

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.: 208140 (DTPa-HBV 005) |
| Title: Randomised comparative clinical study to assess the immunogenicity and reactogenicity of the SmithKline Beecham Biologicals' combined diphtheria, tetanus, acellular pertussis, hepatitis B vaccine and SmithKline Beecham Biologicals' <i>Haemophilus influenzae</i> type b tetanus conjugate vaccine, when administered simultaneously in two separate injections or in one single injection, as a primary vaccination course to healthy infants at the age of 2, 4 and 6 months. DTPa-HBV: GlaxoSmithKline Biologicals' (GSK) [formerly SmithKline Beecham (SB)] combined diphtheria, tetanus, acellular pertussis, hepatitis B vaccine. Hib: GSK Biologicals' <i>Haemophilus influenzae</i> type b tetanus conjugate vaccine. |
| ORationale: The purpose of the study was to assess the safety and immunogenicity of the primary vaccination course of DTPa-HBV and Hib vaccines when administered either simultaneously in opposite thighs or combined in a single injection to healthy infants at 2, 4 and 6 months of age. |
| Phase: III |
| Study Period: 10 January 1994 to 13 September 1994. |
| Study Design: The pilot phase of the study was an open, randomised study with two groups. |
| Centres: 1 centre in Canada. |
| Indication: Primary vaccination against diphtheria, tetanus, pertussis, hepatitis B and <i>Haemophilus influenzae</i> type b in healthy infants. |
| Treatment: The study groups were as follows: <ul style="list-style-type: none"> • DTPa-HBV+Hib Group: received 3 simultaneous intramuscular administrations of DTPa-HBV vaccine in the left limb and Hib vaccine in the right limb. • DTPa-HBV/Hib Group: received 3 reconstituted intramuscular administrations of DTPa-HBV and Hib vaccines in the left limb. |
| Objectives: To assess the safety and immunogenicity of DTPa-HBV and Hib vaccines when administered either simultaneously in opposite thighs or combined in a single injection, to healthy infants, as a three-dose primary vaccination course at 2, 4 and 6 months of age. |
| Primary Outcome/Efficacy Variable: <i>Immunogenicity</i> Prior to vaccination, two months after the second vaccination (post Dose 2) and one month after the third vaccination (post Dose 3). <ul style="list-style-type: none"> • Anti-hepatitis B (anti-HBs) antibody concentration ≥ 10 IU/mL and Geometric Mean concentrations (GMC). • Vaccine response to pertussis toxoid (PT), filamentous hemagglutinin (FHA) and 69 kDa and GMCs. Vaccine response (VR) is defined as: <ul style="list-style-type: none"> - appearance of antibodies (concentration ≥ 5 EL.U/ml when undetectable concentration prior to vaccination. - post vaccination concentrations higher than or equal to pre vaccination concentrations in initially seropositive subjects. • Anti-diphtheria and anti-tetanus antibodies concentration ≥ 0.1 IU/mL and GMCs. • Anti-polyribosyl ribitol phosphate (PRP) antibodies concentration ≥ 0.15 μg/mL and 1.0 μg/mL and GMCs. <i>Safety</i> <ul style="list-style-type: none"> • Occurrence and intensity of solicited local and general symptoms within 48 hours and during the 4-day follow up period after each vaccination. • Occurrence and relationship to vaccination of unsolicited adverse events within 30 days after each vaccination. • Occurrence of serious adverse events (SAEs) during the study period. Outcome variables were not differentiated into primary and secondary in the study protocol, hence all were considered as primary outcome variables. |
| Secondary Outcome/Efficacy Variable(s): Not Applicable. |
| Statistical Methods: The analysis was performed on Intention-to-Treat (ITT) cohort and the Total Vaccinated Cohort. <ul style="list-style-type: none"> - The Total Vaccinated cohort included all vaccinated subjects - The ITT cohort included all subjects vaccinated whom data were available except those who were eliminated for eligibility criteria as defined in the protocol |

Analysis of immunogenicity

The analysis was performed on the ITT cohort. GMC and seropositivity rates were calculated with their 95% confidence interval (CI) for each antibody measured at each blood sampling time point. Also, vaccine response rates to each of the pertussis antigens (PT, FHA, 69kDa) were calculated with 95%CI. Antibody concentrations below the assay cut-off were given an arbitrary value of one half of the cut-off value.

