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Safety and immunogenicity of an investigational meningococcal ACWY conjugate vaccine (MenACWY-CRM) in healthy Indian subjects aged 2 to 75 years

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SUMMARY

Background: This phase 3, multi-center, open-label study evaluated the immunogenicity and safety of a quadrivalent meningococcal conjugate vaccine (MenACWY-CRM, Menveo®; Novartis Vaccines and Diagnostics S.r.l., Siena, Italy) in healthy Indian subjects aged 2–75 years, to provide data for licensure in India.

Methods: A total of 180 subjects were enrolled (60 subjects 2–10 years, 60 subjects 11–18 years, and 60 subjects 19–75 years) and received one dose of MenACWY-CRM. Serum bactericidal activity with human complement (hSBA) was measured before and 1 month after vaccination. Adverse events were collected throughout the 29-day study period.

Results: Percentages of subjects with post-vaccination hSBA ≥8 were 72%, 95%, 94%, and 90% for serogroups A, C, W, and Y, respectively. Geometric mean titers rose 7-fold to 42-fold against the four serogroups. Similar immune responses were observed for the age subgroups 2–10 years, 11–18 years, and 19–75 years. Seroresponse rates at 1 month following vaccination were 72%, 88%, 55%, and 71% for serogroups A, C, W, and Y, respectively. The vaccine was well tolerated with no safety concerns.

Conclusion: A single dose of MenACWY-CRM induced a robust immune response against all four meningococcal serogroups and was well tolerated in an Indian population 2–75 years of age.

1. Introduction

Invasive meningococcal disease is one of the most devastating global bacterial infections. There are an estimated 500 000 cases of meningococcal disease every year, causing 50 000 deaths worldwide.[1] The highest rates of disease occur in infants <1 year of age, and a second peak occurs in adolescents, the population with the highest carriage.[2–4] Meningococcal disease has a high fatality rate of up to 10% and can lead to death within 24 hours.[5] Of those who survive, 20% endure life-long disabilities such as amputations, deafness, and neurodevelopmental deficits.[6] Based on antigenic differences in their capsular polysaccharide, at least 12 serogroups have been identified. The vast majority of invasive meningococcal disease (≥90%) can be attributed to one of six immunologically distinct serogroups: A, B, C, W-135, X, and Y.[6,7]

The incidence and serogroup distribution varies with age group and geographical location, and changes over time. Serogroups B and C are most prevalent in Europe, Australia, and New Zealand, serogroups A, C, and W-135 are most common in Asia and Africa, serogroups B, C, and Y predominate in the USA, Canada, Latin America, and the Caribbean, and serogroup X has caused sporadic and clustered meningitis cases in Sub-Saharan Africa.[8,9] There is

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limited information available on meningococcal epidemiology in India, however pattern similarities with African epidemics suggest that serogroup A is predominant.[10] Occasional epidemics of meningococcal disease (mainly serogroup A) in the past century have been reported, most recently in 2005 in Delhi and surrounding districts.[11] Between March and July 2005, 444 cases and 62 deaths were recorded.[11]

MenACWY-CRM (Menveo®; Novartis Vaccines and Diagnostics S.r.l., Siena, Italy – a GSK company) is a quadrivalent (serogroups A, C, W-135, and Y) meningococcal polysaccharide conjugate vaccine that includes *Corynebacterium diphtheria* cross-reactive material 197 (CRM_{197}) as the carrier protein. Previous clinical studies have shown that MenACWY-CRM is highly immunogenic against all four meningococcal serogroups and is well tolerated in a wide range of age groups, beginning from 2 months of age.[12–14] MenACWY-CRM is currently approved in 64 countries. The vaccine has been approved for use in infants, children, adolescents, and adults, and is also Halal certified, which is relevant to many in the Indian population.

When this study was planned, only unconjugated meningococcal polysaccharide vaccines were available in India. Recently, a quadrivalent meningococcal conjugate vaccine was licensed (Menactra®; Sanofi Pasteur, Swiftwater, PA, USA). The purpose of this study is to support licensure of the GSK MenACWY-CRM vaccine in India. This phase 3, multi-center, open-label study was designed to evaluate the immunogenicity and safety of a single dose of the quadrivalent conjugate vaccine, MenACWY-CRM, in healthy Indian subjects aged 2–75 years.

