

The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

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| Study No.: 217744/035 (DTPa-HBV-IPV-035) |
| Title: A phase II randomized booster vaccination study of one dose of SB Biologicals' DTPa-HBV-IPV vaccine, co-administered with two formulations of SB Biologicals' Hib conjugate vaccine, either mixed in one syringe or injected simultaneously in two concomitant injections into opposite limbs at the same visit, in healthy children who previously participated in Study 217744/011 (DTPa-HBV-IPV-011) or Groups 1, 2 and 3 of Study 217744/016 (DTPa-HBV-IPV-016). DTPa-HBV-IPV: GlaxoSmithkline (GSK) Biologicals (previously SmithKline Beecham Biologicals) combined diphtheria, tetanus and acellular pertussis, recombinant hepatitis B vaccine and inactivated polio vaccine. <i>Hiberix</i> TM (Hib): GSK Biologicals (previously SmithKlineBeecham Biologicals) <i>Haemophilus influenzae</i> type b tetanus toxoid conjugate vaccine. |
| Rationale: The purpose of the study was to evaluate the safety and immunogenicity of administration of a DTPa-HBV-IPV vaccine mixed with 2 formulations of Hib vaccine in a single injection compared to administration in 2 concomitant injections of the same vaccines into opposite limbs as a booster dose in the second year of life. Please refer to the CTRS on (217744/011) for the primary vaccination data. |
| Phase: II |
| Study Period: 22 December 1997 to 31 December 1998 |
| Study Design: Double-blind, randomized, multicenter study with 4 parallel groups (5:5:1:1). |
| Centers: 75 centers in Germany. |
| Indication: Booster vaccination against diphtheria, tetanus, poliomyelitis and <i>haemophilus influenzae</i> type b in healthy children in their second year of life. |
| Treatment: The treatment groups were as follows: <ul style="list-style-type: none"> • DTPa-HBV-IPV/Hib FB Group: received a single dose of DTPa-HBV-IPV vaccine reconstituted with Hib vaccine, formulation B. • DTPa-HBV-IPV/Hib FA Group: received reconstituted DTPa-HBV-IPV vaccine mixed with Hib vaccine of formulation A. • DTPa-HBV-IPV + Hib FA Group: received DTPa-HBV-IPV vaccine and Hib vaccine of formulation A concomitantly. • DTPa-HBV-IPV + Hib FB Group: received DTPa-HBV-IPV vaccine and Hib vaccine of formulation B concomitantly. DTPa-HBV-IPV vaccine was administered intramuscularly into the left anterolateral thigh, when administered alone or mixed with Hib vaccine (formulation A/formulation B). Hib vaccine (formulation A/formulation B) was administered into the right anterolateral thigh when administered alone. Hib vaccine formulation A = the commercially available vaccine (Hib) |
| Objectives: To evaluate and compare the safety of the DTPa-HBV-IPV vaccine mixed with 2 formulations of Hib conjugate vaccine. |
| Primary Outcome/Efficacy Variable: <i>Safety:</i> <ul style="list-style-type: none"> • Occurrence, nature and relationship to vaccination of solicited symptoms in each group. |
| Secondary Outcome/Efficacy Variable(s): <i>Immunogenicity:</i> <ul style="list-style-type: none"> • Antibody concentrations to diphtheria, tetanus, pertussis toxoid (PT), filamentous haemagglutinin (FHA), pertactin (PRN), hepatitis B surface antigens (HBs), polio virus types 1, 2 and 3 and polyribosyl ribitol phosphate (PRP), before and one month after the booster dose of the study vaccines. • Seroprotection before and one month after the booster dose of the study vaccines, defined as: <ul style="list-style-type: none"> - Anti-PRP antibody concentrations $\geq 0.15 \mu\text{g/mL}$ and $\geq 1.0 \mu\text{g/mL}$. - Anti-polio types 1, 2 and 3 antibody titers ≥ 8. - Anti-tetanus antibody concentrations $\geq 0.1 \text{ IU/mL}$. - Anti-diphtheria antibody concentrations $\geq 0.1 \text{ IU/mL}^*$ (ELISA). - Anti-HBs antibody concentrations $\geq 10 \text{ mIU/mL}$ • Seropositivity, before and one month after the booster dose of the study vaccines, defined as: <ul style="list-style-type: none"> - Anti-PT, anti-FHA and anti-PRN antibody concentrations $\geq 5 \text{ EL.U/mL}$. |

- Vaccine response to pertussis antigens (PT, FHA, and PRN), defined as appearance of antibodies in subjects who are seronegative prior to booster vaccination, and at least a two fold increase from pre-booster vaccination antibody concentrations to post-booster vaccination antibody concentrations, in those who are seropositive prior to booster vaccination.

*N.B: samples with anti-diphtheria antibody concentrations <0.1 IU/mL before the booster dose were re-tested using the VERO cell neutralising test (cut-off for neutralising antibody concentrations was ≥ 0.016 IU/mL).

Safety:

- Occurrence of any local symptoms within 4 days after vaccination.
- Occurrence of any general symptoms within 4 days after vaccination.
- Occurrence of any symptoms within 4 days after vaccination.
- Occurrence of unsolicited symptoms within 30 days after vaccination.
- Occurrence of serious adverse events (SAEs) throughout the entire study up to and including 30 days post-vaccination.

Statistical Methods:

The analyses were performed on the Total Vaccinated Cohort (TVC), the Intention to Treat (ITT) Cohort for safety, and ITT Cohort for post-booster immunogenicity.