Analysis of safety

The analysis was performed on the ITT cohort and the Total Vaccinated Cohort. The percentage of subjects reporting each individual solicited local and general symptom within 48 hours (only general symptom) and during the 4-day follow-up (local and general symptom) was tabulated with 95% CI. The same tabulation was performed for grade 3 symptoms and for general symptoms with relationship to vaccination. The percentage of subjects with at least one report of unsolicited adverse events, and their relationship to vaccination, classified by the World Health Organization (WHO) preferred term and reported within 30 days after each vaccination was tabulated. The occurrence of SAEs during the study period was tabulated per group according to the WHO preferred terms.

Study Population: Healthy male and female subjects, aged 8 to 12 weeks at the time of the first vaccination. Written informed consent was obtained from the parents or guardians of the subjects.

| Number of Subjects: | DTPa-HBV+Hib Group | DTPa-HBV/Hib Group |
|---|--------------------|--------------------|
| Planned, N | 90 | 90 |
| Randomised, N (Total Cohort) | 90 | 90 |
| Completed, n (%) | 82 (91.1) | 87 (96.7) |
| Total Number Subjects Withdrawn, n (%) | 8 (8.9) | 3 (3.3) |
| Withdrawn due to Adverse Events n (%) | 1 (1.1) | 0 (0.0) |
| Withdrawn due to Lack of Efficacy n (%) | 0 (0.0) | 0 (0.0) |
| Withdrawn for other reasons n (%) | 7 (7.8) | 3 (3.3) |
| Demographics | DTPa-HBV+Hib Group | DTPa-HBV/Hib Group |
| N (Total Cohort) | 90 | 90 |
| Females: Males | 44:46 | 38:52 |
| Mean Age, weeks (SD) | 8.4 (0.8) | 8.5 (0.9) |
| White, n (%) | 58 (64.4) | 64(71.1) |

Primary Efficacy Results: Distribution of individual anti-HBs antibody concentrations and GMCs (ITT Cohort)

| Group | Timing | N | ≥10 mIU/mL | | | | GMC (mIU/mL) | | | |
|--------------|--------|----|------------|------|--------|------|--------------|--------|------|--|
| | | | n | % | 95% CI | | Value | 95% CI | | |
| | | | | | LL | UL | | LL | UL | |
| DTPa-HBV+Hib | Pre | 71 | 7 | 9.9 | 4.4 | 19.8 | 7 | 5 | 9 | |
| | PII | 71 | 68 | 95.8 | 87.3 | 98.9 | 257 | 179 | 367 | |
| | PIII | 71 | 71 | 100 | 93.6 | 100 | 930 | 697 | 1240 | |
| DTPa-HBV/Hib | Pre | 81 | 13 | 16.0 | 9.2 | 26.3 | 9 | 7 | 12 | |
| | PII | 81 | 76 | 93.8 | 85.6 | 97.7 | 143 | 103 | 199 | |
| | PIII | 81 | 79 | 97.5 | 90.5 | 99.6 | 497 | 355 | 697 | |

N = total number of subjects

n(%) = number (percentage) of subjects within a given range

Pre = pre-vaccination (Day 0)

PII = approximately two months after Dose 2 (Day 112)

PIII = approximately one month after Dose 3 (Day 140)