2. Methods

2.1. Study design and objectives

This phase 3, multi-center, open-label study was conducted at three study centers in India during the period March 2012 to May 2014 (ClinicalTrials.gov identifier NCT01547715; Clinical Trial Registry of India identifier CTRI/2012/02/002452). The study was conducted according to Good Clinical Practice as well as the Ethical Guidelines for Biomedical Research on Human Subjects issued by the Indian Council for Medical Research, India. Ethics review committees approved the study protocol, and written informed consent was obtained from every participant and their parents or legal guardians, where appropriate, prior to enrolment. Enrolment was age-stratified with de-escalation by age, commencing with adults, then adolescents, and then children, with interim safety evaluations of adults and of adolescents.

The immunogenicity objectives of a single dose of MenACWY-CRM was measured by the percentage of subjects with hSBA (serum bactericidal activity using human complement) $\geq$8, the seroresponse rate at 1 month after vaccination (day 29) (primary objective), and hSBA geometric mean titers (GMTs). Immune responses were assessed as serum bacterial activity using human complement against *Neisseria meningitidis* serogroups A, C, W, and Y. Safety objectives were to assess the number and percentage of subjects with solicited local and systemic and unsolicited adverse events (AEs) during the 7 days following vaccination. Serious AEs (SAEs), medically attended AEs, and AEs leading to premature study withdrawal were collected throughout the study period, from day 1 to the end of the study.

2.2. Study participants

A total of 180 subjects were enrolled in this study, 60 in each age group: 2–10 years, 11–18 years, and 19–75 years. Eligible study participants were healthy subjects of either sex aged between 2 and 75 years. Female participants of childbearing potential were required to have a negative urine pregnancy test prior to enrolment. Subjects were excluded from the study if they did not provide informed consent, if they had a history of any meningococcal vaccine administration, if they had disease caused by *N. meningitidis*, or if there had been intimate exposure to an individual with laboratory confirmed *N. meningitidis*. Additional exclusion criteria were a significant infection within 7 days or fever $\geq$38 °C within 3 days of enrolment, known reactions to vaccine components, any serious chronic or progressive disease, known or suspected immune disease or impairment, known bleeding diathesis, receipt of blood products, medical history or illness likely to interfere with the results, receipt of any vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrollment, or previous receipt (within 28 days before study start) or intent to receive any investigational agent or vaccines prior to completion of the study.

2.3. Vaccines

MenACWY-CRM was prepared by extemporaneous mixing of the lyophilized MenA component with the liquid MenCWY component. Each 0.5-ml vaccine dose contained 10 μg of meningococcal serogroup A and 5 μg each of capsular polysaccharide of serogroups C, W-135, and Y conjugated to CRM_{197}. The vaccine was administered as an intramuscular injection into the deltoid muscle of the non-dominant arm.

2.4. Immunogenicity

Blood samples for immunogenicity analyses were obtained on day 1 (pre-vaccination) and day 29 (1 month post-vaccination). Immune responses were assessed as hSBA against meningococcal serogroups A, C, W-135, and Y, according to validated methods, in the laboratories of GSK Vaccines (Marburg, Germany). Pre- and post-vaccination antibody responses were expressed as the percentage of subjects with hSBA $\geq$8, percentage of subjects with a seroresponse, hSBA GMT, and post-vaccination to pre-vaccination geometric mean ratio (GMR). Seroresponse was defined as a post-vaccination hSBA $\geq$8 in subjects with a pre-vaccination hSBA $<$4, and at least 4-fold increase in post-vaccination hSBA in subjects with a pre-vaccination hSBA $\geq$4.

2.5. Safety

Subjects were observed for a minimum of 30 min post-vaccination to monitor for immediate adverse reactions. Subjects or guardians recorded solicited AEs and any other AEs on diary cards for 7 days after the vaccination. In children 2–5 years of age, injection site tenderness, erythema, and induration, and systemic reactions such as a change in eating habits, sleepiness, irritability, vomiting, diarrhea, and rash were collected. In children 6 years of age and older, injection site pain, erythema, and induration, and systemic reactions including chills, nausea, malaise, myalgia, arthralgia, headache, and rash were collected. Body temperature (fever $\geq$38 °C) and use of antipyretic medication was also recorded for all subjects. Participants were contacted on day 3 post-vaccination to remind them to complete the diary card.

Serious AEs or AEs resulting in premature withdrawal and other medically attended events were collected from day 1 to day 29. The investigators assessed the AEs for seriousness, severity, and relation to study vaccines. The severity of AEs was categorized as mild, moderate, or severe, if they resulted in no limitation, some limitation, or inability to perform normal daily activities, respectively. Some local AEs such as erythema, induration, and swelling were categorized based on measurements. Assessments of the causal relationship of spontaneous AEs to the study vaccines were classified as not related, possibly related, or probably related by the investigator.