Original Article

A Safety and Immunogenicity Study of a Single Dose of a Meningococcal (Groups A, C, W, and Y) Polysaccharide Diphtheria Toxoid Conjugate Vaccine (MEN-ACWY-D) in Healthy Japanese Participants

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SUMMARY: Meningococcal disease can cause significant disability and mortality. The quadrivalent meningococcal polysaccharide diphtheria toxoid conjugate vaccine (Men-ACWY-D) protects against invasive meningococcal disease caused by serogroups A, C, W, and Y. This phase III, open-label, single-arm, multicenter study evaluated the safety and immunogenicity of a single vaccine dose in healthy Japanese adults. The study enrolled 200 participants between 2 and 55 years of age. Immunogenicity was assessed by quantifying the seroprotection rates (the proportion of participants with antibody titers $\geq 1:128$ against the capsular polysaccharide from all 4 serogroups measured 28 days after vaccination). Safety endpoints included occurrence, nature, time to onset, duration, intensity, relationship to vaccination, and outcome of solicited and unsolicited adverse events (AEs) and serious AEs (SAEs). Participants included 194 adults, 2 adolescents, and 4 children. Among adults, the seroprotection rates for serogroups A, C, W, and Y were 91.2%, 80.2%, 89.1%, and 93.8%, respectively. Seroconversion rates (the proportion of participants with pre-vaccination titers of $< 1:4$ and a ≥ 4 -fold rise from baseline) were 87.3%, 83.0%, 94.4%, and 96.4%, respectively. No immediate AEs, adverse reactions, SAEs, or deaths were reported for any age group. Men-ACWY-D is well tolerated and immunogenic, eliciting antibodies against capsular polysaccharides from all 4 serogroups in Japanese adults.

INTRODUCTION

Meningococcal meningitis has been a notifiable disease in Japan since 1918 (1). Following a peak of over 4,000 cases annually around 1945, the incidence dropped to < 10 cases annually by the 1990s (1). The combined reporting of meningococcal meningitis and sepsis as “invasive meningococcal infection” was introduced in April 2013 and may have contributed to the increase in the number of reported cases (1), with 59 cases reported in 2013–2014 (2).

Although the incidence of invasive meningococcal disease (IMD) is relatively low in Japan, the case fatality rate is high at 19% (2). Therefore, prevention with an effective vaccine is important. The quadrivalent meningococcal polysaccharide diphtheria toxoid conjugate vaccine (Men-ACWY-D) has been shown to be safe and

immunogenic, both in clinical trials and during a > 10 -year period following licensure in the US, and to provide durable protection against IMD (3–8). It was licensed in Japan in July 2014 (9,10).

The objective of this study was to evaluate the safety and immunogenicity of a single dose of Men-ACWY-D in Japanese adults. The study was conducted to generate data for the Japanese population, in addition to the overseas data. The study design and protocol were agreed upon with the Pharmaceuticals and Medical Devices Agency (PMDA) prior to the initiation of the trial.

MATERIALS AND METHODS

Study design: This phase III, open-label, single-arm trial enrolled 200 healthy persons, aged 2 through 55 years. The majority (194) were between 18 and 55 years of age. All participants received a single dose of the vaccine intramuscularly (IM) and provided blood samples for immunogenicity assessments before vaccination, on Day 0, and on Day 28.

The protocol was approved by the institutional review board at each site. The study complied with the Declaration of Helsinki and the International Conference on Harmonization (ICH) guidelines for Good Clinical Practice. Written informed consent was obtained from each participant or a parent/legal representative for participants between 2 and 19 years of age. This study was registered at ClinicalTrials.gov (NCT01519713).

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Participants: The exclusion criteria included a history of or previous vaccination against meningococcal disease, congenital or acquired immunodeficiency, receipt of immunosuppressive therapy within 6 months or systemic corticosteroid therapy for > 2 consecutive weeks within 3 months, thrombocytopenia, a bleeding disorder or receipt of anticoagulants in the 3 weeks preceding enrollment, or a history of Guillain-Barré Syndrome.

Vaccine: Each 0.5-mL dose of Men-ACWY-D (Menactra[®], Sanofi Pasteur Inc., Swiftwater, PA, USA; batch number: U4243AA) contained 4 µg of capsular polysaccharide from each serogroup (A, C, W, and Y), conjugated to 48 µg of the diphtheria toxoid protein in sterile, isotonic sodium chloride solution. A single dose was administered IM in the deltoid region on Day 0. Participants were observed for 30 min to assess for the occurrence of immediate adverse events or reactions.