95% CI = 95% confidence interval

Primary Efficacy Results: Vaccine response and pre- and post-vaccination GMCs for pertussis components (ITT Cohort)

| Antibody | Group | Pre-vaccination serological status | N | Vaccine Response PIII | | | | N | GMC (EL.U/mL) PRE | | | | N | GMC (EL.U/mL) PII | | | | N | GMC (EL.U/mL) PIII | | | |
|----------|--------------|------------------------------------|----|-----------------------|-----|-------|----|----|-------------------|-------|-----|--------|----|-------------------|----|--------|-------|----|--------------------|--|--|--|
| | | | | n | % | 95%CI | | | Val ue | 95%CI | | Val ue | | 95%CI | | Val ue | 95%CI | | | | | |
| | | | | | | LL | UL | | | LL | UL | | | LL | UL | | LL | | UL | | | |
| Anti-PT | DTPa-HBV+Hib | Seronegative | 52 | 52 | 100 | | | 52 | 2.5 | 2.5 | 2.5 | 54 | 43 | 37 | 50 | 54 | 73 | 63 | 84 | | | |

| | | | | | | | | | | | | | | | | | | | |
|-----------------|------------------|--------------|----|----|------|------|------|----|-----|-----|-----|----|-----|-----|-----|----|-----|-----|-----|
| | | Seropositive | 17 | 14 | 82.4 | | | 17 | 14 | 9 | 22 | 17 | 26 | 19 | 36 | 17 | 50 | 37 | 66 |
| | | All | 69 | 66 | 95.7 | 87.1 | 98.9 | 69 | 4 | 3 | 5 | 71 | 38 | 33 | 44 | 71 | 67 | 58 | 76 |
| | DTPa- HBV/Hib | Seronegative | 56 | 56 | 100 | | | 56 | 2.5 | 2.5 | 2.5 | 57 | 36 | 30 | 43 | 57 | 65 | 55 | 77 |
| | | Seropositive | 24 | 24 | 100 | | | 24 | 8 | 7 | 9 | 24 | 24 | 21 | 28 | 24 | 46 | 38 | 55 |
| | | All | 80 | 80 | 100 | 94.3 | 100 | 80 | 4 | 3 | 4 | 81 | 32 | 28 | 37 | 81 | 59 | 52 | 67 |
| Anti-FHA | DTPa- HBV+Hib | Seronegative | 21 | 21 | 100 | | | 21 | 2.5 | 2.5 | 2.5 | 24 | 158 | 127 | 198 | 24 | 334 | 267 | 416 |
| | | Seropositive | 47 | 46 | 97.9 | | | 47 | 15 | 11 | 19 | 46 | 106 | 86 | 131 | 47 | 263 | 224 | 309 |
| | | All | 68 | 67 | 98.5 | 90.9 | 99.9 | 68 | 9 | 7 | 11 | 70 | 122 | 104 | 143 | 71 | 285 | 250 | 325 |
| | DTPa- HBV/Hib | Seronegative | 28 | 28 | 100 | | | 28 | 2.5 | 2.5 | 2.5 | 30 | 123 | 101 | 150 | 30 | 261 | 214 | 320 |
| | | Seropositive | 51 | 50 | 98.0 | | | 51 | 15 | 12 | 18 | 48 | 84 | 70 | 100 | 51 | 222 | 193 | 256 |
| | | All | 79 | 78 | 98.7 | 92.1 | 99.9 | 79 | 8 | 6 | 10 | 78 | 97 | 84 | 112 | 81 | 236 | 210 | 265 |
| Anti- 69 kDa | DTPa- HBV+Hib | Seronegative | 46 | 46 | 100 | | | 46 | 2.5 | 2.5 | 2.5 | 47 | 104 | 82 | 132 | 47 | 272 | 223 | 332 |
| | | Seropositive | 24 | 21 | 87.5 | | | 24 | 16 | 10 | 23 | 24 | 34 | 23 | 50 | 24 | 172 | 122 | 243 |
| | | All | 70 | 67 | 95.7 | 87.1 | 98.9 | 70 | 5 | 4 | 6 | 71 | 71 | 56 | 90 | 71 | 233 | 194 | 280 |
| | DTPa- HBV/Hib | Seronegative | 58 | 58 | 100 | | | 58 | 2.5 | 2.5 | 2.5 | 58 | 81 | 67 | 99 | 58 | 216 | 183 | 255 |
| | | Seropositive | 23 | 23 | 100 | | | 23 | 13 | 9 | 17 | 23 | 35 | 26 | 48 | 23 | 160 | 119 | 216 |
| | | All | 81 | 81 | 100 | 94.4 | 100 | 81 | 4 | 3 | 5 | 81 | 64 | 54 | 77 | 81 | 198 | 171 | 230 |

