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| Study No.: 208108/091 (Hib-091) and 208108/092 (Hib-092) |
| Title: A phase II, double-blind, randomized study to compare the immunogenicity, safety and reactogenicity of GlaxoSmithKline (GSK) Biologicals' <i>Tritanrix</i> TM -HepB/Hib _{2.5} to GSK Biologicals' <i>Tritanrix</i> TM -HepB/ <i>Hiberix</i> TM when administered as a three-dose primary vaccination course to healthy infants at 6, 10 and 14 weeks of age. A dose of unconjugated Hib vaccine (plain PRP booster) will be administered at the age of 10 months to 50% of the subjects. <i>Tritanrix</i> TM -HepB/Hib _{2.5} : combined diphtheria, tetanus, whole cell pertussis, hepatitis B vaccine with low thiomersal content and <i>Haemophilus influenzae</i> type b conjugate vaccine containing 2.5 µg PRP (DTPw-HBV/ Hib _{2.5}). <i>Tritanrix</i> TM -HepB: combined diphtheria, tetanus, whole cell pertussis and hepatitis B vaccine (DTPw-HBV). <i>Hiberix</i> TM : <i>Haemophilus influenzae</i> type b conjugate vaccine (Hib) |
| Rationale: The aim of this study was to assess the immunogenicity and safety of the DTPw-HBV/Hib _{2.5} vaccine. Subjects received primary vaccination in study 208108/091. Of these subjects 50% participated in the PRP (polyribosyl-ribitol-phosphate) challenge study 208108/092. |
| Phase: II. |
| Study Period: Primary study: 21 August 2003 to 14 January 2004. Challenge study: 18 May 2004 to 19 August 2004. |
| Study Design: Primary study: Double blind, randomized study with 2 groups (1:1) Challenge study: Open, randomized study with 2 groups (1:1). |
| Centers: One study center in the Philippines. |
| Indication: Primary vaccination of healthy infants at 6, 10 and 14 weeks of age. Challenge dose of unconjugated Hib vaccine at 10 months of age to 50% of the subjects. |
| Treatment: Study groups were as follows: <ul style="list-style-type: none"> • Group 1: subjects received 3 doses of DTPw-HBV/Hib_{2.5} in the primary study. • Group 2: subjects received 3 doses of DTPw-HBV/Hib in the primary study. At 10 months of age, 50% of the subjects in each group were administered a challenge dose of unconjugated PRP vaccine. All study vaccines were administered intramuscularly in the left anterolateral thigh. All subjects concomitantly received an oral polio vaccine. |
| Objectives: <i>Primary study:</i> <ul style="list-style-type: none"> • To demonstrate the non-inferiority of DTPw-HBV/Hib_{2.5} vaccine as compared to DTPw-HBV/Hib with respect to the immunogenicity of PRP antigen after the primary vaccination course. |
| Primary Outcome/Efficacy Variables: <ul style="list-style-type: none"> • One month after Dose 3 of the primary vaccination course: anti-PRP antibody concentrations ≥ 0.15 µg/mL |
| Secondary Outcome/Efficacy Variable(s): Immunogenicity: <i>One month after Dose 3 of the primary vaccination course:</i> <ul style="list-style-type: none"> • Anti-diphtheria antibody concentrations ≥ 0.1 IU/mL by ELISA assay or ≥ 0.016 IU/mL by neutralization assay on Vero cells (for subjects seronegative by ELISA) • Anti-tetanus antibody concentrations ≥ 0.1 IU/mL • Anti-<i>Bordetella pertussis</i> toxoid (anti-BPT) antibody concentrations ≥ 15 EL.U/mL , • Vaccine response rates to the <i>Bordetella pertussis</i> antigen, defined as: <ul style="list-style-type: none"> • Appearance of antibodies (concentrations ≥ 15 EL.U/mL) in initially seronegative subjects, or • Post-vaccination antibody concentrations \geq pre-vaccination concentration in initially seropositive subjects. • Anti-PRP antibody concentrations ≥ 1 µg/mL, • Anti-Hepatitis B surface antigen (anti-HBs) antibody concentrations ≥ 10 mIU/mL, • Geometric mean concentrations (GMCs) for antibodies against all vaccine antigens. <i>Before Dose 1 of the primary vaccination course:</i> <ul style="list-style-type: none"> • Seropositivity/seroprotection rates and GMCs for antibodies against all vaccine antigens. |

Before and one month after the plain PRP challenge:

- Anti-PRP antibody concentrations $\geq 0.15 \mu\text{g/mL}$ and $\geq 1 \mu\text{g/mL}$.

Safety:

- Occurrence of solicited local and general symptoms during the 4-day (Day 0-3) follow-up period after each dose,
- Occurrence of unsolicited adverse events (AEs) during the 31-day (Day 0-30) follow-up period after each dose,
- Occurrence of serious adverse events (SAEs) over the full course of the study.

Statistical Methods:

The analyses were performed on the Total Vaccinated Cohort and the According-To-Protocol (ATP) cohort for immunogenicity.

- The Total Vaccinated Cohort included all subjects who received at least one vaccine dose.
- The ATP cohort for immunogenicity included all evaluable subjects who complied with the procedures defined in the protocol and for whom immunogenicity data were available.

Analysis of immunogenicity:

The analysis of immunogenicity was performed on the ATP cohort for immunogenicity.

Geometric Mean Concentrations (GMCs) and seroprotection/seropositivity rates for all antibodies were summarized at pre-vaccination and one month after Dose 3 with their 95% confidence interval (CI). Antibody concentration below the cut-off of the assay was given an arbitrary value of half the cut-off for the purpose of GMC calculation.

In subjects belonging to the PRP challenge subset, GMCs and seroprotection rates for anti-PRP antibodies were also summarized at pre- and post-challenge dose plain PRP vaccination with their 95% CI.

