Investigational Product:	Meningococcal (group C vaccine) Oligosaccharide Diptheria CRM_{197} Conjugate Vaccine (Menjugate™)
Active ingredient:	Neisseria meningitidis group C (strain C11) oligosaccharide conjugated to corynebacterium diphtheriae CRM197 protein
Indication:	Prophylaxis of *Neisseria meningitidis* serogroup C
Sponsor:	Novartis Vaccines & Diagnostics S.r.l.
Date of the CSR:	21 Apr 09

Title of Study: A Phase III, Multi-Center, Open-Label, Controlled, Randomized Study to Evaluate the Immunogenicity, Safety, Tolerability and the Ability to Prime for Memory of Chiron Meningococcal C Conjugate Vaccine Menjugate® When Administered to Healthy Infants as One Dose Given at 2 or 6 Months of Age with a Booster at 12-16 Months of Age, in Comparison to Two Doses in the First Year of Life, Given Two Months Apart, With a Booster at 12-16 Months of Age; and in Comparison to One Dose Given at 12-16 Months of age

Protocol Number: M14P6

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Study Centers: The trial was carried out across 5 study sites in Germany and 4 study sites in Poland.

Publication (reference): None

Study Period:	**Phase of Development:** Phase 3
Date of first enrollment:28 Oct 2005 Date of last visit: 17 Apr 2008	

Objectives:
Immunogenicity Objectives
Primary

- To demonstrate non-inferiority, 10 days after the booster vaccination, of the memory antibody response (in terms of percent responders) to *Neisseria meningitidis* serogroup C after 1 dose of Menjugate® at 2 months of age plus a booster in the second year of life (2 Months group) in comparison with the memory antibody response after 2 doses of Menjugate at 2 and 4 months of age plus a booster in the second year of life (2+4 Months group), as measured by bactericidal assay using rabbit complement (rBCA).

Secondary

- To compare the memory antibody response (in terms of percent responders) to *Neisseria meningitidis* serogroup C after 1 dose of Menjugate® at 6 months of age plus a booster in the second year of life (6 Months group) with the memory antibody response after 2 doses of Menjugate at 2 and 4 months of age plus a booster in the second year of life (2+4 Months group), as measured by rBCA. Geometric mean titers (GMTs) were also evaluated.
- To compare the memory antibody response to *Neisseria meningitidis* serogroup C after 2 doses of Menjugate® given during infancy, and a third (booster) dose in the second year of life (2+4 Months group) in comparison to the antibody response after a single dose of Menjugate given in the second year of life (12-16 Months group), as measured by BCA using rabbit complement (rBCA).
- To evaluate the antibody response (in terms of GMT and percent responders) to *Neisseria meningitidis* serogroup C one month after one dose of Menjugate® at either 2 or 6 months of age (2 Months and 6 Months groups, respectively) as measured by rBCA.
- To compare the antibody response (in terms of GMT and percent responders) to *Neisseria meningitidis* serogroup C one month after one dose of Menjugate® at either 2 or 6 months of age (2 Months and 6 Months groups, respectively) with the antibody response one month after 2 doses of Menjugate at 2 and 4 months of age (2+4 Months group) as measured by rBCA.
- To evaluate the persistence of the antibody response (in terms of GMT and percent responders) to *Neisseria meningitidis* serogroup C after one dose of Menjugate® at either 2 or 6 months of age (2 Months and 6 Months groups, respectively) and the persistence of antibody response after 2 doses of Menjugate at 2 and 4 months of age (2+4 Months group), before the administration of the booster at 12-16 months of age as measured by rBCA.
- To evaluate the memory antibody response (in terms of GMT and percent responders) to *Neisseria meningitidis* serogroup C after one dose of Menjugate® at either 2 or 6 months of age plus a booster dose in the second year of life (2 Months and 6 Months groups, respectively) as measured by rBCA.
- To evaluate the persistence of antibody response (in terms of GMT and percent responders) at ≥8 to ≤10 months of age after the primary vaccination, at 12 to 16 months of age before the booster vaccination, and at 24 months of age after booster vaccination (2+4 Months, 2 Months and 6 Months groups) or primary vaccination (12-16 Months group) as measured by rBCA.

- To evaluate the immunological response to the components of the hexavalent vaccine (diphtheria, tetanus, acellular Pertussis, polio, *Haemophilus influenzae* type b and hepatitis B), with a priority on *Haemophilus influenzae* type b, when administered concomitantly to Menjugate®, in as many subjects as possible, depending on the availability of serum in those young children.

A responder is defined as a subject showing an rBCA titer of at least 1:128 after vaccination, i.e., rBCA ≥ 1:128. Data may also be presented as at least four-fold rises in rBCA titers and as percent of subjects reaching rBCA titers ≥1:8.

Safety Objectives

To evaluate the safety and tolerability of Menjugate® administered to healthy infants at 2 to 6 months of age, and as first, second or third dose in the second year of life.

Methodology: The number of subjects enrolled is summarized in the section entitled "Number of Subjects (planned and analyzed)". For additional details, please refer to the Time and Events Table.

In this phase III, multi-center, open-label, controlled, randomized study, infants were randomized into one of four groups in a 1:1:1:1 ratio to receive:

Group 1 or 2+4 Months group (2-doses): at 2 and 4 months of age, together with the 1st and 3rd (Germany) or 1st and 2nd (Poland) dose of routine hexavalent infant immunization, with a booster at 12-16 months of age.

Group 2 or 2 Months group (1-dose): at 2 months of age, together with 1st dose of routine hexavalent infant immunization, with a booster at 12-16 months of age.

Group 3 or 6 Months group (1-dose): at 6 months of age, together with the 3rd dose (in Poland), but respectively 2 months after the 3rd dose (in Germany) of routine hexavalent infant immunization, with a booster at 12-16 months of age.

Group 4 or 12-16 Months group (1 dose in the second year of life, control group): at 12-16 months of age (together with the 4th dose of routine hexavalent infant immunization).

A physical examination was performed at study entry and at each subsequent visit. Local reactions at the site of injection of the investigational product (i.e., tenderness, erythema, swelling and induration) and systemic reactions (i.e., change in eating habits, sleepiness, unusual crying, vomiting, diarrhea and irritability) were observed for 30 min after each immunization and on the following seven days, including the day of vaccination. All Adverse Events as well as the rectal temperature and the use of analgesic/antipyretic medication were collected during the same seven-day periods. All Serious Adverse Events and/or Adverse Events necessitating a physician's visit (if medically significant as judged by the investigator) and/or resulting in premature withdrawal from the study were collected throughout the study and recorded by study personnel during each of the study visits. All medically relevant prescription medication (excepting minerals and vitamins) taken at any time during the trial were recorded.

From every subject in groups 1 through 3, a total of 5 blood samples of 3 – 5 mL each were taken:

1st Blood sample at 1 month after either the 2nd vaccination within the study (2+4 Months group) or the 1st vaccination within the study (2 Months and 6 Months groups), (time window: 28 – 42 days)

2nd Blood sample at ≥8 to ≤10 months of life
3rd Blood sample prior to booster vaccination at 12-16 months of life
4th Blood sample at 10 days after booster vaccination (time window: 7 – 14 days)
5th Blood sample at the end of the study, at approx. 24 months of age

From every subjects in 12-16 Months group, a total of 4 blood samples of 3 – 5 mL each were taken:

1st Blood sample at study visit 1, baseline at 2 months of age
2nd Blood sample prior to first vaccination at 12-16 months of age
3rd Blood sample at 1 month after vaccination (time window: 28 – 42 days)
4th Blood sample at the end of the study, at approx. 24 months of age

Immunogenicity was assessed by evaluating serum antibody responses to *N. meningitidis* serogroup C by measuring bactericidal antibody titers using rabbit complement (rBCA). Other measures were performed to further assess immunogenicity.

Serological tests on the response to the components of the hexavalent vaccine were conducted, with the evaluation of titers against *Haemophilus influenzae* type b as the first priority. Diphtheria, tetanus, pertussis, PRP-T Hib and HBsAg (Hepatitis B surface antigen) antibody titers were measured using specific ELISAs. Poliovirus antibody titers were measured by the neutralization test (NT). These serological tests were carried out on the first sample obtained after completion of the primary hexavalent schedule (not necessarily at 1 month after last dose of the primary series) and on the sample provided after the hexavalent booster vaccination in the second year of life.

Number of Subjects (planned and analyzed): 260 subjects were planned to be enrolled in the study, 65 subjects per group. A total of 257 subjects were actually enrolled in the study.

	Group 1 2+4 Months	**Group 2 2 Months**	**Group 3 6 Months**	**Group 4 12-16 Months**
Planned	65	65	65	65
Enrolled and vaccinated	64	64	63	66
Per Protocol	64 (100%)	62 (97%)	57 (90%)	61 (92%)

Group 1-2-dose-group; Group 2-1-dose-group; Group 3-1-dose-group; Group 4- Control group

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria: Infants eligible to be enrolled in the study were healthy infants (7 to 11 weeks of age), who were born after full-term pregnancy with an estimated gestational age ≥ 37 weeks and a birth weight ≥ 2.5 kg and for whom the parents/legal guardians had given written informed consent after the nature of the study had been explained; were available for all the visits scheduled in the study; were in good health as determined medical history, physical examination and clinical judgment of the investigator.

