu)**2/(2*sige*sige));
IF s=0 THEN ll=probnorm((cutoff -mu)/sqrt(sige*sige));
L=log(ll);
MODEL yc~general(L);
RANDOM a b ~normal([0, 0],[sig1, sig12, sig2]) SUBJECT=pid;
estimate 'group 1 at duration=Year 10' alpha1 + beta*10*365+ assay / cl ;
estimate 'group 2 at duration=Year 10' alpha2 + beta*10*365 + assay / cl ;
RUN;

OR
Model 2 – random intercept:
PROC NLMIXED data=sero QTOL=1E-5 itdetails /* maxiter=20 tech=newraph*/;
PARMS sig1=&sig1. sige=&sige. alpha1=&alpha1.  alpha2=&alpha2.  beta=&beta.;
pi=2*arcsin(1);
if group_nb=1 then grp1=1; else grp1=0;
if group_nb=2 then grp2=1; else grp2=0;
mu=alpha1*grp1+alpha2*grp2+beta*duration + gamma*assay + a;
IF s=1 THEN ll=(1/(sqrt(2*pi*sige*sige)))*exp(-(yc-mu)**2/(2*sige*sige));
IF s=0 THEN ll=probnorm((cutoff -mu)/sqrt(sige*sige));
L=log(ll);
MODEL yc~general(L);
RANDOM a ~normal(0,sig1) SUBJECT=pid;
estimate 'group 1 at duration=Year 10' alpha1 + beta*10*365 + assay / cl ;
estimate 'group 2 at duration=Year 10' alpha2 + beta*10*365 + assay / cl ;
RUN;
6.3. Analysis of safety

6.3.1. Within groups assessment

The primary analysis will be based on the TVC. If the percentage of vaccinated subjects excluded from the ATP cohort for analysis of safety is more than 5%, a second analysis based on this ATP cohort will be performed to complement the analysis of the TVC.

Safety data will be analyzed by subject incidence rates of solicited and unsolicited adverse events in the vaccine schedules treatment groups by solicited local and general symptom terms, and, for unsolicited AEs, by MedDRA preferred term and system organ class. Safety data will be summarized for all subjects by treatment group.

The incidence of solicited local and general symptoms occurring during 4 days after vaccination will be tabulated with exact 95% CI for each treatment group. The same calculations will be performed for symptoms of any intensity, those with intensity grade ≥ 2, and those with intensity of grade 3, as well as for solicited general events with relationship to vaccination and events requiring medical attention, respectively. Note that all solicited local adverse events will be considered to be causally related.

The percentage of subjects with at least one report of an unsolicited adverse event classified by MedDRA up to 31 days after vaccine will be tabulated with exact 95% CI for each treatment group. The same tabulation will be performed for grade 3 unsolicited adverse events, AEs resulting in a medically attended visit and for unsolicited adverse events that are considered by the investigator to be possibly related to vaccination.

Serious adverse events will be summarized from Day 0 to 31 days post-vaccination.

Serious adverse events, large injection site reaction (defined as swelling with a diameter >100 mm, noticeable diffuse swelling or noticeable increase of limb circumference) and withdrawals due to adverse event(s) will be described in detail.

6.3.2. Between groups assessment

The standardized asymptotic 95% CI for the difference between the two groups and the associated 2-sided p-value to detect group difference will be computed for the following endpoints:

- For each solicited symptom, the percentage of subjects reporting the symptom within 4 days after vaccination (any grade, grade 3, causally related, respectively).
- The percentage of subjects reporting adverse events within 31 days post vaccination (any, grade 3, causally related, requiring medical attention).
Statistical Analysis Plan

Study alias & e-track number(s): DTPA 0.3 (BOOSTRIX)-012 EXT:001 (116570)

- The percentage of subjects reporting serious adverse events (any, causally related) during the study period.

P-value below 5% will be used to identify events that are recognised as worthy of further investigation. It is to be noted that the use of such analyses has the potential to identify a large number of events which may or may not have a causal relationship to treatment due to unadjustment for multiplicity. In order to put these in perspective, the analysis will be complemented by a permutation test that will quantify the probability of identifying erroneously an event according to the threshold p-value. In addition, clinical judgment and biological plausibility should be taken into account when performing overall assessment.

The following local adverse events will be solicited:

- Pain at injection site
- Redness at injection site
- Swelling at injection site

The following general adverse events will be solicited:

- Fatigue
- Fever
- Gastrointestinal symptoms
- Headache

The intensity of the following solicited AEs will be assessed as described:

<table>
<thead>
<tr>
<th>Adults</th>
<th>Adverse Event</th>
<th>Intensity grade</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pain at injection site</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>Mild: Any pain neither interfering with nor preventing normal every day activities.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>Moderate: Painful when limb is moved and interferes with every day activities.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>Severe: Significant pain at rest. Prevents normal every day activities.</td>
</tr>
<tr>
<td></td>
<td>Redness at injection site</td>
<td></td>
<td>Record greatest surface diameter in mm</td>
</tr>
<tr>
<td></td>
<td>Swelling at injection site</td>
<td></td>
<td>Record greatest surface diameter in mm</td>
</tr>
<tr>
<td></td>
<td>Fever*</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>Mild: Headache that is easily tolerated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>Moderate: Headache that interferes with normal activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>Severe: Headache that prevents normal activity</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>Mild: Fatigue that is easily tolerated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>Moderate: Fatigue that interferes with normal activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>Severe: Fatigue that prevents normal activity</td>
</tr>
</tbody>
</table>
Statistical Analysis Plan

Study alias & e-track number(s): DTPA 0.3 (BOOSTRIX)-012 EXT:001 (116570)

<table>
<thead>
<tr>
<th>Gastrointestinal symptoms (nausea, vomiting, diarrhea and/or abdominal pain)</th>
<th>0</th>
<th>Gastrointestinal symptoms normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild: Gastrointestinal symptoms that are easily tolerated</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Moderate: Gastrointestinal symptoms that interfere with normal activity</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Severe: Gastrointestinal symptoms that prevent normal activity</td>
<td></td>
</tr>
</tbody>
</table>

*(Fever is defined as temperature $\geq 99.5^\circ F$ for oral, axillary or tympanic route, or $\geq 100.4^\circ F$ for rectal route. The preferred route for recording temperature in this study will be oral.)*

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals as follows:

| 0 | Absent |
| 1 | $\leq 20$ mm |
| 2 | $> 20$ mm and $\leq 50$ mm |
| 3 | $> 50$ mm |

The maximum intensity of fever will be scored at GSK Biologicals as follows:

<table>
<thead>
<tr>
<th>Oral/Axillary</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the investigator’s clinical judgment.

