Original Article

The Immunogenicity and Safety Profile for KM-248, a Combined Measles, Mumps, and Rubella Vaccine, and Its Noninferiority to the Measles Vaccine in Healthy Japanese Children: a Phase 3 Randomized Multicenter Single-Blind Clinical Trial

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SUMMARY: The domestic combined measles-mumps-rubella (MMR) vaccine was withdrawn in Japan in 1993 following an outbreak of aseptic meningitis attributed to the mumps component of the cocktail. KM-248 is an MMR vaccine (M-M-R[®]II), manufactured by Merck & Co., Inc. (Kenilworth, NJ, USA) and registered and approved in 74 countries, but which has not been approved in Japan. This multicenter, randomized, single-blind study, was designed to evaluate the noninferiority of the KM-248 measles component in terms of immunogenicity when compared to the control measles vaccine already approved in Japan and the seroconversion rates for these three viruses following KM-248 administration. Vaccination with KM-248 in children aged 12–90 months ($n = 178$) induced robust immune responses to measles, mumps, and rubella viruses. The seroconversion rate for the measles virus by the measles component of KM-248 ($n = 172$) was shown to be non-inferior to that of the control measles vaccine ($n = 85$). No serious adverse reactions, such as aseptic meningitis or anaphylaxis, were observed. Fever is one of the most common adverse reactions associated with vaccination and was observed in approximately half of the participants. KM-248 administered to healthy Japanese children aged between 12 and 90 months demonstrated a comparable safety and efficacy profile to the control vaccine.

INTRODUCTION

Measles, mumps, and rubella infections generally result in mild cases of these diseases; however, serious complications can occur, leading to potentially fatal illness, disability, and death (1–3). Vaccines with well-tolerated safety profiles have been developed and proven effective in the prevention of these diseases. Vaccination with combined measles-mumps-rubella (MMR) vaccines is highly effective in reducing the morbidity and mortality associated with these childhood illnesses (4,5). In 1989, a domestic MMR vaccine was introduced into the Japanese immunization program (6). However, in 1993, all MMR vaccines were withdrawn from the program due to the incidence of serious aseptic meningitis (7). Monovalent vaccines have been used since this withdrawal, but the incidence of measles increased, with around 10,000–30,000 cases of measles

reported each year during the late 1990s and early 2000s (8,9). Mumps immunization is not mandatory, and the prevalence of mumps immunization among eligible children is only about 30%, contributing to mumps outbreaks every 3–4 years (10,11). The vaccination coverage of the rubella vaccine dropped to approximately 50% after the withdrawal of the MMR vaccine (12). In 2003, a measles-rubella combination vaccine was introduced into the market and although these individual vaccination rates have improved (13), an MMR vaccine could improve overall compliance with the vaccination program and reduce the number of health care visits and costs for vaccination in young children. Therefore, an alternate MMR vaccine with a lower risk of aseptic meningitis is highly desirable (14).

M-M-R[®]II is a combination vaccine that contains a measles vaccine (more attenuated Edmonston/Enders strain, 50% tissue culture infectious dose [TCID₅₀] $\geq 1,000$), a mumps vaccine (Jeryl Lynn strain, TCID₅₀ $\geq 5,000$), and a rubella vaccine (Wistar RA 27/3 strain, TCID₅₀ $\geq 1,000$), manufactured by Merck & Co., Inc. (Kenilworth, NJ, USA), which was first approved in 1978 in the USA, and continues to have broad global use with registration and approval in 74 countries. In Japan, M-M-R[®]II is considered investigational and is

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referred to as KM-248. In the USA, high vaccination coverage led to the elimination of endemic measles in the year 2000 (15) and endemic rubella in 2004 (16), while the incidence of mumps decreased by > 90% compared to the pre-vaccination era (17). In addition, longitudinal evaluations of KM-248 suggest that the risk of aseptic meningitis is limited (18,19). Japan has completed both early and late phase 2 studies of KM-248, with these studies including 41 and 395 healthy Japanese children, respectively. The major adverse reactions (ADRs) in both studies were fever (64.1% and 47.7%) and rash (53.8% and 26.2%, respectively) and no cases of aseptic meningitis were observed in either study. The aim of this phase 3 study was to evaluate the immunogenicity and safety profile of KM-248 in healthy Japanese children aged between 12 and 90 months in comparison to the current frontline measles vaccine used in Japan.