The non-inferiority of DTPw-HBV/Hib_{2.5} as compared to DTPw-HBV/Hib with respect to the immunogenicity of PRP antigen after the first three vaccine doses was concluded if, one month after Dose 3, the upper limit of the 95% CI for the difference in the proportion of subjects with anti-PRP antibody concentration $\geq 0.15 \mu\text{g/mL}$ (DTPw-HBV/Hib minus DTPw-HBV/Hib_{2.5}) was $< 10\%$.

Analysis of safety:

The analysis of safety was performed on the Total Vaccinated Cohort.

For each solicited symptom, the percentage of subjects with the symptom reported during the 4-day (Day 0-3) follow-up period was summarized after each dose, across doses and, in subjects belonging to the PRP challenge subset, after the challenge dose vaccination for each group with exact 95% CI. The percentage of subjects with unsolicited AEs within 31 days (Day 0-30) after each vaccination was tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) preferred term for each group after the primary vaccination course and, in subjects belonging to the PRP challenge subset, after the challenge dose vaccination. The occurrence of SAEs was tabulated according to the MedDRA preferred term for each group during the entire study period after the primary vaccination course and, in subjects belonging to the PRP challenge subset, after the challenge dose vaccination.

Study Population: Male or female infants, between 6 and 8 weeks of age at the time of the first vaccination, born after a gestation period of 36 to 42 weeks, to hepatitis B seronegative mothers. Subjects were free of obvious health problems as established by medical history and clinical examination before entering the study. Written informed consent was obtained from the parent(s) or guardian(s) of the subject prior to study entry.

| Primary study | | |
|--|----------------|----------------|
| Number of subjects | Group 1 | Group 2 |
| Planned, N | 96 | 96 |
| Randomized, N (Total Vaccinated Cohort) | 96 | 96 |
| Completed, n (%) | 95 (99.0) | 95 (99.0) |
| Total Number Subjects Withdrawn, n (%) | 1 (1.0) | 1 (1.0) |
| Withdrawn due to Adverse Events, n (%) | 0 (0.0) | 0 (0.0) |
| Withdrawn due to Lack of Efficacy, n (%) | Not applicable | Not applicable |
| Withdrawn for other reasons, n (%) | 1 (1.0) | 1 (1.0) |
| Demographics | Group 1 | Group 2 |
| N (Total Vaccinated Cohort) | 96 | 96 |
| Females:Males | 38:58 | 50:46 |
| Mean Age, weeks (SD)* | 6.1 (0.26) | 6.0 (0.14) |
| East/South East Asian, n (%) | 96 (100) | 96 (100) |
| * Age at first dose. | | |
| PRP challenge study | | |
| Number of subjects | Group 1 | Group 2 |
| Planned, N | 48 | 48 |
| Randomized*, N (Total Vaccinated Cohort, PRP challenge subset) | 46 | 47 |

| Completed, n (%) | | 46 (100) | 47 (100) | | | | | | | | | | |
|---|----------|----------------|----------------------------|--------------------------|--------|--------|---------------------------|-------------|--------|-------|---------------------------|--------|--------|
| Total Number Subjects Withdrawn, n (%) | | 0 (0.0) | 0 (0.0) | | | | | | | | | | |
| Withdrawn due to Adverse Events, n (%) | | 0 (0.0) | 0 (0.0) | | | | | | | | | | |
| Withdrawn due to Lack of Efficacy, n (%) | | Not applicable | Not applicable | | | | | | | | | | |
| Withdrawn for other reasons, n (%) | | 0 (0.0) | 0 (0.0) | | | | | | | | | | |
| Demographics | | Group 1 | Group 2 | | | | | | | | | | |
| N (Total Vaccinated Cohort, PRP challenge subset) | | 46 | 47 | | | | | | | | | | |
| Females:Males | | 22:24 | 24:23 | | | | | | | | | | |
| Mean Age, weeks (SD) | | 44.1 (1.04) | 44.0 (0.62) | | | | | | | | | | |
| East/South East Asian, n (%) | | 46 (100) | 47 (100) | | | | | | | | | | |
| * Subjects were randomized in the primary study. | | | | | | | | | | | | | |
| Primary Efficacy Results: Difference in anti-PRP seroprotection rates between groups one month after the third vaccine Dose (ATP cohort for immunogenicity). | | | | | | | | | | | | | |
| Antibody | Group 1 | | | Group 2 | | | Group 2 minus Group 1 | | | | | | |
| | N | n | % | N | n | % | Difference (%) | 95%CI | | | | | |
| | | | | | | | | LL | UL | | | | |
| Anti-PRP $\geq 0.15\mu\text{g/mL}$ | 95 | 95 | 100 | 94 | 94 | 100 | 0.0 | -3.9 | 3.9* | | | | |
| N: Number of subjects with available results n (%): Number (percentage) of subjects with antibody concentration \geq assay cut-off value 95%CI: 95% confidence interval; LL: lower limit; UL: upper limit * Non-inferiority concluded. | | | | | | | | | | | | | |
| Primary Efficacy Results: Seroprotection rates and GMCs for anti-PRP antibodies (ATP cohort for immunogenicity) | | | | | | | | | | | | | |
| Group | Timing | N | $\geq 0.15 \mu\text{g/mL}$ | | | | $\geq 1 \mu\text{g/mL}^*$ | | | | GMC ($\mu\text{g/mL}$)* | | |
| | | | n | % | 95% CI | | n | % | 95% CI | | Value | 95% CI | |
| | | | | | LL | UL | | | LL | UL | | LL | UL |
| 1 | Pre | 95 | 62 | 65.3 | 54.8 | 74.7 | 18 | 18.9 | 11.6 | 28.3 | 0.285 | 0.219 | 0.371 |
| | Post III | 95 | 95 | 100 | 96.2 | 100 | 89 | 93.7 | 86.8 | 97.6 | 15.285 | 11.624 | 20.100 |
| 2 | Pre | 93 | 60 | 64.5 | 53.9 | 74.2 | 19 | 20.4 | 12.8 | 30.1 | 0.318 | 0.240 | 0.420 |
| | Post III | 94 | 94 | 100 | 96.2 | 100 | 89 | 94.7 | 88.0 | 98.3 | 13.868 | 10.816 | 17.780 |
| N: Number of subjects with available results n (%): Number (percentage) of subjects with the specified antibody concentrations 95%CI: 95% confidence interval; LL: lower limit; UL: upper limit Pre: Pre-vaccination Post III: One month after Dose 3 * Secondary outcome variable | | | | | | | | | | | | | |
| Secondary Outcome Variable(s): Seropositivity rates and GMCs for anti-diphtheria and anti-tetanus antibodies (ATP cohort for immunogenicity). | | | | | | | | | | | | | |
| Antibody | Group | Timing | N | $\geq 0.1 \text{ IU/mL}$ | | | | GMC (IU/mL) | | | | | |
| | | | | n | % | 95% CI | | Value | 95% CI | | | | |
| | | | | | | LL | UL | | LL | UL | | | |
| Anti-diphtheria | 1 | Pre | 94 | 27 | 28.7 | 19.9 | 39.0 | 0.075 | 0.064 | 0.087 | | | |
| | | Post III | 94 | 84 | 89.4 | 81.3 | 94.8 | 0.767 | 0.588 | 1.001 | | | |
| | 2 | Pre | 94 | 29 | 30.9 | 21.7 | 41.2 | 0.081 | 0.068 | 0.096 | | | |
| | | Post III | 94 | 82 | 87.2 | 78.8 | 93.2 | 0.576 | 0.439 | 0.757 | | | |
| Anti-tetanus | 1 | Pre | 95 | 85 | 89.5 | 81.5 | 94.8 | 2.136 | 1.509 | 3.024 | | | |
| | | Post III | 95 | 95 | 100 | 96.2 | 100 | 3.198 | 2.636 | 3.880 | | | |
| | 2 | Pre | 94 | 84 | 89.4 | 81.3 | 94.8 | 1.740 | 1.216 | 2.490 | | | |
| | | Post III | 94 | 94 | 100 | 96.2 | 100 | 3.565 | 2.977 | 4.268 | | | |
| N: Number of subjects with available results n (%): Number (percentage) of subjects with the specified antibody concentrations 95%CI: 95% confidence interval; LL: lower limit; UL: upper limit Pre: Pre-vaccination Post III: One month after Dose 3 | | | | | | | | | | | | | |