Immunogenicity: The primary immunogenicity objective was to determine the seroprotection rate to vaccine antigens, defined as the proportion of study participants with a post-vaccination antibody titer $\geq 1:128$, as measured by a serum bactericidal assay using a baby rabbit complement (SBA-BR) 28 days post-vaccination. The secondary immunogenicity objectives were to evaluate the geometric mean titers (GMTs), GMT ratios (GMTRs) between the Day 28/Day 0 titers, and the seroconversion rates. Seroconversion was defined as a pre-vaccination titer of < 1:4 and a ≥ 4 -fold rise in the post-vaccination titer.

Safety: The safety endpoints included the occurrence, nature, duration, intensity, and relationship to vaccination of unsolicited, systemic adverse events (AEs) reported within 30 min; the occurrence, time to onset, duration, and intensity of pre-defined (solicited) injection site reactions and systemic reactions occurring from day 0 through day 7; the occurrence, nature, time to onset, duration, maximum intensity (for non-serious AEs only), and causal relationship to vaccination (for systemic AEs only) of unsolicited (spontaneously reported) AEs within 28 days; and the occurrence, nature, time to onset, duration, relationship to vaccination, and outcome of serious AEs (SAEs) occurring during the entire study duration. Adverse events were defined using the preferred terms from the Medical Dictionary for Regulatory Activities, version 14.1.

There have been no safety concerns among the recipients of this vaccine between the ages of 2 and 18 (4,5,8). However, detailed safety data for this age group were not presented in this report, as the number of participants was low. For participants ≥ 12 years, pain at the injection site was graded as follows: grade 1, no interference with activity; grade 2, some interference with activity; and grade 3, significant interference and prevents daily activity. Erythema and swelling at the injection site were graded as follows: grade 1, ≥ 25 to ≤ 50 mm; grade 2, ≥ 51 to ≤ 100 mm; and grade 3, > 100 mm. In all participants, solicited systemic reactions were graded as follows: fever—grade 1, $\geq 37.5^{\circ}\text{C}$ to $\leq 38.4^{\circ}\text{C}$; grade 2, $\geq 38.5^{\circ}\text{C}$ to $\leq 38.9^{\circ}\text{C}$; and grade 3, $\geq 39.0^{\circ}\text{C}$, while headache, malaise, and myalgia were graded as follows: grade 1, no interference with activity; grade 2, some interference with activity; and grade 3, significant interference and prevents activity. At the request of the Japanese

regulatory authorities and as set forth by the Japanese immunization guidelines, a grade 1 fever was defined in this study as a body temperature between 37.5°C and 38.4°C .

Unsolicited adverse events were AEs that did not fulfil the conditions prelisted in the electronic Case Report Form, either in terms of the symptoms or the time of onset post-vaccination. Adverse reactions were AEs for which a causal relationship between the vaccine and the AE was at least a reasonable possibility. For all safety endpoints, the proportions of participants experiencing at least one event were determined.

Serologic evaluations: The functional meningococcal antibody activity against the capsular polysaccharide antigens from the serogroups contained in Men-ACWY-D was measured using the SBA-BR, as previously described (4,8). All assays were performed by Global Clinical Immunology at Sanofi Pasteur Inc.

Statistical analyses: The number of participants was designed to provide immunogenicity and safety data for the vaccine when administered as a single dose. A sample size of 180 evaluable participants allowed, with 95% probability, for the detection of an AE occurring with a frequency of $\geq 1.6\%$. Assuming the expected proportions of participants with SBA-BR $\geq 1:128$ of 99.8%, 98.8%, 97.1%, and 97.0% for serogroups A, C, W, and Y, respectively, a sample size of 180 participants would have ensured a lower limit of the 95% confidence interval (CI) above the pre-set level with a global power over 90%.

No hypothesis was tested. All analyses were descriptive. A 95% CI was constructed around the point estimates of the single proportions for the immunogenicity endpoints and for safety events based on the exact binomial method (Clopper-Pearson method) (11). The 95% CI constructed around the point estimates of the GMTs was based on the normal approximation of the $\log_2$ titers, followed by back transformation. No imputation for missing data was performed. Statistical analyses were performed using SAS[®] software, version 9.2 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Participants: This study was conducted between January 20 and March 24, 2012, and included 200 participants (194 adults, 2 adolescents, and 4 children). The characteristics and disposition of the adult participants are shown in Table 1. All participants received a single vaccine dose, provided blood samples for the immunogenicity assessment at baseline and on Day 28, completed the study, and were included in the immunology and safety analysis sets.

Immunogenicity: The results from the 2 adolescents and 4 children were similar to those observed for the adult population. As the number of these participants was too small to provide meaningful immunogenicity data, we focused on the analysis of the adult population.