- The ITT Cohort for safety included all subjects who were previously primed in 217744/011 and for whom safety data were available.
- The ITT for Cohort for post-booster immunogenicity included all subjects who were previously primed in 217744/011 and for whom immunogenicity data were available.
- The Total Vaccinated Cohort included all vaccinated subjects.

Analysis for immunogenicity

The analyses were performed on the ITT Cohort for post-booster immunogenicity.

The seropositivity/seroprotection rates, pertussis antigen vaccine response rates and geometric mean titers/concentrations (GMTs/GMCs) one month after booster vaccination were tabulated with their 95% Confidence Intervals (CIs) for each antibody according to the booster vaccination study groups. For the purposes of GMT/GMC calculation, when a serological result was below the antibody assay detection cut-off, an arbitrary value of half the cut-off was used for the purpose of GMT/GMC calculation.

Analysis for safety

The analyses were performed on the ITT Cohort for safety.

The percentage of subjects with individual solicited local and general symptoms during the 4 days (day 0-3) solicited follow-up period was tabulated with their exact 95% CIs. The same tabulated was performed for Grade 3 symptoms and for general symptoms with probable or suspected relationship to vaccination. The percentage of subjects with at least one report of unsolicited adverse event (AE) classified according to the World Health Organisation's (WHO) preferred terms and reported up to 31 days (day 0-30) after vaccination was tabulated. The occurrence of SAEs throughout the entire study period, up to and including 30 days post-vaccination, was tabulated according to WHO preferred terms.

Study Population: Healthy male/female subjects between 13 and 24 months of age at the time of booster vaccination who were previously primed at the age of 3, 4 and 5 months in study 217744/011. Written informed consent was obtained from the subjects' parents or guardians.

| Number of Subjects: | DTPa-HBV-IPV/Hib FB Group | DTPa-HBV-IPV/Hib FA Group | DTPa-HBV-IPV+Hib FA Group | DTPa-HBV-IPV+Hib FB Group |
|---|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Planned, N | 1500 | 1500 | 300 | 300 |
| Randomized N(ITT cohort) | 686 | 702 | 150 | 163 |
| Completed, n (%) | 682 (99.4) | 695 (99.0) | 149 (99.3) | 160 (98.2) |
| Total Number Subjects Withdrawn, n (%) | 4 (0.6) | 7 (1.0) | 1 (0.7) | 3 (1.9) |
| Withdrawn due to Adverse Events n (%) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| Withdrawn due to Lack of Efficacy n (%) | Not applicable | Not applicable | Not applicable | Not applicable |
| Withdrawn for other reasons n (%) | 4 (0.6) | 6 (0.9) | 1 (0.7) | 3 (1.9) |
| Demographics | DTPa-HBV-IPV/Hib FB Group | DTPa-HBV-IPV/Hib FA Group | DTPa-HBV-IPV+Hib FA Group | DTPa-HBV-IPV+Hib FB Group |
| N (ITT Cohort) | 686 | 702 | 150 | 163 |
| Females: Males | 344:342 | 343:359 | 78:72 | 79:84 |
| Mean Age, Months (SD) | 16.5 (2.88) | 16.3 (2.76) | 15.9 (2.66) | 16.3 (3.06) |