Exclusion criteria: Individuals were not included in this study if their parents/legal guardians were unwilling or unable to give written informed consent to their child's participation in the study; previously received meningococcal C vaccine of any kind; had

a previous ascertained or suspected disease caused by *N. meningitidis*, *Corynebacterium diphtheriae*, *Clostridium tetani*, poliovirus, Hepatitis B or *H. influenzae* type b, history of microbiologically proven *Bordetella pertussis*, or clinical condition of spasmodic cough for a period longer than or equal to 2 weeks associated with apnea or whooping; have had household contact with and/or intimate exposure to an individual with microbiologically proven *N. meningitidis* serogroup C or *Bordetella pertussis*, within the previous 60 days; had either received, or for whom there was intent to immunize with, any vaccines or investigational agents within 60 days prior to enrolment, through to 30 days following any study vaccine administration; except for the vaccination against tuberculosis which was allowed to be given to the subjects in the Polish sites since this was a legally required infant vaccination in Poland given to the child at birth and except for Hepatitis B vaccination given in Poland at birth as well and except for vaccination with DTaP-IPV-HBV/Hib, which as routine infant vaccination was allowed to be given concomitantly to the study medication; had a history of any anaphylactic shock, asthma, urticaria or other allergic reaction after previous vaccinations or hypersensitivity to any vaccine component; received prior vaccination with DTaP-IPV-HBV/Hib or any of the components (before the age of 2 months), unless the exception for hepatitis B in Poland applied; had experienced fever (rectal temperature ≥ 38.5°C) within the past 3 days or were suffering from a present acute infectious disease; had experienced significant acute or chronic infections requiring systemic antibiotic treatment or antiviral therapy within the past 10 days; had any present or suspected serious chronic disease such as cardiac or autoimmune disease or insulin dependent diabetes; had leukemia, lymphomas, neoplasm; had a history of serologically or clinically confirmed HIV, hepatitis B or hepatitis C infection; with a known or suspected impairment of the immune function, or those receiving immunosuppressive therapy, or having received immunosuppressive therapy, including use of corticosteroids known to be associated with suppression of hypothalamic-pituitary-adrenal (HPA) axis (i.e., systemic corticosteroids [eg 1 mg/kg/day of prednisone or its equivalent] or chronic use of inhaled high-potency corticosteroids [budesonide 800 µg per day or fluticasone 750 µg per day]); had received blood, blood products or a parenteral immunoglobulin preparation; with a known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time; had any other serious chronic disease (e.g., with signs of cardiac or renal failure or severe malnutrition), including progressive neurological disease; had a history of seizure disorder; a genetic anomaly (known cytogenic disorders) e.g., Down's syndrome; who with their parents/legal guardians were planning to leave the area of the study site before the end of the study period; with any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

Contraindications for the subsequent immunizations were the development of any condition specified in the initial exclusion criteria and any serious vaccine related reaction to investigational agent or concomitant vaccines which in the opinion of the investigator could have altered the course of subsequent study or concomitant DTaP-IPV-HBV/Hib vaccinations.

Test Product, Dose, Mode of Administration, Lot Number: Novartis Meningococcal C Conjugate vaccine Menjugate® - Lot number *UA9476A.*

All subjects assigned to groups 1 through 4 received three (2+4 Months group) or two (2 Months and 6 Months groups) doses or 1 dose (12-16 Months group) of the MenCC vaccine, which was injected IM into the antero-lateral area of the right thigh by using a suitable needle, administered in the subject's pediatrician's practice/ hospital.

Only valid for Poland:

GlaxoSmithKline Biologicals S.A., Belgium hexavalent infant vaccine Infanrix® Hexa - Lot number *A21CA270B*

Each 0.5 mL dose contained diphtheria toxoid ≥ 30 IU, tetanus toxoid ≥ 40 IU, pertussis toxoid 25 μg, pertussis FHA 25 μg, Pertactin 8 μg, Hepatitis B surface antigen recombinant 10.0 μg, inactivated poliovirus type 1, 2 and 3, *Haemophilus influenzae* type b polysaccharide (10 μg) conjugated to tetanus toxoid, adsorbed on aluminum hydroxide /aluminum phosphate, sodium chloride, water for injection

All subjects assigned to groups 1 through 4 received four doses of the hexavalent infant vaccine Infanrix® Hexa as recommended in Poland and Germany with 3 doses under 6 months of age and a booster dose in the second year of life, administered IM into the antero-lateral area of the left thigh by using a suitable needle, in the subject's pediatrician's practice/ hospital.

Duration of Study: The actual duration of the study was approximately 30 months (28 October 2005 to 17 April 2008) including approximately 7 months of enrolment (28 October 05 to 31 May 2006) and 22 months of individual study participation.

Reference Therapy, Dose, Mode of Administration, Lot Number:

Concomitant vaccines: Routine hexavalent infant immunization: Infanrix® Hexa, Lot number *A21CA270B*, as recommended in Poland and Germany with 3 doses under 6 months of age and a booster dose in the second year of life, administered into the antero-lateral area of the left thigh.

Criteria for Evaluation:

Immunogenicity:

- The geometric mean antibody titers (GMTs) as measured by rBCA and the proportion of subjects with rBCA ≥ 1:128 and rBCA ≥ 1:8 were calculated.
- The geometric mean antibody concentrations (GMCs) against components of the hexavalent vaccines (i.e., diphtheria, tetanus, acellular pertussis, PRP-T Hib, HbsAg, polio type I, II, III) as measured by ELISA and the proportion of subjects achieving protective titers against components of the hexavalent vaccine (i.e., diphtheria ≥ 0.1 IU/mL, tetanus ≥ 0.1 IU/mL, PRP-T Hib ≥ 0.15 mcg/mL, HbsAg ≥ 10 IU/L, polio type I, II, III ≥ 1:8) were calculated.
- GMCs for the acellular pertussis component were evaluated pre (for 12-16 Months group) and post (groups 1-4) basic immunization in the first year of life (after three doses). Geometric mean increases were calculated based in GMC.

Safety:

The proportion of subjects experiencing local and systemic reactions, the number of subjects reporting SAEs and/ or AEs necessitating a physician's visit and/ or resulting in

premature withdrawal from the study were summarized, according to severity and relatedness.

Statistical Methods:

Statistical Hypothesis:

The null hypothesis associated with the primary immunogenicity objective was that the proportion of responders, defined as subjects showing a rBCA ≥ 1:128, after 1 dose of Menjugate® at 2 months of age plus a booster in the second year of life (2 Months group) was inferior to the proportion of responders after 2 doses of Menjugate at 2 and 4 months of age plus a booster in the second year of life (2+4 Months group), by more than 10%.

The associated alternative hypothesis was that the difference in those proportions (proportion in 2 Months group minus proportion in 2+4 Months group) was greater than -10%.

Statistical Power Considerations:

When the sample size in each group is 55, a two-group test of proportions with a one-sided 2.5% significance level will have 86% power to reject the null hypothesis that the 1 dose group is inferior to the 2 dose group (the difference in proportions is 10% or farther from zero in the same direction) in favor of the alternative hypothesis that the 1 dose group is non-inferior to the 2 dose group (2+4 Months group), assuming that the expected difference in proportions is 1% and the proportion in the 2 doses group is 98%.

In order to foresee for a drop-out rate of approximately 15%, 65 subjects were enrolled in each group, with a total of 260 subjects.

Summary and Conclusions:

Immunogenicity results

As measured by rBCA titers 10 days after the booster vaccination, non-inferiority of the memory antibody response to *Neisseria meningitidis* serogroup C for the 2 Months group in comparison with 2+4 Months group was not demonstrated (lower limit of the two-sided 95% CI around the difference in the percentages of rBCA seroresponders 2 Months group minus 2+4 Months group was not greater than -10%).

All subjects were seroresponders (i.e. rBCA ≥ 1:128) in the 6 Months group as well as in the 2+4 Months group. However, the percentage of responders in the 12-16 Months group was only 52%. Non-inferiority of the memory antibody response to *Neisseria meningitidis* serogroup C was also not demonstrated for 6 Months group in comparison with 2+4 Months group as well as for 12-16 Months group in comparison with 2+4 Months group.

The GMTs increased substantially 10 days after booster (522 to 635-fold increase from pre-booster levels) across 2+4 Months, 2 Months and 6 Months vaccine groups. However, the rise in GMT as measured by rBCA at one month after one dose given at 12-16 months of age for 12-16 Months group was much lower (27-fold).

The proportion of subjects achieving protective titers (i.e., rBCA ≥ 128) against *Neisseria meningitidis* serogroup C at 1 month after the primary immunization was lower in the 2 Months and 6 Months groups (51% and 64% respectively) as compared to

the 2+4 Months group (percentage of responders 93%). The GMTs as measured by rBCA at 1 month after primary immunization were also lower in the 2 Months and 6 Months groups (GMT: 57 and 108 respectively) as compared to the 2+4 Months group (GMT: 653).