MATERIALS AND METHODS

Study design and participants: This was a multicenter, randomized, single-blind, comparative study. The study was conducted at 42 sites across Japan from September 2000 to August 2001.

The study protocol and informed consent form were approved by the institutional review board at each participating site. All guardians, and if appropriate the subjects, provided written informed consent before the initiation of any study-specific procedures. The study was conducted in accordance with the ethical principles originating in or derived from the Declaration of Helsinki and Good Clinical Practice guidelines.

Healthy male or female Japanese children aged 12 to 90 months with no history of measles, mumps, or rubella infection, as determined by serological evaluation, or vaccination against these infections were enrolled in this study. Key exclusion criteria included any children with a fever of $\geq 37.5^{\circ}\text{C}$ immediately prior to vaccination, with any serious acute condition, and with a history of an anaphylactic reaction to eggs or any component of the vaccines such as gelatin or aminoglycoside antimicrobials.

The participants were randomly assigned in a 2:1 ratio to either KM-248 or a control measles vaccine using a variable block method (block size of 3, 6, or 9 subjects). The control vaccine was a freeze-dried live attenuated measles vaccine named MVT (Schwarz FF-8 strain, $\text{TCID}_{50} \geq 5,000$) which was manufactured by Takeda Pharmaceutical Company Limited (Osaka, Japan). A single dose (0.5 mL) of the assigned study drug was administered subcutaneously in the lateral aspect of the upper arm under single-blinded conditions. Two blood samples were obtained: one immediately before vaccination (day 0) and the other between days 42 and 56 post-vaccination. Those subjects who received the MVT vaccine were allowed to receive KM-248 after the end of the study if the subjects/guardian requested it. Safety was assessed in these subjects for an additional 35 days after the second vaccination.

Study assessments: The primary endpoints were noninferiority of the immune response (seroconversion rate) against the measles virus when comparing KM-248 and MVT, and a lower limit of 95% confidence

interval (CI) exceeding 85% for seroconversion rates for measles, mumps, and rubella following vaccination with KM-248. The secondary endpoints included antibody titers in pre- and post-vaccination sera as determined by the hemagglutination inhibition method for measles and rubella, and enzyme-linked immunosorbent assay (ELISA) for mumps. The seroconversion rate was determined based on the percentage of subjects whose antibody titers exceeded the cutoff value ($\geq 1:8$ [2^3] for measles, $\geq 1:2$ [2^1] for mumps, and $\geq 1:8$ [2^3] for rubella) on days 42–56 for those participants whose antibody titers were below the cutoff value prior to vaccination. Safety was assessed based on adverse events (AEs) including body temperature, and objective and subjective symptoms. The investigators instructed the subjects/guardians to record temperature, signs and symptoms associated with fever including nausea, rash, anorexia, morose, cough, rhinorrhea, diarrhea, and any other symptoms, and medications in the study diary from 3 hours before the vaccination until day 35 post-vaccination. Nasopharyngeal swabs were performed on day 21 post-vaccination. If measles or mumps viruses were detected, virus identification was performed using polymerase chain reaction (PCR). Any signs and symptoms of suspected aseptic meningitis were followed, and available spinal fluid samples were evaluated for mumps using PCR in order to establish a definitive diagnosis and further differentiate the vaccine strains from wild-type strains.

Statistical analyses: The sample size was estimated based on the expected seroconversion rates of 95% for measles virus observed in previous KM-248 studies (20) and reported in MVT (21). We determined the population size for this study using an one-sided α level of 2.5% and 90% power and a clinically acceptable maximum difference (δ) of 10%. These evaluations determined that we needed 150 subjects for the KM-248 and 75 subjects for MVT treatment groups in order to evaluate noninferiority. The sample size needed to demonstrate that the antibody response for each of the three vaccine components was not below the 85% acceptable limit was determined using an one-sided α level of 2.5% and 95% power which estimated the subject number to be 110 subjects. Assuming a 10% protocol deviation rate and that 15% of subjects would be seropositive for measles, mumps, or rubella virus at baseline we determined that the target sample size was at least 200 for the KM-248 group and 100 for the MVT group.