| | | | | | | | | | | | | |
|---|---------------------------|---------|----------------|---------------------------|----------------|----------------|---------------------------|----------------|----------------|---------------------------|----------------|----------------|
| White, n (%) | 658 (95.9) | | 672 (95.7) | | 144 (96.0) | | 159 (97.5) | | | | | |
| Primary Efficacy Results: The incidence of solicited local symptoms reported during the 4-day (day 0-3) follow-up period after booster vaccination (ITT cohort for safety analysis) | | | | | | | | | | | | |
| | | | Pain | | | Redness | | | Swelling | | | |
| Group | N | Vaccine | n | % | 95%CI (LL; UL) | n | % | 95%CI (LL; UL) | N | % | 95%CI (LL; UL) | |
| DTPa-HBV-IPV/Hib FB | 670 | Any | 224 | 33.4 | 29.9; 37.1 | 315 | 47.0 | 43.2; 50.9 | 223 | 33.3 | 29.7; 37.0 | |
| DTPa-HBV-IPV/Hib FA | 691 | Any | 307 | 44.4 | 40.7; 48.2 | 323 | 46.7 | 43.0; 50.5 | 242 | 35.0 | 31.5; 38.7 | |
| DTPa-HBV-IPV+Hib FA | 145 | Any | 59 | 40.7 | 32.6; 49.2 | 76 | 52.4 | 44.0; 60.8 | 54 | 37.2 | 29.4; 45.7 | |
| DTPa-HBV-IPV+Hib FB | 157 | Any | 61 | 38.9 | 31.2; 46.9 | 71 | 45.2 | 37.3; 53.4 | 57 | 36.3 | 28.8; 44.3 | |
| Any = local symptom for any vaccination site (for local symptoms following multiple injections, a symptom was counted once even if reported at multiple sites). | | | | | | | | | | | | |
| N = number of subjects with at least one symptom sheet completed | | | | | | | | | | | | |
| n (%) = number (percentage) of subjects reporting a specified symptom | | | | | | | | | | | | |
| 95% CI: Exact 95% confidence interval; LL, UL= Lower limit, Upper limit | | | | | | | | | | | | |
| Primary Efficacy Results: The incidence of Grade 3 solicited local symptoms reported during the 4-day (day 0-3) follow-up period after booster vaccination (ITT cohort for safety analysis) | | | | | | | | | | | | |
| | | | Pain | | | Redness | | | Swelling | | | |
| Group | N | Vaccine | n | % | 95%CI (LL; UL) | n | % | 95%CI (LL; UL) | n | % | 95%CI (LL; UL) | |
| DTPa-HBV-IPV/Hib FB | 670 | Any | 23 | 3.4 | 2.2; 5.1 | 74 | 11.0 | 8.8; 13.7 | 44 | 6.6 | 4.8; 8.7 | |
| DTPa-HBV-IPV/Hib FA | 691 | Any | 55 | 8.0 | 6.1; 10.2 | 71 | 10.3 | 8.1; 12.8 | 48 | 6.9 | 5.2; 9.1 | |
| DTPa-HBV-IPV+Hib FA | 145 | Any | 11 | 7.6 | 3.8; 13.2 | 23 | 15.9 | 10.3; 22.8 | 16 | 11.0 | 6.4; 17.3 | |
| DTPa-HBV-IPV+Hib FB | 157 | Any | 5 | 3.2 | 1.0; 7.3 | 24 | 15.3 | 10.0; 21.9 | 13 | 8.3 | 4.5; 13.7 | |
| Any = local symptom for any vaccination site (for local symptoms following multiple injections, a symptom was counted once even if reported at multiple sites). | | | | | | | | | | | | |
| N = number of subjects with at least one symptom sheet completed | | | | | | | | | | | | |
| n (%) = number (percentage) of subjects reporting a specified symptom | | | | | | | | | | | | |
| 95% CI: Exact 95% confidence interval; LL, UL= Lower limit, Upper limit | | | | | | | | | | | | |
| Grade 3 pain: cried when the limb was moved | | | | | | | | | | | | |
| Grade 3 redness and swelling > 20 mm in diameter | | | | | | | | | | | | |
| Primary Efficacy Results: Incidence of all solicited general symptoms reported during the 4-day (day 0-3) follow-up period after booster vaccination (ITT cohort for safety analysis). | | | | | | | | | | | | |
| Symptoms | DTPa-HBV-IPV/Hib FB Group | | | DTPa-HBV-IPV/Hib FA Group | | | DTPa-HBV-IPV+Hib FA Group | | | DTPa-HBV-IPV+Hib FB Group | | |
| | N = 670 | | | N = 691 | | | N = 145 | | | N = 157 | | |
| | n | % | 95%CI (LL; UL) | n | % | 95%CI (LL; UL) | n | % | 95%CI (LL; UL) | n | % | 95%CI (LL; UL) |
| Diarrhea | 85 | 12.7 | 10.3; 15.4 | 102 | 14.8 | 12.2; 17.6 | 19 | 13.1 | 8.1; 19.7 | 23 | 14.6 | 9.5; 21.2 |
| Fussiness | 194 | 29.0 | 25.5; 32.6 | 274 | 39.7 | 36.0; 43.4 | 57 | 39.3 | 31.3; 47.8 | 58 | 36.9 | 29.4; 45.0 |
| Loss of appetite | 154 | 23.0 | 19.8; 26.4 | 199 | 28.8 | 25.4; 32.3 | 44 | 30.3 | 23.0; 38.5 | 38 | 24.2 | 17.7; 31.7 |
| Restlessness | 151 | 22.5 | 19.4; 25.9 | 157 | 22.7 | 19.6; 26.0 | 29 | 20.0 | 13.8; 27.4 | 39 | 24.8 | 18.3; 32.4 |
| Sleepiness | 126 | 18.8 | 15.9; 22.0 | 177 | 25.6 | 22.4; 29.0 | 31 | 21.4 | 15.0; 29.0 | 29 | 18.5 | 12.7; 25.4 |
| Fever | 249 | 37.2 | 33.5; 40.9 | 336 | 48.6 | 44.8; 52.4 | 62 | 42.8 | 34.6; 51.2 | 59 | 37.6 | 30.0; 45.7 |
| Vomiting | 36 | 5.4 | 3.8; 7.4 | 30 | 4.3 | 2.9; 6.1 | 3 | 2.1 | 0.4; 5.9 | 9 | 5.7 | 2.7; 10.6 |
| N = number of subjects with at least one symptom sheet completed | | | | | | | | | | | | |
| n (%) = number (percentage) of subjects reporting a specified symptom | | | | | | | | | | | | |
| 95% CI= Exact 95% confidence interval; LL, UL= Lower limit, Upper limit | | | | | | | | | | | | |
| Fever = rectal temperature $\geq 38.0^{\circ}\text{C}$ ($\geq 100.4^{\circ}\text{F}$) or axillary, oral and tympanic temperature $\geq 37.5^{\circ}\text{C}$ ($\geq 99.5^{\circ}\text{F}$) | | | | | | | | | | | | |
| Primary Efficacy Results: Incidence of all Grade 3 solicited general symptoms reported during the 4-day (day 0-3) follow-up period after booster vaccination (ITT cohort for safety analysis). | | | | | | | | | | | | |
| Symptoms | DTPa-HBV-IPV/Hib FB Group | | | DTPa-HBV-IPV/Hib FA Group | | | DTPa-HBV-IPV+Hib FA Group | | | DTPa-HBV-IPV+Hib FB Group | | |
| | N = 670 | | | N = 691 | | | N = 145 | | | N = 157 | | |
| | n | % | 95%CI | n | % | 95%CI | n | % | 95%CI | n | % | 95%CI |