The proportion of subjects maintaining protective antibody titers (rBCA ≥ 128) against *Neisseria meningitidis* serogroup C after the primary immunization at 8 to 10 months of age was higher in the 2+4 Months group (46%) than in the 2 Months and 6 Months groups (0 and 14% respectively) whereas at 12 to 16 months of age it was similar across these three vaccine groups (3% to 10%). At 24 months of age none of the subjects in the 12-16 Months group had seroprotective titers whereas the proportion of subjects maintaining rBCA titers ≥ 128 after booster dose was lower in 2+4 Months group (26%) as compared to 2 Months and 6 Months groups (44% and 43% respectively).

Antibody persistence as measured by rBCA GMTs after primary immunization series at 8-10 months of age was lower for 2 Months group (GMT: 5.07) as compared to 2+4 Months and 6 Months groups (GMTs: 61 and 37 respectively), however at 12-16 months of age GMTs were similar across the three vaccine groups (4 to 6.64). At 24 months of age rBCA GMT was lower (GMT: 2.83) in the 12-16 Months group than in the other vaccine groups receiving one or two doses of Menjugate in the first year of life and a booster dose at 12-16 months of age. These groups showed similar rBCA GMTs (28 to 47).

In order to evaluate the immunological response to the components of the hexavalent vaccine (diphtheria, tetanus, acellular pertussis, polio, *Haemophilus influenzae* type b and hepatitis B), when administered concomitantly to Menjugate®, further serological tests were conducted in as many subjects as possible.

At one month after primary hexavalent vaccination all subjects in the 2+4 Months group (Germany only) and 6 Months group (Poland only) achieved antidiphtheria, antitetanus and anti-PRP protective titers. These antibody titers in subjects receiving hexavalent vaccine concomitantly with Menjugate (groups 2+4 Months, 2 Months and 6 Months) were evaluated up to 4-6 months after primary vaccination series at 2, 3, 4 months of age or 2-4 months after primary vaccination series at 2, 4, 6 months of age and were still very high (range: 93% to 100%). All subjects achieved protective diphtheria and tetanus antibody titers 10 days (groups 2+4 Months, 2 Months and 6 Months) or one month (group 12-16 Months) after booster vaccination. However, 94% to 100% subjects achieved protective anti-PRP antibody titers 10 days (groups 2+4 Months, 2 Months and 6 Months) or one month (group 12-16 Months) after booster vaccination.

Almost 95% to 100% subjects in the 2+4 Months group (Germany only) and all subjects in the 6 Months group (Poland only) achieved anti-polio (types I, II and III) protective titers at one month after primary hexavalent vaccination. Anti-polio antibody titers in subjects receiving hexavalent vaccine concomitantly with Menjugate (groups 2+4 Months, 2 Months and 6 Months) were evaluated up to 4-6 months after primary vaccination series at 2, 3, 4 months of age or 2-4 months after primary vaccination series at 2, 4, 6 months of age and were still very high (range: 74% to 100%). All subjects achieved protective anti-polio antibody titers 10 days (groups 2+4 Months, 2 Months and 6 Months) or one month (group 12-16 Months) after booster vaccination.

Geometric mean anti-PT antibody titer was lower (2.91 to 2.92) than geometric mean anti-FHA (8.36 to 9.91) and anti-PRN (7.76 to 8.53) antibody titers prior to the first hexavalent vaccination in the 12-16 Months group. A much greater increase from baseline was seen for anti-FHA and anti-PRN antibody titers (> 30-fold) as compared to anti-PT antibody titer (> 20 fold) one month after the booster vaccination.

At one month after primary hexavalent vaccination geometric mean anti-PT antibody titers in the 2+4 Months group (Germany only) and the 6 Months group (Poland only) were similar (34 and 41 respectively). Geometric mean anti-PT antibody titers in subjects receiving hexavalent vaccine concomitantly with Menjugate (groups 2+4 Months, 2 Months and 6 Months) were evaluated up to 4-6 months after primary vaccination series at 2, 3, 4 months of age or 2-4 months after primary vaccination series at 2, 4, 6 months of age and were slightly lower (range: 14 to 29). The GMTs were slightly higher 10 days after booster vaccination (range: 33 to 72).

At one month after primary hexavalent vaccination geometric mean anti-FHA antibody titers in the 2+4 Months group (Germany only) and the 6 Months group (Poland only) were similar (138 and 167 respectively). Geometric mean anti-FHA antibody titers in subjects receiving hexavalent vaccine concomitantly with Menjugate (groups 2+4 Months, 2 Months and 6 Months) were evaluated up to 4-6 months after primary vaccination series at 2, 3, 4 months of age or 2-4 months after primary vaccination series at 2, 4, 6 months of age and were slightly lower (range: 71 to 101). However, the GMTs were much higher 10 days after booster vaccination (range: 220 to 606).

At one month after primary hexavalent vaccination geometric mean anti-PRN antibody titers in the 2+4 Months group (Germany only) and the 6 Months group (Poland only) were similar (94 and 119 respectively). Geometric mean anti-PRN antibody titers in subjects receiving hexavalent vaccine concomitantly with Menjugate (groups 2+4 Months, 2 Months and 6 Months) were evaluated up to 4-6 months after primary vaccination series at 2, 3, 4 months of age or 2-4 months after primary vaccination series at 2, 4, 6 months of age and were lower (range: 46 to 86). However, GMTs were much higher 10 days after booster vaccination (range: 276 to 524).

At one month after primary hexavalent vaccination anti-HbsAg protective titers were achieved by 95% of the subjects in the 2+4 Months group (Germany only) and all subjects in the 6 Months group (Poland only). Anti-HbsAg antibody titers in subjects receiving hexavalent vaccine concomitantly with Menjugate (the 2+4 Months, 2 Months, and 6 Months groups) were evaluated up to 4-6 months after primary vaccination series at 2, 3, 4 months of age or 2-4 months after primary vaccination series at 2, 4, 6 months of age and were still very high (range: 94% to 100%). The percentages of subjects achieving protective anti-HbsAg antibody titers 10 days after booster vaccination (for the 2+4 Months, 2 Months, and 6 Months groups) ranged between 90% and 100%. All subjects achieved protective anti-HbsAg antibody titers at one month (for the 12-16 Months group) after booster vaccination.

Safety results

A total of 257 subjects were enrolled in this study to evaluate the safety and tolerability of Menjugate® administered to healthy infants at 2 to 6 months of age and as first, second or third dose in the second year of life. All subjects were included in the safety population.

When vaccine was administered at 2-6 months of age, the percentages of subjects who had any solicited adverse events (i.e., local, systemic, or other reactions observed during the 7 days after vaccination) were similar to those observed when vaccine was administered in the second year of life (67% to 75% as compared to 72% to 82%). Rates of any solicited adverse events were also comparable at subsequent vaccinations within each vaccine group.

An increase in the percentages of subjects experiencing solicited local reactions was observed with subsequent vaccinations within the groups (28%, 33% and 55% in the 2+4 Months group; 34% to 70% in the 2 Months group and 44% to 50% in the 6 Months group). In contrast, there was a decrease in the percentages of subjects experiencing solicited systemic reactions with subsequent vaccinations (67%, 55% and 50% in the 2+4 Months group; 73% to 52% in the 2 Months group and 53% to 50% in the 6 Months group).

Overall, when vaccine was administered at 2-6 months of age, lower percentages of subjects had solicited local reactions than when vaccine was administered in the second year of life. Higher percentage of subjects had tenderness, swelling and erythema after first vaccination in the 12-16 Months group (43%, 16% and 39%) as compared to the other vaccine groups. However, induration after first vaccination was more commonly seen in the 6 Months group (38%) than in the other vaccine groups. The majority of reactions were mild to moderate in severity. Only 2% to 5% of subjects were observed with swelling, erythema or induration >50 mm or severe tenderness (definition: baby cried when injected limb was moved).

Across all vaccine groups, comparable reporting rates were seen for solicited systemic reactions after the first vaccination, except for the rate for sleepiness, which was lower in the 6 Months group (16%) as compared to the other vaccine groups (45% to 48%). Also, the percentages of subjects with any solicited systemic reaction were similar to those seen with subsequent vaccinations within the group. Fever rates (> 38.5°C rectally) at similar ages (i.e., 12-16 months of age) were similar in all groups, whether Menjugate was preceded by 0, 1 or 2 Menjugate vaccinations (20%, 15%, 14% or 15% for the 2+4 Months, 2 Months, 6 Months and 12-16 Months groups, respectively). Only one subject in the 6 Months group had rectal temperature ≥40.5°C after second vaccination in the second year of life.

Unsolicited AEs within one month after vaccination were similar regardless of the vaccine being administered at 2-6 months of age or in the second year of life in the 2+4 Months, 2 Months and 6 Months groups. However, rates of unsolicited AEs were higher in subjects receiving only one dose of vaccination at 12-16 months (the 12-16 Months group). Overall, the percentages of subjects experiencing any unsolicited AE were lower in the 6 Months group (38%) as compared to the other three vaccine groups (50% to 56%). The MedDRA System Organ Class (SOC) most commonly affected by unsolicited AEs was “Infections and Infestations” (25% to 41%), followed by “Gastrointestinal Disorders” (5% to 11%), “Skin and Subcutaneous Disorders” (3% to 11%) and “General Disorders and Administration Site Conditions” (3% to 9%).