The intensity should be assigned to one of the following categories:

1 (mild) = An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

2 (moderate) = An AE which is sufficiently discomforting to interfere with normal everyday activities.

3 (severe) = An AE which prevents normal, everyday activities (In adults such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy.)
7. STATISTICAL CALCULATIONS

7.1. Derived and transformed data

- **Immunogenicity**
  - The cut-off value is defined by the laboratory before the analysis.
  - A seronegative subject is a subject whose titer is below the assay cut-off value.
  - A seropositive subject is a subject whose titer is greater than or equal to the assay cut-off value.

- A seroprotected subject is a subject whose antibody concentration/titer is greater than or equal to the level defining clinical protection. The following seroprotection thresholds are applicable:
  - Anti-D antibody concentrations \( \geq 0.1 \text{ IU/mL} \).
  - Anti-T antibody concentrations \( \geq 0.1 \text{ IU/mL} \).

- **Other cut-offs to be considered:**
  - Anti-D antibody concentrations \( \geq 1.0 \text{ IU/mL} \).
  - Anti-T antibody concentrations \( \geq 1.0 \text{ IU/mL} \).

1. Booster response for D & T:
   - initially seronegative subjects (pre-booster antibody concentration below the assay cut-off) with an increase of at least four times the assay cut-off one month after vaccination,
   - initially seropositive subjects (pre-booster antibody concentration \( \geq \) assay cut-off) with an increase of at least four times the pre-booster antibody concentration one month after vaccination

2. Booster response for pertussis:
   - initially seronegative subjects (pre-booster antibody concentration below the assay cut-off) with an increase of at least four times the assay cut-off one month after vaccination,
   - initially seropositive subjects with anti-body concentration \(< four times the assay cut-off with an increase of at least four times the pre-booster antibody concentration one month after vaccination
   - initially seropositive subjects with anti-body concentration \( \geq four times the assay cut-off with an increase of at least two times the pre-booster antibody concentration one month after vaccination
3. Alternative Booster response to D and T antigens is defined as:
   - for initially seronegative subjects (pre-vaccination concentration below the assay cut-off): antibody concentrations at least four times the assay cut-off one month after vaccination, and
   - for initially seropositive subjects with pre-vaccination concentration <1.0 IU/mL: antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.
   - for initially seropositive subjects with pre-vaccination concentration in [1.0; 6.0] IU/mL: antibody concentrations of at least two times the pre-vaccination concentration, one month after vaccination.

- Subjects with pre-vaccination concentration ≥ 6.0 IU/mL are not evaluable for vaccine response.

4. Alternative Booster response to PT, FHA and PRN antigens is defined as:
   - for initially seronegative subjects (pre-vaccination concentration below the assay cut-off): antibody concentrations at least four times the assay cut-off one month after vaccination, and
   - for initially seropositive subjects with pre-vaccination antibody concentration ≥ assay cut-off and < 60 IU/mL: antibody concentration increase of at least 30 EL.U/mL from the pre-vaccination concentration, one month after vaccination.
   - for initially seropositive subjects with pre-vaccination antibody concentration ≥ 60 EL.U/mL: at least 1.5 fold increase of antibody concentration from the pre-vaccination concentration, one month after vaccination.

- The Geometric Mean Concentrations (GMC) calculations are performed by taking the anti-log of the mean of the log concentration/titer transformations. Antibody concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC calculation.
- The 95% CI for GMTs/GMCs will be obtained within each group separately. The 95% CI for the mean of log-transformed titre/concentration will be first obtained assuming that log-transformed values were normally distributed with unknown variance. The 95% CI for the GMTs/GMCs will then be obtained by exponential-transformation of the 95% CI for the mean of log-transformed titre/concentration.
# Statistical Analysis Plan

Study alias & e-track number(s): DTPA 0.3 (BOOSTRIX)-012 EXT:001 (116570)

7.2. **Number of decimals**

The following decimal description from the decision rules will be used for the demography, immunogenicity and safety/reactogenicity.

<table>
<thead>
<tr>
<th>Display Table</th>
<th>Parameters</th>
<th>Number of decimal digits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td>Mean, median age</td>
<td>1</td>
</tr>
<tr>
<td>Demographic characteristics</td>
<td>SD (age)</td>
<td>2</td>
</tr>
<tr>
<td>Immunogenicity (Anti-D, Anti-T)</td>
<td>GMC/GMC ratio</td>
<td>2/3</td>
</tr>
<tr>
<td>Immunogenicity (Anti-PT, Anti-FHA, Anti-PRN)</td>
<td>GMC/GMC ratio</td>
<td>1/2</td>
</tr>
<tr>
<td>Reactogenicity</td>
<td>Mean, Min, Q1, Median, Q3, Max for duration</td>
<td>1</td>
</tr>
<tr>
<td>All summaries</td>
<td>% of count, including LL &amp; UL of CI</td>
<td>1</td>
</tr>
<tr>
<td>All summaries</td>
<td>% of difference, including LL &amp; UL of CI</td>
<td>2</td>
</tr>
</tbody>
</table>
### Statistical Analysis Plan

<table>
<thead>
<tr>
<th>Study alias &amp; e-track number(s): DTPA 0.3 (BOOSTRIX)-012 EXT:001 (116570)</th>
</tr>
</thead>
</table>

#### 7.3. Handling of missing data

#### 7.3.1. Handling of missing immunogenicity data

For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.

