Results from the MenA conjugate vaccine (PsA-TT) randomized controlled trials in infants and young children

Executive summary

prepared by the Meningitis Vaccine Project & partners

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Background and vaccine development rationale

To overcome the limited immunogenicity of the meningococcal group A (MenA) polysaccharide (Ps) vaccine, the protein conjugation technology was applied to the development of MenAfriVac® (Serum Institute of India Ltd.). The MenA Ps is covalently conjugated to a protein, which acts as an immunologic carrier. MenAfriVac is a purified MenA polysaccharide tetanus toxoid (TT) conjugated vaccine (10 µg of conjugate per dose). In December 2009, Drug Controller General of India (DCGI), the Indian National Regulatory Agency, granted MenAfriVac a Marketing Authorization (MA) and WHO prequalification was obtained on 23 June 2010.

Efficacy assessment was based on serological data showing that MenAfriVac induces superior functional immune responses, both in terms of post vaccination serum bactericidal antibody (SBA) levels and induction of immunological memory, when compared to meningococcal A Ps containing vaccines. MenAfriVac's current indication is active immunization of individuals aged 1 to 29 years against invasive meningococcal disease caused by *Neisseria meningitidis* group A.

From December 2010, MenAfriVac was introduced in Africa (first in Burkina Faso, Mali and Niger) with mass vaccination in the age group of 1-29 years old. One year after vaccine introduction, experience from Burkina Faso provided early evidence that mass vaccination was associated with a significantly reduced risk of meningitis in the targeted population, as well as among the unvaccinated age groups (less than 1 year and over 29 years of age) suggesting vaccine induced herd protection [1]. The data indicate a virtual disappearance of group A meningococci and the lowest number of acute meningitis cases in the past 15 years in Burkina Faso. This latter finding is consistent with the disappearance of *N. meningitidis* group A carriage among both vaccinated and unvaccinated individuals in Burkina Faso within one year of vaccination implementation [2]. The phased introduction of MenAfriVac in Chad just prior to the 2012 epidemic provided the opportunity to assess the effectiveness of the vaccine by comparing incidence rates of meningitis in vaccinated and unvaccinated areas over the same observation period (2.48/100,000 versus 43.8/100,000) indicating a 94% reduction in crude incidence rate. Furthermore, a 98% decrease in the prevalence of MenA carriage was shown in all age groups living in one vaccinated area, as compared to recent pre-vaccination time period [3]. Adverse events following immunization (AEFIs) were monitored in approximately 11 million MenAfriVac vaccinees in Burkina Faso in 2010, through both countrywide enhanced passive and sentinel active surveillance. The observations did not indicate any outstanding safety issue [4]. Safety reports periodically updated after administration of more than 153 million doses have confirmed the reactogenicity and safety profile of MenAfriVac. Altogether these observations indicate an acceptable safety profile, high vaccine efficacy and establishment of herd protection against MenA disease of MenAfriVac. Introduction of MenAfriVac for mass vaccination in the age group of 1-29 year old has now been implemented in 12 African countries of the meningitis belt since December 2010, with the expectation to control group A meningococcal disease.

Although MenAfriVac is highly efficacious, MenA epidemics are likely to return in countries where mass vaccination have been introduced because the susceptible population, mainly the new birth cohorts, will increase yearly. It will therefore be critical to ensure that population immunity is sustained following the initial mass vaccination in the age group of 1-29 year old. Maintaining population immunity could then be achieved either through repeated periodic mass immunization campaigns that would target the age group of 1-4 year old, or through routine vaccination of infants. With this latter approach in mind, two options, which could be considered for the incorporation of MenAfriVac into the Expanded Programme on Immunization (EPI) schedule depending on the age of vaccination, have been evaluated in the studies presented here.

- Option 1: When immunization starts in early infancy two doses of MenAfriVac are administered: one dose at age 14 weeks (with PENTA3 and OPV) and a second dose at age 9 months (with Measles and Yellow Fever vaccines, and possibly Rubella vaccine).

- Option 2: When administration starts later, one dose of MenAfriVac is administered at age 9-12 months (with Measles and Yellow Fever vaccines, possibly Rubella vaccine), followed if deemed necessary by a 2nd dose at age 15-18 months.

Whereas the antigenic content of MenAfriVac, i.e. 10 µg polysaccharide A conjugated to tetanus toxoid (PsA-TT) was initially selected in line with other meningococcal conjugate vaccines licensed at time of its development, dose ranging studies were conducted to define the infant dosage. Indeed, clinical trials were designed to define the optimal dosage and immunization schedules that would fit within the EPI in infants living in the African meningitis belt. Because of the very high demonstrated immunogenicity of MenAfriVac in 12-23 month old children [5], and the likelihood that more than one dose might be required for effective immunization of the youngest infants, it seemed appropriate to assess reduced antigenic content. Further, the risk of immunological interference with co-administration of vaccines is unpredictable and occurs most frequently in early life. These concerns are thus related to both the need to co-administer a range of antigens simultaneously to infants and a relatively immature immune system of recipients [6]. Furthermore, consideration was given to the clinical experience with other conjugated vaccines; including an investigational group A and C meningococcal conjugate vaccine [7]. Finally, these considerations are also consistent with existing meningococcal conjugate vaccines that contain oligo- or polysaccharides quantity less than 10 µg.

Hence, two studies (PsA-TT-004 and PsA-TT-007) were conducted to evaluate reduced antigenic contents of the vaccine compared to MenAfriVac, - 5 µg and 2.5 µg polysaccharide A conjugated to tetanus toxoid, in one trial carried out in the younger age group (14 weeks) and - 5 µg polysaccharide A conjugated to tetanus toxoid, in the other trial conducted in 9 month old infants, when given according to the proposed immunization schemes fitting in the EPI schedule.

The safety and immunogenicity data support the use of MenAfriVac, 5µg dosage, for active immunization for the protection against invasive meningococcal disease caused by *Neisseria meningitidis* group A in young children from the age of 3 months to 24 months.

Overview of clinical immunogenicity/efficacy and safety studies

For the purpose of the present indication variation, the clinical development plan of the MenAfriVac 5 µg conjugate vaccine included two additional clinical studies, conducted between November 2008 and September 2013, in the intended target age population, living in two countries of the African meningitis belt: a phase II dose ranging study (PsA-TT-004) conducted in healthy infants and toddlers in Ghana and a phase III study (PsA-TT-007) also conducted in healthy infants and toddlers in Mali. A detailed description of these two studies is presented in Table 1. In both double-blind randomized controlled studies, the reference group received the 10 µg dosage (MenAfriVac). Two additional dosages, 5 µg and 2.5 µg (in study PsA-TT-004), or one additional dosage, 5 µg (in study PsA-TT-007), were assessed. Study vaccines were concomitantly given with EPI and rubella

vaccines. A control group in each of the studies received only EPI vaccines [8]. A total of 2700 subjects were enrolled and randomized and 2698 were vaccinated in the two clinical studies.

The studies were designed to assess safety and immunogenicity of different antigen amounts of PsA-TT vaccine and different schedules before 2 years of age. In addition, both studies assessed the ability of PsA-TT to induce immune memory and to evaluate the safety and immunogenicity of concomitantly administered EPI and rubella vaccines in this age group. The phase II study (PsATT-004) also evaluated the antibody persistence till 36 months of age. On the average subjects were followed up for at least 7 months in study PsA-TT-007 and for 30 months in study PsA-TT-004 since enrolment.

The evaluation of the efficacy of the PsA-TT 5 µg vaccine was based on its ability to induce levels of bactericidal antibodies non-inferior to those induced by MenAfriVac, the reference licensed PsA-TT 10 µg vaccine [9]. The field experience with use of MenAfriVac in countries of the African meningitis belt has since 2010 provided compelling evidence that the vaccine prevents meningococcal invasive disease as well as infection. This confirms experience with other licensed meningococcal vaccines for which data indicate that the presence of induced serum capsular bactericidal antibodies (SBA) correlates to protection and, therefore, can be considered a valid surrogate marker of protection [10]. A primary criterion in determining noninferior immunogenicity of the lower dosages of vaccine in comparison with immunogenicity of the reference 10 µg vaccine dosage was the percentage of vaccinees having a fourfold or greater response in bactericidal antibody in relation to the baseline values [11]. The antibody assays used to evaluate immunogenicity were standardized to yield reproducible data and fully validated. The functional antibody titer in human sera to MenA was measured with a serum bactericidal antibody assay using baby rabbit complement (rSBA) [12].