| | | | | | | LL | UL | | LL | UL |
|---------------------|---------------------|------|----|-------|-------|-------|--------|--------|--------|--------|
| Anti-polio type 1 | DTPa-HBV-IPV/Hib FB | Pre | 65 | 64 | 98.5 | 91.7 | 100.0 | 294.1 | 213.8 | 404.6 |
| | | Post | 65 | 65 | 100.0 | 94.5 | 100.0 | 1840.8 | 1459.4 | 2321.9 |
| | DTPa-HBV-IPV/Hib FA | Pre | 57 | 57 | 100.0 | 93.7 | 100.0 | 194.8 | 151.1 | 251.1 |
| | | Post | 57 | 57 | 100.0 | 93.7 | 100.0 | 2073.0 | 1568.9 | 2739.0 |
| | DTPa-HBV-IPV+Hib FA | Pre | 56 | 56 | 100.0 | 93.6 | 100.0 | 302.8 | 220.9 | 415.0 |
| | | Post | 56 | 56 | 100.0 | 93.6 | 100.0 | 1700.9 | 1345.0 | 2151.0 |
| DTPa-HBV-IPV+Hib FB | Pre | 64 | 62 | 96.9 | 89.2 | 99.6 | 231.1 | 168.2 | 317.7 | |
| | Post | 64 | 64 | 100.0 | 94.4 | 100.0 | 1950.5 | 1514.6 | 2511.8 | |
| Anti-polio type 2 | DTPa-HBV-IPV/Hib FB | Pre | 65 | 65 | 100.0 | 94.5 | 100.0 | 462.8 | 351.3 | 609.9 |
| | | Post | 65 | 65 | 100.0 | 94.5 | 100.0 | 2125.8 | 1735.9 | 2603.3 |
| | DTPa-HBV-IPV/Hib FA | Pre | 57 | 57 | 100.0 | 93.7 | 100.0 | 450.7 | 353.2 | 575.0 |
| | | Post | 57 | 57 | 100.0 | 93.7 | 100.0 | 2611.8 | 2045.2 | 3335.3 |
| | DTPa-HBV-IPV+Hib FA | Pre | 56 | 56 | 100.0 | 93.6 | 100.0 | 487.3 | 370.4 | 641.1 |
| | | Post | 56 | 56 | 100.0 | 93.6 | 100.0 | 1754.3 | 1414.6 | 2175.7 |
| DTPa-HBV-IPV+Hib FB | Pre | 64 | 64 | 100.0 | 94.4 | 100.0 | 401.5 | 314.6 | 512.4 | |
| | Post | 64 | 64 | 100.0 | 94.4 | 100.0 | 1919.1 | 1559.5 | 2361.5 | |
| Anti-polio type 3 | DTPa-HBV-IPV/Hib FB | Pre | 65 | 65 | 100.0 | 94.5 | 100.0 | 214.8 | 164.1 | 281.2 |
| | | Post | 65 | 65 | 100.0 | 94.5 | 100.0 | 3274.1 | 2600.2 | 4122.6 |
| | DTPa-HBV-IPV/Hib FA | Pre | 57 | 57 | 100.0 | 93.7 | 100.0 | 159.4 | 117.9 | 215.4 |
| | | Post | 57 | 57 | 100.0 | 93.7 | 100.0 | 4171.2 | 3257.5 | 5341.3 |
| | DTPa-HBV-IPV+Hib FA | Pre | 56 | 56 | 100.0 | 93.6 | 100.0 | 213.8 | 157.8 | 289.6 |
| | | Post | 56 | 56 | 100.0 | 93.6 | 100.0 | 2912.5 | 2030.0 | 4178.6 |
| DTPa-HBV-IPV+Hib FB | Pre | 64 | 64 | 100.0 | 94.4 | 100.0 | 159.0 | 118.6 | 213.2 | |
| | Post | 64 | 64 | 100.0 | 94.4 | 100.0 | 3635.9 | 2875.7 | 4597.0 | |

N = number of subjects with available results

n (%) = number / percentage of subjects with titers within the specified range

95% CI = 95% confidence interval; LL, UL= Lower limit, Upper limit.

Pre = Pre-vaccination blood sample obtained immediately before the booster dose

Post = Post vaccination blood sample obtained one month after the booster dose

Secondary Outcome Variable(s): Seroprotection rate and GMC for anti-tetanus antibodies (ITT cohort for post-booster immunogenicity analysis).

| Group | Timing | N | ≥ 0.1 IU/mL | | | | GMC | | |
|---------------------|--------|----|-------------|-------|--------|-------|--------|--------|--------|
| | | | n | % | 95% CI | | IU/mL | 95% CI | |
| | | | | | LL | UL | | LL | UL |
| DTPa-HBV-IPV/Hib FB | Pre | 65 | 63 | 96.9 | 89.3 | 99.6 | 0.521 | 0.415 | 0.654 |
| | Post | 65 | 65 | 100.0 | 94.5 | 100.0 | 7.833 | 6.444 | 9.522 |
| DTPa-HBV-IPV/Hib FA | Pre | 57 | 54 | 94.7 | 85.4 | 98.9 | 0.377 | 0.290 | 0.489 |
| | Post | 57 | 57 | 100.0 | 93.7 | 100.0 | 7.848 | 6.371 | 9.667 |
| DTPa-HBV-IPV+Hib FA | Pre | 56 | 55 | 98.2 | 90.4 | 100.0 | 0.603 | 0.470 | 0.773 |
| | Post | 56 | 56 | 100.0 | 93.6 | 100.0 | 11.981 | 8.946 | 16.046 |
| DTPa-HBV-IPV+Hib FB | Pre | 64 | 62 | 96.9 | 89.2 | 99.6 | 0.455 | 0.349 | 0.593 |
| | Post | 64 | 64 | 100.0 | 94.4 | 100.0 | 11.427 | 9.495 | 13.753 |

N = number of subjects with available results

n (%) = number / percentage of subjects with concentrations within the specified range

95% CI = 95% confidence interval; LL, UL= Lower limit, Upper limit.