#### 7.3.2. Handling of missing safety data

- For a given subject and the analysis of solicited symptom within 4 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the TVC will include only vaccinated subjects and doses with documented safety data (i.e. symptom screen completed).

- For analysis of unsolicited adverse events, such as serious adverse events or adverse events by primary MedDRA term, and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.

- For summaries reporting both solicited and unsolicited adverse events, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.
8. CONDUCT OF ANALYSES

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

8.1. Sequence of analyses

The analysis will be performed in two steps. The first analysis (analysis E1_01) will include only the safety data up to one month post the booster dose. The final analysis (analysis E1_02) will include all demography, safety and immunogenicity analysis. These analyses will be the basis for the study report of the booster phase. Results will not be shared with the investigator before study conclusion.

8.2. Statistical considerations for interim analyses

All analyses will be conducted on final data and therefore no statistical adjustment for interim analyses is required.
9. CHANGES FROM PLANNED ANALYSES

- The vaccine responses were redefined in light of the change in assay cut-off.
- Sensitivity analysis of persistence data was initially based on imputation method. The method was replaced by a repeated mixed model.
- For the assessment of anti-PT, anti-FHA and anti-PRN antibody concentrations, the two-sided 95% CIs of the GMC ratios between subjects in the Tdap group (divided by) the Infanrix Group in APV-039 one month after vaccination (one month after vaccination for Tdap group, one month after the third dose of Infanrix for Infanrix group in APV-039) will be computed using the method proposed by G.Y. Zou and A. Donner [Zou, 2008] in order to account heterogeneity of variance between this study and APV-039. The APV-039 annex report dated 23May2016 will be used as reference for this comparison.
10. REFERENCES

- The exact CIs for a proportion within a group will be computed using SAS, [Clopper, 1934].
- The standardized asymptotic 95% CI or 97.5% CI for the group difference in proportion will be based on Method 6 as published by Newcombe [Newcombe, 1998].
11. **ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ATP</td>
<td>According-To-Protocol</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>GMT</td>
<td>Geometric Mean Titre</td>
</tr>
<tr>
<td>GSK</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>TVC</td>
<td>Total Vaccinated cohort</td>
</tr>
</tbody>
</table>
Documentation of inter-laboratory standardization methods and quality assurance procedures

Not Applicable
Publications based on the study

Not Applicable
Important publications referenced in the report

Not Applicable
CRF /eCRFs for deaths, other SAEs and withdrawals due to adverse events

Not Applicable
### Detailed Title:
An open, phase III, non-randomized, multi-center study to assess the immunogenicity and safety of a booster dose of GlaxoSmithKline (GSK) Biologicals’ combined reduced antigen content diphtheria-tetanus toxoids and acellular pertussis vaccine (*Boostrix™*), when administered in young adults, 10 years after previous booster vaccination in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].

### SAP version
Amendment 1

### SAP date
20-Apr-2017

### Scope:
All data pertaining to the above study

### Co-ordinating author:
PPD / PPD

### Other author(s):
PPD and PPD for previous versions

### This version is approved by:

<table>
<thead>
<tr>
<th>Role</th>
<th>PPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Research and Development Lead</td>
<td></td>
</tr>
<tr>
<td>Project Statistician</td>
<td></td>
</tr>
<tr>
<td>Lead Statistician</td>
<td></td>
</tr>
</tbody>
</table>
# Statistical Analysis Plan

**Study alias & e-track number(s):** DTPA 0.3 (BOOSTRIX)-012 EXT:001 (116570)

## TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>TABLE</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. DOCUMENT HISTORY</td>
<td>5</td>
</tr>
<tr>
<td>2. STUDY DESIGN</td>
<td>6</td>
</tr>
<tr>
<td>2.1. Design Overview</td>
<td>6</td>
</tr>
<tr>
<td>2.2. Duration of the study</td>
<td>7</td>
</tr>
<tr>
<td>2.3. Groups description</td>
<td>7</td>
</tr>
<tr>
<td>2.4. Sub-Groups description</td>
<td>7</td>
</tr>
<tr>
<td>3. OBJECTIVES</td>
<td>8</td>
</tr>
<tr>
<td>3.1. Primary Objectives</td>
<td>8</td>
</tr>
<tr>
<td>3.2. Secondary Objectives</td>
<td>8</td>
</tr>
<tr>
<td>4. ENDPOINTS</td>
<td>10</td>
</tr>
<tr>
<td>4.1. Primary endpoints</td>
<td>10</td>
</tr>
<tr>
<td>4.2. Secondary endpoints</td>
<td>10</td>
</tr>
<tr>
<td>5. STUDY POPULATION</td>
<td>12</td>
</tr>
<tr>
<td>5.1. Total vaccinated cohort</td>
<td>12</td>
</tr>
<tr>
<td>5.2. According-to-protocol cohort for analysis of safety</td>
<td>12</td>
</tr>
<tr>
<td>5.3. According-to-protocol cohort for analysis of immunogenicity</td>
<td>12</td>
</tr>
<tr>
<td>6. STATISTICAL METHODS</td>
<td>13</td>
</tr>
<tr>
<td>6.1. Analysis of demographics/baseline characteristics</td>
<td>13</td>
</tr>
<tr>
<td>6.2. Analysis of immunogenicity</td>
<td>13</td>
</tr>
<tr>
<td>6.2.1. Within groups assessment</td>
<td>13</td>
</tr>
<tr>
<td>6.2.2. Between groups assessment</td>
<td>13</td>
</tr>
<tr>
<td>6.2.3. Sensitivity analysis of persistence</td>
<td>14</td>
</tr>
<tr>
<td>6.3. Analysis of safety</td>
<td>16</td>
</tr>
<tr>
<td>6.3.1. Within groups assessment</td>
<td>16</td>
</tr>
<tr>
<td>6.3.2. Between groups assessment</td>
<td>16</td>
</tr>
<tr>
<td>7. STATISTICAL CALCULATIONS</td>
<td>19</td>
</tr>
<tr>
<td>7.1. Derived and transformed data</td>
<td>19</td>
</tr>
<tr>
<td>7.2. Number of decimals</td>
<td>21</td>
</tr>
<tr>
<td>7.3. Handling of missing data</td>
<td>22</td>
</tr>
<tr>
<td>7.3.1. Handling of missing immunogenicity data</td>
<td>22</td>
</tr>
<tr>
<td>7.3.2. Handling of missing safety data</td>
<td>22</td>
</tr>
<tr>
<td>8. CONDUCT OF ANALYSES</td>
<td>23</td>
</tr>
<tr>
<td>8.1. Sequence of analyses</td>
<td>23</td>
</tr>
<tr>
<td>8.2. Statistical considerations for interim analyses</td>
<td>23</td>
</tr>
<tr>
<td>9. CHANGES FROM PLANNED ANALYSES</td>
<td>24</td>
</tr>
</tbody>
</table>
10. REFERENCES .................................................................................................................. 25