The primary serological assay used to assess the immunogenicity of the PsA-TT vaccine was thus a validated rSBA to measure functional antibody activity in human sera to group A *Nm*. This is consistent with the World Health Organization (WHO) recommendation for the evaluation of meningococcal polysaccharide and conjugate vaccines [9]. The primary endpoint in study PsA-TT-004 was the percentage of subjects who showed a seroconversion for MenA antibodies measured by rSBA assay, i.e. a 4-fold or higher response in post-immunization serum MenA rSBA antibody titer with respect to pre-immunization serum MenA rSBA antibody titer, at 28 days after each vaccine dose. An almost identical endpoint, the percentage of subjects who showed a seroconversion for MenA antibodies measured by rSBA assay at 28 days after the last vaccine dose, was one of the primary endpoints in study PsA-TT-007. A co-primary endpoint, geometric mean titer (GMT) of MenA antibody titers measured by rSBA assay at 28 days after the last vaccine dose, is included in the study PsA-TT -007.

The main secondary immunogenicity endpoints in the clinical studies included: (1) for MenA antibodies measured by rSBA: percentage of subjects reaching a threshold of 1:128 for MenA rSBA antibody titer and geometric mean titer (GMT); (2) for MenA capsular polysaccharide antibodies measured by ELISA [13]: percentage of subjects who showed a seroconversion for MenA IgG ELISA concentrations, i.e. a 4-fold or higher response in post-immunization MenA IgG ELISA concentration with respect to pre-immunization concentration; percentage of subjects reaching a threshold of 2 µg/ml for MenA IgG ELISA concentrations and geometric mean concentration (GMC). For immune response to EPI antigens, percentage of subjects with specific IgG concentration or neutralizing antibody titer above predefined discriminatory thresholds and GMC/GMT for each of the specific IgG concentration or neutralizing antibody titer.

Table 1 Overview of clinical immunogenicity/efficacy and safety studies

Study ID Phase	Number of Study Centers, Locations	Study start Study end Total enrollment/ goal	Design Control type	Dose, Route	Study & Control Vaccines	#Subjects by arm	Study objective	Duration	Gender F/M Median age at first vaccination (Range)	Primary endpoint(s)	# subjects with at least 1 dose (2 doses) PsA-TT 10µg PsA-TT 5µg PsA-TT 2.5µg
PsA-TT-004 II	1, Ghana	November 2008 to May 2012 1200/1200	Randomized double- blind control dose-ranging	1 or 2 doses of different PsA-TT dosages IM	PsA-TT 10 µg PsA-TT 5 µg PsA-TT 2.5 µg EPI vaccines	200 per group	Safety and immunogenicity, concomitant administration with EPI vaccines, immune persistence	33 months	597/601*, 14 weeks (min-max, 13-18 weeks)	4-fold or higher response in rSBA titers**	579 (192) 200 (191) 200 (194)
PsA-TT 007 III	1, Mali	March 2012 to September 2013 1500/1500	Randomized double-blind control dose-ranging	1 or 2 doses of different PsA-TT dosages IM	PsA-TT 10µg PsA-TT 5µg EPI vaccines	300 per group	Safety and immunogenicity, concomitant administration with EPI vaccines	7 to 10 months	725/775, 9 months (min-max, 9-13 months)	4-fold or higher response in rSBA titers and rSBA geometric mean titers (GMT)***	600 (280) 600 (279)

* 2 volunteers noted not to be qualified before vaccination
** Sero-conversion from baseline just prior to vaccination to 28 days after vaccination with two doses
*** Sero-conversion from baseline just prior to vaccination to 28 days after last vaccination, GMT ratio 28 days after last vaccination

Clinical trials

Both clinical studies, PsA-TT-004 and PsA-TT-007, were conducted in accordance with the International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) regulations and guidelines, and all applicable regulatory and ethical requirements.

STUDY PsA-TT-004

The study was conducted in Navrongo, Ghana from November 2008 to May 2012 (Principal Investigator: Dr. Abraham Hodgson, Navrongo Health Research Centre, Ghana Health Services, Navrongo, Ghana).

The primary objective was to demonstrate that the MenAfriVac 5 µg vaccine and the 2.5 µg PsA-TT vaccine elicited antibody responses that showed non-inferiority to those achieved by the 10 µg PsA-TT vaccine, i.e. MenAfriVac, 28 days after each dose. Hence, this study includes a double-blind, randomized, and controlled comparison of the immunogenicity and the safety of three different dosages of MenAfriVac (group 1A), MenAfriVac 5 µg (group 1B), and 2.5 µg PsA-TT (group 1C) - when administered to healthy infants in a two dose schedule at 14 weeks and 9 months of age. In addition, the safety and immunogenicity of one dose of MenAfriVac when given at 9 months (group 2) or at 12 months (group 3) of age were also evaluated. Group 4 received only the recommended EPI vaccines, i.e. OPV and DTwPHBVHib at 14 weeks of age, Measles and Yellow Fever vaccines at 9 months of age, and DTwPHBVHib at 12 months of age. PsA-TT immunogenicity data were obtained before and 28 days after each dose of PsA-TT and up to the age of 24 and 36 months, i.e. 18 to 27 months after the last PsA-TT dose depending on the study group. The immunogenicity of concomitantly administered vaccines - OPV, DTwPHBVHib, Measles and Yellow Fever according to the EPI, was also measured one month after vaccination.

The study was powered to demonstrate non-inferiority of the MenA rSBA antibody response elicited by MenAfriVac 5 µg and the 2.5 µg dosage of PsA-TT to that of MenAfriVac. The percentage of vaccinees with a 4-fold or higher response in rSBA titer compared to baseline was used as primary immunogenicity endpoint and the upper limit of the 97.5% confidence interval of the difference in response rates between MenAfriVac group (group 1A) and lower dosage group (group 1B or group 1C) was set to be less than 10% (a predefined non-inferiority margin) in order to claim non-inferiority of lower dosage of PsA-TT to MenAfriVac [14;15]. Differences in response rates that are within 10% are unlikely to represent a medically significant change in vaccine efficacy. Such predefined margin of non-inferiority has generally been considered acceptable for the purpose of evaluation of other conjugate vaccines recently licensed [16;17]. Under the assumptions of a response rate of 90% for MenAfriVac in group 1A, power set at 80% and one-sided alpha risk at 0.0125, the required sample size for the evaluable immunogenicity population was 188 per study group.

Twelve hundreds (1200) infants aged 14 to 18 weeks whose medical history did not show any obvious health problem and who had been fully vaccinated according to the local EPI schedule were randomly allocated to one of six groups: 1A, 1B, 1C, 2, 3 and 4 (200 each). Overall 157 subjects (13.1%) were discontinued between the age of 14 weeks (visit 1) and 36 months (visit 11). Discontinuation was predominantly due to lost to follow up (29.9%), out-migration (26.8%), protocol violation (21.7%) and deaths (11.5%). The per protocol population for immunogenicity evaluation 28 days after the second dose at 9 months of age comprised of 180 infants in group 1A, 184 infants in group1B and 185 individuals in group 1C providing a power higher than 80% to the primary statistical analysis with extremely high percentages of subjects with a seroconversion 28 days after the second dose. A total of 1043 subjects completed the last visit at the age of 3 years (visit 11). They were distributed in the 6 groups as follows: 176 in group 1A, 178 in group 1B, 169 in group 1C, 171 in group 2, 181 in group 3 and 168 in group 4. These figures indicate a high completion rate for a trial lasting 33 months and an acceptable balance among the study groups.

At time of enrollment, there were no medically relevant differences in demographic and clinical criteria. Baseline rSBA GMTs were very low, ranging from 2.04 (group1C) to 2.29 (group 1B) in the overall group1. Although the slight variation reached statistical significance, baseline rSBA levels can be considered comparable.

Analysis of immunogenicity data

Per protocol evaluable population was the primary data set for the evaluation of immunogenicity data. Of note, the analysis in the ITT population yielded similar results.