The safety analysis set was defined as subjects who received vaccination but excluded those who did not have any observation/examination data post vaccination. Efficacy analysis Set A was defined as subjects whose antibodies against the three viruses were all negative before vaccination and presenting with immunogenicity after vaccination. Efficacy analysis Set B was defined as subjects after excluding participants from efficacy analysis Set A, who reported protocol violation.

The noninferiority of KM-248 to MVT in terms of seroconversion rate was assessed in the measles cohort of the efficacy analysis Set B using the Dunnett–Gent method (22,23). Confirmation was supplied when the lower limit of the two-sided 95% CI of the differences between the KM-248 and MVT participants was $\leq 10\%$.

Fig. 1. Patient disposition. * One subject was withdrawn due to mumps infection after vaccination with KM-248. MVT, measles vaccine (Schwarz FF-8 strain) Takeda®.

Seroconversion rates of KM-248 for measles, mumps, and rubella were calculated in the corresponding measles, mumps, and rubella cohorts of the efficacy analysis set A. Positive seroconversion rates for measles, mumps, and rubella following KM-248 treatment were confirmed when the lower limit of the 95% CI of each seroconversion rate was $> 85\%$. The descriptive statistics of the measles, mumps, and rubella antibody titers in the KM-248 group were evaluated. AEs were coded using the Medical Dictionary for Regulatory Activities Japanese Edition ver. 5.0. Fever was assessed using the following categories: $\geq 37.5^{\circ}\text{C}$, $\geq 38.0^{\circ}\text{C}$, and $\geq 39.0^{\circ}\text{C}$. The odds ratios of the incidence of fever and rash and their 95% CIs were calculated. All analyses were performed using SAS software ver. 6.12 (SAS Institute, Cary, NC, USA).

RESULTS

Participants: A total of 316 subjects were randomly assigned to either KM-248 ($n = 210$) or MVT ($n = 106$) and received the assigned vaccine (Fig. 1). One subject in the mumps cohort was excluded because of spontaneous infection during the study. The baseline characteristics for each cohort are summarized in Table 1.

Immunogenicity: The positive seroconversion rate for measles virus was 98.8% (170/172) in the KM-248 group and 100.0% (85/85) in the MVT group, and the difference between the groups was -1.2% (95%

CI, -2.8% – 0.4%), supporting the noninferiority of KM-248 in comparison to MVT ($P < 0.025$) (Table 2). The point estimates of the seroconversion rates for measles, mumps, and rubella viruses were 98.9%, 96.0%, and 100.0%, respectively (Table 2), indicating that the immunogenicity induced by KM-248 was within the pre-specified range of $> 85\%$. Evaluation of the secondary endpoints revealed that the geometric mean measles antibody titer in the KM-248 and MVT groups for efficacy analysis Set B were $2^{5.7}$ and $2^{5.6}$, respectively. The difference between the groups was $2^{0.07}$ (95% CI, $2^{-0.17}$ – $2^{0.31}$), indicating that there was no statistically significant difference in these values ($P = 0.570$) (Table 3). The geometric mean mumps and rubella antibody titers for KM-248 in efficacy analysis Set B were $2^{6.3}$ and $2^{6.9}$, respectively.

Safety: The overall incidence of any AEs in the KM-248 and MVT groups was 98.6% (1,801 events in 207/210) and 99.1% (800 events in 105/106), respectively. The incidence of ADRs in the KM-248 and MVT groups was 73.3% (518 events in 154/210) and 57.5% (180 events in 61/106), respectively. The AEs with a frequency of $\geq 10\%$ in any group included fever, rhinorrhea, cough, diarrhea, vomiting, rash, eczema, morose, and anorexia (Table 4). ADRs with a frequency of $\geq 10\%$ in any group included fever, rhinorrhea, cough, diarrhea, rash, morose, and anorexia (Table 4). Injection site edema was reported in two (1.0%) patients in the KM-248 group, but neither redness nor pain was reported as an administration site ADR in either