11. ABBREVIATIONS .............................................................................................................. 26
LIST OF TABLES

Table 1  Study groups in the study  ................................................................. 7
The SAP is divided into 2 parts: the first part detailing the analyses to be performed (current document) and a second part, annexes (called TFL) describing the flow and format of tables, figures and listings to be annexed to the SR.

1. DOCUMENT HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Version</th>
<th>Description</th>
<th>Protocol Version</th>
</tr>
</thead>
<tbody>
<tr>
<td>02-JUL-2014</td>
<td>Final</td>
<td></td>
<td>DTPA 0.3 (BOOSTRIX)-012 EXT 001 (116570) Protocol Amendment 2 (03-Oct-2013).docx</td>
</tr>
<tr>
<td>20-Apr-2017</td>
<td>Amendment 1</td>
<td>The definition of booster response was adapted to the new assay cut-off (see section 7.1) The sensitivity analysis was clarified: this will be based on a repeated mixed model.</td>
<td>DTPA 0.3 (BOOSTRIX)-012 EXT 001 (116570) Protocol Amendment 2 (03-Oct-2013).docx</td>
</tr>
</tbody>
</table>
2. STUDY DESIGN

2.1. Design Overview

Experimental design: A phase III, open-label, non-randomized, multi-centric, single-country study with two parallel groups
2.2. **Duration of the study**

Duration of the study: The intended duration of the study, for each subject will be approximately one month;

- Booster epoch: Starting at Visit 1 (Day 0) and ending at Visit 2 (Day 30).

2.3. **Groups description**

The following group names will be used for the statistical analyses:

**Table 1** Study groups in the study

<table>
<thead>
<tr>
<th>Group order in tables</th>
<th>Group label in tables</th>
<th>Group definition for footnote</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Td</td>
<td>Subjects receiving the first dose of Tdap vaccine</td>
</tr>
<tr>
<td>2</td>
<td>Tdap</td>
<td>Subjects receiving a second dose of Tdap vaccine</td>
</tr>
</tbody>
</table>

2.4. **Sub-Groups description**

No sub-groups analysis
3. OBJECTIVES

3.1. Primary Objectives

Immunogenicity

- To demonstrate that a second dose of Tdap vaccine (administered to the Tdap Group) is non-inferior to a first dose of Tdap vaccine (administered to the Td Group), with respect to immune response to diphtheria and tetanus antigens.

  The criteria for meeting the above objective are defined as:
  - One month after vaccination, the lower limits of the 95% CI on the difference of the seroprotection rates [second dose of Tdap (Tdap Group) minus first dose of Tdap (Td Group)] for anti-diphtheria, anti-tetanus antibody concentrations are greater than or equal to -10% (clinical limit for non-inferiority).

- To demonstrate that a second dose of Tdap vaccine, (administered to the Tdap group) is non-inferior to a three dose series of Infanrix vaccine in infants who received this vaccine in German household contact efficacy study APV-039, with respect to antibodies against pertussis toxoid (anti-PT), antibodies against filamentous hemagglutinin (anti-FHA) and antibodies against pertactin (anti-PRN) antibody concentrations.

  The criteria for meeting the above objective are defined as:
  - One month after vaccination, the lower limits of the 95%CI on the anti-PT, anti-FHA and anti-PRN GMC ratios (Tdap Group divided by Infanrix Group in APV-039) are greater than or equal to 0.67.

3.2. Secondary Objectives

- To assess the persistence of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 10 years after the previous booster dose of the Tdap vaccine in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].

- To assess the immunogenicity of the Tdap vaccine in terms of seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies, one month after vaccination.

- To explore the potential difference in terms of booster response* to anti-D, anti-T, anti-PT, anti-FHA and anti-PRN between the second dose of Tdap vaccine (administered to the Tdap Group) and the first dose of Tdap vaccine (administered to the Td Group).

- To explore the potential difference in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations between a second dose of Tdap vaccine (administered to the Tdap Group) and a first dose of Tdap vaccine (administered to the Td Group).
Statistical Analysis Plan

Study alias & e-track number(s): DTPA 0.3 (BOOSTRIX)-012 EXT:001 (116570)

- To evaluate and compare the safety of a second dose of Tdap vaccine (administered to the Tdap group) and a first dose of Tdap vaccine (administered to the Td group), with respect to solicited symptoms (local and general), unsolicited symptoms and serious adverse events (SAEs).
4. **ENDPOINTS**

4.1. **Primary endpoints**

**Immunogenicity**

- Anti-D and anti-T antibody concentrations $\geq 0.1$ IU/mL by ELISA, one month after vaccination.
- Anti-pertussis (PT, FHA and PRN) antibodies GMCs one month after vaccination.
- Anti-pertussis (PT, FHA and PRN) antibodies GMCs one month after the third dose of *Infanrix* in Study APV-039 Total Vaccinated cohort.