Following the first dose at 14 weeks of age, the percentages of infants with a seroconversion (defined as at least a 4-fold response in MenA rSBA antibody titers 28 days after vaccination with respect to baseline) were high in all groups: 93.9% (95% CI 89.3 - 96.9), 94.1% (95% CI 89.7 - 97.0), and 96.7% (95% CI 93.0 - 98.8) in groups 1A, 1B, and 1C, respectively. The differences (and 97.5% CI) in percentage of subjects with a seroconversion were -0.2% (-6.3 - 5.7) between Groups 1A and 1B and -2.9% (-8.6 - 2.4) between groups 1A and 1C. Following the second dose at 9 months of age, infants with a seroconversion in relation to baseline were: 99.4% (95% CI 96.8 - 100.0), 99.4% (95% CI 96.8 - 100.0), and 99.4% (95% CI 96.9 - 100.0) in groups 1A, 1B, and 1C, respectively. The differences (and 97.5%CI) in percentage of subjects with a seroconversion were -0.0% (-3.4 - 3.3) between groups 1A and 1B and -0.0% (-3.4 - 3.2) between groups 1A and 1C. Hence relating to the primary study objective, non-inferiority of MenAfriVac 5 µg and 2.5 µg PsA-TT vaccine to MenAfriVac was demonstrated after the first dose given at 14 weeks of age (window 14 to 18 weeks) and after the second dose at 9 months of age (window 9 to 12 months).

There was no difference among the three study groups with respect to the secondary endpoints of the MenA rSBA response, i.e. the percentage achieving an antibody titer ≥1:128 and GMTs after the first and second dose. One month after the second dose, GMTs of MenA rSBA titer were 4932.68 (95% CI 4239.02 - 5739.86), 5048.63 (95% CI 4429.28 - 5754.59), and 4238.04 (95% CI 3560.38 - 5044.67) in Groups 1A, 1B and 1C, respectively, indicating very high antibody levels compared to the controls, 3.25 (95% CI 2.57 - 4.12) in group 4. They were also higher than levels achieved by one dose of MenAfriVac given at 9 months of age to naïve infants of group 2, 2845.72 (95% CI 2346.96 - 3450.47), demonstrating the priming effect of the first dose given at 14 weeks. In group 3, one dose of MenAfriVac at 12-18 months of age (median 15 months) induced a high GMT of MenA rSBA antibody titer, 3196.90 (95% CI 2667.08 – 3831.97). Comparison of GMTs of MenA rSBA antibody titer achieved one month after one dose of MenAfriVac in groups 1A, 2 and 3 indicates an age related increase, which is likely attesting to the maturation of the infant immune system.

The design of the study provides data on the persistence of antibody until the age of 24 months (i.e. 12 to 15 months after last dose in groups 1 and 2) and until the age of 36 months (i.e. 18 to 27 months after the last dose in groups 1 and 2). High levels of MenA rSBA antibody were maintained until the age 36 months. Whereas antibody levels dropped substantially during the first 12-15 month time period after the last PsA-TT vaccine dose, the percentages of subjects with MenA rSBA antibody titer ≥ 1:128 remained high: 85.0% (95% CI 78.7 - 90.1), 86.8% (95% CI 80.8 - 91.4), 87.8% (95% CI 81.8 - 92.4), 82.4% (95% CI 75.8 - 87.8), 92.5% (95% CI 87.6 - 96.0) in groups 1A, 1B, 1C, 2, and 3, respectively *vs.* 47.9% (95% CI 40.1 - 55.8) in the control group 4. Furthermore, GMTs are indicative of long-term seroprotection in all vaccinated groups. At the age of 24 months, GMTs for MenA rSBA antibodies were: 343.73 (95% CI 256.02 - 461.50), 419.53 (95% CI 309.45 - 568.78), 480.55 (95% CI 358.05 - 644.96), 369.50 (95% CI 261.00 - 523.10) and 790.40 (95% CI 593.85 - 1052.01) in groups 1A, 1B, 1C, 2, and 3, respectively *vs.* 30.57 (95% CI 19.60 - 47.67) in the control group 4. There were no further decrease in antibody levels between 24 and 36 months of age. At the age of 36 months, the percentages of subjects with MenA rSBA antibody titer ≥ 1:128 remained high: 81.7% (95% CI 74.9 - 87.3), 88.1% (95% CI 82.2 - 92.6), 87.3% (95% CI 81.0 - 92.0), 88.1% (95% CI 82.1 - 92.7), 91.2% (95% CI 85.9 - 95.0) in groups 1A, 1B, 1C, 2, and 3, respectively *vs.*69.9% (95% CI 62.0 - 76.9) in control Group 4. GMTs for MenA rSBA antibodies were: 355.97 (95% CI 242.22 - 523.13), 553.75 (95% CI 402.75 - 761.37), 483.44 (95% CI 333.75 - 700.28), 488.17 (95% CI 344.25 - 692.26) and 812.75 (95% CI 597.86 - 1104.87) in groups 1A, 1B, 1C, 2, and 3, respectively and 139.28 (95% CI 88.57 - 219.01) in control group 4. Gradually increasing MenArSBA antibody levels were noted among controls from the age of 10 months to 36 months. Such an observation may be the result of

encountering group A meningococcus, other meningococcal serogroups, other *Neisseria* species such as *N. lactamica* which may plays a role in the development of immunity to meningococcus, or cross reacting enteric bacteria or moieties [18-20]. At age of 24 months, the differences (and 97.5% CI) in percentage of subjects with a seroconversion were 0.1% (-7.7 - 7.8) between Groups 1A and 1B and -2.4% (-10.0 - 5.0) between Groups 1A and 1C. At age of 36 months, the differences (and 97.5% CI) in percentage of subjects with a seroconversion were -8.5% (-17.4 - 0.0) between groups 1A and 1B and -4.5% (-13.9 – 4.9) between groups 1A and 1C. Non-inferiority of MenAfriVac 5µg and the 2.5 µg dosage to MenAfriVac was demonstrated at the ages of 24 and 36 months, in terms of the immune response expressed as percentage of subjects with a seroconversion. The conclusion was confirmed by percentage of subjects with MenA rSBA titer ≥ 1:128 or GMT of MenA rSBA antibodies at the ages of 24 and 36 months.

Analysis of reactogenicity and safety data

Safety evaluation included monitoring of immediate reactions within one hour of vaccination, solicited reactions and AEs during a time window of 4 days, as the majority of local and systemic reactions occur usually within 2 days of vaccination, and AEs for four weeks after each vaccination. Serious adverse events were recorded during the entire study duration. All safety evaluations were performed on the ITT population (there was no instance of wrong treatment assignment).

Immediate reactions

There were no immediate local reactions noted at the site of PsA-TT injection for any dose given at 14 weeks, 9 months or 12 months of age. Immediate mild and transient systemic reactions were recorded in 3 subjects following concomitant vaccinations with Measles and Yellow fever at 9 months of age [1 subject in Group 1B, 2 subjects in pooled Control Group (Groups 3 and 4)] and following vaccination with DTwPHBVHiB only at 12 months of age in one subject in group 1A, one subject in group 1B, and one subject in group 4, but none after concomitant vaccination with PsA-TT 10 µg in group 3.

Solicited local reactions

Local reactions at the site of injection of PsA-TT at 14 weeks of age were predominantly mild and transient tenderness. Induration were less frequent, lasted a little longer and never reached 50 mm of diameter. Local reactions were noted in 11.5%, 8.0% and 12.5% of subjects at the site of PsA-TT injection for groups 1A, 1B and 1C, respectively, whereas higher rates were observed at the DTwPHBVHib injection site (23.0% of subjects in group 1B to 30.5% in group 1C). Local reactions at the site of PsA-TT injection were less common after the second dose of PsA-TT given at 9 months of age, with frequencies of 4.7%, 3.7% and 2.1% of subjects for groups 1A, 1B and 1C, respectively, suggesting a trend for a dosage related increase in local reactions. Local reactions at the site of PsA-TT injection were less frequent in naïve subjects receiving a first dose of MenAfriVac (Group 2). Mild and transient tenderness was the most common reaction and no induration reached 50 mm of diameter. Local reactions at the site of PsA-TT injection after a first dose of MenAfriVac given at 12 months of age were noted in 8.9% of group 3 subjects whereas higher rates were noted at the DTwPHBVHib injection site (28.4%) in the same group. Mild and transit tenderness was the most frequent reaction and no induration reached 20 mm of diameter. Altogether these observations indicate that local reactions at the injection site of PsA-TT are mainly mild and transient and do not increase after the second dose. The data also suggest that concomitant administration of DTwPHBVHib which is more reactogenic may influence reporting of local reactions at the PsA-TT site.