Secondary Outcome Variable(s): Seroprotection rate to diphtheria taking into account ELISA and Vero-cell assay for subjects seronegative by ELISA one month after the third vaccine dose (ATP cohort for immunogenicity)

| Group | N | Sero-negativity assessed by ELISA | | Seronegativity assessed by Vero for subjects seronegative by ELISA | | Overall seronegativity for anti-diphtheria antibodies | | Estimated proportion of subjects seroprotected | | |
|-------|----|-----------------------------------|------|--|------|---|-----|--|--------|------|
| | | n/N | % | n'/N' | % | n/N x n'/N' | % | SP | 95% CI | |
| 1 | 95 | 10/95 | 10.5 | 7/10 | 70 | 10/95x7/10 | 7.4 | 92.6 | 84.9 | 96.7 |
| 2 | 94 | 12/94 | 12.8 | 7/12 | 58.3 | 12/94x7/12 | 7.4 | 92.6 | 84.8 | 96.7 |

N = number of subjects tested by ELISA
n/N = number of subjects with titres below the 0.1 IU/mL / number of subjects tested by ELISA
n'/N' = number of subjects with titres below the 0.016 IU/mL / number of subjects tested by neutralization test on Vero cells
% = proportion of subjects with titres below the considered cut-off (0.1 for ELISA IU/mL and 0.016 IU/mL for Vero)
n/N x n'/N' = the multiplication of the two proportions = overall seronegativity for anti-diphtheria antibody
Overall= based on both the ELISA and the Vero testing
SP = estimated proportion of subjects with protective antibodies
95% CI = exact 95% confidence interval

Secondary Outcome Variable(s): Seropositivity rates and GMCs for anti-BPT antibodies one month after the third vaccine dose (ATP cohort for immunogenicity).

| Group | Timing | N | ≥ 15 EL.U/mL | | | | GMC (EL.U/mL) | | | |
|-------|----------|----|--------------|------|--------|------|---------------|--------|-------|--|
| | | | n | % | 95% CI | | Value | 95% CI | | |
| | | | | | LL | UL | | LL | UL | |
| 1 | Pre | 95 | 9 | 9.5 | 4.4 | 17.2 | 8.4 | 7.8 | 9.1 | |
| | Post III | 94 | 94 | 100 | 96.2 | 100 | 118.2 | 105.0 | 133.0 | |
| 2 | Pre | 94 | 4 | 4.3 | 1.2 | 10.5 | 7.8 | 7.5 | 8.2 | |
| | Post III | 92 | 91 | 98.9 | 94.1 | 100 | 79.5 | 68.8 | 91.9 | |

N: Number of subjects with available results
n (%): Number (percentage) of subjects with the specified antibody concentrations.
95%CI: 95% confidence interval; LL: lower limit; UL: upper limit
Pre: Pre-vaccination
Post III: One month after Dose 3

Secondary Outcome Variable(s): Vaccine response to BPT one month after the third vaccine dose (ATP cohort for immunogenicity).