The seroprotection rates for serogroups A, C, W, and Y were 91.2% (95% CI 86.3, 94.8), 80.2% (73.9, 85.6), 89.1% (83.8, 93.1), and 93.8% (89.3, 96.7), respectively (Table 2). The GMTs on Day 0 were lower for serogroups C and W than for serogroups A and Y (Table 3). By Day 28, the GMTs for all the serogroups increased

Table 1. Demographic characteristics and disposition of adult participants

Variable	(N = 194)
Age (years)	
Mean (SD)	35.6 (11.2)
Median	33.0
Minimum:Maximum	18:55
Sex (n [%])	
Male	97 (50)
Female	97 (50)
Race (n [%])	
Asian/Oriental	194 (100)
Weight (kilograms)	
Mean (SD)	60.63 (12.60)
Median	58.50
Minimum:Maximum	38.2:118.9

SD, standard deviation.

Table 2. Immunogenicity findings at day 28 post-vaccination in adult participants

Serogroup	Seroprotection rate (SBA-BR titer $\geq$ 1:128)		Seroprotection rate (SBA titers $\geq$ 1:8)	
	n/M	% (95%CI)	n/M	% (95%CI)
A	177/194	91.2 (86.3, 94.8)	180/194	92.8 (88.2, 96.0)
C	154/192	80.2 (73.9, 85.6)	167/192	87.0 (81.4, 91.4)
W	172/193	89.1 (83.8, 93.1)	186/193	96.4 (92.7, 98.5)
Y	180/192	93.8 (89.3, 96.7)	190/192	99.0 (96.3, 99.9)

n, number of participants with respective SBA-BR; M, number of participants with valid serology data; CI, confidence interval.

Table 3. Pre-vaccination and post-vaccination GMTs and GMTRs in adult participants

Serogroup	Pre-vaccination GMT (Day 0)		Pre-vaccination GMT (Day 28)		GMTR (95%CI)
	M	GMT (95%CI)	M	GMT (95%CI)	
A	193	26.0 (17.4, 38.9)	194	1,202.6 (876.2, 1,650.6)	31.9 (21.7, 46.8)
C	193	5.6 (4.2, 7.4)	192	389.1 (274.4, 551.8)	40.8 (28.3, 58.9)
W	193	12.8 (9.3, 17.6)	193	995.0 (737.9, 1,341.7)	53.6 (38.9, 73.9)
Y	193	64.2 (45.1, 91.5)	192	1,244.4 (991.3, 1,562.2)	16.1 (11.6, 22.2)

M, number of participants with valid serology data; GMT, geometric mean titer; GMTR, geometric mean titer ratio (geometric mean of the ratio of post-vaccination GMT/pre-vaccination GMT); CI, confidence interval.

Table 4. Seroconversion¹⁾ rates at day 28 post-vaccination in adult participants

Serogroup	n/M	% (95%CI)
A	89/102	87.3 (79.2, 93.0)
C	122/147	83.0 (75.9, 88.7)
W	102/108	94.4 (88.3, 97.9)
Y	54/56	96.4 (87.7, 99.6)

¹⁾: Seroconversion was defined as a pre-vaccination titer of $< 1:4$ dilution and a ≥ 4 -fold rise in post-vaccination antibody titer.

n, number of participants with seroconversion; M, number of participants with pre-vaccination titer $< 1:4$ and a valid serology result on day 28; CI, confidence interval; NA, not applicable.

Table 5. Summary of solicited AEs in adult participants

Participants experiencing at least one event or reaction	n/M	% (95%CI)
Solicited injection site reaction	63/194	32.5 (25.9, 39.6)
Injection site pain	60/194	30.9 (24.5, 37.9)
Grade 1	55/194	28.4 (22.1, 35.2)
Grade 2	5/194	2.6 (0.8, 5.9)
Grade 3	0/194	0 (0.0, 1.9)
Injection site erythema	5/194	2.6 (0.8, 5.9)
Grade 1	4/194	2.1 (0.6, 5.2)
Grade 2	1/194	0.5 (0.0, 2.8)
Grade 3	0/194	0 (0.0, 1.9)
Injection site swelling	2/194	1.0 (0.1, 3.7)
Grade 1	1/194	0.5 (0.0, 2.8)
Grade 2	1/194	0.5 (0.0, 2.8)
Grade 3	0/194	0 (0.0, 1.9)
Solicited systemic reaction	67/194	34.5 (27.9, 41.7)
Fever	3/194	1.5 (0.3, 4.5)
Grade 1	3/194	1.5 (0.3, 4.5)
Grade 2	0/194	0 (0.0, 1.9)
Grade 3	0/194	0 (0.0, 1.9)
Headache	22/194	11.3 (7.2, 16.7)
Grade 1	15/194	7.7 (4.4, 12.4)
Grade 2	7/194	3.6 (1.5, 7.3)
Grade 3	0/194	0 (0.0, 1.9)
Malaise	30/194	15.5 (10.7, 21.3)
Grade 1	20/194	10.3 (6.4, 15.5)
Grade 2	7/194	3.6 (1.5, 7.3)
Grade 3	3/194	1.5 (0.3, 4.5)
Myalgia	48/194	24.7 (18.8, 31.4)
Grade 1	40/194	20.6 (15.2, 27.0)
Grade 2	7/194	3.6 (1.5, 7.3)
Grade 3	1/194	0.5 (0.0, 2.8)