Higher percentages of subjects experienced unsolicited AE possibly or probably related to treatment in the 2 Months group (17%) as compared to the other three vaccine groups

(2% to 6%). The SOC "General Disorders and Administration Site Conditions" was most commonly possibly or probably related to treatment (2% to 9% across all vaccine groups).

There were no deaths in this study. Overall, a total of 40 SAEs were reported. None of the SAEs were assessed as related to the study vaccine.

Conclusions

The results of the analysis of the primary objective demonstrated that memory antibody response to *Neisseria meningitidis* serogroup C (as measured by percentage of rBCA ≥128) after 1 dose of Menjugate® (at 2 months of age) followed by a booster in the second year of life did not meet the non-inferiority criteria versus the response after 2 doses (at 2 and 4 months of age) plus a booster in the second year of life.

The memory response of Menjugate® given as 1 dose at 6 months of age plus a booster in the second year of life was comparable with that of 2 doses at 2 and 4 months of age plus a booster in the second year of life, with 100% of the subjects achieving protective titers in both groups. However, the antibody response (percentage of responders and GMTs) one month after a single dose of Menjugate given in the second year of life was much lower compared to the memory antibody response in subjects receiving 2 doses at 2 and 4 months of age plus a booster in the second year of life.

In the first year of life, the immune responses (percentage of responders and GMTs) to Menjugate one month after the primary immunization were lower in the one-dose groups as compared to the two-dose group. Therefore, it can be concluded that a two-dose schedule elicited better seroprotection than the one-dose schedule during the first year of life.

Persistence of antibody response to *Neisseria meningitidis* serogroup C after primary vaccination at 8 to 10 months of age was lower in the one-dose groups than in the two-dose group, however, at 12 to 16 months of age all three groups showed similar persistent titers.

At 24 months of age, persistence was lowest after a single dose of Menjugate given in the second year of life as compared to the groups receiving a primary series (one or two doses) of Menjugate in the first year of life. Of note, persistence at 24 months of age was higher in the groups that received only one dose of Menjugate during the first year of life (either at 2 or 6 months of age) compared to the group that received two doses (at 2 and 4 months of age). However, sample size was too small to draw further conclusions.

The immunological response to the components of the hexavalent vaccine (diphtheria, tetanus, acellular pertussis, polio and *Haemophilus influenzae* type b), when administered concomitantly with Menjugate®, was similar among groups regardless of the dosing schedule of Menjugate.

The safety profile of Menjugate was comparable whether it was administered at 2-6 months of age or as first, second or third dose in the second year of life. No serious or other clinically significant adverse events considered to be related to the study vaccine were reported. There were no deaths in the study.

It can be concluded that Menjugate® was generally safe and well tolerated at all dose regimens evaluated in this study.

Table 2-1: Time and Events

Months of age (study months)/ Group	**2 (0)**	**3 (1)**	**4 (2)**	**5 (3)**	**6 (4)**	**7 (5)**	**8-10 (7)**	**12-16 (12)**	**12-16 (12) +10 days* +28days****	**24 (22)**
Hexavalent vaccine, ***Germany***	*Infanrix® Hexa*	*Infanrix® Hexa*	*Infanrix® Hexa*					*Infanrix® Hexa Booster*		
Hexavalent vaccine, ***Poland***	*Infanrix® Hexa*		*Infanrix® Hexa*		*Infanrix® Hexa*			*Infanrix® Hexa Booster*		
Group 1 2-dose-group	MenCC		MenCC	**Blood Sample**			**Blood Sample**	**Blood Sample** + Booster MenCC	**Blood Sample**	**Blood Sample**
Group 2 1-dose-group	MenCC	**Blood Sample**					**Blood Sample**	**Blood Sample** + Booster MenCC	**Blood Sample**	**Blood Sample**
Group 3 1-dose-group					MenCC	**Blood Sample**	**Blood Sample**	**Blood Sample** + Booster MenCC	**Blood Sample**	**Blood Sample**
Group 4 Control group	**Blood Sample**							**Blood Sample** + MenCC	**Blood Sample**	**Blood Sample**

* Group 1 – 3; ** Group 4

Table 2-2: Blood Draw Time Points for Evaluation of Concomitant Antigens

Months of age	Infanrix Hexa Vaccination Germany	Poland	Group 1 2-dose-group	Group 2 1-dose-group	Group 3 1-dose-group	Group 4 Control group
2	X	X				BD – Day 0 Germany and Poland
3		X				
4	X	X				
5			BD 1 month after 3rd dose Germany			
6		X				
7					BD 1 month after 3rd dose Poland 3 months after 3rd dose Germany	
8-10			BD 2-4 months after 3rd dose Poland	BD 2-4 months after 3rd dose Poland 4-6 months after 3rd dose Germany		
12-16	X	X				BD - Pre-booster 6-10 months after 3rd dose Poland 8-10 months after 3rd dose Germany
12-16 +10 days * +28 days **			BD 10 days after booster Poland and Germany	BD 10 days after booster Poland and Germany	BD 10 days after booster Poland and Germany	BD 28 days after booster Poland and Germany

BD: Blood Draw; *: Group 1 – 3; **: Group 4

Table 2-3: Population Analyzed

Vaccine Group	Number (%) of Subjects			
	Group 1 2+4 months N=64	Group 2 2 months N=64	Group 3 6 months N=63	Group 4 12-16 months N=66
Population:				
Enrolled Population	64 (100%)	64 (100%)	63 (100%)	66 (100%)
Exposed Population	64 (100%)	64 (100%)	63 (100%)	66 (100%)
Safety Population	64 (100%)	64 (100%)	63 (100%)	66 (100%)
MITT Population	64 (100%)	63 (98%)	58 (92%)	62 (94%)
Any PP Immuno Population	41 (64%)	36 (56%)	37 (59%)	37 (56%)

MITT -Modified Intention-To-Treat; PP- per Protocol; Group 1-2-dose-group; Group 2-1-dose-group; Group 3-1-dose-group; Group 4- Control group

Table 2-4: Summary of Study Termination

Primary Withdrawal Reason	Number (%) of Subjects			
	Group 1 2+4 months N=64	Group 2 2 months N=64	Group 3 6 months N=63	Group 4 12-16 months N=66
Completed	64 (100%)	62 (97%)	57 (90%)	61 (92%)
Completed Protocol	64 (100%)	62 (97%)	57 (90%)	61 (92%)
Premature Withdrawal	0	2 (3%)	6 (10%)	5 (8%)
Withdrawal Of Consent	0	1 (2%)	3 (5%)	3 (5%)
Lost To Follow-Up	0	1 (2%)	1 (2%)	1 (2%)
Protocol Deviation/Violation	0	0	0	1 (2%)
Unable To Classify	0	0	2 (3%)	0

Group 1-2-dose-group; Group 2-1-dose-group; Group 3-1-dose-group; Group 4- Control group

Table 2-5: Demographic and Other Baseline Characteristics by Vaccine Group – Enrolled Population

Variable	Group 1 2+4 months N=64	Group 2 2 months N=64	Group 3 6 months N=63	Group 4 12-16 months N=66
Age (Days±SD):	62.1±10.3	63±10.4	61.6±10.1	63.1±9.9
Sex (N [percentages]):				
Male	32 (50%)	34 (53%)	36 (57%)	39 (59%)
Female	32 (50%)	30 (47%)	27 (43%)	27 (41%)
Race (N [percentages])::				
Caucasian	64 (100%)	63 (100%)	58 (100%)	62 (100%)
Weight (kg±SD):	5.45±0.62	5.39±0.63	5.35±0.70	5.46±0.61
Height (cm±SD):	59.2±2.8	59.1±2.8	58.4±2.7	58.9±2.8
Met Protocol Criteria:				
Yes	63 (98%)	63 (98%)	62 (98%)	66 (100%)
No	1 (2%)	1 (2%)	1 (2%)	0

Categorical parameters: N(%), non-categorical parameters: Mean±Std ; Group 1-2-dose-group; Group 2-1-dose-group; Group 3-1-dose-group; Group 4- Control group

Table 2-6: Percentage of Responders[a] as Measured by rBCA Titers Against *N.meningitidis* serogroup C at 10 Days After The Booster Dose and Vaccine Group Differences – Vaccine Groups 1 and 2 – Per-Protocol Population

	Number (Percentages) (95%CI)		Vaccine Group Difference
	Vaccine Groups		
	Group 2	Group 1	Group 2 – Group 1
	2 months	2+4 months	2months – 2+4months
	N=36	N=41	(95% CI)
Pre-Booster	1 (3%) (0.070-15)	4 (10%) (3-23)	(-7%) (-20, 6)
10 Days After Booster	26 (90%) (73-98) N=29	36 (100%) (90-100) N=36	(-10%) (-26, 0)

[a]: A responder is defined as a subject with rBCA titer ≥1:128 10 days after vaccination; Group 1-2-dose-group; Group 2-1-dose-group

Table 2-7: Percentage of Responders[a] (95% CI) as Measured by rBCA Titers Against *N.meningitidis* serogroup C at 10 Days After The Booster Dose and Vaccine Group Differences – Vaccine Groups 1 and 3 – Per-Protocol Population

	Number (Percentages) (95%CI)		Vaccine Group Difference
	Vaccine Groups		
	Group 3	Group 1	Group 3 – Group 1
	6 months	2+4 months	6months – 2+4months
	N=36	N=41	(95% CI)
Pre-Booster	1 (3%) (0.070-15)	4 (10%) (3-23)	(-7%) (-20, 6)
10 Days After Booster	32 (100%) (89-100) N=32	36 (100%) (90-100) N=36	(0%) (-11, 10)

[a]: A responder is defined as a subject with rBCA titer ≥1:128 10 days after vaccination; Group 1-2-dose-group; Group 3-1-dose-group.