4.2. **Secondary endpoints**

**Immunogenicity**

- Anti-D* and anti-T antibody concentrations $\geq 0.1$ IU and $\geq 1.0$ IU/mL by ELISA or $\geq 0.01$ IU/ml by Vero cell testing for subjects with post-vaccination ELISA anti-diphtheria toxoid antibody concentration $< 0.1$ IU/ml, prior to and one month after vaccination.
- Anti-PT, anti-FHA and anti-PRN antibody concentrations $\geq 5$ EL.U/mL, anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations prior to and one month after vaccination.
- Booster response to the diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens one month after vaccination

* Sera with ELISA concentrations $< 0.1$ IU/mL will be tested for neutralizing antibodies using a Vero-cell neutralization assay.

**Reactogenicity**

Solicited local and general symptoms

- Occurrence of each solicited local and general symptoms (any and Grade 3) within 4 days (Day 0 – 3) after vaccination.
- Occurrence of large injection site reactions (defined as swelling with a diameter $> 100$ mm, noticeable diffuse swelling or noticeable increase of limb circumference) within 4 days (Day 0 - 3) after vaccination.

Unsolicited adverse events

- Occurrence of unsolicited AEs within 31 days (Day 0 – 30) after vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
Serious adverse events

– Occurrence of serious adverse events from the administration of the vaccinatedose up to 31 days following vaccination.
5. STUDY POPULATION

5.1. Total vaccinated cohort

The TVC will include all subjects with a study vaccine administration dose documented:

- A safety analysis based on the TVC will include all vaccinated subjects.
- An immunogenicity analysis based on the TVC will include all vaccinated subjects for whom immunogenicity results are available.

5.2. According-to-protocol cohort for analysis of safety

The ATP cohort for analysis of safety will include all eligible and vaccinated subjects

- Who have received the dose of study vaccine.
- For whom administration site of study vaccine is known.
- Who did not receive a vaccine leading to elimination from an ATP analysis.

5.3. According-to-protocol cohort for analysis of immunogenicity

The ATP cohort for analysis of immunogenicity will include all evaluable subjects from the ATP cohort for analysis of safety:

- Who meet all eligibility criteria.
- Who comply with the procedures and intervals defined in the protocol.
- Who do not meet any of the criteria for elimination from an ATP analysis during the study.
- Who did not receive a product leading to elimination from an ATP analysis.
- Who did not present with a medical condition leading to elimination from an ATP analysis, before the visit 2 blood sample.
- For whom data concerning immunogenicity endpoint measures are available. This will include subjects for whom assay results are available for antibodies against at least one study vaccine antigen component after vaccination.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Elimination codes</th>
<th>Eli Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP cohort for analysis of immunogenicity</td>
<td>1010-2500</td>
<td>MA</td>
</tr>
<tr>
<td>ATP cohort for analysis of safety</td>
<td>1010-1500</td>
<td>MA</td>
</tr>
</tbody>
</table>
6. STATISTICAL METHODS

6.1. Analysis of demographics/baseline characteristics

Demographic characteristics (age at vaccination visit in years, gender, geographical ancestry and ethnicity) will be summarized by group using descriptive statistics:

- Frequency tables will be generated for categorical variable such as center.
- Mean, median, standard deviation will be provided for continuous data such as age.

In addition, a summary of the tracking log-sheet documenting outcomes of the contacts made with subjects for enrolment will be provided.

6.2. Analysis of immunogenicity

The primary analysis will be based on the ATP cohort for analysis of immunogenicity. If, in any vaccine group, the percentage of vaccinated subjects with serological results excluded from the ATP cohort for analysis of immunogenicity is 5% or more, a second analysis based on the TVC will be performed to complement the ATP analysis.

6.2.1. Within groups assessment

For each group and each antigen:

- Seropositivity/seroprotection rate at pre-vaccination, one month post-vaccination will be calculated with exact 95% confidence intervals (CIs).
- GMCs at pre-vaccination, one month post-vaccination will be tabulated with 95% CIs.
- Booster response rate one month post-vaccination will be calculated with exact 95% CIs.
- Alternative response rate one month post-vaccination will be calculated with exact 95% CIs.
- Antibody concentrations distribution at pre-vaccination and one month post-vaccination will be displayed using reverse cumulative curves (RCC).

6.2.2. Between groups assessment

- For anti-D, anti-T seroprotection rates, the two-sided standardized asymptotic 95% CI for the group differences (Tdap Group – Td Group) will be calculated.
Statistical Analysis Plan

Study alias & e-track number(s): DTPA 0.3 (BOOSTRIX)-012 EXT:001 (116570)

- For anti-D, anti-T antibody response, the two-sided 95% CIs of the GMC ratios between subjects in the Tdap Group and (divided by) the Td Group one month after vaccination will be computed using an analysis of covariance (ANCOVA) model on the logarithm$_{10}$ transformation of the concentrations adjusted to pre-vaccination titer in 776423/001 [DTPA 0.3 (BOOSTRIX)-001] study.

- For the assessment of anti-PT, anti-FHA and anti-PRN antibody concentrations, the two-sided 95% CIs of the GMC ratios between subjects in the Tdap group (divided by) the Infanrix Group in APV-039 one month after vaccination (one month after vaccination for Tdap group, one month after the third dose of Infanrix for Infanrix group in APV-039) will be computed using the method proposed by G.Y. Zou and A. Donner [Zou, 2008] in order to account heterogeneity of variance between this study and APV-039.

- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN booster response, the two-sided standardized asymptotic 95% CI for the group differences (Tdap Group - Td Group) will be calculated.