AEs, adverse events; n, number of participants reporting event; M, number of participants with available data; CI, confidence interval.

compared to the pre-vaccination levels. On Day 28, the GMTRs were 31.9 (95% CI 21.7, 46.8) for serogroup A, 40.8 (28.3, 58.9) for serogroup C, 53.6 (38.9, 73.9) for serogroup W, and 16.1 (11.6, 22.2) for serogroup Y. The seroconversion rates for serogroups A, C, W, and Y were 87.3% (79.2, 93.0), 83.0% (75.9, 88.7), 94.4% (88.3, 97.9), and 96.4% (87.7, 99.6), respectively (Table 4).

Safety: We have reported the safety data for all the age groups. No immediate AEs, AEs leading to early

study discontinuation, SAEs, or deaths were reported. Pain was the most frequently reported injection site reaction in 60 of 194 adults (30.9%) (Table 5). Most of the injection site reactions were grade 1 in intensity, occurred within 0–3 days, and resolved within 7 days. One adolescent participant experienced erythema on days 0–6, which was only rated as grade 3 on day 1. In adults, the most common solicited systemic reactions were myalgia, observed in 48 of 194 (24.7%) participants, and

Table 6. Summary of unsolicited AEs and ARs in adult participants ($N = 194$)

Participants experiencing at least one event or reaction	n/M	% (95%CI)
Unsolicited AE	39/194	20.1 (14.7, 26.4)
Unsolicited AR	6/194	3.1 (1.1, 6.6)
Unsolicited injection site AR	2/194	1.0 (0.1, 3.7)
Unsolicited systemic AE	38/194	19.6 (14.2, 25.9)
Unsolicited systemic AR	4/194	2.1 (0.6, 5.2)

AE, adverse event; AR, adverse reaction; n , number of participants reporting event; M , number of participants with available data; CI, confidence interval.

malaise, reported by 30 of 194 (15.5%) participants; no adolescents or children experienced any solicited systemic reactions. Most of the solicited systemic reactions in adults were grade 1 in intensity, occurred within 0–3 days, and resolved within 7 days. Solicited systemic reactions in adults that were grade 3 in intensity included malaise, observed in 3 of 194 (1.5%) participants, and myalgia, reported by 1 of 194 (0.5%) participants. A total of 38 adults reported an unsolicited systemic AE: nasopharyngitis (7.7%), headache (2.6%), and diarrhea (2.1%) (Table 6). Most of the unsolicited systemic AEs were grade 1–2 in intensity; grade 3 events of nasopharyngitis were reported by 3 participants. Four events (hypoesthesia, diarrhea, eczema, and arthralgia) were considered related to study vaccination. One unsolicited systemic AE (grade 1 dental caries) was reported in an adolescent, and another (grade 1 otitis media) was reported in a child.

DISCUSSION

This study assessed the safety and immunogenicity of Men-ACWY-D to support the registration of the first meningococcal polysaccharide diphtheria toxoid conjugate vaccine (Men-ACWY-D; Menactra®) in Japan.

The results showed that Men-ACWY-D induced a robust immune response in all the adult participants. This conclusion, consistent with and supported by data from the United States, was based on the high GMTs and seroconversion rates. Although the seroprotection rate for serogroup C (80.2%) in adults was lower than those of the other serogroups (89.1%–93.8%), 87% of the adult participants had a serogroup C titer $\geq 1:8$ 28 days after vaccination, which is considered as protective (Table 2).

Outside of Japan, the meningococcal polysaccharide vaccine has been used for several years. However, it elicits T-cell-independent responses that provide insufficient protection in the very young and may result in hyporesponsiveness after repeated vaccination (12,13). In contrast, conjugate vaccines elicit T-cell-dependent responses that provide durable protection through memory B cells, which facilitate booster antibody responses to subsequent doses (14,15). Furthermore, conjugate vaccines are postulated to contribute to herd protection by reducing the asymptomatic nasopharyngeal carriage of *Neisseria meningitidis* (16).