Pre = Pre-vaccination blood sample obtained immediately before the booster dose

Post = Post vaccination blood sample obtained one month after the booster dose

Secondary Outcome Variable(s): Seroprotection rate and GMC for anti-diphtheria antibodies (ITT cohort for post-booster immunogenicity analysis).

| Group | Timing | N | ≥ 0.1 IU/mL | | | | GMC | | |
|-------|--------|---|-------------|---|--------|----|-------|--------|----|
| | | | n | % | 95% CI | | IU/mL | 95% CI | |
| | | | | | LL | UL | | LL | UL |

| | | | | | | | | | |
|---------------------|------|----|----|-------|------|-------|-------|-------|-------|
| DTPa-HBV-IPV/Hib FB | Pre | 65 | 46 | 70.8 | 58.2 | 81.4 | 0.163 | 0.129 | 0.206 |
| | Post | 65 | 64 | 98.5 | 91.7 | 100.0 | 3.335 | 2.618 | 4.248 |
| DTPa-HBV-IPV/Hib FA | Pre | 57 | 37 | 64.9 | 51.1 | 77.1 | 0.129 | 0.104 | 0.160 |
| | Post | 57 | 57 | 100.0 | 93.7 | 100.0 | 3.413 | 2.632 | 4.426 |
| DTPa-HBV-IPV+Hib FA | Pre | 56 | 39 | 69.6 | 55.9 | 81.2 | 0.179 | 0.136 | 0.236 |
| | Post | 56 | 55 | 98.2 | 90.4 | 100.0 | 3.749 | 2.703 | 5.201 |
| DTPa-HBV-IPV+Hib FB | Pre | 64 | 38 | 59.4 | 46.4 | 71.5 | 0.132 | 0.102 | 0.171 |
| | Post | 64 | 64 | 100.0 | 94.4 | 100.0 | 3.134 | 2.532 | 3.878 |

N = number of subjects with available results;
n (%) = number (percentage) of subjects with concentrations within the specified range
95% CI = 95% confidence interval; LL, UL= Lower limit, Upper limit.
Pre = Pre-vaccination blood sample obtained immediately before the booster dose
Post = Post vaccination blood sample obtained one month after the booster dose

Secondary Outcome Variable(s): Seroprotection rate and GMCs for anti-HBs antibodies (ITT cohort for post-booster immunogenicity analysis).

| Group | Timing | N | ≥ 10 mIU/mL | | | | GMC | | |
|---------------------|--------|----|-------------|-------|-------|-------|--------|--------|--------|
| | | | n | % | 95%CI | | mIU/mL | 95%CI | |
| | | | | | LL | UL | | LL | UL |
| DTPa-HBV-IPV/Hib FB | Pre | 41 | 39 | 95.1 | 83.5 | 99.4 | 212.8 | 128.1 | 353.4 |
| | Post | 41 | 41 | 100.0 | 91.4 | 100.0 | 5521.9 | 3166.6 | 9629.1 |
| DTPa-HBV-IPV/Hib FA | Pre | 35 | 34 | 97.1 | 85.1 | 99.9 | 227.1 | 149.5 | 345.0 |
| | Post | 35 | 35 | 100.0 | 90.0 | 100.0 | 6366.9 | 3820.3 | 10611 |
| DTPa-HBV-IPV+Hib FA | Pre | 38 | 35 | 92.1 | 78.6 | 98.3 | 206.1 | 123.4 | 344.1 |
| | Post | 38 | 37 | 97.4 | 86.2 | 99.9 | 6272.7 | 2969.2 | 13251 |
| DTPa-HBV-IPV+Hib FB | Pre | 48 | 46 | 95.8 | 85.7 | 99.5 | 193.2 | 119.4 | 312.8 |
| | Post | 48 | 46 | 95.8 | 85.7 | 99.5 | 4650.5 | 2577.3 | 8391.5 |

N = number of subjects with available results
n (%) = number (percentage) of subjects with concentrations within the specified range
95% CI = 95% confidence interval; LL, UL= Lower limit, Upper limit.
Pre = Pre-vaccination blood sample obtained immediately before the booster dose
Post = Post vaccination blood sample obtained one month after the booster dose

Secondary Outcome Variable(s): Vaccine response to PT (ITT cohort for post-booster immunogenicity analysis).

| Antigen | Group | Pre-vaccination Status | Vaccine Response | | | | |
|---------|---------------------|------------------------|------------------|----|------|--------|------|
| | | | N | n | % | 95% CI | |
| | | | | | | LL | UL |
| PT | DTPa-HBV-IPV/Hib FB | S+ | 48 | 46 | 95.8 | 89.3 | 99.6 |
| | | S- | 17 | 17 | 100 | | |
| | | Total | 65 | 63 | 96.9 | | |
| | DTPa-HBV-IPV/Hib FA | S+ | 38 | 36 | 94.7 | 87.9 | 99.6 |
| | | S- | 19 | 19 | 100 | | |
| | | Total | 57 | 55 | 96.5 | | |
| | DTPa-HBV-IPV+Hib FA | S+ | 38 | 37 | 97.4 | 87.7 | 99.6 |
| | | S- | 18 | 17 | 94.4 | | |
| | | Total | 56 | 54 | 96.4 | | |
| | DTPa-HBV-IPV+Hib FB | S+ | 35 | 33 | 94.3 | 89.2 | 99.6 |
| | | S- | 29 | 29 | 100 | | |
| | | Total | 64 | 62 | 96.9 | | |

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

n (%) = number / percentage of subjects showing a vaccine response

95% CI = 95% confidence interval; LL, UL= Lower limit, Upper limit.