Table 1. Baseline characteristics (efficacy analysis Set A)

		Measles and rubella cohort		Mumps cohort
		MVT N = 89	KM-248 N = 178	KM-248 N = 177
Age	0 years old (< 12 months)	1	0	0
	1 year old (≥ 12 months and < 24 months)	77	163	162
	2 years old (≥ 24 months and < 36 months)	5	7	7
	3 years old (≥ 36 months and < 48 months)	5	4	4
	4 years old (≥ 48 months and < 60 months)	1	2	2
	5 years old (≥ 60 months and < 72 months)	0	1	1
	6 years old (≥ 72 months and < 84 months)	0	1	1
	7 years old (≥ 84 months and ≤ 90 months)	0	0	0
	Total	89	178	177
Mean ± SD (Age [months])		17.0 ± 7.6	17.0 ± 9.4	17.0 ± 9.4
Range (Age [months])		11–48	12–83	12–83
Gender	Male	46	101	100
	Female	43	77	77
	Total	89	178	177

MVT, measles vaccine (Schwarz FF-8 strain) Takeda®; SD, standard deviation.

Table 2. Positive seroconversion rates for measles, mumps, and rubella viruses

	Efficacy analysis set	Group	No. of subjects who became positive	Response rate (%)	95% CI	Dunnett-Gent test (95% CI of the difference)
Measles	B	KM-248	170/172	98.8	95.9–99.9	Z = incalculable P < 0.025
		MVT	85/85	100.0	95.8–100.0	–1.2 (–2.8–0.4)
Measles	A	KM-248	176/178	98.9	96.0–99.9	–
Mumps	A	KM-248	170/177	96.0	92.0–98.4	–
Rubella	A	KM-248	178/178	100.0	97.9–100.0	–

MVT, measles vaccine (Schwarz FF-8 strain) Takeda®; CI, confidence interval.

group. No deaths were reported during the trial. A total of six subjects in the KM-248 group reported Serious AEs (SAEs) and these included asthmatic bronchitis, asthma/pneumonia, tonsillitis/inflammation of the upper respiratory tract/herpetic gingivostomatitis, otitis media acute, pseudocroup, and hepatic impairment; none of these SAEs were thought to be related to KM-248. No SAEs were reported in the MVT group. Of the ADRs observed during the 35 day post vaccination period the incidence of fever ≥ 37.5°C, ≥ 38.0°C, and ≥ 39.0°C were 57.6%, 44.3%, and 20.5% in the KM-248 group, and 44.3%, 31.1%, and 14.2% in the MVT group, respectively (Table 5). No significant difference was found in the incidence of fever ≥ 39.0°C, but fevers at ≥ 37.5°C and ≥ 38.0°C were significantly more common in the KM-248 group than in the MVT group. The onset times of the maximum temperature for these fevers were in the range of 0–23 days (median 9 days) in the KM-248 group and 0–20 days (median 8 days) in the MVT group. The incidence of rash was significantly higher in the KM-248 group. Febrile convulsion was reported in 2 subjects (1.0%) in the KM-248 group and one (0.9%) in the MVT group. Other AEs accompanying fever in

the KM-248 group included rhinorrhea, morose, cough, and anorexia. The gelatin IgE antibody evaluations were negative in 208 subjects following vaccination. No vaccine strain mumps or measles viruses were identified in the nasopharyngeal shedding samples, suggesting that there was no productive infection in response to the vaccine. No serious ADRs such as aseptic meningitis, anaphylaxis, or acute thrombocytopenia purpura were noted. A total of 41 of the children in the MVT group received a second vaccination with KM-248 at the end of the study, but no serious ADRs, including aseptic meningitis, were observed in any of these patients.