The vaccine was well tolerated. Most of the local and systemic reactions were transient and grades 1–2 in intensity. Nasopharyngitis was reported in 7.7% of adult

participants. Malaise and myalgia of grade 3 intensity were observed in 1.5% and 0.5% of adult participants, respectively. Four events (hypoesthesia, diarrhea, eczema, and arthralgia) were considered to be related to the study vaccine. Although the low number of children and adolescents enrolled in the study precluded direct comparisons with the findings of other studies, the safety profile in adults was comparable with that demonstrated overseas.

The vaccine, licensed in 2005 in the United States, has been shown to have a favorable safety profile and induce durable protection against meningococcal disease (4,5,8,17). It was assessed in infants aged 9 months, toddlers aged 12 months, children aged 2–10 years, and adolescents aged 11–18 years in the United States and demonstrated high seroprotection rates against all serogroups, when administered with and without routine childhood vaccines (4,5,8). However, direct comparisons between studies may be difficult because of the potential differences in the study populations, including the different degrees of natural priming by circulating organisms in geographically different environments (18) or differences in the ages of the study participants.

No meningococcal vaccine was licensed in Japan at the start of this study. However, IMD exhibits mortality as high as 19% in Japan (2). A meningococcal vaccine is needed by those who travel to perform Hajj (the annual Islamic pilgrimage to Mecca), by those who travel to the meningococcal belt area, and by those who study abroad. These travelers have been looking forward to the approval of a meningococcal vaccine in Japan. An outbreak of meningococcal disease in a high school dormitory in the Miyazaki Prefecture was reported in 2011 that resulted in one death (19). More recently, 6 cases of laboratory-confirmed meningococcal infection, caused by serogroup W, were confirmed among Scottish and Swedish attendees of a World Scout Jamboree held in 2015 in the Yamaguchi Prefecture, following their return home (20). These outbreaks highlight the increased risk of meningococcal disease in closed communities, suggesting that IMD is of concern not only to travelers but also to the local Japanese population. A safe and effective vaccine has the potential to play an important role in the prevention of meningococcal disease in Japan.

This study used a quadrivalent conjugate vaccine that did not include serogroup B antigens. Recent data on IMD in Japan show that up to 43% of the cases reported between 2013 and 2015 were caused by serogroup Y, with serogroups C, B, and W accounting for up to 12%, 7%, and 9.5% of cases, respectively (2,21). No cases caused by serogroup A were reported during this time-frame. This is in contrast to the serogroup distribution among the cases reported between 2005 and 2013, where as many as 19.1% of cases were caused by serogroup B, and serogroups Y, W, and C accounted for 15.7%, 2.6%, and 1.7% of the cases, respectively (1). Data indicating the recent increase in cases caused by the serogroups included in the Men-ACWY-D vaccine suggest that its widespread use is likely to have a positive impact through the prevention of a significant number of infections. However, given that the serogroup responsible for disease was unknown in up to a third of the cases, the surveillance system may need improvement.

In countries in which the vaccine is routinely used, it

is administered prior to the start of group living, which represents a high risk for meningococcal infection. In addition, cohorts with an increased risk of IMD have been identified and include patients with genetic deficiencies in complement pathway components, individuals with anatomic or functional asplenia, laboratory personnel who routinely handle meningococcal isolates, people living in close quarters (e.g., college students), and individuals exposed to second hand smoke (22–29). It is highly desirable that these cohorts in Japan should receive Men-ACWY-D.

This study has a few limitations. First, we cannot rule out the possible variability in the AE reports, as this study was open-label and single-arm. However, the lack of a control group was justified by the data demonstrating that Men-ACWY-D is approved in the United States and Canada, as well as in multiple countries in Europe, the Middle East, and Asia, with high immunogenicity and tolerable safety (30,31). Second, the limited number of adolescents and children enrolled make further assessments imperative for strict interpretation. However, the data from the adults confirmed the previously documented safety and immunogenicity of the vaccine in earlier trials that had been conducted overseas (4,5).

In conclusion, this trial showed that Men-ACWY-D was well tolerated and induced a robust immune response, eliciting antibodies against meningococcal disease caused by serogroups A, C, W, and Y in healthy Japanese adults. These findings enabled the licensure of the vaccine in Japan. The implementation and expanded use of Men-ACWY-D has the potential to decrease the incidence of serious disability and death caused by IMD in Japan.

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