| Group | Pre-vaccination status | N | Vaccine response rate | | | | |
|-------|------------------------|----|-----------------------|------|--------|-----|--|
| | | | n | % | 95% CI | | |
| | | | | | LL | UL | |
| 1 | S+ | 9 | 9 | 100 | 66.4 | 100 | |
| | S- | 85 | 85 | 100 | 95.8 | 100 | |
| | Total | 94 | 94 | 100 | 96.2 | 100 | |
| 2 | S+ | 4 | 4 | 100 | 39.8 | 100 | |
| | S- | 88 | 87 | 98.9 | 93.8 | 100 | |
| | Total | 92 | 91 | 98.9 | 94.1 | 100 | |

N: number of subjects with both pre- and post-vaccination results available
n (%): Number (percentage) of responders
S-/S+: seronegative/seropositive subjects at pre-vaccination
Total: subjects either seropositive or seronegative at pre-vaccination
95%CI: exact 95% confidence interval; LL: lower limit; UL: upper limit

Secondary Outcome Variable(s): Seroprotection rates and GMCs for anti-HBs (ATP cohort for immunogenicity).

| Group | Timing | N | ≥ 10 mIU/mL | | | | GMC (mIU/mL) | | | |
|-------|----------|----|-------------|------|--------|------|--------------|--------|-------|--|
| | | | n | % | 95% CI | | Value | 95% CI | | |
| | | | | | LL | UL | | LL | UL | |
| 1 | Pre | 93 | 25 | 26.9 | 18.2 | 37.1 | 12.8 | 9.0 | 18.0 | |
| | Post III | 93 | 83 | 89.2 | 81.1 | 94.7 | 108.9 | 77.9 | 152.2 | |

| | | | | | | | | | |
|---|----------|----|----|------|------|------|------|------|------|
| 2 | Pre | 93 | 21 | 22.6 | 14.6 | 32.4 | 11.4 | 8.1 | 16.2 |
| | Post III | 93 | 73 | 78.5 | 68.8 | 86.3 | 67.1 | 47.0 | 96.0 |

N: Number of subjects with available results
n (%): Number (percentage) of subjects with the specified antibody concentrations
95%CI: 95% confidence interval; LL: lower limit; UL: upper limit
Pre: Pre-vaccination
Post III: One month after Dose 3

Secondary Outcome Variable(s): Seroprotection rates and GMCs for anti-PRP antibodies before and 1 month after the PRP challenge dose (ATP cohort for immunogenicity, PRP challenge subset).

| Group | Timing | N | ≥ 0.15 µg/mL | | | | ≥ 1 µg/mL | | | | GMC (µg/mL) | | |
|-------|------------|----|--------------|-----|--------|-----|-----------|------|--------|------|-------------|--------|--------|
| | | | n | % | 95% CI | | n | % | 95% CI | | Value | 95% CI | |
| | | | | | LL | UL | | | LL | UL | | LL | UL |
| 1 | PIII(M3) | 46 | 46 | 100 | 92.3 | 100 | 43 | 93.5 | 82.1 | 98.6 | 17.487 | 12.319 | 24.822 |
| | PIII(M8.5) | 46 | 46 | 100 | 92.3 | 100 | 38 | 82.6 | 68.6 | 92.2 | 4.716 | 2.959 | 7.516 |
| | PIV(M9.5) | 46 | 46 | 100 | 92.3 | 100 | 45 | 97.8 | 88.5 | 99.9 | 57.270 | 37.044 | 88.539 |
| 2 | PIII(M3) | 47 | 47 | 100 | 92.5 | 100 | 45 | 95.7 | 85.5 | 99.5 | 14.524 | 10.136 | 20.810 |
| | PIII(M8.5) | 47 | 47 | 100 | 92.5 | 100 | 44 | 93.6 | 82.5 | 98.7 | 6.322 | 4.377 | 9.130 |
| | PIV(M9.5) | 47 | 47 | 100 | 92.5 | 100 | 46 | 97.9 | 88.7 | 99.9 | 41.989 | 28.010 | 62.945 |

N: Number of subjects with available results
n (%): Number (percentage) of subjects with the specified antibody concentrations
95%CI: 95% confidence interval; LL: lower limit; UL: upper limit
PIII(M3): 1 month after Dose 3 of primary vaccination
PIII(M8.5): 6.5 months after Dose 3, before the challenge dose
PIV (M9.5): 1 month after the challenge dose.

Secondary Outcome Variable(s): Number and percentage of subjects with solicited local symptoms during the 4-day (Day 0-3) follow-up period (Total Vaccinated Cohort).