Table 2-8: Percentage of Responders[a] as Measured by rBCA Titers Against *N.meningitidis* serogroup C at 10 days After The Booster Dose and One Month After One Dose Given at 12-16 Months of Age and Vaccine Group Difference – Vaccine Groups 1 and 4 – PP Population

	Number (Percentages) (95%CI)		Vaccine Group Difference
	Vaccine Groups		
	Group 4	Group 1	Group 4 – Group 1
	12-16 mo	2+4 months	12-16mo - 2+4months
	N=37	N=41	(95% CI)
Pre-Vaccination	0 (0%) (0-9)	4 (10%) (3-23)	(-10%) (-23, 0)
10 or 28* Days After Vaccination	16 (52%) (33-70) N=31	36 (100%) (90-100) N=36	(-48%) (-65, -32)

[a]: A responder is defined as a subject with rBCA titer ≥ 1:128 after vaccination; Group 1-2-dose-group; Group 4- Control group * 28 days after vaccination for group 4

Table 2-9: Geometric Mean rBCA Titers Against *N.meningitidis* serogroup C at 10 Days After Booster and Vaccine Group Ratios – Vaccine Groups 1, 2, and 3 – PP Population

GMT	GMT (95%CI) and GMRs (95%CI)			Vaccine Group Ratios	
	Vaccine Groups				
	Group 3	Group 2	Group 1	Group 2 /Group 1	Group 3 /Group 1
	6 months	2 months	2+4 months	2 months : 2+4 months	6 months : 2+4 months
	N=36	N=36	N=41	(95% CI)	(95% CI)
GMT Pre-Booster	6.60 (4.00-11)	4.00 (2.56-6.24)	6.64 (4.05-11)	0.60 (0.31-1.17)	0.99 (0.51, 1.93)
GMT 10 Days After Booster	3922 (2653-5799) N=32	2664 (1411-5031) N=29	2953 (2023-4309) N=36	0.90 (0.47-1.72)	1.33 (0.71, 2.48)
GMR Post-Booster / Pre-Booster	548 (309-972) N=31	635 (294-1370) N=29	522 (333-819) N=36	1.22 (0.54-2.74)	1.05 (0.47-2.33)

Group 1-2-dose-group; Group 2-1-dose-group; Group 3-1-dose-group

Table 2-10: Geometric Mean rBCA Titers Against *N.meningitidis* serogroup C at 10 days After Booster and One Month After One Dose Given at 12-16 Months of Age and Vaccine Group Ratio – Vaccine Groups 1 and 4 – PP Population

GMT	GMT (95%CI) and GMRs (95%CI)		Vaccine Group Ratio
	Vaccine Groups		
	Group 4	Group 1	Group 4 /Group 1
	12-16 MO	2+4 MONTHS	12-16 MO : 2+4 MONTHS
	N=37	N=41	(95% CI)
GMT Pre-Vaccination	2.20 (1.82-2.66)	6.64 (4.05-11)	0.33 (0.19, 0.57)
GMT 10 or 28* Days After Vaccination	60 (29-123) N=31	2953 (2023-4309) N=36	0.020 (0.0094, 0.044)
GMR Post-Vaccination /Pre-Vaccination	27 (13-54) N=31	522 (333-819) N=36	0.051 (0.023, 0.11)

* 28 days after Vaccination for group 4; Group 1-2-dose-group; Group 4- Control group

Table 2-11: Percentage of Responders[a] as Measured by rBCA Titers Against *N.meningitidis* serogroup C at 1 Month After Infant Vaccination and Vaccine Group Differences – Vaccine Groups 1, 2 and 3 – PP Population

	Number (Percentages) (95%CI)				Vaccine Group Differences	
	Vaccine Groups					
	Group 3	Group 2	Group 4	Group 1	Group 3 – Group 1	Group 2 – Group 1
	6 MONTHS	2 MONTHS	12-16 MO	2+4 MONTHS	6MONTHS - 2+4MONTHS	2MONTHS - 2+4MONTHS
	N=36	N=35	N=36	N=40	(95% CI)	(95% CI)
Day 0	NA	NA	1 (3%) (0.070-15)	NA	NA	NA
One Month After Infant Vaccination	23 (64%) (46-79)	18 (51%) (34-69)	NA	37 (93%) (80-98)	(-29%) (-46, -11)	(-41%) (-58, -22)

[a]: A responder is defined as a subject with rBCA titer ≥ 1:128 after vaccination; Group 1-2-dose-group; Group 2-1-dose-group; Group 3-1-dose-group; Group 4- Control group

Table 2-12: Geometric Mean rBCA Titers (95% CI) Against *N.meningitidis* serogroup C at 1 Month After Infant Vaccination And Vaccine Group Ratios – Vaccine Groups 1, 2 and 3

	GMTs (95%CI)				Vaccine Group Ratios	
	Vaccine Groups					
	Group 3	Group 2	Group 4	Group 1	Group 2 / Group 1	Group 3 / Group 1
	6 Months	2 Months	12-16 Months	2+4 Months	2 months : 2+4 months	6 months : 2+4 months
	N=36	N=35	N=36	N=40	(95% CI)	(95% CI)
Day 0	NA	NA	2.33 (1.71-3.19)	NA	NA	NA
One Month After Infant Vaccination	108 (78-149)	57 (32-100)	NA	653 (436-977)	0.087 (0.048, 0.16)	0.16 (0.091, 0.30)

Group 1-2-dose-group; Group 2-1-dose-group; Group 3-1-dose-group; Group 4- Control group

Table 2-13: Percentage of Subjects With rBCA Titers ≥ 1:128 Against *N.meningitidis* serogroup C - Persistence of Antibody After Infant Vaccination or Vaccination at 12-16 Months of Age – All Vaccine Groups – PP Population

	Number (Percentages) of Subjects (95%CI)			
	Group 1	**Group 2**	**Group 3**	**Group 4**
	2+4 months	**2 months**	**6 months**	**12-16 mo**
	N=41	**N=36**	**N=36**	**N=31**
One Month After Infant Vaccination	37 (93%) (80-98) N=40	18 (51%) (34-69) N=35	23 (64%) (46-79)	NA
Persistence at 8-10 Months of Age	17 (46%) (29-63) N=37	0 (0%) (0-10) N=35	5 (14%) (5-30) N=35	NA
Persistence at 12-16 Months of Age	4 (10%) (3-23)	1 (3%) (0.070-15)	1 (3%) (0.070-15)	NA
10 Days After Booster	36 (100%) (90-100) N=36	26 (90%) (73-98) N=29	32 (100%) (89-100) N=32	NA
28 Days After 1st Dose at 12-16 Months of Age	NA	NA	NA	16 (52%) (33-70)
Persistence at 24 Months of Age	8 (26%) (12-45) N=31	11 (44%) (24-65) N=25	10 (43%) (23-66) N=23	0 (0%) (0-15) N=22

Group 1-2-dose-group; Group 2-1-dose-group; Group 3-1-dose-group; Group 4- Control group

Table 2-14: Summary of Geometric Mean rBCA Titers – Persistence of Antibody After Infant Vaccination or Vaccination at 12-16 Months of Age - All Vaccine Groups – PP Population

	GMTs (95%CI)			
	Group 1	**Group 2**	**Group 3**	**Group 4**
	2+4 months	**2 months**	**6 months**	**12-16 mo**
	N=41	**N=36**	**N=36**	**N=31**
One Month After Infant Vaccination	653 (436-977) N=40	57 (32-100) N=35	108 (78-149)	NA
Persistence at 8-10 Months of Age	61 (35-106) N=37	5.07 (3.23-7.96) N=35	37 (26-52) N=35	NA
Persistence at 12-16 Months of Age	6.64 (4.05-11)	4.00 (2.56-6.24)	6.60 (4.00-11)	NA
10 Days After Booster	2953 (2023-4309) N=36	2664 (1411-5031) N=29	3922 (2653-5799) N=32	NA
28 Days After 1st Dose at 12-16 Months of Age	NA	NA	NA	60 (29-123)
Persistence at 24 Months of Age	28 (14-57) N=31	36 (14-93) N=25	47 (21-105) N=23	2.83 (2.17-3.68) N=22

Group 1-2-dose-group; Group 2-1-dose-group; Group 3-1-dose-group; Group 4- Control group

Table 2-15: Percentages of Subjects With Anti-Diphtheria Antibody Titer ≥ 0.1 IU/mL - PP Population