DISCUSSION

This study demonstrates that the vaccination of 12–90-month-old Japanese children with KM-248 induces robust immune responses to measles, mumps, and rubella viruses. It is of particular interest that this study confirmed that the seroconversion rate for the measles portion of this vaccine (more attenuated Edmonston/Enders strain) was not inferior to that of MVT (Schwarz FF-8 strain), which is widely

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Table 3. Antibody titers against measles, mumps, and rubella viruses in the KM-248 and measles vaccine

Antibody titer		Efficacy analysis Set A		Efficacy analysis Set B	
		KM-248 N = 178	MVT N = 89	KM-248 N = 172	MVT N = 85
Measles antibody titer (2 ⁿ)	< 3	2	0	2	0
	3	1	2	1	2
	4	9	6	9	6
	5	55	25	54	24
	6	83	49	79	46
	7	27	5	26	5
	8	1	2	1	2
No. of subjects who became positive		176	89	170	85
Minimum (2 ⁿ)		< 3	3	< 3	3
Maximum (2 ⁿ)		8	8	8	8
Geometric mean (2 ⁿ)		5.7	5.6	5.7	5.6
95% CI		5.6–5.8	5.4–5.8	5.5–5.8	5.4–5.8
Two sample <i>t</i> -test		DF = 265, <i>t</i> = 0.63, <i>P</i> = 0.531		DF = 255, <i>t</i> = 0.57, <i>P</i> = 0.570	
95% CI of the difference		0.07 (–0.16–0.30)		0.07 (–0.17–0.31)	
Mumps antibody titer	Ab < 2.0	–	–	7	–
	2.0 ≤ Ab < 4.0	–	–	1	–
	4.0 ≤ Ab < 8.0	–	–	2	–
	8.0 ≤ Ab < 16.0	–	–	8	–
	16.0 ≤ Ab < 32.0	–	–	18	–
	32.0 ≤ Ab < 64.0	–	–	35	–
	64.0 ≤ Ab < 128.0	–	–	51	–
	128.0 ≤ Ab < 256.0	–	–	39	–
	256.0 ≤ Ab < 512.0	–	–	9	–
	512.0 ≤ Ab < 1024.0	–	–	2	–
No. of subjects who became positive		165			
Minimum		< 2.0			
Maximum		758.8			
Geometric mean		62.3			
95% CI		51.6–75.3			
Rubella antibody titer (2 ⁿ)	< 3	–	–	0	–
	3	–	–	0	–
	4	–	–	1	–
	5	–	–	18	–
	6	–	–	28	–
	7	–	–	78	–
	8	–	–	41	–
	9	–	–	6	–
No. of subjects who became positive		172			
Minimum (2 ⁿ)		4			
Maximum (2 ⁿ)		9			
Geometric mean (2 ⁿ)		6.9			
95% CI		6.8–7.1			

Ab, antibody titer; MVT, measles vaccine (Schwarz FF-8 strain) Takeda®; CI, confidence interval.

Table 4. Adverse events and adverse reactions classified by primary system organ class and preferred term (preferred term incidence $\geq 2\%$) (safety analysis set)

	Adverse events		Adverse drug reactions	
	KM-248 <i>N</i> = 210 <i>n</i> (%)	MVT <i>N</i> = 106 <i>n</i> (%)	KM-248 <i>N</i> = 210 <i>n</i> (%)	MVT <i>N</i> = 106 <i>n</i> (%)
General disorders and administration site conditions				
Fever	159 (75.7)	67 (63.2)	121 (57.6)	47 (44.3)
Respiratory, thoracic and mediastinal disorders				
Rhinorrhoea	176 (83.8)	96 (90.6)	32 (15.2)	22 (20.8)
Cough	160 (76.2)	79 (74.5)	28 (13.3)	11 (10.4)
Sneezing	9 (4.3)	6 (5.7)	1 (0.5)	0 (0.0)
Sputum increased	8 (3.8)	2 (1.9)	2 (1.0)	0 (0.0)
Wheezing	9 (4.3)	1 (0.9)	3 (1.4)	0 (0.0)
Nasal congestion	6 (2.9)	3 (2.8)	1 (0.5)	0 (0.0)
Pharyngolaryngeal pain	0 (0.0)	3 (2.8)	0 (0.0)	0 (0.0)
Gastrointestinal disorders				
Diarrhoea NOS	114 (54.3)	58 (54.7)	30 (14.3)	13 (12.3)
Vomiting NOS	88 (41.9)	38 (35.8)	18 (8.6)	7 (6.6)
Diarrhoea infectious	12 (5.7)	9 (8.5)	0 (0.0)	0 (0.0)
Stomatitis	7 (3.3)	2 (1.9)	4 (1.9)	0 (0.0)
Skin and subcutaneous tissue disorders				
Rash	103 (49.0)	34 (32.1)	94 (44.8)	27 (25.5)
Eczema NOS	21 (10.0)	7 (6.6)	0 (0.0)	0 (0.0)
Viral rash NOS	9 (4.3)	1 (0.9)	0 (0.0)	0 (0.0)
Psychiatric disorders				
Morose	126 (60.0)	42 (39.6)	61 (29.0)	18 (17.0)
Metabolism and nutritional disorders				
Anorexia	111 (52.9)	46 (43.4)	53 (25.2)	18 (17.0)
Eye disorders				
Eye discharge	17 (8.1)	6 (5.7)	3 (1.4)	0 (0.0)
Ocular hyperaemia	1 (0.5)	3 (2.8)	0 (0.0)	1 (0.9)