| Symptom | Intensity | Group 1 | | | | Group 2 | | | |
|----------|-----------|---------------------|------|--------|------|---------------|------|--------|------|
| | | n | % | 95% CI | | n | % | 95% CI | |
| | | | | LL | UL | | | LL | UL |
| | | Dose 1 | | | | | | | |
| | | N = 96 | | | | N = 96 | | | |
| Pain | Any | 82 | 85.4 | 76.7 | 91.8 | 79 | 82.3 | 73.2 | 89.3 |
| | Grade 3 | 18 | 18.8 | 11.5 | 28.0 | 16 | 16.7 | 9.8 | 25.6 |
| Redness | Any | 52 | 54.2 | 43.7 | 64.4 | 55 | 57.3 | 46.8 | 67.3 |
| | > 20 mm | 3 | 3.1 | 0.6 | 8.9 | 13 | 13.5 | 7.4 | 22.0 |
| Swelling | Any | 66 | 68.8 | 58.5 | 77.8 | 62 | 64.6 | 54.2 | 74.1 |
| | > 20 mm | 43 | 44.8 | 34.6 | 55.3 | 38 | 39.6 | 29.7 | 50.1 |
| | | Dose 2 | | | | | | | |
| | | N = 96 | | | | N = 95 | | | |
| Pain | Any | 67 | 69.8 | 59.6 | 78.7 | 57 | 60.0 | 49.4 | 69.9 |
| | Grade 3 | 7 | 7.3 | 3.0 | 14.4 | 3 | 3.2 | 0.7 | 9.0 |
| Redness | Any | 41 | 42.7 | 32.7 | 53.2 | 35 | 36.8 | 27.2 | 47.4 |
| | > 20 mm | 3 | 3.1 | 0.6 | 8.9 | 3 | 3.2 | 0.7 | 9.0 |
| Swelling | Any | 46 | 47.9 | 37.6 | 58.4 | 36 | 37.9 | 28.1 | 48.4 |
| | > 20 mm | 27 | 28.1 | 19.4 | 38.2 | 13 | 13.7 | 7.5 | 22.3 |
| | | Dose 3 | | | | | | | |
| | | N = 96 | | | | N = 95 | | | |
| Pain | Any | 54 | 56.3 | 45.7 | 66.4 | 48 | 50.5 | 40.1 | 60.9 |
| | Grade 3 | 5 | 5.2 | 1.7 | 11.7 | 3 | 3.2 | 0.7 | 9.0 |
| Redness | Any | 35 | 36.5 | 26.9 | 46.9 | 36 | 37.9 | 28.1 | 48.4 |
| | > 20 mm | 3 | 3.1 | 0.6 | 8.9 | 3 | 3.2 | 0.7 | 9.0 |
| Swelling | Any | 38 | 39.6 | 29.7 | 50.1 | 33 | 34.7 | 25.3 | 45.2 |
| | > 20 mm | 13 | 13.5 | 7.4 | 22.0 | 11 | 11.6 | 5.9 | 19.8 |
| | | Across Doses | | | | | | | |
| | | N = 96 | | | | N = 96 | | | |

| | | | | | | | | | |
|----------|---------|----|------|------|------|----|------|------|------|
| Pain | Any | 87 | 90.6 | 82.9 | 95.6 | 87 | 90.6 | 82.9 | 95.6 |
| | Grade 3 | 20 | 20.8 | 13.2 | 30.3 | 21 | 21.9 | 14.1 | 31.5 |
| Redness | Any | 64 | 66.7 | 56.3 | 76.0 | 66 | 68.8 | 58.5 | 77.8 |
| | > 20 mm | 7 | 7.3 | 3.0 | 14.4 | 17 | 17.7 | 10.7 | 26.8 |
| Swelling | Any | 78 | 81.3 | 72.0 | 88.5 | 66 | 68.8 | 58.5 | 77.8 |
| | > 20 mm | 46 | 47.9 | 37.6 | 58.4 | 41 | 42.7 | 32.7 | 53.2 |

N: number of subjects with a symptom sheet completed
n (%): number (percentage) of subjects for whom the symptom was reported
Any: incidence of a particular symptom regardless of grade
Grade 3 pain: cried when limb was moved/spontaneously painful
95% CI: exact 95% confidence interval; LL: lower limit, UL: upper limit

Secondary Outcome Variable(s): Number and percentage of subjects with solicited local symptoms during the 4-day (Day 0-3) follow-up period after the PRP vaccination (Total Vaccinated Cohort, PRP challenge subset).

| Symptom | Intensity | Group 1 (N = 46) | | | | Group 2 (N = 47) | | | |
|----------|-----------|------------------|------|--------|------|------------------|------|--------|------|
| | | n | % | 95% CI | | n | % | 95% CI | |
| | | | | LL | UL | | | LL | UL |
| Pain | Any | 15 | 32.6 | 19.5 | 48.0 | 7 | 14.9 | 6.2 | 28.3 |
| | Grade 3 | 0 | 0.0 | 0.0 | 7.7 | 0 | 0.0 | 0.0 | 7.5 |
| Redness | Any | 13 | 28.3 | 16.0 | 43.5 | 9 | 19.1 | 9.1 | 33.3 |
| | > 20 mm | 0 | 0.0 | 0.0 | 7.7 | 1 | 2.1 | 0.1 | 11.3 |
| Swelling | Any | 8 | 17.4 | 7.8 | 31.4 | 7 | 14.9 | 6.2 | 28.3 |
| | > 20 mm | 0 | 0.0 | 0.0 | 7.7 | 0 | 0.0 | 0.0 | 7.5 |

N: number of subjects with a symptom sheet completed
n (%): number (percentage) of subjects for whom the symptom was reported
Any: incidence of a particular symptom regardless of grade
Grade 3 pain: cried when limb was moved/spontaneously painful
95% CI: exact 95% confidence interval; LL: lower limit, UL: upper limit

Secondary Outcome Variable(s): Number and percentage of subjects with solicited general symptoms during the 4-day (Day 0-3) follow-up period (Total Vaccinated Cohort).