Solicited systemic reactions

After the first PsA-TT dose given simultaneously with DTwPHBVHib, similar rates of systemic reactions were reported in 12.5% of subjects in group 1A, 11.0% of subjects in group 1B and 14.0% of subjects in group 1C and 9.9% of subjects in the pooled control group (pooled group of groups 2, 3, and 4). Systemic reactions were predominantly mild and transient. The most common systemic reactions were diarrhea (ranging 6.5% in group 1B to 8.0% in group 1C), persistent crying (ranging from 2.5% in groups 1A and 1B to 3.0% in group 1C), loss of appetite (ranging from 1.0% in group 1B to 2.5% in group 1A), and vomiting (ranging from 0.5% in group 1B to 2.0%in group 1C). All fevers were ≤38.9°C. After the second dose given simultaneously with Measles and Yellow Fever, similar rates of systemic reactions were reported in 4.1% of subjects in group 1A, 6.3% in group 1B and 3.1% of group 1C, and 4.4% in the pooled control group (pooled group of groups 3 and 4).

Systemic reactions were predominantly mild and transient. Among the group 1, the most common systemic reactions were diarrhea (ranging 0.5% in group 1C to 4.2% in group 1B), fever (ranging from 1.0% in group 1A to 2.1% in groups 1B and 1C), and vomiting (ranging from 0% in group 1C to 1.0% in group 1B). All fevers were ≤ 39.9°C. Rate of systemic reactions in group 2 (first dose of MenAfriVac administered with Measles and Yellow Fever vaccines) was 6.9%.

Adverse events within 28 days of dose 1

Adverse events (including local and systemic reactions ongoing beyond Day 4) within 28 days of the first vaccination given at 14 weeks of age occurred with similar frequency and were reported in 42.0% of subjects, 42.5%, 46.0% and 39.6% in groups 1A, 1B, 1C and the pooled control group (pooled group of groups 2, 3, and 4), respectively. The AEs, other than persisting reactions, were reported in 35.0% of subjects, 35.0%, 35.0% and 31.3% of groups 1A, 1B, 1C and the pooled control group, respectively. The most commonly reported adverse events were gastroenteritis occurring in 13.4% of subjects, induration predominantly at the DTwPHBVHiB injection site that did not resolve by Day 4 or that began after Day 4 (11.5%), respiratory tract infection (11.2%) and malaria (8.3%). The percentages of infants reporting each specific event were similar among study groups. All related AEs were local or systemic reactions ongoing beyond Day 4, or with onset after Day 4.

Adverse events within 28 days of dose 2

Rates of adverse events (including local and systemic reactions ongoing beyond Day 4) within 28 days of vaccination given at 9 months were similar and reported in 46.6% of subjects, 41.4%, 45.4%, 40.2% and 46.4% in groups 1A, 1B, 1C, 2 and the pooled control group (pooled group of groups 3 and 4), respectively. The most commonly reported adverse events were malaria occurring in 20.8% of subjects, respiratory tract infection (18.0%) and gastroenteritis (11.0%). The percentages of infants reporting each specific event were similar among study groups, with the exception of on-going systemic reactions, mainly diarrhea, that were more frequent in the pooled PsA-TT group than in the pooled control group, 4.8% versus 1.4%. Overall, adverse events were transient and of mild or moderate intensity in most of the cases, and unrelated to any vaccine except for solicited post-immunization reactions ongoing (or occurring) beyond Day 4. The rates of AEs, other than on-going reactions, occurring within 28 days of vaccination increased with age at vaccination: overall percentages were 33.1 % of subjects after vaccination at 14 weeks of age, 43% after vaccination at 9 months of age and 49.2% after vaccination at 12 months of age. Infections and infestations were largely the predominating causes of AEs within 28 days of vaccination, including gastroenteritis, malaria and respiratory tract infections. The increasing rates of malaria and to a lesser extent of respiratory tract infections, with age contributed to these observations.

Serious adverse events (SAEs) and deaths

Overall, there were 408 serious adverse events reported in the study. Most of them (89.0%) were due to infective causes, 5.9% from blood and lymphatic disorders, 2.7% from injuries and poisoning, and 2.4% from other causes including respiratory, gastrointestinal, congenital, metabolic, nervous, general, and ear and labyrinth disorders. Among the SAEs classified as “Infections and infestations”, severe malaria and gastroenteritis of moderate intensity were most commonly reported. Three cases of meningitis were reported during study period, two were due to *N. meningitidis* group W135 (one each in group 1C and group 1A) and one (group 1A) due to an unspecified pathogen. SAEs with onset with 28 days of the first (14 weeks of age), second (9 months of age) and third vaccination (12 months of age) were 11, 22 and 9 cases (2 cases with day of onset beyond 28 days after the third vaccination were included due to late follow-up visit), respectively and were not found to occur at significantly different rates among the PsA-TT groups and the pooled control groups. They were all considered unrelated to study vaccines except the 2 following cases which were one case of febrile seizure that occurred on day 0 and resolved within 24 hours (group 3 after concomitant vaccination of MenAfriVac and DTwPHBVHib) and one case of facial oedema with onset on the day of vaccination and resolving within 48 hours (group 1A after concomitant vaccination of the second dose of MenAfriVac and DTwPHBVHib). Twenty subjects died during the entire study period. Eighteen (90%) died of infective causes, and one each died of malnutrition and foreign body aspiration. None of the 20 deaths was assessed related to the study vaccine.

STUDY PsA-TT-007

The study was conducted in Bamako (Mali) from March 2012 to September 2013 (Principal Investigator: Professor Samba Sow, Centre pour le Développement des Vaccins, CVD-Mali, Ministry of Health, Bamako, Mali).

The primary objective of study PsA-TT-007 was to compare 28 days after the last vaccination of PsA-TT the immunogenicity of two PsA-TT vaccine dosages, MenAfriVac 5µg and MenAfriVac, when administered in a one-dose schedule at 9 months of age or a two-dose schedule at 9 and 15 months of age, in order to determine the optimal dosage and schedule fitting in routine immunization sessions, in co-administration with EPI vaccines (Measles, Yellow Fever and Rubella vaccines). In this double-blind, randomized, and controlled study, healthy infants aged 9 months were randomly allocated to one of the following groups to receive:

- Group 1: Two doses of PsA-TT vaccine concomitantly with Measles and Yellow Fever vaccines at 9 months of age and with combined Measles-Rubella vaccines at 15 months of age, with Group 1A: MenAfriVac® and Group 1B: MenAfriVac 5µg;
- Group 2: One single dose of PsA-TT vaccine concomitantly with Measles and Yellow Fever vaccines at 9 months of age and one dose of combined Measles-Rubella vaccines at 15 months of age, with Group 1A: MenAfriVac® and Group 1B: MenAfriVac 5µg;
- Group 3: One dose of Measles and Yellow Fever vaccines at 9 months of age and one of combined Measles-Rubella vaccines at 15 months of age (control group).

The five-group design allowed the evaluation of two different formulations (MenAfriVac 5 µg and MenAfriVac) and the relevance of a booster dose (two-dose schedule with MenAfriVac 5µg and MenAfriVac). Furthermore, the safety profile of the study vaccine given concomitantly with the recommended EPI vaccines was assessed in reference to controls (group 3), as well as possible immunological interferences due to simultaneous administration.