MVT, measles vaccine (Schwarz FF-8 strain) Takeda®; NOS, not otherwise specified.

used as a vaccination against measles virus in Japan. These 2 measles strains have been reported to have similar immunogenicity (24). A global clinical study evaluating KM-248 across 6 countries, excluding Japan, demonstrated that the seroconversion rates for measles, mumps, and rubella post-vaccination were 96.9%, 96.9%, and 99.5%, respectively (20), which were comparable to our findings (98.9% for measles, 96.0% for mumps, and 100.0% for rubella). These results were also similar to those previously reported for the domestic MMR vaccine which had seroconversion rates for measles, mumps, and rubella of 98.3%, 92.5%, and 99.4%, respectively (25).

The domestic MMR vaccines manufactured by 3 Japanese companies and routinely applied between 1989 and 1993 until withdrawal from the national immunization program due to an unacceptable number of aseptic meningitis cases (7). The incidence of aseptic meningitis has been reported to range from 1/7,000 to 1/405 (14,26–27). The nationwide surveys and tests conducted by the Ministry of Health, Welfare, and Labor found that the Urabe mumps strain used in the domestic MMR vaccine was the cause of these cases of aseptic meningitis. Miller et al. (18) reported that all

cases of vaccine-associated aseptic meningitis in MMR vaccines were derived from the Urabe mumps strain, although the risk associated with the MMR vaccine was approximately 1/4 of that associated with infections of the wild mumps virus. On the other hand, the UK reported no cases of aseptic meningitis when using an MMR vaccine containing the Jeryl Lynn mumps strain (18), which is the mumps component in the KM-248 vaccine. There were no cases of aseptic meningitis in the three previous Japanese clinical trials during the study period. Between 1978 and 2010, over 575 million doses of KM-248 were used in the USA, Europe, and other countries. During this same period, 57 cases of aseptic meningitis were reported, but the Jeryl Lynn mumps strain-derived virus used in the vaccine was not identified in any of these cases (28). According to the Worldwide Adverse Experience System (WAES) maintained by Merck & Co., Inc., the frequency of aseptic meningitis in KM-248 administrations is 1.2 per 10 million doses (in-house data).

KM-248 uses hydrolyzed gelatin as a stabilizer, which carries the potential risk of inducing anaphylaxis. Anti-gelatin antibody (IgE) titers were evaluated in all of the participants in this study using an ELISA,

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Table 5. Incidence of maximum fever and the odds ratio observed within 35 days after vaccination (safety analysis set)