| Symptom | Intensity/ Relationship | Group 1 | | | | Group 2 | | | |
|------------------|----------------------------|---------|------|--------|------|---------|------|--------|------|
| | | n | % | 95% CI | | n | % | 95% CI | |
| | | | | LL | UL | | | LL | UL |
| | | Dose 1 | | Dose 2 | | Dose 1 | | Dose 2 | |
| N = 96 | | N = 96 | | N = 96 | | N = 95 | | | |
| Drowsiness | Any | 65 | 67.7 | 57.4 | 76.9 | 52 | 54.2 | 43.7 | 64.4 |
| | Grade 3 | 3 | 3.1 | 0.6 | 8.9 | 3 | 3.1 | 0.6 | 8.9 |
| | Related | 64 | 66.7 | 56.3 | 76.0 | 52 | 54.2 | 43.7 | 64.4 |
| Irritability | Any | 71 | 74.0 | 64.0 | 82.4 | 68 | 70.8 | 60.7 | 79.7 |
| | Grade 3 | 4 | 4.2 | 1.1 | 10.3 | 2 | 2.1 | 0.3 | 7.3 |
| | Related | 71 | 74.0 | 64.0 | 82.4 | 68 | 70.8 | 60.7 | 79.7 |
| Loss of Appetite | Any | 25 | 26.0 | 17.6 | 36.0 | 22 | 22.9 | 15.0 | 32.6 |
| | Grade 3 | 0 | 0.0 | 0.0 | 3.8 | 0 | 0.0 | 0.0 | 3.8 |
| | Related | 25 | 26.0 | 17.6 | 36.0 | 20 | 20.8 | 13.2 | 30.3 |
| Fever (axillary) | ≥ 37.5°C | 78 | 81.3 | 72.0 | 88.5 | 64 | 66.7 | 56.3 | 76.0 |
| | > 39.0°C | 3 | 3.1 | 0.6 | 8.9 | 0 | 0.0 | 0.0 | 3.8 |
| | Related | 76 | 79.2 | 69.7 | 86.8 | 63 | 65.6 | 55.2 | 75.0 |
| | | Dose 2 | | | | | | | |
| | | N = 96 | | N = 95 | | N = 96 | | N = 95 | |
| Drowsiness | Any | 53 | 55.2 | 44.7 | 65.4 | 33 | 34.7 | 25.3 | 45.2 |
| | Grade 3 | 0 | 0.0 | 0.0 | 3.8 | 0 | 0.0 | 0.0 | 3.8 |
| | Related | 53 | 55.2 | 44.7 | 65.4 | 33 | 34.7 | 25.3 | 45.2 |
| Irritability | Any | 65 | 67.7 | 57.4 | 76.9 | 45 | 47.4 | 37.0 | 57.9 |
| | Grade 3 | 1 | 1.0 | 0.0 | 5.7 | 2 | 2.1 | 0.3 | 7.4 |
| | Related | 65 | 67.7 | 57.4 | 76.9 | 45 | 47.4 | 37.0 | 57.9 |
| Loss of | Any | 23 | 24.0 | 15.8 | 33.7 | 9 | 9.5 | 4.4 | 17.2 |

| | | | | | | | | | |
|------------------|----------|---------------------|------|------|------|---------------|------|------|------|
| Appetite | Grade 3 | 0 | 0.0 | 0.0 | 3.8 | 0 | 0.0 | 0.0 | 3.8 |
| | Related | 23 | 24.0 | 15.8 | 33.7 | 9 | 9.5 | 4.4 | 17.2 |
| Fever (axillary) | ≥ 37.5°C | 56 | 58.3 | 47.8 | 68.3 | 52 | 54.7 | 44.2 | 65.0 |
| | > 39.0°C | 1 | 1.0 | 0.0 | 5.7 | 1 | 1.1 | 0.0 | 5.7 |
| | Related | 53 | 55.2 | 44.7 | 65.4 | 49 | 51.6 | 41.1 | 62.0 |
| | | Dose 3 | | | | | | | |
| | | N = 96 | | | | N = 95 | | | |
| Drowsiness | Any | 31 | 32.3 | 23.1 | 42.6 | 34 | 35.8 | 26.2 | 46.3 |
| | Grade 3 | 2 | 2.1 | 0.3 | 7.3 | 2 | 2.1 | 0.3 | 7.4 |
| | Related | 31 | 32.3 | 23.1 | 42.6 | 34 | 35.8 | 26.2 | 46.3 |
| Irritability | Any | 51 | 53.1 | 42.7 | 63.4 | 43 | 45.3 | 35.0 | 55.8 |
| | Grade 3 | 3 | 3.1 | 0.6 | 8.9 | 1 | 1.1 | 0.0 | 5.7 |
| | Related | 51 | 53.1 | 42.7 | 63.4 | 43 | 45.3 | 35.0 | 55.8 |
| Loss of Appetite | Any | 14 | 14.6 | 8.2 | 23.3 | 16 | 16.8 | 9.9 | 25.9 |
| | Grade 3 | 0 | 0.0 | 0.0 | 3.8 | 0 | 0.0 | 0.0 | 3.8 |
| | Related | 14 | 14.6 | 8.2 | 23.3 | 16 | 16.8 | 9.9 | 25.9 |
| Fever (axillary) | ≥ 37.5°C | 50 | 52.1 | 41.6 | 62.4 | 31 | 32.6 | 23.4 | 43.0 |
| | > 39.0°C | 1 | 1.0 | 0.0 | 5.7 | 0 | 0.0 | 0.0 | 3.8 |
| | Related | 47 | 49.0 | 38.6 | 59.4 | 30 | 31.6 | 22.4 | 41.9 |
| | | Across Doses | | | | | | | |
| | | N = 96 | | | | N = 96 | | | |
| Drowsiness | Any | 78 | 81.3 | 72.0 | 88.5 | 65 | 67.7 | 57.4 | 76.9 |
| | Grade 3 | 5 | 5.2 | 1.7 | 11.7 | 3 | 3.1 | 0.6 | 8.9 |
| | Related | 77 | 80.2 | 70.8 | 87.6 | 65 | 67.7 | 57.4 | 76.9 |
| Irritability | Any | 83 | 86.5 | 78.0 | 92.6 | 80 | 83.3 | 74.4 | 90.2 |
| | Grade 3 | 7 | 7.3 | 3.0 | 14.4 | 3 | 3.1 | 0.6 | 8.9 |
| | Related | 83 | 86.5 | 78.0 | 92.6 | 80 | 83.3 | 74.4 | 90.2 |
| Loss of Appetite | Any | 39 | 40.6 | 30.7 | 51.1 | 34 | 35.4 | 25.9 | 45.8 |
| | Grade 3 | 0 | 0.0 | 0.0 | 3.8 | 0 | 0.0 | 0.0 | 3.8 |
| | Related | 39 | 40.6 | 30.7 | 51.1 | 32 | 33.3 | 24.0 | 43.7 |
| Fever (axillary) | ≥ 37.5°C | 88 | 91.7 | 84.2 | 96.3 | 80 | 83.3 | 74.4 | 90.2 |
| | > 39.0°C | 5 | 5.2 | 1.7 | 11.7 | 1 | 1.0 | 0.0 | 5.7 |
| | Related | 87 | 90.6 | 82.9 | 95.6 | 78 | 81.3 | 72.0 | 88.5 |