Pre-vac status = pre-booster vaccination serological status

S+: subjects with concentrations equal to or above the assay cut-off at pre-vaccination (= initially seropositive)

S-: subjects with concentrations below the assay cut-off at pre-vaccination (= initially seronegative)

Vaccine response: appearance of antibodies (i.e. concentration \geq cut-off 5 EL.U/mL) in subjects who are initially seronegative or at least a two-fold increase of pre-vaccination antibody concentrations in those who are initially seropositive

Secondary Outcome Variable(s): Vaccine response to FHA (ITT cohort for post-booster immunogenicity analysis).

| Antigen | Group | Pre-vaccination Status | N | Vaccine Response | | | |
|---------|---------------------|------------------------|----|------------------|------|--------|------|
| | | | | n | % | 95% CI | |
| | | | | | | LL | UL |
| FHA | DTPa-HBV-IPV/Hib FB | S+ | 51 | 50 | 98.0 | 90.1 | 100 |
| | | S- | 3 | 3 | 100 | | |
| | | Total | 54 | 53 | 98.1 | | |
| | DTPa-HBV-IPV/Hib FA | S+ | 42 | 42 | 100 | 92.5 | 100 |
| | | S- | 5 | 5 | 100 | | |
| | | Total | 47 | 47 | 100 | | |
| | DTPa-HBV-IPV+Hib FA | S+ | 42 | 40 | 95.2 | 81.3 | 98.6 |
| | | S- | 2 | 1 | 50.0 | | |
| | | Total | 44 | 41 | 93.2 | | |
| | DTPa-HBV-IPV+Hib FB | S+ | 52 | 50 | 96.2 | 87.9 | 99.6 |
| | | S- | 5 | 5 | 100 | | |
| | | Total | 57 | 55 | 96.5 | | |

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

n (%) = number / percentage of subjects showing a vaccine response

95% CI = 95% confidence interval; LL, UL= Lower limit, Upper limit.

Pre-vac status = pre-booster vaccination serological status

S+: subjects with concentrations equal to or above the assay cut-off at pre-vaccination(= initially seropositive)

S-: subjects with concentrations below the assay cut-off at pre-vaccination(= initially seronegative)

Vaccine response: appearance of antibodies (i.e. concentrations \geq cut-off 5 EL.U/mL) in subjects who are initially seronegative or at least a two-fold increase of pre-vaccination antibody concentrations in those who are initially seropositive

Secondary Outcome Variable(s): Vaccine response to PRN (ITT cohort for post-booster immunogenicity analysis).

| Antigen | Group | Pre-vaccination Status | N | Vaccine Response | | | |
|---------|---------------------|------------------------|----|------------------|------|--------|------|
| | | | | n | % | 95% CI | |
| | | | | | | LL | UL |
| PRN | DTPa-HBV-IPV/Hib FB | S+ | 63 | 59 | 93.7 | 85.0 | 98.3 |
| | | S- | 2 | 2 | 100 | | |
| | | Total | 65 | 61 | 93.8 | | |
| | DTPa-HBV-IPV/Hib FA | S+ | 56 | 54 | 96.4 | 87.9 | 99.6 |
| | | S- | 1 | 1 | 100 | | |
| | | Total | 57 | 55 | 96.5 | | |
| | DTPa-HBV-IPV+Hib FA | S+ | 56 | 52 | 92.9 | 82.7 | 98.0 |
| | | S- | 56 | 52 | 92.9 | | |
| | | Total | 59 | 56 | 94.9 | | |
| | DTPa-HBV-IPV+Hib FB | S+ | 5 | 5 | 100 | 86.9 | 99.0 |
| | | S- | 64 | 61 | 95.3 | | |
| | | Total | 63 | 59 | 93.7 | | |

N = number of subjects with both pre- and post-vaccination results available
n (%) = number (percentage) of subjects showing a vaccine response
95% CI = 95% confidence interval; LL, UL= Lower limit, Upper limit.
Pre-vac status = pre-booster vaccination serological status
S+: subjects with concentrations equal to or above the assay cut-off at pre-vaccination(= initially seropositive)
S-: subjects with concentrations below the assay cut-off at pre-vaccination(= initially seronegative)
Vaccine response: appearance of antibodies (i.e. concentration \geq cut-off 5 EL.U/mL) in subjects who are initially seronegative or at least a two-fold increase of pre-vaccination antibody concentrations in those who are initially seropositive

Secondary Outcome Variable(s): Seropositivity rates and GMCs of anti-PT, anti-FHA and anti-PRN antibodies (ITT cohort for post-booster immunogenicity analysis)