	KM-248 (N = 210)			MVT (N = 106)			Odds ratio (95% CI)
	n	Cumulative (n)	% (95% CI)	n	Cumulative (n)	% (95% CI)	
Adverse events							
≥ 39.0°C	71	71	33.8 (27.4–40.6)	30	30	28.3 (20.0–37.9)	1.294 (0.757–2.241)
38.0–38.9°C	51	122	58.1 (51.1–64.8)	20	50	47.2 (37.4–57.1)	1.553 (0.945–2.553)
37.5–37.9°C	37	159	75.7 (69.3–81.4)	17	67	63.2 (53.3–72.4)	1.815 (1.058–3.096)
< 37.5°C ¹⁾	51	210	100.0	39	106	100.0	
Mean ± SD (°C)		38.35 ± 1.01			38.12 ± 1.03		
Range (°C)		36.7–41.4			36.4–41.0		
Onset day, Median (range)		8 (0–35) days			8 (0–32) days		
Adverse reactions							
≥ 39.0°C	43	43	20.5 (15.2–26.6)	15	15	14.2 (8.1–22.3)	1.562 (0.797–3.195)
38.0–38.9°C	50	93	44.3 (37.5–51.3)	18	33	31.1 (22.5–40.9)	1.758 (1.047–2.982)
37.5–37.9°C	28	121	57.6 (50.6–64.4)	14	47	44.3 (34.7–54.3)	1.707 (1.037–2.811)
< 37.5°C ¹⁾	89	210	100.0	59	106	100.0	
Onset day, Median (range)		9 (0–23) days			1 (0–20) days		

¹⁾: Temperature < 37.5°C or ≥ 37.5°C without casualty were not counted as ADR.

ADR, adverse reaction; CI, confidence interval; MVT, measles vaccine (Schwarz FF-8 strain) Takeda®; SD, standard deviation.

and all of the results were negative. In the WAES, the frequency of anaphylaxis was 2.3 per 10 million doses through January 17, 2003 (in-house data).

Overall, the risk of serious ADRs due to KM-248 in Japanese children is very low, with the risk of aseptic meningitis and anaphylaxis being extremely rare.

Fever is a common ADR following any measles vaccination, including MMR vaccines (29). It was reported (12) that the incidence of fever at ≥ 38.5°C after measles vaccination was 13.4% and fever-related convulsion was 0.2% in a national survey of self-reported health problems in Japan, while the incidence of fever in the control measles vaccine (MVT) used in this study was higher than these reported statistics. However, this is not unexpected as this was a clinical trial and subjects/guardians were instructed to measure the body temperature daily under identical conditions using a standardized protocol. Given this hypervigilance, it is possible that this procedure might have been found to have no notable fever in post-marketing pharmacovigilance in the real world. However, physicians and subjects/guardians receiving KM-248 should be informed of the incidence of fever ≥ 39.0°C in about 20% of subjects. The incidence of rash associated with fever was significantly higher in the KM-248 group than in the MVT group, but febrile convulsions was rare in both groups. Other major symptoms, including rhinorrhea, morose, cough, and anorexia, are typical of measles and thus they were not considered secondary symptoms associated with fever; rather, they were considered independent symptoms due

to vaccination.

This study has some limitations. First, this was a single-blind study. However, all procedures were conducted in a double-blind setting, except for the double dummy method. A commercially available measles vaccine (MVT) was used as a comparator; therefore, the appearance of the vials and colors of the solutions were different. Second, the trial was not powered to detect rare ADRs such as aseptic meningitis and anaphylaxis; however, the larger safety data outside of Japan provides a context for understanding the safety profile of this vaccine.

In conclusion, we demonstrated that KM-248 induced sufficient antibodies against measles, mumps, and rubella viruses after one vaccination. The seroconversion rate for the measles virus by the measles vaccine component (more attenuated Edmonston/Enders strain) of KM-248 was shown to be non-inferior to that of the measles Schwarz FF-8 strain vaccine. While fever was observed for both KM-248 and MVT, no serious ADRs such as aseptic meningitis and anaphylaxis were observed in either group.

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Conflict of interest KMB covered all of the expenses for this study. KM-248, investigational vaccine used for this study, was provided by the company. Dr. Kohji Ueda received fees from KMB for consultation and lectures. Heather Platt is an employee of Merck Sharp & Dohme Corp. (Kenilworth, NJ, USA, a subsidiary of Merck & Co., Inc.), and Shinji Tochihiro and Yoshiaki Oda are employees of KMB.

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