The study was powered to demonstrate non-inferiority of the MenA rSBA antibody response elicited by the two-dose schedule with MenAfriVac 5µg (group 1B), one-dose of MenAfriVac (group 2A) or one-dose of MenAfriVac 5µg (group 2B) to the immune response elicited by the two-dose schedule with MenAfriVac (group 1A). Two primary endpoints (percentage of vaccinees with a 4-fold or higher response in MenA rSBA titer compared to baseline and MenA rSBA GMTs determined 28 days after the last vaccine dose) were used. Non-inferiority was declared if the upper 98.3% confidence bound of the difference in percentage of the 4-fold responders between relevant study groups was less than 10% as in study PsA-TT-004 ***and*** if the upper 98.3% confidence bound of the GMT ratio was less than 1.5, an additional stringent criterion. Under the assumptions of a seroconversion rate of 90% for MenAfriVac group 1A, power set at 90% and one-sided alpha risk at 0.0083, the required sample size for the evaluable immunogenicity population was 265 per study group. This estimated sample size provided a power of 97% to detect a non-inferiority margin of 1.5 for GMT ratio using a one-sided, two-sample t-test, at one-sided significance level of 0.0083 and assuming the standard deviation of $\log_2$-transformed titers was 1.58 (based on the results of the infant study PsA-TT-004 performed in Ghana).

Fifteen hundreds (1500) infants aged 9 to 12 months, whose medical history did not show any obvious health problem and who had been fully vaccinated according to the local EPI schedule, were randomly allocated to one of the 5 study groups, 1A, 1B, 2A, 2B and 3 (300 each). Overall 111 subjects (7.4%) were discontinued between the age of 9 (visit 1) and 15 months (visit 6). Discontinuation was predominantly due to consent withdrawal (73.9%) and out-migration (18%). Deaths were the cause of 3.6% discontinuations. A total of 1389 subjects completed the study until visit 6. They were distributed in the 5 groups as follows: 278 in group 1A, 278 in group 1B, 280 in group 2A, 277 in group 2B and 276 in group 3. These figures indicate a high completion rate with an acceptable balance among the study groups.

At time of enrollment, there were no medically relevant differences in demographic (except for distribution of sex) and clinical criteria among the 5 groups. Baseline rSBA GMTs were very low and similar across study groups.

Analysis of immunogenicity data

Per protocol evaluable population was the primary data set for the evaluation of immunogenicity data. Of note, the analysis in the ITT population yielded similar results.

Relating to the primary study objective, high percentages of subjects developed a 4-fold or higher response in MenA rSBA titer 28 days after the last dose of PsA-TT vaccine with respect to baseline in all groups: 100% (95% CI 98.9 - 100.0), 99.6% (95% CI 97.9 - 100.0), 98.6% (95% CI 96.4 - 99.6), and 97.2% (95% CI 94.5 - 98.8) in groups 1A, 1B, 2A, and 2B, respectively. The difference (and 98.3% CI) in seroconversion rates was: 0.4% (-1.8 - 2.8) between group 1A and group 1B, 1.4% (-0.8 - 4.4) between group 1A and group 2A and 2.8% (0.6 - 6.3) between group 1A and group 2B. GMTs of MenA rSBA titers measured 28 days after the last dose of PsA-TT vaccine were 12108.3 (95% CI 10960.6 - 13376.2), 11095.9 (95% CI 9901.4 - 12434.4), 4883.1 (4244.2 - 5618.1), and 4167.3 (95% CI 3508.2 - 4950.3) in groups 1A, 1B, 2A, and 2B, respectively; GMTs in groups 1A and 1B in which subjects received two doses of PsA-TT vaccine were more than twice the GMTs in groups 2A and 2B in which subjects received only one dose of PsA-TT vaccine. The GMT ratios (and 98.3% CI) of group 1A versus group 1B, group 1A versus group 2A, and group 1A versus group 2B were: 1.1 (0.9 - 1.3), 2.5 (2.0 - 3.1), and 2.9 (2.3 - 3.7), respectively. Thus, non-inferiority of MenAfriVac 5µg (group 1B) administered in a two-dose schedule to MenAfriVac administered in a two-dose schedule was demonstrated. As the second dose of PsA-TT induced a substantial increase in antibody levels, non-inferiority of the one-dose schedule could not be demonstrated for the GMT endpoint, despite high antibody levels achieved 28 days after one dose given at 9 months of age. Nonetheless, one dose schedule, no matter with what PsA-TT dosage (10 µg or 5 µg), was non-inferior to MenAfriVac administered in a two-dose schedule when the seroconversion endpoint is considered.

The study design allows also comparing the immune responses induced by MenAfriVac 5µg with those to MenAfriVac after a first dose given at 9 months of age. Pooled MenAfriVac 5µg group (pooled group of groups 1B and 2B) was non-inferior to the pooled MenAfriVac group (pooled group of groups 1A and 2A) based on the percentages of subjects with a 4-fold or higher response in MenA rSBA antibody titer one month after vaccination with respect to baseline, 97.3% (95% CI 95.6 - 98.5) in the pooled MenAfriVac 5µg group versus 98.2% (95% CI 96.8 - 99.1) in the pooled MenAfriVac group with a difference of 0.9% (98.3% CI -1.3 - 3.3) between the pooled MenAfriVac group and the pooled MenAfriVac 5µg group. When considering the other MenA rSBA related endpoints, -percentage of subjects with MenA rSBA titer ≥ 1:8 and percentage of subjects with MenA rSBA titer ≥ 1:128 one month after vaccination, statistically significant differences were noted in favor of MenAfriVac. Of note the differences were numerically minimal and high proportions of subjects achieved these threshold, -for instance, the percentage of subjects with MenA rSBA titer ≥ 1:128 were 99.5% (95% CI 98.5 - 99.9) in the pooled MenAfriVac group and 97.9% (95% CI 96.3 - 98.9) in the pooled 5µg-dosage group. A similar trend was found for GMT of MenA rSBA titers. The ratio of GMTs of the pooled MenAfriVac group versus the pooled 5 µg group after adjusting baseline titer, sex, and visit was 1.3 (95%CI 1.1 - 1.5). One month after the first dose given at 9 months, the reverse cumulative distribution (RCD) curves of MenA rSBA titers for groups 1A, 1B , 2A and 2B are clearly shifted to the right compared to that among controls (group 3), and do not exhibit any actual decrease before the value of 1:512. These differences between MenAfriVac 5µg and MenAfriVac were not persisting 7 months after one dose. The MenAfriVac 5µg group (2B) was non-inferior to the MenAfriVac group (2A) based on the percentage with a 4-fold or higher response in MenA rSBA antibody titer 7 months after one dose with respect to baseline, 95.8% (95% CI 92.6 - 97.9) in group 2B versus 96.9% (95% CI 94.0 - 98.7) in group 2A with a difference of 1.1% (98.3% CI -3.2 - 5.6) between groups 2A and 2B. Similar GMTs of MenA rSBA titers were observed in group 2A (2195.6 (95% CI 1810.6 - 2662.5)) and 2B (2382.7 (95% 1951.9 – 2908.6)) 7 months after one dose and the ratio of GMTs of group 2A versus group 2B was 1.0 (95% CI 0.8 - 1.3) after adjusting for baseline titer, sex, and visit. Other endpoints, -percentage of subjects with MenA rSBA titer ≥ 1:8 and percentage of subjects with MenA rSBA titer ≥ 1:128 were not different between the two groups seven months after vaccination; the percentage of subjects with MenA rSBA titer ≥ 1:128 were 96.9% (95% CI 94.0 – 98.7) in group 2A and 96.6% (95% CI 93.6 - 98.4) in group 2B.

Analysis of reactogenicity and safety data

Safety evaluation included monitoring of immediate reactions within 30 minutes of vaccination, solicited reactions and AEs during a time window of 4 days as the majority of local and systemic reactions occur usually within 2 days of vaccination and AEs for four weeks after each vaccination. Serious adverse events were recorded during the entire study duration. All safety evaluations were performed on the ITT population (there was no instance of wrong treatment assignment).

Immediate reactions

There were neither any immediate local reactions noted at the site of PsA-TT injection nor any immediate systemic reactions for any dose given at 9 months or 15 months of age.

Solicited local reactions

Local reactions at the injection site of PsA-TT given at 9 months of age were rare (<1%), mild and transient (resolving within 2 days) tenderness. Local reactions were similarly uncommon (<1%), mild and transient at the Yellow Fever and Measles injection sites. There were no local reactions after the second dose of PsA-TT given at 15 months of age, except one case of mild and transient tenderness in group 1B reported at the site of PsA-TT injection. Altogether these observations indicate that local reactions at the injection site of PsA-TT are rare, mild and transient and do not increase after the second dose.