N: number of subjects with a symptom sheet completed

n (%): number (percentage) of subjects for whom the symptom was reported

Any: incidence of a particular symptom regardless of grade or relationship to study vaccination

Grade 3 drowsiness: drowsiness which prevented normal everyday activities

Grade 3 irritability: crying that could not be comforted

Grade 3 Loss of appetite: not eating at all

Related: the investigator considered that there was a reasonable possibility that the vaccine contributed to the symptom

95% CI: exact 95% confidence interval; LL: lower limit, UL: upper limit

Secondary Outcome Variable(s): Number and percentage of subjects with solicited general symptoms during the 4-day (Day 0-3) follow-up period after the PRP vaccination (Total Vaccinated Cohort, PRP challenge subset).

| Symptom | Intensity/ Relationship | Group 1 (N = 46) | | | | Group 2 (N = 47) | | | |
|------------------|----------------------------|------------------|------|--------|------|------------------|------|--------|------|
| | | n | % | 95% CI | | n | % | 95% CI | |
| | | | | LL | UL | | | LL | UL |
| Drowsiness | Any | 9 | 19.6 | 9.4 | 33.9 | 6 | 12.8 | 4.8 | 25.7 |
| | Grade 3 | 0 | 0.0 | 0.0 | 7.7 | 1 | 2.1 | 0.1 | 11.3 |
| | Related | 9 | 19.6 | 9.4 | 33.9 | 6 | 12.8 | 4.8 | 25.7 |
| Irritability | Any | 7 | 15.2 | 6.3 | 28.9 | 6 | 12.8 | 4.8 | 25.7 |
| | Grade 3 | 0 | 0.0 | 0.0 | 7.7 | 0 | 0.0 | 0.0 | 7.5 |
| | Related | 7 | 15.2 | 6.3 | 28.9 | 6 | 12.8 | 4.8 | 25.7 |
| Loss of appetite | Any | 3 | 6.5 | 1.4 | 17.9 | 4 | 8.5 | 2.4 | 20.4 |
| | Grade 3 | 0 | 0.0 | 0.0 | 7.7 | 1 | 2.1 | 0.1 | 11.3 |
| | Related | 3 | 6.5 | 1.4 | 17.9 | 4 | 8.5 | 2.4 | 20.4 |

| | | | | | | | | | | |
|---|----------|----|------|------|------|---------------------------|---------------------------|------|------|--|
| Fever (axillary) | ≥ 37.5°C | 10 | 21.7 | 10.9 | 36.4 | 14 | 29.8 | 17.3 | 44.9 | |
| | > 39.0°C | 3 | 6.5 | 1.4 | 17.9 | 1 | 2.1 | 0.1 | 11.3 | |
| | Related | 9 | 19.6 | 9.4 | 33.9 | 14 | 29.8 | 17.3 | 44.9 | |
| <p>N: number of subjects with a symptom sheet completed n (%): number (percentage) of subjects for whom the symptom was reported Any: incidence of a particular symptom regardless of grade or relationship to study vaccination Grade 3 drowsiness: drowsiness which prevented normal everyday activities Grade 3 irritability: crying that could not be comforted Grade 3 loss of appetite: not eating at all Related: the investigator considered that there was a reasonable possibility that the vaccine contributed to the symptom 95% CI: exact 95% confidence interval; LL: lower limit, UL: upper limit</p> | | | | | | | | | | |
| Safety Results: Number (%) of subjects with unsolicited AEs within 31 days (Day 0-30) after vaccination (Total Vaccinated Cohort). | | | | | | | | | | |
| Most Frequent AEs - On-Therapy (occurring within Day 0-30 following vaccination) | | | | | | Group 1 N = 96 | Group 2 N = 96 | | | |
| Subjects with any AE(s), n (%) | | | | | | 65 (67.7) | 59 (61.5) | | | |
| Upper respiratory tract infection | | | | | | 29 (30.2) | 28 (29.2) | | | |
| Injection site induration | | | | | | 15 (15.6) | 13 (13.5) | | | |
| Rhinitis | | | | | | 13 (13.5) | 11 (11.5) | | | |
| Pneumonia | | | | | | 12 (12.5) | 10 (10.4) | | | |
| Gastroenteritis | | | | | | 4 (4.2) | 12 (12.5) | | | |
| Bronchitis acute | | | | | | 4 (4.2) | 7 (7.3) | | | |
| Nasopharyngitis | | | | | | 7 (7.3) | 4 (4.2) | | | |
| Viral infection | | | | | | 2 (2.1) | 4 (4.2) | | | |
| Human herpesvirus 6 infection | | | | | | 3 (3.1) | 0 (0.0) | | | |
| Otitis media acute | | | | | | 2 (2.1) | 1 (1.0) | | | |
| Pyrexia | | | | | | 1 (1.0) | 2 (2.1) | | | |
| Dermatitis contact | | | | | | 1 (1.0) | 1 (1.0) | | | |
| Convulsion | | | | | | 0 (0.0) | 1 (1.0) | | | |
| Gingival abscess | | | | | | 0 (0.0) | 1 (1.0) | | | |
| Injection site erythema | | | | | | 0 (0.0) | 1 (1.0) | | | |
| Somnolence | | | | | | 0 (0.0) | 1 (1.0) | | | |
| Vomiting | | | | | | 0 (0.0) | 1 (1.0) | | | |
| Safety Results: Number (%) of subjects with unsolicited AEs within 31 days (Day 0-30) after the PRP challenge vaccination (Total Vaccinated Cohort, PRP challenge subset). | | | | | | | | | | |
| Most Frequent AEs - On-Therapy (occurring within Day 0-30 following vaccination) | | | | | | Group 1 N = 46 | Group 2 N = 47 | | | |
| Subjects with any AE(s), n (%) | | | | | | 9 (19.6) | 9 (19.1) | | | |
| Upper respiratory tract infection | | | | | | 2 (4.3) | 4 (8.5) | | | |
| Bronchitis acute | | | | | | 2 (4.3) | 1 (2.1) | | | |
| Human Herpesvirus 6 infection | | | | | | 0 (0.0) | 2 (4.3) | | | |
| Gastroenteritis | | | | | | 2 (4.3) | 0 (0.0) | | | |
| Rhinitis | | | | | | 1 (2.2) | 1 (2.1) | | | |
| Excoriation | | | | | | 1 (2.2) | 0 (0.0) | | | |
| Impetigo | | | | | | 0 (0.0) | 1 (2.1) | | | |
| Otitis media acute | | | | | | 1 (2.2) | 0 (0.0) | | | |
| Pharyngotonsillitis | | | | | | 0 (0.0) | 1 (2.1) | | | |
| Viral infection | | | | | | 0 (0.0) | 1 (2.1) | | | |
| Viral rash | | | | | | 1 (2.2) | 0 (0.0) | | | |
| Safety Results: Number (%) of subjects with SAEs over the full course of the primary vaccination study (Total Vaccinated Cohort). | | | | | | | | | | |
| SAEs, n (%) [n considered by the investigator to be related to study medication] | | | | | | | | | | |
| All SAEs | | | | | | Group 1 N = 96 | Group 2 N = 96 | | | |
| Subjects with any SAE(s), n (%) [n related] | | | | | | 6 (6.3) [0] | 5 (5.2) [0] | | | |
| Pneumonia | | | | | | 4 (4.2) [0] | 3 (3.1) [0] | | | |