- For anti-PT, anti-FHA and anti-PRN antibody response, the two-sided 95% CI of the GMC ratios between subjects in the Tdap Group and Td Group one month after vaccination will be computed using an ANCOVA model on the logarithm$_{10}$ transformation of the concentrations adjusted to pre-vaccination titer in Boostrix-001.

- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN alternative booster response, the two-sided standardized asymptotic 95% CI for the group differences (Tdap Group - Td Group) will be calculated.

6.2.3. Sensitivity analysis of persistence

An analysis of persistence will be carried out by using a repeated generalised linear model. This model will use all results from 776423/001 [DTPA 0.3 (BOOSTRIX)-001], post vaccination visit and pre booster results of the current study. Analyses will be based on the ATP cohort of 776423/001 [DTPA 0.3 (BOOSTRIX)-001] and 116570 studies respectively.

Serology results below cut-off will be considered as left censored at the assay cut-off.

The model will include the fixed group effect, the fixed effect of time since last vaccination, the random intercept effect and, if data allows, the random slope effect [Reference: Thiébaut R. and Jacqmin-Gadda H]. It should be noted that since the assay changed between studies 776423/001 and 116570, the slope estimate will combine both the decrease in concentration and the effect in assay change.
The following SAS-code will be applied to obtain prediction in term of log10-transformed GMC and to estimate log10-transformed group GMC ratio for antigen D, T, PT, FHA, PRN:

*** start value derived from a simple ANCOVA;
*** duration is the time since vaccination in study 776423/001;
*** assay indicator (1 when same assay used as in study 776423/001, 0 otherwise);

Model 1 – random intercept & slope
PROC NLMIXED data=sero QTOL=1E-5 itdetails /* maxiter=20 tech=newraph*/;
PARMS sig1=&sig1. sig12=0 sig2=&sig2. sige=&sige. alpha1=&alpha1. alpha2=&alpha2. beta=&beta. ;
pi=2*arsin(1);
if group_nb=1 then grp1=1; else grp1=0;
if group_nb=2 then grp2=1; else grp2=0;
mu=alpha1*grp1+alpha2*grp2+beta*duration + a + b*duration + gamma*assay;
IF s=1 THEN ll=(1/(sqrt(2*pi*sige*sige)))*exp(-(yc-mu)**2/(2*sige*sige));
IF s=0 THEN ll=probnorm((cutoff-mu)/sqrt(sige*sige));
L=log(ll);
MODEL yc~general(L);
RANDOM a b ~normal([0, 0],[sig1, sig12, sig2]) SUBJECT=pid;
estimate 'group 1 at duration=Year 10' alpha1 + beta*10*365 + assay / cl;
estimate 'group 2 at duration=Year 10' alpha2 + beta*10*365+ assay / cl;
RUN;

OR
Model 2 – random intercept:
PROC NLMIXED data=sero QTOL=1E-5 itdetails /* maxiter=20 tech=newraph*/;
PARMS sig1=&sig1. sige=&sige. alpha1=&alpha1. alpha2=&alpha2. beta=&beta.;
pi=2*arsin(1);
if group_nb=1 then grp1=1; else grp1=0;
if group_nb=2 then grp2=1; else grp2=0;
mu=alpha1*grp1+alpha2*grp2+beta*duration + gamma*assay + a;
IF s=1 THEN ll=(1/(sqrt(2*pi*sige*sige)))*exp(-(yc-mu)**2/(2*sige*sige));
IF s=0 THEN ll=probnorm((cutoff-mu)/sqrt(sige*sige));
L=log(ll);
MODEL yc~general(L);
RANDOM a ~normal(0,sig1) SUBJECT=pid;
estimate 'group 1 at duration=Year 10' alpha1 + beta*10*365 + assay / cl;
estimate 'group 2 at duration=Year 10' alpha2 + beta*10*365 + assay / cl;
RUN;
6.3. Analysis of safety

6.3.1. Within groups assessment

The primary analysis will be based on the TVC. If the percentage of vaccinated subjects excluded from the ATP cohort for analysis of safety is more than 5%, a second analysis based on this ATP cohort will be performed to complement the analysis of the TVC.

Safety data will be analyzed by subject incidence rates of solicited and unsolicited adverse events in the vaccine schedules treatment groups by solicited local and general symptom terms, and, for unsolicited AEs, by MedDRA preferred term and system organ class. Safety data will be summarized for all subjects by treatment group.

The incidence of solicited local and general symptoms occurring during 4 days after vaccination will be tabulated with exact 95% CI for each treatment group. The same calculations will be performed for symptoms of any intensity, those with intensity grade \( \geq 2 \), and those with intensity of grade 3, as well as for solicited general events with relationship to vaccination and events requiring medical attention, respectively. Note that all solicited local adverse events will be considered to be causally related.

The percentage of subjects with at least one report of an unsolicited adverse event classified by MedDRA up to 31 days after vaccine will be tabulated with exact 95% CI for each treatment group. The same tabulation will be performed for grade 3 unsolicited adverse events, AEs resulting in a medically attended visit and for unsolicited adverse events that are considered by the investigator to be possibly related to vaccination.

Serious adverse events will be summarized from Day 0 to 31 days post-vaccination.

Serious adverse events, large injection site reaction (defined as swelling with a diameter \( >100 \text{ mm} \), noticeable diffuse swelling or noticeable increase of limb circumference) and withdrawals due to adverse event(s) will be described in detail.

6.3.2. Between groups assessment

The standardized asymptotic 95% CI for the difference between the two groups and the associated 2-sided p-value to detect group difference will be computed for the following endpoints:

- For each solicited symptom, the percentage of subjects reporting the symptom within 4 days after vaccination (any grade, grade 3, causally related, respectively).
- The percentage of subjects reporting adverse events within 31 days post vaccination (any, grade 3, causally related, requiring medical attention).
The percentage of subjects reporting serious adverse events (any, causally related) during the study period.