Vaccine response definition:

- pre-vaccination seronegative infants: appearance of antibodies (i.e. concentration \geq cut-off [5 EL.U/mL])
- pre-vaccination seropositive infants: post-vaccination concentration \geq pre-vaccination concentration

N = total number of subjects

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

Pre = pre-vaccination (Day 0)

PII = approximately two months after Dose 2 (Day 112)

PIII = approximately one month after Dose 3 (Day 140)

95% CI = 95% confidence interval

Primary Efficacy Results: Distribution of individual anti-diphtheria and anti-tetanus antibody concentrations and GMCs (ITT Cohort)

| Antibody | Group | Timing | N | ≥ 0.1 IU/mL | | | | | GMC (IU/mL) | | |
|-----------------|------------------|--------|----|------------------|------|--------|------|-------|-------------|-------|--|
| | | | | n | % | 95% CI | | Value | 95% CI | | |
| | | | | | | LL | UL | | LL | UL | |
| Anti-diphtheria | DTPa- HBV+Hib | Pre | 70 | 24 | 34.3 | 23.6 | 46.7 | 0.087 | 0.071 | 0.107 | |
| | | PII | 71 | 70 | 98.6 | 91.3 | 99.9 | 0.743 | 0.605 | 0.912 | |
| | | PIII | 71 | 71 | 100 | 93.6 | 100 | 1.962 | 1.672 | 2.303 | |
| | DTPa- HBV/Hib | Pre | 81 | 23 | 28.4 | 19.2 | 39.7 | 0.080 | 0.066 | 0.097 | |
| | | PII | 81 | 80 | 98.8 | 92.4 | 99.9 | 0.685 | 0.569 | 0.826 | |
| | | PIII | 81 | 81 | 100 | 94.4 | 100 | 1.581 | 1.344 | 1.860 | |
| Anti-tetanus | DTPa- HBV+Hib | Pre | 70 | 45 | 64.3 | 51.9 | 75.1 | 0.222 | 0.163 | 0.301 | |
| | | PII | 71 | 71 | 100 | 93.6 | 100 | 1.088 | 0.836 | 1.416 | |
| | | PIII | 71 | 71 | 100 | 93.6 | 100 | 3.078 | 2.546 | 3.720 | |
| | DTPa- HBV/Hib | Pre | 81 | 59 | 72.8 | 61.6 | 81.9 | 0.268 | 0.200 | 0.358 | |
| | | PII | 81 | 81 | 100 | 94.4 | 100 | 1.239 | 0.996 | 1.542 | |
| | | PIII | 81 | 81 | 100 | 94.4 | 100 | 3.007 | 2.531 | 3.572 | |

N = total number of subjects

n(%) = number (percentage) of subjects within a given range

Pre = pre-vaccination (day 0)