		Number (Percentages) of Subjects (95%CI)			
		Group 1	**Group 2**	**Group 3**	**Group 4**
		2+4 months	**2 months**	**6 months**	**12-16 mo**
		N=20	**N=19**	**N=19**	**N=20**
Day 0	Germany	NA	NA	NA	9 (45%) (23-68)
	Poland	NA	NA	NA	3 (18%) (4-43) N=17
1 mo After Primary	Germany	20 (100%) (83-100)	NA	NA	NA
	Poland	NA	NA	17 (100%) (80-100) N=17	NA
2-4 mo After Primary	Poland	16 (100%) (79-100) N=16	15 (100%) (78-100) N=15	NA	NA
3 mo After Primary	Germany	NA	NA	14 (93%) (68-100) N=15	NA
4-6 mo After Primary	Germany	NA	19 (100%) (82-100)	NA	NA
6-10 mo After Primary	Poland	NA	NA	NA	15 (79%) (54-94) N=19
8-12 mo After Primary	Germany	NA	NA	NA	14 (82%) (57-96) N=17
10 Days After Booster	Germany	19 (100%) (82-100) N=19	15 (100%) (78-100) N=15	14 (100%) (77-100) N=14	NA
	Poland	18 (100%) (81-100) N=18	15 (100%) (78-100) N=15	19 (100%) (82-100)	NA
28 Days After Booster	Germany	NA	NA	NA	14 (100%) (77-100) N=14
	Poland	NA	NA	NA	18 (100%) (81-100) N=18

Group 1-2-dose-group; Group 2-1-dose-group; Group 3-1-dose-group; Group 4- Control group

Table 2-16: Percentages of Subjects With Anti-Tetanus Antibody Titer ≥ 0.1 IU/mL - PP Population

		Number (Percentages) of Subjects (95%CI)			
		Group 1	**Group 2**	**Group 3**	**Group 4**
		2+4 months	**2 months**	**6 months**	**12-16 mo**
		N=20	**N=19**	**N=19**	**N=20**
Day 0	Germany	NA	NA	NA	17 (85%) (62-97)
	Poland	NA	NA	NA	17 (100%) (80-100) N=17
1 mo After Primary	Germany	20 (100%) (83-100)	NA	NA	NA
	Poland	NA	NA	17 (100%) (80-100) N=17	NA
2-4 mo After Primary	Poland	16 (100%) (79-100) N=16	15 (100%) (78-100) N=15	NA	NA
3 mo After Primary	Germany	NA	NA	15 (100%) (78-100) N=15	NA
4-6 mo After Primary	Germany	NA	19 (100%) (82-100)	NA	NA
6-10 mo After Primary	Poland	NA	NA	NA	18 (95%) (74-100) N=19
8-12 mo After Primary	Germany	NA	NA	NA	17 (100%) (80-100) N=17
10 Days After Booster	Germany	19 (100%) (82-100) N=19	15 (100%) (78-100) N=15	14 (100%) (77-100) N=14	NA
	Poland	18 (100%) (81-100) N=18	15 (100%) (78-100) N=15	19 (100%) (82-100)	NA
28 Days After Booster	Germany	NA	NA	NA	14 (100%) (77-100) N=14
	Poland	NA	NA	NA	18 (100%) (81-100) N=18

Group 1-2-dose-group; Group 2-1-dose-group; Group 3-1-dose-group; Group 4- Control group

Table 2-17: Percentages of Subjects With Anti-PRP Antibody Titer ≥ 0.15 µg/mL - PP Population

		Number (Percentages) of Subjects (95%CI)			
		Group 1	**Group 2**	**Group 3**	**Group 4**
		2+4 months	**2 months**	**6 months**	**12-16 mo**
		N=20	**N=19**	**N=19**	**N=20**
Day 0	Germany	NA	NA	NA	19 (95%) (75-100)
	Poland	NA	NA	NA	15 (88%) (64-99) N=17
1 mo After Primary	Germany	20 (100%) (83-100)	NA	NA	NA
	Poland	NA	NA	17 (100%) (80-100) N=17	NA
2-4 mo After Primary	Poland	16 (100%) (79-100) N=16	15 (100%) (78-100) N=15	NA	NA
3 mo After Primary	Germany	NA	NA	15 (100%) (78-100) N=15	NA
4-6 mo After Primary	Germany	NA	18 (95%) (74-100)	NA	NA
6-10 mo After Primary	Poland	NA	NA	NA	18 (95%) (74-100) N=19
8-12 mo After Primary	Germany	NA	NA	NA	17 (100%) (80-100) N=17
10 Days After Booster	Germany	19 (100%) (82-100) N=19	15 (100%) (78-100) N=15	14 (100%) (77-100) N=14	NA
	Poland	17 (94%) (73-100) N=18	15 (100%) (78-100) N=15	19 (100%) (82-100)	NA
28 Days After Booster	Germany	NA	NA	NA	14 (100%) (77-100) N=14
	Poland	NA	NA	NA	17 (94%) (73-100) N=18

Group 1-2-dose-group; Group 2-1-dose-group; Group 3-1-dose-group; Group 4- Control group

Table 2-18: Percentages of Subjects With Anti-Polio Type I Antibody Titer ≥ 1:8 - PP Population

		Number (Percentages) of Subjects (95%CI)			
		Group 1	**Group 2**	**Group 3**	**Group 4**
		2+4 months	**2 months**	**6 months**	**12-16 mo**
		N=20	**N=19**	**N=19**	**N=20**
Day 0	Germany	NA	NA	NA	15 (75%) (51-91)
	Poland	NA	NA	NA	12 (71%) (44-90) N=17
1 mo After Primary	Germany	20 (100%) (83-100)	NA	NA	NA
	Poland	NA	NA	17 (100%) (80-100) N=17	NA
2-4 mo After Primary	Poland	16 (100%) (79-100) N=16	15 (100%) (78-100) N=15	NA	NA
3 mo After Primary	Germany	NA	NA	12 (92%) (64-100) N=13	NA
4-6 mo After Primary	Germany	NA	18 (95%) (74-100)	NA	NA
6-10 mo After Primary	Poland	NA	NA	NA	18 (100%) (81-100) N=18
8-12 mo After Primary	Germany	NA	NA	NA	14 (82%) (57-96) N=17
10 Days After Booster	Germany	18 (100%) (81-100) N=18	15 (100%) (78-100) N=15	13 (100%) (75-100) N=13	NA
	Poland	18 (100%) (81-100) N=18	15 (100%) (78-100) N=15	19 (100%) (82-100)	NA
28 Days After Booster	Germany	NA	NA	NA	14 (100%) (77-100) N=14
	Poland	NA	NA	NA	18 (100%) (81-100) N=18

Group 1-2-dose-group; Group 2-1-dose-group; Group 3-1-dose-group; Group 4- Control group

Table 2-19: Percentages of Subjects With Anti-Polio Type II Antibody Titer ≥ 1:8 - PP Population

		Number (Percentages) of Subjects (95%)			
		Group 1	**Group 2**	**Group 3**	**Group 4**
		2+4 months	**2 months**	**6 months**	**12-16 mo**
		N=20	**N=19**	**N=19**	**N=20**
Day 0	Germany	NA	NA	NA	8 (40%) (19-64)
	Poland	NA	NA	NA	11 (65%) (38-86) N=17
1 mo After Primary	Germany	19 (95%) (75-100)	NA	NA	NA
	Poland	NA	NA	17 (100%) (80-100) N=17	NA
2-4 mo After Primary	Poland	16 (100%) (79-100) N=16	15 (100%) (78-100) N=15	NA	NA
3 mo After Primary	Germany	NA	NA	12 (92%) (64-100) N=13	NA
4-6 mo After Primary	Germany	NA	14 (74%) (49-91)	NA	NA
6-10 mo After Primary	Poland	NA	NA	NA	16 (89%) (65-99) N=18
8-12 mo After Primary	Germany	NA	NA	NA	15 (88%) (64-99) N=17
10 Days After Booster	Germany	18 (100%) (81-100) N=18	15 (100%) (78-100) N=15	13 (100%) (75-100) N=13	NA
	Poland	18 (100%) (81-100) N=18	15 (100%) (78-100) N=15	19 (100%) (82-100)	NA
28 Days After Booster	Germany	NA	NA	NA	14 (100%) (77-100) N=14
	Poland	NA	NA	NA	18 (100%) (81-100) N=18

Group 1-2-dose-group; Group 2-1-dose-group; Group 3-1-dose-group; Group 4- Control group

Table 2-20: Percentages of Subjects With Anti-Polio Type III Antibody Titer ≥ 1:8 - PP Population

		Number (%) of Subjects			
		Group 1	**Group 2**	**Group 3**	**Group 4**
		2+4 months	**2 months**	**6 months**	**12-16 mo**
		N=20	**N=19**	**N=19**	**N=20**
Day 0	Germany	NA	NA	NA	13 (65%) (41-85)
	Poland	NA	NA	NA	1 (6%) (0-29) N=17
1 mo After Primary	Germany	20 (100%) (83-100)	NA	NA	NA
	Poland	NA	NA	17 (100%) (80-100) N=17	NA
2-4 mo After Primary	Poland	16 (100%) (79-100) N=16	15 (100%) (78-100) N=15	NA	NA
3 mo After Primary	Germany	NA	NA	13 (100%) (75-100) N=13	NA
4-6 mo After Primary	Germany	NA	17 (89%) (67-99)	NA	NA
6-10 mo After Primary	Poland	NA	NA	NA	18 (100%) (81-100) N=18
8-12 mo After Primary	Germany	NA	NA	NA	14 (82%) (57-96) N=17
10 Days After Booster	Germany	18 (100%) (81-100) N=18	15 (100%) (78-100) N=15	13 (100%) (75-100) N=13	NA
	Poland	18 (100%) (81-100) N=18	15 (100%) (78-100) N=15	19 (100%) (82-100)	NA
28 Days After Booster	Germany	NA	NA	NA	14 (100%) (77-100) N=14
	Poland	NA	NA	NA	18 (100%) (81-100) N=18