| Antibody | Group | Timing | N | ≥ 5 EL.U/mL | | | GMC EL.U/mL | 95%CI | | |
|----------|---------------------|--------|----|------------------|-------|----------------|----------------|-------|-------|-------|
| | | | | n | % | 95%CI (LL; UL) | | LL | UL | |
| Anti-PT | DTPa-HBV-IPV/Hib FB | Pre | 65 | 48 | 73.8 | 61.5 | 84.0 | 7.9 | 6.3 | 9.9 |
| | | Post | 65 | 64 | 98.5 | 91.7 | 100.0 | 124.2 | 101.0 | 152.8 |
| | DTPa-HBV-IPV/Hib FA | Pre | 57 | 38 | 66.7 | 52.9 | 78.6 | 7.1 | 5.5 | 9.1 |
| | | Post | 57 | 57 | 100.0 | 93.7 | 100.0 | 108.7 | 90.7 | 130.3 |
| | DTPa-HBV-IPV+Hib FA | Pre | 56 | 38 | 67.9 | 54.0 | 79.7 | 8.1 | 6.2 | 10.6 |
| | | Post | 56 | 55 | 98.2 | 90.4 | 100.0 | 111.6 | 86.9 | 143.2 |
| | DTPa-HBV-IPV+Hib FB | Pre | 64 | 35 | 54.7 | 41.7 | 67.2 | 5.6 | 4.4 | 7.1 |
| | | Post | 64 | 64 | 100.0 | 94.4 | 100.0 | 122.4 | 101.8 | 147.2 |
| Anti-FHA | DTPa-HBV-IPV/Hib FB | Pre | 64 | 61 | 95.3 | 86.9 | 99.0 | 23.2 | 18.4 | 29.2 |
| | | Post | 55 | 54 | 98.2 | 90.3 | 100.0 | 194.7 | 158.0 | 240.0 |
| | DTPa-HBV-IPV/Hib FA | Pre | 56 | 51 | 91.1 | 80.4 | 97.0 | 21.3 | 16.4 | 27.7 |
| | | Post | 47 | 47 | 100.0 | 92.5 | 100.0 | 216.0 | 182.9 | 255.1 |
| | DTPa-HBV-IPV+Hib FA | Pre | 55 | 53 | 96.4 | 87.5 | 99.6 | 20.7 | 16.6 | 25.9 |
| | | Post | 44 | 43 | 97.7 | 88.0 | 99.9 | 180.1 | 136.0 | 238.5 |
| | DTPa-HBV-IPV+Hib FB | Pre | 64 | 59 | 92.2 | 82.7 | 97.4 | 17.0 | 13.0 | 22.2 |
| | | Post | 57 | 57 | 100.0 | 93.7 | 100.0 | 202.5 | 172.7 | 237.4 |
| Anti-PRN | DTPa-HBV-IPV/Hib FB | Pre | 65 | 63 | 96.9 | 89.3 | 99.6 | 32.8 | 26.8 | 40.2 |
| | | Post | 65 | 65 | 100.0 | 94.5 | 100.0 | 467.0 | 348.0 | 626.7 |
| | DTPa-HBV-IPV/Hib FA | Pre | 57 | 56 | 98.2 | 90.6 | 100.0 | 27.3 | 21.7 | 34.3 |
| | | Post | 57 | 56 | 98.2 | 90.6 | 100.0 | 582.8 | 420.2 | 808.4 |
| | DTPa-HBV-IPV+Hib FA | Pre | 56 | 56 | 100.0 | 93.6 | 100.0 | 31.3 | 24.4 | 40.2 |
| | | Post | 56 | 55 | 98.2 | 90.4 | 100.0 | 467.4 | 320.4 | 681.8 |
| | DTPa-HBV-IPV+Hib FB | Pre | 64 | 59 | 92.2 | 82.7 | 97.4 | 26.7 | 20.2 | 35.4 |
| | | Post | 64 | 64 | 100.0 | 94.4 | 100.0 | 560.5 | 441.2 | 712.2 |

N = number of subjects with available results
n (%) = number / percentage of subjects with concentrations within the specified range
95% CI = 95% confidence interval; LL, UL= Lower limit, Upper limit.
Pre = Pre-vaccination blood sample obtained immediately before the booster dose
Post = Post vaccination blood sample obtained one month after the booster dose

Secondary Outcome Variable(s): Incidence and nature of all, local and general symptoms reported during the 4-day (day 0-3) follow-up period after booster vaccination (ITT cohort for safety analysis).

| Group | N | All symptoms | | | General symptoms | | | Local* symptoms | | |
|---------------------|-----|--------------|------|----------------|------------------|------|----------------|-----------------|------|----------------|
| | | n | % | 95%CI (LL; UL) | n | % | 95%CI (LL; UL) | n | % | 95%CI (LL; UL) |
| DTPa-HBV-IPV/Hib FB | 670 | 527 | 78.7 | 75.4; 81.7 | 439 | 65.5 | 61.8; 69.1 | 378 | 56.4 | 52.6; 60.2 |
| DTPa-HBV-IPV/Hib FA | 692 | 566 | 81.8 | 78.7; 84.6 | 508 | 73.4 | 70.0; 76.7 | 418 | 60.4 | 56.7; 64.1 |
| DTPa-HBV-IPV+Hib FA | 145 | 119 | 82.1 | 74.8; 87.9 | 104 | 71.7 | 63.7; 78.9 | 92 | 63.4 | 55.1; 71.3 |
| DTPa-HBV-IPV+Hib FB | 157 | 124 | 79.0 | 71.8; 85.1 | 107 | 68.2 | 60.3; 75.4 | 90 | 57.3 | 49.2; 65.2 |

This table includes both solicited and unsolicited symptoms reported during the 4 day follow-up period.
*Local: Number of documented doses reporting at least one local symptom whatever the number of injections.
For local symptoms and multiple injections, a symptom was counted once even if reported on multiple sites.
N = number of subjects with at least one documented dose