| PII = approximately two months after Dose 2 (Day 112) PIII = approximately one month after Dose 3 (Day 140) 95% CI = 95% confidence interval | | | | | | | | | | | | | | | | | | | |
|---|-----------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|------|------|---|-----|----|------|
| Primary Efficacy Results: Distribution of individual anti-PRP antibody concentrations and GMCs (ITT Cohort) | | | | | | | | | | | | | | | | | | | |
| Group | Timing | N | ≥0.15 µg/mL | | | | ≥1.0 µg/mL | | | | GMC (µg/mL) | | | | | | | | |
| | | | n | % | 95% CI | | n | % | 95% CI | | Value | 95% CI | | | | | | | |
| | | | | | LL | UL | | | LL | UL | | LL | UL | | | | | | |
| DTPa-HBV+Hib | Pre | 71 | 21 | 29.6 | | | 2 | 2.8 | | | 0.127 | 0.100 | 0.161 | | | | | | |
| | PII | 71 | 50 | 70.4 | | | 26 | 36.6 | | | 0.529 | 0.360 | 0.766 | | | | | | |
| | PIII | 71 | 68 | 95.8 | 87.4 | 98.9 | 62 | 87.3 | 76.8 | 93.7 | 5.939 | 4.157 | 8.485 | | | | | | |
| DTPa-HBV/Hib | Pre | 81 | 15 | 18.5 | | | 2 | 2.5 | | | 0.102 | 0.087 | 0.119 | | | | | | |
| | PII | 81 | 50 | 61.7 | | | 19 | 23.5 | | | 0.343 | 0.247 | 0.476 | | | | | | |
| | PIII | 81 | 73 | 90.1 | 80.9 | 95.3 | 47 | 58.0 | 46.5 | 68.7 | 1.210 | 0.883 | 1.658 | | | | | | |
| N = total number of subjects n(%) = number (percentage) of subjects within a given range Pre = pre-vaccination (Day 0) PII = approximately two months after Dose 2 (Day 112) PIII = approximately one month after Dose 3 (Day 140) 95% CI = 95% confidence interval | | | | | | | | | | | | | | | | | | | |
| Primary Efficacy Results: Incidence of all and grade 3 solicited local symptoms during the first 4 days following vaccination, for each dose administered in each group (ITT cohort) | | | | | | | | | | | | | | | | | | | |
| Symptoms* | Intensity | Dose 1 | | | | Dose 2 | | | | Dose 3 | | | | | | | | | |
| | | DTPa-HBV+Hib Group N = 88 | | DTPa-HBV/Hib Group N = 88 | | DTPa-HBV+Hib Group N = 87 | | DTPa-HBV/Hib Group N = 86 | | DTPa-HBV+Hib Group N = 81 | | DTPa-HBV/Hib Group N = 85 | | | | | | | |
| | | DTPa-HBV | | Hib | | DTPa-HBV | | Hib | | DTPa-HBV | | Hib | | | | | | | |
| | | n | % | n | % | n | % | n | % | n | % | n | % | | | | | | |
| Pain | Any | 15 | 17.0 | 13 | 14.8 | 19 | 21.6 | 16 | 18.4 | 11 | 12.6 | 10 | 11.6 | 8 | 9.9 | 5 | 6.2 | 11 | 12.9 |
| | Grade 3 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 1.1 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Redness | Any | 14 | 15.9 | 9 | 10.2 | 11 | 12.5 | 13 | 14.9 | 6 | 6.9 | 15 | 17.4 | 24 | 29.6 | 8 | 9.9 | 17 | 20.0 |
| | >20mm | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 2 | 2.5 | 0 | 0.0 | 0 | 0.0 |
| Swelling | Any | 9 | 10.2 | 4 | 4.5 | 6 | 6.8 | 7 | 8.0 | 4 | 4.6 | 10 | 11.6 | 18 | 22.2 | 6 | 7.4 | 14 | 16.5 |
| | >20mm | 3 | 3.4 | 1 | 1.1 | 1 | 1.1 | 2 | 2.3 | 1 | 1.1 | 0 | 0.0 | 5 | 6.2 | 0 | 0.0 | 1 | 1.2 |
| *All symptoms occurred during the first 48 hours following vaccination. N = total number of doses with a symptom sheet returned n(%) = total number (percentage) of doses followed by the specified symptom All = occurrence of any solicited local symptom regardless of their intensity grade Grade 3 pain = Pain that prevented normal everyday activities | | | | | | | | | | | | | | | | | | | |
| Primary Efficacy Results: Incidence of all solicited general symptoms, and incidence of severe solicited general symptoms, during the first 4 days and during the first 48 hours following vaccination, for each dose administered in each group (ITT cohort) | | | | | | | | | | | | | | | | | | | |
| Symptoms | Intensity | Time of Onset | Dose 1 | | | | Dose 2 | | | | Dose 3 | | | | | | | | |
| | | | DTPa-HBV+Hib Group N = 88 | | DTPa-HBV/Hib Group N = 88 | | DTPa-HBV+Hib Group N = 87 | | DTPa-HBV/Hib Group N = 86 | | DTPa-HBV+Hib Group N = 81 | | DTPa-HBV/Hib Group N = 85 | | | | | | |
| | | | n | % | n | % | n | % | n | % | n | % | n | % | | | | | |
| Fever | Any | 4 days | 6 | 6.8 | 6 | 6.8 | 12 | 13.8 | 6 | 7.0 | 7 | 8.6 | 5 | 5.9 | | | | | |
| | | 48 hours | 6 | 6.8 | 6 | 6.8 | 12 | 13.8 | 6 | 7.0 | 5 | 6.2 | 4 | 4.7 | | | | | |
| | >39.5°C* | 4 days | 0 | 0.0 | 0 | 0.0 | 1 | 1.1 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | | | | | |
| Unusual Crying | Any | 4 days | 26 | 29.5 | 21 | 23.9 | 19 | 21.8 | 12 | 14.0 | 14 | 17.3 | 12 | 14.1 | | | | | |
| | | 48 hours | 24 | 27.3 | 21 | 23.9 | 19 | 21.8 | 12 | 14.0 | 14 | 17.3 | 12 | 14.1 | | | | | |
| | Grade 3* | 4 days | 1 | 1.1 | 1 | 1.1 | 1 | 1.1 | 0 | 0.0 | 2 | 2.5 | 0 | 0.0 | | | | | |
| Vomiting | Any | 4 days | 10 | 11.4 | 11 | 12.5 | 5 | 5.7 | 1 | 1.2 | 3 | 3.7 | 5 | 5.9 | | | | | |
| | | 48 hours | 10 | 11.4 | 8 | 9.1 | 4 | 4.6 | 1 | 1.2 | 3 | 3.7 | 5 | 5.9 | | | | | |
| | Grade 3* | 4 days | 0 | 0.0 | 0 | 0.0 | 1 | 1.1 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | | | | | |

| | | | | | | | | | | | | | | |
|------------------|----------|----------|----|------|----|------|----|------|----|------|----|------|----|------|
| Diarrhoea | Any | 4 days | 9 | 10.2 | 7 | 8.0 | 7 | 8.0 | 3 | 3.5 | 5 | 6.2 | 5 | 5.9 |
| | | 48 hours | 8 | 9.1 | 6 | 6.8 | 6 | 6.9 | 3 | 3.5 | 5 | 6.2 | 3 | 3.5 |
| | Grade 3* | 4 days | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Loss of appetite | Any | 4 days | 12 | 13.6 | 9 | 10.2 | 9 | 10.3 | 9 | 10.5 | 5 | 6.2 | 6 | 7.1 |
| | | 48 hours | 12 | 13.6 | 9 | 10.2 | 9 | 10.3 | 8 | 9.3 | 5 | 6.2 | 5 | 5.9 |
| | Grade 3* | 4 days | 1 | 1.1 | 0 | 0.0 | 1 | 1.1 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Restlessness | Any | 4 days | 41 | 46.6 | 27 | 30.7 | 35 | 40.2 | 26 | 30.2 | 31 | 38.3 | 25 | 29.4 |
| | | 48 hours | 40 | 45.5 | 27 | 30.7 | 35 | 40.2 | 26 | 30.2 | 30 | 37.0 | 25 | 29.4 |
| | Grade 3* | 4 days | 1 | 1.1 | 2 | 2.3 | 1 | 1.1 | 0 | 0.0 | 2 | 2.5 | 1 | 1.2 |

N = total number of doses with a symptom sheet returned

N(%) = total number (percentage) of doses followed by the specified symptom

*The onset of all severe general symptoms was within 48 hours of vaccination.