Group 1-2-dose-group; Group 2-1-dose-group; Group 3-1-dose-group; Group 4- Control group

Table 2-21: Summary of Geometric Mean Anti-PT Antibody Titer - PP Population

		Group 1 2+4 months N=20	Group 2 2 months N=19	Group 3 6 months N=19	Group 4 12-16 mo N=20
Day 0	Germany	NA	NA	NA	2.91 (2.34-3.62)
	Poland	NA	NA	NA	2.92 (2.29-3.73) N=17
1 mo After Primary	Germany	34 (24-47)	NA	NA	NA
	Poland	NA	NA	41 (27-63) N=17	NA
2-4 mo After Primary	Poland	29 (21-41) N=16	17 (12-24) N=15	NA	NA
3 mo After Primary	Germany	NA	NA	27 (19-38) N=15	NA
4-6 mo After Primary	Germany	NA	14 (9.68-21)	NA	NA
6-10 mo After Primary	Poland	NA	NA	NA	5.83 (4.00-8.48) N=19
8-12 mo After Primary	Germany	NA	NA	NA	6.14 (3.99-9.47) N=17
10 Days After Booster	Germany	68 (43-106) N=19	52 (29-92) N=15	59 (31-109) N=14	NA
	Poland	72 (46-113) N=18	33 (20-56) N=15	42 (27-68)	NA
28 Days After Booster	Germany	NA	NA	NA	70 (45-109) N=14
	Poland	NA	NA	NA	75 (50-112) N=18

Group 1-2-dose-group; Group 2-1-dose-group; Group 3-1-dose-group; Group 4- Control group

Table 2-22: Summary of Geometric Mean Anti-FHA Antibody Titer - PP Population

		Group 1 2+4 months N=20	Group 2 2 months N=19	Group 3 6 months N=19	Group 4 12-16 mo N=19
Day 0	Germany	NA	NA	NA	8.36 (5.01-14)
	Poland	NA	NA	NA	9.91 (7.09-14) N=17
1 mo After Primary	Germany	138 (101-189)	NA	NA	NA
	Poland	NA	NA	167 (133-209) N=17	NA
2-4 mo After Primary	Poland	98 (77-123) N=16	77 (52-115) N=15	NA	NA
3 mo After Primary	Germany	NA	NA	101 (69-147) N=15	NA
4-6 mo After Primary	Germany	NA	71 (53-95)	NA	NA
6-10 mo After Primary	Poland	NA	NA	NA	53 (33-83)
8-12 mo After Primary	Germany	NA	NA	NA	52 (31-87) N=17
10 Days After Booster	Germany	606 (356-1032) N=19	294 (181-477) N=15	278 (172-450) N=14	NA
	Poland	220 (156-309) N=18	223 (136-367) N=15	226 (162-317)	NA
28 Days After Booster	Germany	NA	NA	NA	348 (241-502) N=14
	Poland	NA	NA	NA	355 (257-490) N=18

Group 1-2-dose-group; Group 2-1-dose-group; Group 3-1-dose-group; Group 4- Control group

Table 2-23: Summary of Geometric Mean Anti-PRN Antibody Titer - PP Population

		Group 1 2+4 months N=20	Group 2 2 months N=19	Group 3 6 months N=19	Group 4 12-16 mo N=20
Day 0	Germany	NA	NA	NA	8.53 (5.08-14)
	Poland	NA	NA	NA	7.76 (5.53-11) N=17
1 mo After Primary	Germany	94 (65-136)	NA	NA	NA
	Poland	NA	NA	119 (82-171) N=17	NA
2-4 mo After Primary	Poland	66 (41-106) N=16	46 (23-91) N=15	NA	NA
3 mo After Primary	Germany	NA	NA	86 (49-151) N=15	NA
4-6 mo After Primary	Germany	NA	49 (33-73)	NA	NA
6-10 mo After Primary	Poland	NA	NA	NA	37 (24-56) N=19
8-12 mo After Primary	Germany	NA	NA	NA	35 (18-69) N=17
10 Days After Booster	Germany	464 (289-745) N=19	524 (343-799) N=15	394 (192-810) N=14	NA
	Poland	380 (236-614) N=18	276 (155-490) N=15	398 (250-633)	NA
28 Days After Booster	Germany	NA	NA	NA	465 (314-689) N=14
	Poland	NA	NA	NA	509 (347-747) N=18

Group 1-2-dose-group; Group 2-1-dose-group; Group 3-1-dose-group; Group 4- Control group

Table 2-24: Percentages of Subjects With Anti-HbsAg Antibody Titer ≥ 10 mIU/mL - PP Population

		Number Percentages) of Subjects (95%CI)			
		Group 1	Group 2	Group 3	Group 4
		2+4 months	2 months	6 months	12-16 mo
Day 0	Germany	NA	NA	NA	4 (24%) (7-50) N=17
	Poland	NA	NA	NA	4 (25%) (7-52) N=16
1 month after primary	Germany	20 (95%) (76-100) N=21	NA	NA	NA
	Poland	NA	NA	19 (100%) (82-100) N=19	NA
2-4 months after primary	Poland	18 (100%) (81-100) N=18	14 (100%) (77-100) N=14	NA	NA
3 months after primary	Germany	NA	NA	11 (100%) (72-100) N=11	NA
4-6 months after primary	Germany	NA	15 (94%) (70-100) N=16	NA	NA
6-10 months after primary	Poland	NA	NA	NA	17 (100%) (80-100) N=17
8-12 months after primary	Germany	NA	NA	NA	17 (100%) (80-100) N=17
10 days after booster	Germany	15 (100%) (78-100) N=15	14 (100%) (77-100) N=14	9 (90%) (55-100) N=10	NA
	Poland	18 (100%) (81-100) N=18	15 (100%) (78-100) N=15	19 (100%) (82-100) N=19	NA
28 days after booster	Germany	NA	NA	NA	13 (100%) (75-100) N=13
	Poland	NA	NA	NA	18 (100%) (81-100) N=18

Group 1-2-dose-group; Group 2-1-dose-group; Group 3-1-dose-group; Group 4- Control group

Table 2-25: Overview of Subjects with Solicited Local and Systemic Reactions – Up to 7 days after Each Vaccination

Number (%) of Subjects With Solicited Reactions				
	Group 1 2+4 months N=64	**Group 2 2 months N=64**	**Group 3 6 months N=59**	**Group 4 12-16 mo N=62**
Vaccination 1				
Any	47 (73%)	48 (75%)	44 (75%)	51 (82%)
Local	18 (28%)	22 (34%)	26 (44%)	37 (60%)
Systemic	43 (67%)	47 (73%)	31 (53%)	42 (68%)
Other*	7 (11%)	7 (11%)	8 (14%)	13 (21%)
Vaccination 2				
Any	43 (67%)	50/63 (79%)	42/58 (72%)	NA
Local	21 (33%)	44/63 (70%)	29/58 (50%)	NA
Systemic	35 (55%)	33/63 (52%)	29/58 (50%)	NA
Other*	8 (13%)	15/63 (24%)	6/58 (10%)	NA
Vaccination 3				
Any	46 (72%)	NA	NA	NA
Local	35 (55%)	NA	NA	NA
Systemic	32 (50%)	NA	NA	NA
Other*	11 (17%)	NA	NA	NA

*: Use of analgesic antipyretic medication; Group 1-2-dose-group; Group 2-1-dose-group; Group 3-1-dose-group; Group 4- Control group

Table 2-26: Summary of Solicited Local Reactions by Severity and by Vaccination

			Number (%) of Subjects With Injection Site Reactions			
			Group 1 2+4 months	Group 2 2 months	Group 3 6 months	Group 4 12-16 months
	Vaccination no.		N=64	N=64	N=58	N=61
Tenderness	1	Any	6 (9%)	17 (27%)	8 (14%)	26 (43%)
		Severe[a]	0	3 (5%)	0	1 (2%)
	2	Any	8 (13%)	28/62 (45%)	18/57 (32%)	NA
		Severe	0	1/62 (2%)	1/57 (2%)	NA
	3	Any	21/63 (33%)	NA	NA	NA
		Severe	0	NA	NA	NA
Swelling (mm)	1	Any	1 (2%)	5 (8%)	5 (9%)	10 (16%)
		> 50 mm	0	1 (2%)	0	2 (3%)
	2	Any	7 (11%)	16/62 (26%)	13/57 (23%)	NA
		> 50 mm	0	2/62 (3%)	0	NA
	3	Any	10/63 (16%)	NA	NA	NA
		> 50 mm	1/63 (2%)	NA	NA	NA
Erythema (mm)	1	Any	13 (20%)	7 (11%)	20 (34%)	24 (39%)
		> 50 mm	0	0	0	2 (3%)
	2	Any	15 (23%)	24/62 (39%)	22/57 (39%)	NA
		> 50 mm	0	3/62 (5%)	0	NA
	3	Any	25/63 (40%)	NA	NA	NA
		> 50 mm	0	NA	NA	NA

Group 1-2-dose-group; Group 2-1-dose-group; Group 3-1-dose-group; Group 4- Control group
Note: The numbers (N) in the header is the total number of subjects with documented reactions.
[a] Tenderness was defined as severe if the infant cried when the injected limb was moved.