P-value below 5% will be used to identify events that are recognised as worthy of further investigation. It is to be noted that the use of such analyses has the potential to identify a large number of events which may or may not have a causal relationship to treatment due to unadjustment for multiplicity. In order to put these in perspective, the analysis will be complemented by a permutation test that will quantify the probability of identifying erroneously an event according to the threshold p-value. In addition, clinical judgment and biological plausibility should be taken into account when performing overall assessment.

The following local adverse events will be solicited:

- Pain at injection site
- Redness at injection site
- Swelling at injection site

The following general adverse events will be solicited:

- Fatigue
- Fever
- Gastrointestinal symptoms
- Headache

The intensity of the following solicited AEs will be assessed as described:

<table>
<thead>
<tr>
<th>Adults</th>
<th>Intensity grade</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain at injection site</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Mild: Any pain neither interfering with nor preventing normal every day activities.</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Moderate: Painful when limb is moved and interferes with every day activities.</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Severe: Significant pain at rest. Prevents normal every day activities.</td>
</tr>
<tr>
<td>Redness at injection site</td>
<td></td>
<td>Record greatest surface diameter in mm</td>
</tr>
<tr>
<td>Swelling at injection site</td>
<td></td>
<td>Record greatest surface diameter in mm</td>
</tr>
<tr>
<td>Fever*</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Mild: Headache that is easily tolerated</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Moderate: Headache that interferes with normal activity</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Severe: Headache that prevents normal activity</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Mild: Fatigue that is easily tolerated</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Moderate: Fatigue that interferes with normal activity</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Severe: Fatigue that prevents normal activity</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Mild: Fatigue that is easily tolerated</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Moderate: Fatigue that interferes with normal activity</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Severe: Fatigue that prevents normal activity</td>
</tr>
</tbody>
</table>
Gastrointestinal symptoms
(nausea, vomiting, diarrhea and/or abdominal pain)

<table>
<thead>
<tr>
<th>0</th>
<th>Gastrointestinal symptoms normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild: Gastrointestinal symptoms that are easily tolerated</td>
</tr>
<tr>
<td>2</td>
<td>Moderate: Gastrointestinal symptoms that interfere with normal activity</td>
</tr>
<tr>
<td>3</td>
<td>Severe: Gastrointestinal symptoms that prevent normal activity</td>
</tr>
</tbody>
</table>

*Fever is defined as temperature ≥ 99.5°F for oral, axillary or tympanic route, or ≥100.4°F for rectal route. The preferred route for recording temperature in this study will be oral.

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals as follows:

<table>
<thead>
<tr>
<th>0</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≤ 20 mm</td>
</tr>
<tr>
<td>2</td>
<td>&gt; 20 mm and ≤ 50 mm</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 50 mm</td>
</tr>
</tbody>
</table>

The maximum intensity of fever will be scored at GSK Biologicals as follows:

<table>
<thead>
<tr>
<th>Oral/Axillary</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the investigator’s clinical judgment.

The intensity should be assigned to one of the following categories:

1 (mild) = An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

2 (moderate) = An AE which is sufficiently discomforting to interfere with normal everyday activities.

3 (severe) = An AE which prevents normal, everyday activities (In adults such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy.)
7. STATISTICAL CALCULATIONS

7.1. Derived and transformed data

- **Immunogenicity**
  - The cut-off value is defined by the laboratory before the analysis.
  - A seronegative subject is a subject whose titer is below the assay cut-off value.
  - A seropositive subject is a subject whose titer is greater than or equal to the assay cut-off value.

- A seroprotected subject is a subject whose antibody concentration/titer is greater than or equal to the level defining clinical protection. The following seroprotection thresholds are applicable:
  - Anti-D antibody concentrations \( \geq 0.1 \) IU/mL.
  - Anti-T antibody concentrations \( \geq 0.1 \) IU/mL.

- **Other cut-offs to be considered:**
  - Anti-D antibody concentrations \( \geq 1.0 \) IU/mL.
  - Anti-T antibody concentrations \( \geq 1.0 \) IU/mL.

1. Booster response for D & T:

- Initially seronegative subjects (pre-booster antibody concentration below the assay cut-off) with an increase of at least four times the assay cut-off one month after vaccination,
- Initially seropositive subjects (pre-booster antibody concentration \( \geq \) assay cut-off) with an increase of at least four times the pre-booster antibody concentration one month after vaccination.

2. Booster response for pertussis:

- Initially seronegative subjects (pre-booster antibody concentration below the assay cut-off) with an increase of at least four times the assay cut-off one month after vaccination,
- Initially seropositive subjects with anti-body concentration \(<\) four times the assay cut-off with an increase of at least four times the pre-booster antibody concentration one month after vaccination.
- Initially seropositive subjects with anti-body concentration \(\geq\) four times the assay cut-off with an increase of at least two times the pre-booster antibody concentration one month after vaccination.
3. Alternative Booster response to D and T antigens is defined as:
   − for initially seronegative subjects (pre-vaccination concentration below the assay cut-off): antibody concentrations at least four times the assay cut-off one month after vaccination, and
   − for initially seropositive subjects with pre-vaccination concentration <1.0 IU/mL: antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.
   − for initially seropositive subjects with pre-vaccination concentration in [1.0; 6.0 IU/mL]: antibody concentrations of at least two times the pre-vaccination concentration, one month after vaccination.

4. Alternative Booster response to PT, FHA and PRN antigens is defined as:
   − for initially seronegative subjects (pre-vaccination concentration below the assay cut-off): antibody concentrations at least four times the assay cut-off one month after vaccination, and
   − for initially seropositive subjects with pre-vaccination antibody concentration ≥ assay cut-off and < 60 IU/mL: antibody concentration increase of at least 30 EL.U/mL from the pre-vaccination concentration, one month after vaccination.
   − for initially seropositive subjects with pre-vaccination antibody concentration ≥ 60 EL.U/mL: at least 1.5 fold increase of antibody concentration from the pre-vaccination concentration, one month after vaccination.