Solicited systemic reactions

After the first PsA-TT vaccine dose given simultaneously with Yellow Fever and Measles vaccines, systemic reactions were reported in 16.7% , 18.3%, 19.0% , 19.0% and 17.0% of subjects in groups 1A,1B,2A, 2B and 3 (control). There was no statistically significant difference between the pooled MenAfriVac group (pooled group of groups 1A and 2A) and the pooled MenAfriVac 5µg group (pooled group of groups 1B and 2B) and between each pooled PsA-TT group and the control group 3. Systemic reactions were generally mild and no reaction was rated grade 3 (severe). The most common systemic reactions were diarrhea (ranging 9.0% in group 1B to 13.3% in group 2B), vomiting (ranging from 4.7% in group 3 to 7.0% in group1A) and fever (ranging from 3.7% in groups 2B and 3 to 5.3% in group1B). After the second PsA-TT vaccine dose given simultaneously with Measles-Rubella vaccine, systemic reactions were reported in 6.4% of vaccinees. Rates of systemic reactions were 3.9% of subjects in group 1A, 7.9% in group 1B, 8.9% in group 2A, and 5.7% in group 2B and control group 3 and not statistically different between groups 1A and 1B and between each of groups 1A and 1B and pooled control group (pooled group of groups 2A, 2B and). Systemic reactions were predominantly mild and transient. The most common systemic reactions were diarrhea (ranging 1.8% in group 1A to 5.7% in groups 1B and 2A). All other systemic reactions were reported in similar proportions among groups in less than 3% of subjects in each group.

Adverse events within 28 days of dose 1

Rates of adverse events (including systemic reactions ongoing beyond Day 4) within 28 days of the first vaccination were similar: 63.3%, 67.3%, 65.7%, 68.3% and 63.0%% of subjects in groups 1A,1B, 2A, 2B, and the control group 3, respectively. “Infections and infestations” in the system organ class (SOC) analysis were observed in 50.0%, 55.0%, 53.0% and 54.3% of subjects in groups 1A, 1B, 2A and 2B, respectively and for 51.3% of subjects in control group 3 and were mainly bronchitis, gastroenteritis, diarrhoea infectious, and pharyngitis. “Gastrointestinal disorders”, mainly diarrhoea, were reported by 14.7 % of subjects and “respiratory, thoracic and mediastinal disorders” by 11.9%. The percentages of infants reporting each specific event were similar among study groups. All related AEs were systemic reactions, mainly diarrhoea, ongoing beyond Day 4. There were no statistically significant differences in percentage of subjects with related AEs between study groups compared.

Adverse events within 28 days of dose 2

Adverse events (including systemic reactions ongoing beyond Day 4) within 28 days of vaccination at 15 months of age were occurring with similar rates in the five study groups - 42.5% of subjects in group 1A, 38.0% in group 1B, 35.6% in group 2A, 40.1% in group 2B and 40.9% in group 3. “Infections and infestations” were largely the most common SOC category noted in the five groups: 36.1% of subjects in group 1A, 31.2% in group 1B, and 30.6%, 33.3% and 33.7% of the subjects in groups 2A, 2B and 3, respectively. They were mainly bronchitis, rhinitis and pharyngitis. Overall, the

proportions of subjects reporting each specific event were similar among each of the study groups. All related AEs were systemic reactions ongoing beyond Day 4 and there were no statistically significant differences in the rate of related AEs between study groups compared. All adverse events resolved without sequelae.

Serious adverse events (SAEs) and deaths

Overall, 42 serious adverse event were reported during the entire study period and occurred with similar proportions in the five study groups for each follow up period (i.e. within 28 days of each vaccination and during the interval between the 2 doses). Ten out of the 42 SAEs occurred within 28 days after the first vaccination, six out of the 42 SAEs occurred within 28 days after the second vaccination, and most of them (81%) were infections and infestations according to SOC. Most of the SAEs were resolving within 7 days without sequelae and all were considered unrelated to study vaccines. Four subjects died during the study period. Three died from gastroenteritis and one from injury. None of the 4 deaths was related to the study vaccine.

IMMUNOGENICITY OF CONCOMITANTLY ADMINISTERED VACCINES IN STUDIES PsA-TT-004 AND -007

In both studies, potential interference in the immune response to the EPI vaccines administered concomitantly with PsA-TT vaccine was assessed by examining non-inferiority of immune responses to EPI antigens in PsA-TT groups in which subjects received EPI and PsA-TT vaccines simultaneously to the immune responses in subjects receiving these EPI vaccines alone. Primary immunogenicity endpoints for each vaccine antigen were the percentage of subjects achieving predefined antibody concentrations or titers one month after vaccination. If the upper bound of the 95% CI of the difference in percentages of subjects achieving the predetermined threshold for a given EPI vaccine between the control group (receiving only the EPI vaccine) and a specific study group (receiving simultaneous administration of PsA-TT and the EPI vaccine) was less than 10% (pre-specified non-inferiority margin), the comparator was considered non-inferior to the control. In both studies, the size of the study allowed a number of sera tested for the immunogenicity of EPI vaccines to provide a power over 90% to demonstrate non-inferiority for pair wise comparison between a study group and the respective control, with an assumed response rate of 95% at the predefined threshold for a given EPI antigen.

The non-inferiority of each of PsA-TT groups (EPI with PsA-TT) to the relevant control group (EPI alone) was demonstrated for most of pairwise comparisons in the two studies, in terms of response rate of subjects with immune response to a given EPI antigen reaching predefined threshold. For study PsA-TT-004, the few exceptions relate to the percentages of subjects with *B. pertussis* specific IgG concentration ≥ 11 IU/ml which were much lower (40.7% - 47.5%) than the expected response rate of 95% one month after the third DTwPHBVHib dose in all study groups and for which non-inferiority of three PsA-TT groups (groups 1A, 1B, 1C) to the control group was not demonstrated, percentages of subjects with anti-PRP IgG concentration ≥ 1 µg/ml one month after the third DTwPHBVHib dose for which non-inferiority of group1C to the control group was not shown, percentages of subjects with Measles-specific IgG concentration > 11 DU for which non-inferiority of groups 1B and 2 to the control group 4 was not shown and percentages of subjects with Yellow Fever neutralizing antibody titer ≥ 1:8 one month after vaccination at 9 months of age which were less (69.9% - 79.4%) than the expected response rate in all groups and for which non-inferiority of groups 1C and 2 to group 4 was not demonstrated. Although non-inferiority was not shown, there were no statistically significant differences in GMTs or GMCs for any of these 4 EPI vaccine antigens one month after vaccination after adjusting age, sex, and pre-dose concentration (or titer): GMCs of *B. Pertussis* specific IgG concentrations ranged from 8.0 to 9.1; GMCs of anti-PRP IgG concentration were from 2.5 to 3.2; GMCs of Measles-specific IgG concentrations were from 13.0 to 13.8; GMTs of Yellow Fever neutralizing antibody titer ranged from 12.5 to 16.7 one month after vaccination. Overall, the percentages of subjects with immune response achieving a predefined threshold were similar across study groups. In study PsA-TT-007, non-inferiority of group 2A to the control group 3 was not demonstrated for the percentage of subjects with Yellow Fever neutralizing antibody titer ≥ 1:8 one

month after vaccination at 9 months of age. The percentages were high, ranging from 94.8% to 98.3% and GMTs were similar, ranging from 29.8 to 34.5 one month after vaccination. Noteworthy, antibody measurement for Yellow Fever antigen was performed in only approximately 20% of samples. In study PsA-TT-004, co-administration of MenAfriVac or MenAfriVac 5µg did not interfere with the tetanus antitoxin nor the PRP antibody response (induced by the tetanus toxoid Hib conjugate as in Zilbrix), which indicates the absence of carrier epitopic suppression. Study PsA-TT-007 provides evidence that the carrier protein in MenAfriVac or MenAfriVac 5µg elicited tetanus antitoxin antibody.

The immunogenicity of rotavirus and pneumococcoccal conjugate vaccines which might be simultaneously given with MenAfriVac 5µg has not been formally evaluated in these two studies. Based on the clinical experience with co-administration of Prevenar13 and NeisVac, a meningococcal group C polysaccharide tetanus toxoid conjugated vaccine (10 µg of conjugate per dose), there were no immunological interference as the immunogenicity of the 2 vaccines, Prevenar13 and NeisVac, was not altered. Therefore, it is reasonable to expect similar findings for MenAfriVac 5µg [21;22]. Published data on the concomitant administration of Rotarix with Meningitec, a meningococcal group C polysaccharide CRM_{197} conjugated vaccine, and other recommended infant vaccines and that of Rotateq with NeisVac and other recommended infant vaccines does not provide evidence of any immunological interference[23;24].