Table 2-27: Summary of Solicited Systemic Reactions, by Vaccination

		Number (%) of Subjects With Systemic Reactions			
		Group 1 2+4 months	Group 2 2 months	Group 3 6 months	Group 4 12-16 months
	Vaccination no.	N=64	N=64	N=58	N=62
Systemic					
Diarrhea	1	8 (13%)	6 (9%)	11 (19%)	9/61 (15%)
	2	6 (9%)	8/62 (13%)	10/57 (18%)	NA
	3	6/63 (10%)	NA	NA	NA
Change Eat. Habits	1	17 (27%)	13 (20%)	8 (14%)	15/61 (25%)
	2	12 (19%)	16/62 (26%)	14/57 (25%)	NA
	3	14/63 (22%)	NA	NA	NA
Sleepiness	1	29 (45%)	29 (45%)	9 (16%)	29/61 (48%)
	2	21 (33%)	15/62 (24%)	9/57 (16%)	NA
	3	20/63 (32%)	NA	NA	NA
Unusual Crying	1	15 (23%)	19 (30%)	8 (14%)	9/61 (15%)
	2	19 (30%)	12/62 (19%)	7/57 (12%)	NA
	3	10/63 (16%)	NA	NA	NA
Irritability	1	14 (22%)	16 (25%)	11 (19%)	10/61 (16%)
	2	14 (22%)	11/62 (18%)	11/57 (19%)	NA
	3	15/63 (24%)	NA	NA	NA
Vomiting	1	6 (9%)	2 (3%)	3 (5%)	7/61 (11%)
	2	4 (6%)	4/62 (6%)	3/57 (5%)	NA
	3	2/63 (3%)	NA	NA	NA
Fever* ($\geq$ 38.5C)	1	5 (8%)	7 (11%)	8/57 (14%)	9/60 (15%)
	2	8 (13%)	9/61 (15%)	7/57 (12%)	NA
	3	12/61 (20%)	NA	NA	NA
Other					
Analg. Antipyr. Med.Used	1	7 (11%)	7 (11%)	8 (14%)	13 (21%)
	2	8 (13%)	15/63 (24%)	6/57 (11%)	NA
	3	11 (17%)	NA	NA	NA

Group 1-2-dose-group; Group 2-1-dose-group; Group 3-1-dose-group; Group 4- Control group
Note: The numbers (N) in the header is the total number of subjects with documented reactions.
*: Rectal temperature

Table 2-28: Overview of Subjects with Unsolicited Adverse Events within One Month after Vaccination – By Vaccination

	Number (%) of Subjects with Adverse Events			
	Group 1 2+4 months	**Group 2 2 months**	**Group 3 6 months**	**Group 4 12-16 months**
Vaccination 1	**N=64**	**N=64**	**N=59**	**N=62**
Any AEs	14 (22%)	24 (38%)	20 (34%)	34 (55%)
Serious AEs	0	2 (3%)	1 (2%)	0
Vaccination 2	**N=64**	**N=63**	**N=58**	**N=0**
Any AEs	18 (28%)	23 (37%)	14 (24%)	NA
Serious AEs	1 (2%)	1 (2%)	0	NA
Vaccination 3	**N=64**	**N=0**	**N=0**	**N=0**
Any AEs	19 (30%)	NA	NA	NA
Serious AEs	2 (3%)	NA	NA	NA

Group 1-2-dose-group; Group 2-1-dose-group; Group 3-1-dose-group; Group 4- Control group

Table 29: Serious Adverse events by Preferred Term sorted by System Organ Class

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects [1]			
	Group 1 2+4 months N=64	**Group 2 2 months N=64**	**Group 3 6 months N=63**	**Group 4 12-16 months N=66**
Any Serious Adverse Event	6 (9%)	8 (13%)	8 (13%)	5 (8%)
Infections & Infestations	2 (3%)	6 (9%)	4 (6%)	3 (5%)

Group 1-2-dose-group; Group 2-1-dose-group; Group 3-1-dose-group; Group 4- Control group
1Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

Table 30: Unsolicited AEs Reported by >5% of Subjects by Decreasing Frequency Sorted By System Organ Class

MedDRA SOC	AE	Number (%) of Subjects [1]			
		Group 1 2+4 months N=64	Group 2 2 months N=64	Group 3 6 months N=63	Group 4 12-16 months N=66
Infections & Infestations	Upper Respiratory Tract Infection	25 (39%)	27 (42%)	22 (35%)	22 (33%)
Infections & Infestations	Bronchitis	19 (30%)	20 (31%)	14 (22%)	25 (38%)
Infections & Infestations	Rhinitis	17 (27%)	18 (28%)	21 (33%)	8 (12%)
Infections & Infestations	Otitis Media	18 (28%)	11 (17%)	11 (17%)	8 (12%)
Infections & Infestations	Pharyngitis	13 (20%)	14 (22%)	16 (25%)	14 (21%)
Infections & Infestations	Gastroenteritis	8 (13%)	6 (9%)	5 (8%)	11 (17%)
Infections & Infestations	Conjunctivitis	4 (6%)	7 (11%)	9 (14%)	7 (11%)
Infections & Infestations	Nasopharyngitis	4 (6%)	2 (3%)	6 (10%)	9 (14%)
Metabolism And Nutrition Dis.	Teething	2 (3%)	2 (3%)	7 (11%)	1 (2%)
Gastrointestinal Disorders	Dyspepsia	7 (11%)	3 (5%)	5 (8%)	6 (9%)
Infections & Infestations	Febrile Infection	2 (3%)	7 (11%)	2 (3%)	2 (3%)
Gastrointestinal Disorders	Diarrhoea	4 (6%)	6 (9%)	4 (6%)	7 (11%)
Infections & Infestations	Dermatitis Diaper	5 (8%)	4 (6%)	6 (10%)	6 (9%)
Infections & Infestations	Ear Infection	6 (9%)	5 (8%)	2 (3%)	5 (8%)
Infections & Infestations	Exanthema Subitum	6 (9%)	5 (8%)	2 (3%)	6 (9%)
General disorders and administration site conditions	Pyrexia	2 (3%)	6 (9%)	4 (6%)	3 (5%)
Infections & Infestations	Tonsillitis	3 (5%)	6 (9%)	5 (8%)	5 (8%)
Skin & Subcutaneous Tis. Disorders	Rash	5 (8%)	3 (5%)	3 (5%)	3 (5%)
Infections & Infestations	Viral Infection	5 (8%)	5 (8%)	4 (6%)	4 (6%)
Infections & Infestations	Eczema Infantile	3 (5%)	2 (3%)	4 (6%)	3 (5%)
Infections & Infestations	Laryngitis	3 (5%)	3 (5%)	4 (6%)	2 (3%)

Blood And Lymphateic Sys. Disorder	Anaemia	1 (2%)	4 (6%)	2 (3%)	0
Resp., Thoracic & Mediastinal Dis.	Cough	2 (3%)	4 (6%)	1 (2%)	1 (2%)
Psychiatric disorders	Restlessness	1 (2%)	4 (6%)	1 (2%)	3 (5%)
Gastrointestinal Disorders	Infantile Colic	1 (2%)	1 (2%)	2 (3%)	4 (6%)
Skin and subcutaneous tissue disorders	Oral Candidiasis	3 (5%)	0	1 (2%)	4 (6%)
Skin and subcutaneous tissue disorders	Vulvitis	0	1 (2%)	0	4 (6%)
Skin and subcutaneous tissue disorders	Dermatitis Allergic	2 (3%)	2 (3%)	3 (5%)	3 (5%)
Infections & Infestations	Varicella	3 (5%)	3 (5%)	3 (5%)	1 (2%)
Gastrointestinal disorders	Constipation	1 (2%)	3 (5%)	1 (2%)	1 (2%)
Infections & Infestations	Pneumonia	1 (2%)	3 (5%)	2 (3%)	2 (3%)
Infections & Infestations	Respiratory Tract Infection	0	3 (5%)	1 (2%)	2 (3%)
Skin and subcutaneous tissue disorders	Skin Candida	1 (2%)	3 (5%)	1 (2%)	1 (2%)
Skin and subcutaneous tissue disorders	Stomatitis	3 (5%)	1 (2%)	1 (2%)	1 (2%)
Injury,Poisoning And Procedural Complications	Contusion	1 (2%)	0	0	3 (5%)

Group 1-2-dose-group; Group 2-1-dose-group; Group 3-1-dose-group; Group 4- Control group; 1Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.