Any = occurrence of any solicited general local symptom regardless of their intensity grade

Grade 3 Symptoms = symptoms that prevented normal everyday activities

Primary Efficacy Results: Relationship of solicited general symptoms to vaccination (ITT cohort)

| Symptom | Dose Group | Dose 1 | | Dose 2 | | Dose 3 | | All | |
|------------------|------------|---------------|--------------|---------------|--------------|---------------|--------------|---------------|--------------|
| | | DTPa-HBV +Hib | DTPa-HBV/Hib | DTPa-HBV +Hib | DTPa-HBV/Hib | DTPa-HBV +Hib | DTPa-HBV/Hib | DTPa-HBV +Hib | DTPa-HBV/Hib |
| | Relation | n | | n | | n | | n | |
| Diarrhoea | PR | 7 | 3 | 7 | 1 | 5 | 3 | 19 | 7 |
| | PU | 2 | 4 | 0 | 2 | 0 | 2 | 2 | 8 |
| | R | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | U | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Loss of Appetite | PR | 11 | 9 | 9 | 7 | 5 | 6 | 25 | 22 |
| | PU | 1 | 0 | 0 | 2 | 0 | 0 | 1 | 2 |
| | R | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | U | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Restlessness | PR | 39 | 26 | 35 | 26 | 31 | 25 | 105 | 77 |
| | PU | 2 | 1 | 0 | 0 | 0 | 0 | 2 | 1 |
| | R | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | U | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Temperature | PR | 4 | 3 | 12 | 5 | 7 | 5 | 23 | 13 |
| | PU | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | R | 2 | 3 | 0 | 1 | 0 | 0 | 2 | 4 |
| | U | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Unusual crying | PR | 23 | 21 | 19 | 12 | 14 | 12 | 56 | 45 |
| | PU | 3 | 0 | 0 | 0 | 0 | 0 | 3 | 0 |
| | R | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | U | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Vomiting | PR | 10 | 10 | 5 | 1 | 2 | 4 | 17 | 15 |
| | PU | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 2 |
| | R | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | U | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

PR = possibly related—direct cause and effect relationship has not been demonstrated but it is possible or likely

PU = probably unrelated—direct cause and effect relationship has not been demonstrated; it is improbable but not impossible

R = related—a direct cause and effect relationship exists

U = unrelated—no direct cause and effect relationship exists.

Safety Results: Number (%) of unsolicited adverse events within 30 days according to the WHO preferred term (ITT Cohort)

| Most frequent adverse events - On-Therapy (occurring within day 0-30 following vaccination) | DTPa-HBV+Hib Group N = 88 | DTPa-HBV/Hib Group N = 88 |
|--|---------------------------------|------------------------------|
| Subjects with any AE(s), n (%) | 58 (65.9) | 50 (56.8) |
| Injection site reaction | 25 (28.4) | 9 (10.2) |
| Somnolence | 18 (20.5) | 10 (11.4) |
| Nervousness | 9 (10.2) | 6 (6.8) |

| | | |
|-----------------------------------|---------|---------|
| Upper respiratory tract infection | 6 (6.8) | 6 (6.8) |
| Crying | 5 (5.7) | 4 (4.5) |
| Diarrhoea | 5 (5.7) | 3 (3.4) |
| Vomiting | 3 (3.4) | 4 (4.5) |
| Irritability | 3 (3.4) | 3 (3.4) |
| Respiratory tract infection | 3 (3.4) | 3 (3.4) |
| Toothache | 3 (3.4) | 3 (3.4) |
| Anorexia | - | 5 (5.7) |
| Affect lability | 3 (3.4) | - |
| Application site haematoma | 3 (3.4) | - |
| Cough | - | 3 (3.4) |
| Pyrexia | - | 3 (3.4) |
| Rash | 3 (3.4) | - |