| | | |
|--|----------------------------|----------------------------|
| Bronchopneumonia | 1 (1.0) [0] | 0 (0.0) [0] |
| Convulsion | 0 (0.0) [0] | 1 (1.0) [0] |
| Gastroenteritis | 0 (0.0) [0] | 1 (1.0) [0] |
| Gastroenteritis bacterial | 1 (1.0) [0] | 0 (0.0) [0] |
| Pneumonia bacterial | 1 (1.0) [0] | 0 (0.0) [0] |
| Fatal SAEs | Group 1 N = 96 | Group 2 N = 96 |
| Subjects with fatal SAE(s), n (%) [n related] | 0 (0.0) [0] | 0 (0.0) [0] |
| Safety Results: Number (%) of subjects with SAEs over the full course of the PRP challenge study (Total Vaccinated Cohort, PRP challenge subset). | | |
| SAEs, n (%) [n considered by the investigator to be related to study medication] | | |
| All SAEs | Group 1 N = 46 | Group 2 N = 47 |
| Subjects with any SAE(s), n (%) [n related] | 0 (0.0) [0] | 1 (2.1) [0] |
| Human Herpesvirus 6 infection | 0 (0.0) [0] | 1 (2.1) [0] |
| Fatal SAEs | Group 1 N = 46* | Group 2 N = 47* |
| Subjects with fatal SAE(s), n (%) [n related] | 0 (0.0) [0] | 0 (0.0) [0] |

Conclusion: One month after Dose 3, all subjects had anti-PRP antibody concentrations ≥ 0.15 $\mu\text{g/mL}$ and at least 93.7% of the subjects had anti-PRP antibody concentrations ≥ 1 $\mu\text{g/mL}$; 92.6% of all subjects had anti-diphtheria antibody concentrations $\geq 0.1\text{IU/mL}$ by ELISA or ≥ 0.016 by Vero cell assay; all subjects had anti-tetanus antibody concentrations $\geq 0.1\text{IU/mL}$; and at least 98.9% of all subjects had anti-BPT antibody concentrations $\geq 15\text{EL.U/mL}$; at least 78.5% of all subjects had anti-HBs antibody concentrations $\geq 10\text{mIU/mL}$. One month after the challenge dose, all subjects had anti-PRP antibody ≥ 0.15 $\mu\text{g/mL}$ and at least 97.8% of subjects had antibody concentrations ≥ 1 $\mu\text{g/mL}$. After the primary vaccination course, pain was the most frequently reported solicited local symptom across doses in both groups (90.6%) and fever was the most frequently reported solicited general symptom. After the challenge dose, pain and redness were the most frequently reported solicited local symptom. Irritability and fever were the most frequently reported solicited general symptoms across doses after the primary vaccination course and fever was the most frequently reported solicited general symptom after the challenge dose. After the primary vaccination course, at least one unsolicited AE was reported for 67.7% and 61.5% of the subjects of Groups 1 and 2, respectively. After the challenge dose, at least one unsolicited AE was reported for 19.6% and 19.1% of the subjects of Groups 1 and 2, respectively. After the primary vaccination course SAEs were reported in 6 subjects from Group 1 and in 5 subjects from. After the challenge dose, 1 SAE was reported in Group 2. None of the reported SAEs was considered by the investigator to be related to the study vaccination. No fatal SAEs were reported during the entire study period.

Publications: None.

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