• Subjects with pre-vaccination concentration ≥ 6.0 IU/mL are not evaluable for vaccine response.

The Geometric Mean Concentrations (GMC) calculations are performed by taking the anti-log of the mean of the log concentration/titer transformations. Antibody concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC calculation.

The 95% CI for GMTs/GMCs will be obtained within each group separately. The 95% CI for the mean of log-transformed titre/concentration will be first obtained assuming that log-transformed values were normally distributed with unknown variance. The 95% CI for the GMTs/GMCs will then be obtained by exponential-transformation of the 95% CI for the mean of log-transformed titre/concentration.
7.2. **Number of decimals**

The following decimal description from the decision rules will be used for the demography, immunogenicity and safety/reactogenicity.

<table>
<thead>
<tr>
<th>Display Table</th>
<th>Parameters</th>
<th>Number of decimal digits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td>Mean, median age</td>
<td>1</td>
</tr>
<tr>
<td>Demographic characteristics</td>
<td>SD (age)</td>
<td>2</td>
</tr>
<tr>
<td>Immunogenicity (Anti-D, Anti-T)</td>
<td>GMC/GMC ratio</td>
<td>2/3</td>
</tr>
<tr>
<td>Immunogenicity (Anti-PT, Anti-FHA, Anti-PRN)</td>
<td>GMC/GMC ratio</td>
<td>1/2</td>
</tr>
<tr>
<td>Reactogenicity</td>
<td>Mean, Min, Q1, Median, Q3, Max for duration</td>
<td>1</td>
</tr>
<tr>
<td>All summaries</td>
<td>% of count, including LL &amp; UL of CI</td>
<td>1</td>
</tr>
<tr>
<td>All summaries</td>
<td>% of difference, including LL &amp; UL of CI</td>
<td>2</td>
</tr>
</tbody>
</table>
7.3. **Handling of missing data**

7.3.1. **Handling of missing immunogenicity data**

For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.

7.3.2. **Handling of missing safety data**

- For a given subject and the analysis of solicited symptom within 4 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the TVC will include only vaccinated subjects and doses with documented safety data (i.e. symptom screen completed).

- For analysis of unsolicited adverse events, such as serious adverse events or adverse events by primary MedDRA term, and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.

- For summaries reporting both solicited and unsolicited adverse events, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.
8. CONDUCT OF ANALYSES

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

8.1. Sequence of analyses

The analysis will be performed in two steps. The first analysis (analysis E1_01) will include only the safety data up to one month post the booster dose. The final analysis (analysis E1_02) will include all demography, safety and immunogenicity analysis. These analyses will be the basis for the study report of the booster phase. Results will not be shared with the investigator before study conclusion.

8.2. Statistical considerations for interim analyses

All analyses will be conducted on final data and therefore no statistical adjustment for interim analyses is required.
9. CHANGES FROM PLANNED ANALYSES

- The vaccine responses were redefined in light of the change in assay cut-off.
- Sensitivity analysis of persistence data was initially based on imputation method. The method was replaced by a repeated mixed model.
- For the assessment of anti-PT, anti-FHA and anti-PRN antibody concentrations, the two-sided 95% CIs of the GMC ratios between subjects in the Tdap group (divided by) the Infanrix Group in APV-039 one month after vaccination (one month after vaccination for Tdap group, one month after the third dose of Infanrix for Infanrix group in APV-039) will be computed using the method proposed by G.Y. Zou and A. Donner [Zou, 2008] in order to account heterogeneity of variance between this study and APV-039. The APV-039 annex report dated 23May2016 will be used as reference for this comparison.
10. REFERENCES

- The exact CIs for a proportion within a group will be computed using SAS, [Clopper, 1934].
- The standardized asymptotic 95% CI or 97.5% CI for the group difference in proportion will be based on Method 6 as published by Newcombe [Newcombe, 1998].
11. **ABBREVIATIONS**

AE: Adverse event

ATP: According-To-Protocol

CI: Confidence Interval

GMT: Geometric Mean Titre

GSK: GlaxoSmithKline

SAE: Serious Adverse Event

TVC: Total Vaccinated cohort
PPD - This section contained Curriculum Vitae(s) and has been excluded to protect personal privacy.
CONFIDENTIAL
116570 (DTPA 0.3 (BOOSTRIX)-012 EXT-001)
Report Final

Signature of principal or coordinating investigator
GlaxoSmithKline Biologicals
Vaccines R&D
Investigator Approval Page

STUDY TITLE: An open, phase III, non-randomized, multi-center study to assess the immunogenicity and safety of a booster dose of GlaxoSmithKline (GSK) Biologicals’ combined reduced antigen content diphtheria-tetanus toxoids and acellular pertussis vaccine (Boostrix), when administered in young adults, 10 years after previous booster vaccination in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].

Study: 116570 (DTPA 0.3 (BOOSTRIX)-012 EXT 001) Development Phase: III

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Investigator: Dr Meera Varman
Affiliation/investigational centre: 2412 Cummings Street, Suite 100, Room 1022, Department of Pediatrics, Creighton University School of Medicine, Omaha, Nebraska 68131, United States

Signature of Investigator: [Signature]
Date: 9/28/17

For internal use only
STUDY TITLE: An open, phase III, non-randomized, multi-center study to assess the immunogenicity and safety of a booster dose of GlaxoSmithKline (GSK) Biologicals' combined reduced antigen content diphtheria-tetanus toxoids and acellular pertussis vaccine (Boostrix), when administered in young adults, 10 years after previous booster vaccination in Study 776423/001 [DTPA 0.3 (BOOSTRIX)-001].

Study: 116570 (DTPA 0.3 (BOOSTRIX)-012 EXT 001) Development Phase: III

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory: Narcisa Mesaros

Title of Sponsor Signatory: Clinical and Epidemiology R&D Project Leader, Belgium

Signature:

Date: 26-09-2017