| | | | | |
|--|--|--|--|--|
| n = number of subjects presenting at least one type of symptom | | | | |
| % = percentage of subjects presenting at least one type of symptom | | | | |
| 95% CI= Exact 95% confidence interval; LL, UL= Lower limit, Upper limit. | | | | |
| Safety Results: Number (%) of unsolicited adverse events within 30 days following booster vaccination according to the WHO preferred term (ATP cohort for safety) | | | | |
| Most frequent 5 adverse events - On-Therapy (Occurring between 0-30 days following vaccination) | DTPa-HBV-IPV/Hib FB Group N = 672 | DTPa-HBV-IPV/Hib FA Group N = 694 | DTPa-HBV-IPV+Hib FA Group N = 145 | DTPa-HBV-IPV+Hib FB Group N = 158 |
| Subjects with any AE(s), n(%) | 241 (35.9) | 236 (34.0) | 57 (39.3) | 48 (30.4) |
| Fever | 46 (6.8) | 38 (5.5) | 7 (4.8) | 12 (7.6) |
| bronchitis | 36 (5.4) | 32 (4.6) | 13 (9.0) | 7 (4.4) |
| upper respiratory tract infection | 32 (4.8) | 30 (4.3) | 1 (0.7) | 6 (3.8) |
| infection viral | 24 (3.6) | 21 (3.0) | 5 (3.4) | 6 (3.8) |
| Otitis media | 22 (3.3) | 23 (3.3) | 6 (4.1) | 3 (1.9) |
| rhinitis | 22 (3.3) | 15 (2.2) | 6 (4.1) | 5 (3.2) |
| infection | 20 (3.0) | 15 (2.2) | 2 (1.4) | 9 (5.7) |
| injection site reaction | 15 (2.2) | 16 (2.3) | 5 (3.4) | 4 (2.5) |
| Safety results: Number (%) of subjects with serious adverse events (Total Vaccinated Cohort) | | | | |
| Serious adverse event, n (%) [n considered by the investigator to be related to study medication] | | | | |
| All SAEs | DTPa-HBV-IPV/Hib FB Group N = 686 | DTPa-HBV-IPV/Hib FA Group N = 702 | DTPa-HBV-IPV+Hib FA Group N = 150 | DTPa-HBV-IPV+Hib FB Group N = 163 |
| Subjects with any SAE(s), n(%) [n related] | 5 (0.7) [1] | 4 (0.6) [0] | 0 (0.0) [0] | 3 (1.8) [0] |
| allergic reaction | 0 (0.0) [0] | 1 (0.1) [0] | 0 (0.0) [0] | 0 (0.0) [0] |
| cyanosis | 0 (0.0) [0] | 0 (0.0) [0] | 0 (0.0) [0] | 1 (0.6) [0] |
| fever convulsions | 1 (0.1) [1] | 0 (0.0) [0] | 0 (0.0) [0] | 0 (0.0) [0] |
| gastroenteritis | 4 (0.6) [0] | 1 (0.1) [0] | 0 (0.0) [0] | 2 (1.2) [0] |
| injury | 1 (0.1) [0] | 0 (0.0) [0] | 0 (0.0) [0] | 0 (0.0) [0] |
| neuroblastoma | 0 (0.0) [0] | 1 (0.1) [0] | 0 (0.0) [0] | 0 (0.0) [0] |
| pneumonia | 1 (0.1) [0] | 0 (0.0) [0] | 0 (0.0) [0] | 0 (0.0) [0] |
| pyelonephritis | 0 (0.0) [0] | 1 (0.1) [0] | 0 (0.0) [0] | 0 (0.0) [0] |
| Fatal SAEs | DTPa-HBV-IPV/Hib FB Group N = 686 | DTPa-HBV-IPV/Hib FA Group N = 702 | DTPa-HBV-IPV+Hib FA Group N = 150 | DTPa-HBV-IPV+Hib FB Group N = 163 |
| Subjects with fatal SAEs, n (%) [related] | 0 (0.0) [0] | 0 (0.0) [0] | 0 (0.0) [0] | 0 (0.0) [0] |

Conclusion:
Following vaccination, across groups (DTPa-HBV-IPV/Hib FB, DTPa-HBV-IPV/Hib FA, DTPa-HBV-IPV+Hib FA and DTPa-HBV-IPV+Hib FB), at least 33.4% of the subjects reported pain, 45.2% of the subjects reported redness and 33.3% of the subjects reported swelling. Grade 3 pain, redness and swelling were reported by at least 3.2%, 10.3% and 6.6% of subjects, respectively.
At least one solicited general symptom was reported by 5.4%, 4.3%, 2.1%, and 5.7% in DTPa-HBV-IPV/Hib FB Group, DTPa-HBV-IPV/Hib FA Group, DTPa-HBV-IPV+Hib FA Group, and in DTPa-HBV-IPV+Hib FB Group, respectively. At least one Grade 3 solicited general symptom was reported by 0.6%, 0.3%, 0.7%, and 0.6% of the subjects in DTPa-HBV-IPV/Hib FB Group, DTPa-HBV-IPV/Hib FA Group, DTPa-HBV-IPV+Hib FA Group, and in DTPa-HBV-IPV+Hib FB Group, respectively. Across groups, at least 3.3%, 3.3%, 1.4%, and 2.5% of the subjects in DTPa-HBV-IPV/Hib FB Group, DTPa-HBV-IPV/Hib FA Group, DTPa-HBV-IPV+Hib FA Group, and in DTPa-HBV-IPV+Hib FB Group reported a probable or suspected symptom related to vaccination.
At least one unsolicited AE was reported by 241(35.9%), 236 (34.0%), 57 (39.3%), and 48 (30.4%) subjects in DTPa-

HBV-IPV/Hib FB Group, DTPa-HBV-IPV/Hib FA Group, DTPa-HBV-IPV+Hib FA Group, and in DTPa-HBV-IPV+Hib FB Group, respectively. At least one SAE was reported by 5 (0.7%), 4 (0.6%), and 3 (1.8%) subjects in DTPa-HBV-IPV/Hib FB Group, DTPa-HBV-IPV/Hib FA Group and in DTPa-HBV-IPV+Hib FB Group, respectively. One SAE in the DTPa-HBV-IPV/Hib FB Group was considered to be related to the vaccination by the investigator. No fatal SAEs were reported during the study.

Publications: None.

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