- : Adverse event absent or not meeting the selected rule(s)

Detail of rule: More than 30 subjects per treatment group and <= 3 groups: the most frequent 10 events in each group

Safety Results: Number (%) of subjects with Serious Adverse Events (SAEs) (Total Vaccinated Cohort)

Serious adverse event, n (%) [n considered by the investigator to be related to study medication]

| All SAEs | DTPa-HBV+Hib Group N = 90 | DTPa-HBV/Hib Group N = 90 |
|---|------------------------------|------------------------------|
| Subjects with any SAE(s), n (%) [n related] | 4 (4.4) [0] | 4 (4.4) [0] |
| Respiratory tract infection | 1 (1.1) [0] | 3 (3.3) [0] |
| Bone development abnormal | 1 (1.1) [0] | 0 (0.0) [0] |
| Bronchospasm | 1 (1.1) [0] | 0 (0.0) [0] |
| Cough | 1 (1.1) [0] | 0 (0.0) [0] |
| Eye discharge | 0 (0.0) [0] | 1 (1.1) [0] |
| Injury | 0 (0.0) [0] | 1 (1.1) [0] |
| Nervousness | 0 (0.0) [0] | 1 (1.1) [0] |
| Pyrexia | 0 (0.0) [0] | 1 (1.1) [0] |
| Urinary tract infection | 1 (1.1) [0] | 0 (0.0) [0] |
| Vomiting | 0 (0.0) [0] | 1 (1.1) [0] |
| Fatal SAEs | DTPa-HBV+Hib Group N = 90 | DTPa-HBV/Hib Group N = 90 |
| Subjects with fatal SAE(s), n (%) [n related] | 0 (0.0) [0] | 0 (0.0) [0] |

Conclusion:

In DTPa-HBV+Hib Group, 9.9%, 95.8% and 100% of the subjects had anti-HBs antibodies concentrations ≥ 10 mIU/mL at Day 0, Day 112 and Day 140 respectively. In DTPa-HBV/Hib Group, 16%, 93.8% and 97.5% of the subjects had anti-HBs antibodies concentrations ≥ 10 mIU/mL at Day 0, Day 112 and Day 140 respectively. In DTPa-HBV+Hib Group, 95.7%, 98.5% and 95.7% of the subjects had vaccine response against PT, FHA and PRN antigens, respectively; in DTPa-HBV/Hib Group, 100%, 98.7% and 100% of the subjects had vaccine response against PT, FHA and PRN antigens, respectively. In DTPa-HBV+Hib Group, 34.3%, 98.6% and 100% of the subjects, 64.3%, 100% and 100% at Day 0, Day 112 and Day 140 respectively, had anti-diphtheria and anti-tetanus antibodies concentrations ≥ 0.1 IU/mL respectively. In DTPa-HBV/Hib Group, 28.4%, 98.8% and 100% of the subjects, 72.8%, 100% and 100% at Day 0, Day 112 and Day 140, respectively, had anti-diphtheria and anti-tetanus antibodies concentrations ≥ 0.1 IU/mL, respectively. In DTPa-HBV+Hib Group, 29.6%, 70.4% and 95.8% of the subjects and in DTPa-HBV/Hib Group, 18.5%, 61.7% and 90.1% of the subjects had anti-PRP antibodies concentrations ≥ 0.15 μ g/ml at Day 0, Day 112 and Day 120, respectively

At least one unsolicited adverse event was reported by 58 (65.9%) and by 50 (56.8%) subjects in DTPa-HBV+Hib Group and in DTPa-HBV/Hib Group, respectively. At least one SAE was reported by 4 (4.4%) and by 4 (4.4%) subjects in DTPa-HBV+Hib Group and in DTPa-HBV/Hib Group, respectively. None of these SAEs were considered to be related to the vaccination, by the investigator. No fatal SAEs were reported during the study.

Publications: None.

Date updated: 27 August 2009