Discussion

The clinical studies PsA-TT-004 and PsA-TT-007 address issues related to the potential use of MenAfriVac 5 µg when incorporated into the EPI to maintain population immunity. One ("9 months of age") and two ("14 weeks and 9 months of age", and "9 and 15 months of age") immunization schedules fitting EPI sessions were evaluated.

Safety of MenAfriVac 5 µg

A total of 3315 doses of PsA-TT vaccine were administered in the two studies, including 1651 doses of MenAfriVac, 1270 doses of MenAfriVac 5µg and 394 doses of 2.5 µg PsA-TT. Eleven hundred and seventy nine (1179) and 472 infants received a first and second dose of MenAfriVac, respectively whereas 800 and 470 infants received a first and second dose of MenAfriVac 5µg.

The reactogenicity profile of PsA-TT concomitant with EPI vaccines in infants aged between 14 weeks and 9 months at time of immunization was shown to be similar to that of concomitantly given EPI vaccines. Local reactions at injection sites of PsA-TT and EPI vaccines were predominantly mild and transient. Local reactions at the site of PsA-TT injection were observed in less than 11% of infants. There were no significant increases in systemic reactions due to concomitant vaccination of PsA-TT compared to the EPI vaccines administered alone. No clinically significant differences in the frequency or severity of AEs within 28 days of vaccination were observed among infants receiving PsA-TT simultaneously with the EPI vaccines compared to EPI vaccines alone, indicating a comparable safety profile. In general, reported AEs within 28 days of vaccination corresponded to symptoms associated with medical conditions occurring commonly in subjects of the same age as subjects included in both studies and living in meningitis belt countries. AEs that were considered related to study vaccine were essentially post-immunization reactions ongoing beyond day 4 (mostly induration and gastrointestinal disorders). Overall, reported serious adverse events (SAEs) were not statistically different among study groups at any time during the vaccination series and follow-up observation period. By far, the most frequently reported SAEs were infections and infestations according to SOC. Overall, the safety database shows a comparable safety profile for MenAfriVac 5µg and MenAfriVac when co-administered with the recommended EPI vaccines and does not reveal any signals for a specific adverse event to occur in excess.

Nonetheless, there are limitations to the safety database. The safety of PsA-TT has only been evaluated in healthy infants and the size of the database may be too small to detect rare AEs that would occur at a frequency lower than 0.5%. However, the clinical experience with more than 150 million doses of MenAfriVac administered has clearly shown that MenAfriVac has an acceptable safety profile. In both studies, MenAfriVac was used as comparator which provides added confidence as to the safety profile of MenAfriVac 5µg. Furthermore, it is biologically not plausible that the reduced antigenic content, in the same vaccine formulation considered here, would be associated a different safety profile. Therefore, the usual pharmacovigilance programme will allow to assess whether any AEs, that were too rare to be observed in studies PsA-TT-004 and PsA-TT-007, are associated with MenAfriVac 5µg when used in routine EPI practice.

Immunogenicity of MenAfriVac 5 µg

Immunogenicity data in infants, aged from 14 weeks (study PsA-TT-004) to 9 months (study PsA-TT-007) at time of first vaccination, indicate that MenAfriVac 5µg elicits functional immune responses that are similar to those induced by MenAfriVac. In both studies, non-inferiority of MenAfriVac 5µg to MenAfriVac was demonstrated in terms of the primary immunogenicity endpoint for subjects with a seroconversion in MenA rSBA antibody titer. Specifically, with respect to percentage of subjects with a 4-fold or higher response in MenA rSBA antibody titer with respect to baseline, non-inferiority of MenAfriVac 5 µg administered at 14 weeks and 9 months of age to MenAfriVac administered at 14 weeks and 9 months of age, concomitantly with EPI vaccines, was demonstrated at 28 days after the second dose up to 24 to 27 months after the second dose in study PsA-TT-004; non-inferiority of MenAfrivac 5µg administered in 9 months of age or administered in 9 months and 15 months of age to MenAfriVac administered in 9 months and 15 months of age, concomitantly with EPI vaccines was established at 28 days of the last vaccine dose in study PsA-TT-007.

Findings in study PsA-TT-004 indicate that a schedule consisting of 2 doses of MenAfriVac 5µg given at 14 weeks and 9 months of age was highly immunogenic. One month after the second dose, GMT of MenA rSBA titers was high (5048.6) for MenAfriVac 5µg and significantly greater than that achieved by a single dose of MenAfriVac at 9 months, indicating that the first dose of MenAfriVac 5µg is effectively priming the immune system. MenA rSBA antibody titers ≥ 1/128 were persisting in 88.1% of subjects in the 5µg group at the age of 36 months. In study PsA-TT 007, a co-primary endpoint related to MenA rSBA GMTs was added to assess non-inferiority of alternative schedule and dosage of PsA-TT vaccine to MenAfriVac administered in a two-dose schedule. For this endpoint, the alternative schedule and dosage of PsA-TT can be claimed to be non-inferior to MenAfriVac administered in a two-dose schedule if the 98.3% upper confidence bound of GMT ratio of the alternative schedule and dosage group versus the MenAfriVac group is less than 1.5 at 28 days after the last dose of MenAfriVac, which appears to be a very stringent requirement. Based on this criterion only, two-dose schedule of MenAfriVac 5µg was non-inferior to two-dose schedule of MenAfriVac, but one-dose schedule given at 9 months of age for both MenAfriVac and MenAfriVac 5 µg was not shown non-inferior to two-dose schedule of MenAfriVac given at 9 months and 15 months of age. This is due to the strong antibody increase induced by a second dose of PsA-TT resulting in high MenA rSBA GMTs that were greater than 11,000 for both MenAfriVac and MenAfriVac 5µg. However, such high GMT level may not persist very long. According to one of the pre-licensure studies for MenAfriVac conducted in toddlers (study PsA-TT-002) [5], GMT was 10037.4 at 28 days after two doses of MenAfriVac given at 12 to 23 months of age for the first dose and 10 months later for the second dose, but 14 months after the second dose of MenAfriVac, GMT decreased to 2720.8, which indicated a substantial decline of antibody titers for MenAfriVac within about a year. Even though based on GMT, non-inferiority of the one-dose schedule of PsA-TT with either 10 µg or 5 µg to the two-dose schedule of MenAfriVac was not demonstrated, high MenArSBA titers were already achieved following one dose of PsA-TT given at 9 months of age; GMTs at 28 days after the single dose of PsA-TT were 4883.1 and 4167.3 for the one-dose schedule of MenAfriVac and MenAfriVac 5µg, respectively. Seven months after the single dose, MenArSBA titers remained high: GMTs were 2195.6 and 2382.7 for the one-dose schedule of MenAfriVac and MenAfriVac 5µg, respectively and they were not significantly different from each other after adjusting for baseline titer, sex, and visit.

Antibody persistence depending on PsA-TT dosage, schedule and age at vaccination was modelled using a longitudinal mixed model analysis The analysis was based on MenA rSBA antibody data from studies PsA-TT-004 and -007 presented here, and from the earlier study PsA-TT-002 where MenAfriVac was administered to toddlers and antibody persistence was evaluated up to 4.25 to 5 years after vaccination. The MenAfriVac 5µg vaccine was shown to have an immune response profile over time at least as good as that of MenAfriVac, whether administered in a one-or- two-dose schedule. Based on the immune response profile over an extended period of time of the MenAfriVac vaccine when given in a one-dose or two-dose schedule, it is reasonable to predict that the trajectory of immune response of the MenAfriVac 5µg vaccine will follow a similar trend and that a single dose of MenAfriVac 5µg vaccine given from age 9 months onwards will induce sustained antibody levels over time. It is therefore highly probable that MenAfriVac 5µg would be as effective as MenAfriVac to prevent group A meningococcal disease in infants when given as a two dose schedule at the age of 14 weeks and 9 months, or as one dose schedule given from the age of 9 months.

WHO recommendations on measles vaccination include the administration of a second dose of measles vaccine at 15 to 18 months of age in regions where measles transmission is on-going. This provides an opportunity for MenAfriVac vaccination which justifies considering extending the age indication up to 24 months for MenAfriVac 5µg. A review of immunogenicity data indicate an age related increase in MenAfriVac induced MenArSBA antibody levels from 14 weeks to 18-23 months of age. Since MenAfriVac 5µg demonstrated non inferiority to MenAfriVac at 14 weeks and at 9 months, it is reasonable to project non inferiority up to the age of 24 months. Hence the data support that MenAfriVac 5µg is indicated for: "active immunization for the protection against invasive meningococcal disease caused by *N. meningitidis* serogroup A in young children aged 3 to 24 months", with the following proposed immunization schedules

- From 14 weeks of age, two dose schedule with an interval of at least three months
- From 9 months of age, one dose

Concomitant vaccination

Data from both studies have shown that concomitant administration of MenAfriVac or MenAfriVac 5µg, does not affect the safety profile and the immunogenicity of routinely recommended infant vaccines in the EPI. The immunogenicity profile of all EPI vaccine antigens that were evaluated in these two studies exhibited mostly non-inferior immune responses induced by EPI vaccines co-administered with PsA-TT vaccine compared to the immune responses induced by EPI vaccines alone. Failure to show non-inferiority in some instances were partly due to either lower than expected response rates at the predefined threshold considered for a given antigen or smaller than required number of tested sera. Overall, compared with EPI vaccines administered alone, the percentages of responders and geometric mean levels of vaccine induced antibodies were similar for all EPI antigens when MenAfriVac and PsA-TT vaccines were given concomitantly. These data support that MenAfriVac 5µg vaccine can be safely and effectively given concomitantly with the other EPI vaccines as recommended. This would greatly ease the programmatic challenges related to adding immunization of infants or toddlers against group A meningococcal disease.

Conclusion

The two clinical studies provided convincing evidence that MenAfriVac 5 µg is well tolerated and safe. MenAfriVac 5µg would provide a substantial benefit given its demonstrated ability to elicit sustained functional immune responses in infants from the age of 14 weeks that are non- inferior to the immune responses induced by MenAfriVac which has proven highly effective. Clinical data allow its routine use within recommended EPI. The benefit-to-risk ratio of MenAfriVac 5µg appears to be highly favourable. Monitoring disease caused by group A *N. meningitidis* in countries where routine infant immunisation with MenAfriVac 5µg is implemented will confirm as to whether its impact is associated with sustained population immunity and whether changes in immunisation recommendations such as booster doses would be needed.

References

[1] Novak RT, Kambou JL, Diomande FV, et al. Serogroup A meningococcal conjugate vaccination in Burkina Faso: analysis of national surveillance data. Lancet Infect Dis 2012; 12: 757-64.

[2] Kristiansen PA, Diomande F, Ouedraogo R, et al. Carriage of *Neisseria lactamica* in 1- to 29-year-old people in Burkina Faso: epidemiology and molecular characterization. J Clin Microbiol 2012; 50: 4020-7.

[3] Daugla D, Gami J, Gamougam K, et al. Effect of a serogroup A meningococcal conjugate vaccine (PsA-TT) on serogroup A meningococcal meningitis and carriage in Chad: a community study. Lancet 2014; 383: 40–47.

[4] Djingarey MH, Barry R, Bonkoungou M, et al. Effectively introducing a new meningococcal A conjugate vaccine in Africa: The Burkina Faso experience. Vaccine 2012; 30S: B40– B45.

[5] Sow SO, Okoko BJ, Diallo,A, et al. Immunogenicity and safety of a meningococcal A conjugate vaccine in Africans. N Engl J Med 2011; 364: 2293-2304.

[6] Insel RA. Potential alterations in immunogenicity by combining or simultaneously administering vaccine components. Ann NY Acad Sci 1995; 754: 35-48.

[7] Campagne G, Garba A, Fabre P, et al. Safety and immunogenicity of three doses of a *Neisseria meningitidis* A + C diphtheria conjugate vaccine in infants from Niger. Pediatr Infect Dis J 2000; 19: 144-50.

[8] ICH Harmonised Tripartite Guideline. Choice of control group and related issues in clinical trials. E10. Current Step 4, version dated July 20 2000. ; WHO. Guidelines on clinical evaluation of vaccines: regulatory expectations. WHO Expert Committee on Biological Standardization. Fifty-second report. World Health Organization (WHO): Geneva, 2004. [Annex 1. WHO Technical Report Series, No.924]

[9] WHO (1976). Requirements for meningococcal polysaccharide vaccine (requirements for biological substances no. 23). WHO TRS 594: 50-75. ; WHO (1980). Requirements for meningococcal polysaccharide vaccine. WHO TRS 658.; WHO (2004). Recommendations for the production and control of group C meningococcal conjugate vaccines (Annex 3). WHO TRS 926:64-94.; WHO (2006). Recommendations to assure the quality, safety and efficacy of group A meningococcal conjugate vaccines, Vol. WHO\BS\06.2041-Final.

[10] Frasch C.E., Borrow R. and Donnelly J. Bactericidal antibody is the immunologic surrogate protection against meningococcal disease. Vaccine 2009; 27S: B112-116.

[11] CDC. Prevention and control of meningococcal disease. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm. Rep 49, 1-10. 2000.

[12] Maslanka SE, Gheesling LL, Libutti DE, et al. Standardization and a multilaboratory comparison of *Neisseria meningitidis* serogroup A and C serum bactericidal assays. The Multilaboratory Study Group. Clin Diagn Lab Immunol 1997; 4: 156-167.

[13] Carlone GM, Frasch CE, Siber GR, et al. Multicenter comparison of levels of antibody to the *Neisseria meningitidis* group A capsular polysaccharide measured by using an enzyme-linked immunosorbent assay. J Clin Microbiol 1992; 30: 154-9.

[14] Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4:213-26.

[15] European Agency for the Evaluation of Medicinal Products (EMEA). Guideline on clinical evaluation of new vaccines. Committee for Medicinal Product for Human Use (CHMP). EMEA/CHMP/VWP/164653/2005. 2006.

[16] European Medicine Agency. Synflorix Pneumococcal polysaccharide conjugate vaccine (adsorbed). EMA/703937/2013EMEA/H/C/000973 . 2013.

[17] European Medicine Agency (EMEA). Prevenar 13 pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) . EMA/CHMP/156399/2012 EMEA/H/C/001104 . 2012.

[18] Robbins JB, Myerowitz L, Whisnant JK, et al. Enteric bacteria cross-reactive with *Neisseria meningitidis* groups A and C and Diplococcus pneumoniae types I and 3. Infect Immun 1972; 6: 651-6.

[19] Vann WF, Liu TY, Robbins JB. Bacillus pumilus polysaccharide cross-reactive with meningococcal group A polysaccharide. Infect Immun 1976; 13: 1654-62.

[20] Guirguis N, Schneerson R, Bax A, et al. Escherichia coli K51 and K93 capsular polysaccharides are cross-reactive with the group A capsular polysaccharide of *Neisseria meningitidis*. Immunochemical, biological, and epidemiological studies. J Exp Med 1985; 162: 1837-51.

[21] Vanderkooi OG, Scheifele D, Girgenti D, et al. Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine in healthy infants and toddlers given with routine pediatric vaccinations in Canada. Pediatr Infect Dis J 2012; 31: 72-7.

[22] Martinon-Torres F, Gimenez-Sanchez F, Gurtman A, et al. 13-valent pneumococcal conjugate vaccine given with meningococcal C-tetanus toxoid conjugate and other routine pediatric vaccinations: immunogenicity and safety. Pediatr Infect Dis J 2012; 31: 392-9.

[23] Vesikari T, Karvonen A, Prymula R, et al. Immunogenicity and safety of the human rotavirus vaccine Rotarix co-administered with routine infant vaccines following the vaccination schedules in Europe. Vaccine 2010; 28: 5272-9.

[24] Vesikari T, Karvonen A, Borrow R, et al. Results from a randomized clinical trial of coadministration of RotaTeq, a pentavalent rotavirus vaccine, and NeisVac-C, a meningococcal serogroup C conjugate vaccine. Clin Vaccine Immunol 2011; 18: 878-84.