SYNOPSIS

Name of Sponsor/Company Sanofi Pasteur MSD S.N.C.	**Individual Study Table referring to part of the dossier**	*(For National Authority use only)*
Name of Finished Product VARIVAX®	Volume	
Name of Active Ingredients Live attenuated varicella virus [Oka/ Merck strain]	Page	

Title of the study	A double-blind, randomised, controlled multi-centre safety study of a refrigerator-stable formulation of VARIVAX® in healthy 12 to 15 month-old children. Study Identification Number: **X04-VAR-402** Eudract N°**2004-002669-19**	
Principal investigators	**France:** Vincent GAJDOS, MD Hôpital Antoine BECLERE 157 rue de la Porte Trivaux 92141 CLAMART CEDEX **Italy:** Giuseppe FERRERA, MD Azienda USL n°7 – Ragusa Via G. di Vittorio, 59/c 97100 – RAGUSA – SICILY	
Study centres	39 active centres in France and 1 active centre in Italy.	
Publication	Not applicable	
Study period (years)	First Visit First Subject: 02-December-2004 Last Visit Last Subject: 13-September-2005	**Phase of development** Phase IV
Objective	To describe the safety profile of a refrigerator-stable formulation of VARIVAX® as a first single dose injection in 12 to 15 month old children in the 42-day follow-up period post-vaccination. Because of its demonstrated and well known safety profile, M-M-R™II was selected as the active control for this study.	
Methodology	Double-blind, randomised, two arms, controlled, multi-centre safety study. Both vaccines were administered sequentially to all subjects following a 2x2 cross-over design.	
Number of subjects (planned and analysed)	***Planned:*** 500 subjects (250 subjects per group) ***Randomised:*** 507 subjects (254 subjects in Group 1 and 253 in Group 2) ***Analysed:*** **Safety Set** (507 subjects): all subjects who received a study vaccine and who had safety follow-up data. **Safety subset** (496 subjects): all subjects who received both vaccinations (VARIVAX® followed by M-M-R™II or M-M-R™II followed by VARIVAX®) and with safety follow-up data for both periods.	

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Disposition of subjects

	Group 1 (VARIVAX® then M-M-R™II)		Group 2 (M-M-R™II then VARIVAX®)		All	
	n subjects	(%)	n subjects	(%)	n subjects	(%)
Randomised	254	(100%)	253	(100%)	507	(100%)
Vaccinated	254	(100%)	253	(100%)	507	(100%)
Completed	250	(98.4%)	247	(97.6%)	497	(98.0%)
Withdrawn	4	(1.6%)	6	(2.4%)	10	(2.0%)
Adverse Event (AE)	1	(0.4%)	3	(1.2%)	4	(0.8%)
Deaths	0	(0%)	0	(0%)	0	(0%)
Serious AE	0	(0%)	0	(0%)	0	(0%)
Non-serious AE	1	(0.4%)	3	(1.2%)	4	(0.8%)
Definite contra-indication (C-I)	1	(0.4%)	0	(0%)	1	(0.2%)
Medical definite C-I	0	(0%)	0	(0%)	0	(0%)
Non-medical definite C-I	1	(0.4%)	0	(0%)	1	(0.2%)
Protocol deviation	1	(0.4%)	0	(0%)	1	(0.2%)
Personal reason	0	(0%)	0	(0%)	0	(0%)
Lost to follow-up	0	(0%)	0	(0%)	0	(0%)
Other	1	(0.4%)	3	(1.2%)	4	(0.8%)

All withdrawals for adverse events were due to varicella-like rashes, all assessed as unrelated to the study vaccine.
The definite contra-indication leading to withdrawal was the administration of immunoglobulin to treat an idiopatic thrombocytopenic purpura reported as a vaccine-related serious adverse event following VARIVAX® administration (subject 504009)

Diagnosis and main criteria for inclusion

Healthy children 12 to 15 months of age; parent(s)/legal representative having signed a consent form; no previous clinical history of measles, mumps, rubella, varicella or zoster and no exposure to these diseases in the 30 days prior to first study vaccination; no previous vaccination with any type of measles, mumps, rubella or varicella vaccine and no vaccination with any other vaccine in the 30 days prior to first study vaccination; no history of anaphylactic or anaphylactoid reactions to any components of the study vaccines; no immune impairment or humoral/ cellular deficiency, no receipt of long-term systemic corticosteroids at high dose in the 30 days prior to first study vaccination and no receipt of any blood or blood-derived product in the 150 days prior to first study vaccination.

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Test vaccine, dose and mode of administration, batch number	**VARIVAX®:** live attenuated varicella virus prophylactic vaccine Presentation: powder and solvent for suspension for injection. Dose: 0.5 mL Route: subcutaneous injection into the upper antero-lateral region of the thigh. Storage: +2°C to +8°C. Batch number: HV46780 expiry date 07-October-2005
Reference therapy, dose and mode of administration, batch number	**M-M-R™II:** live attenuated measles, mumps and rubella viruses prophylactic vaccine Presentation: powder and solvent for suspension for injection. Dose: 0.5 mL Route: subcutaneous injection into the upper antero-lateral region of the thigh. Storage: +2°C to +8°C. Batch number: X9600-1 expiry date 30-November-2005
Vaccination schedule	**Group 1:** VARIVAX® at visit 1 (Day 0), then M-M-R™II at visit 2 (Day 42) **Group 2:** M-M-R™II at visit 1 (Day 0), then VARIVAX® at visit 2 (Day 42) 42 days of safety follow-up after the administration of each vaccine in each study group.
Criteria for evaluation	- From Day 0 to Day 4 after each vaccination: • Solicited injection site reactions: injection site erythema, injection site swelling and injection site pain - From Day 0 to Day 42 after each vaccination: • spontaneously reported injection site reactions, • Varicella-like rash, • Measles-like rash, • Rubelliform rash, • Mumps-like illness, • Daily rectal or rectal equivalent temperature (axillary temperature + 0.9°C) Pyrexia was defined as an episode of rectal temperature ≥39.4°C, episode of feverish feeling or fever with no numeric value of temperature, or episode of any temperature that led to withdrawal from the study or judged as an adverse event by the investigator, • Other systemic adverse events. - Throughout the subject study period (from signature of the consent form until the last visit of the concerned subject): • Serious adverse events.
Statistical methods	All vaccinated subjects with safety follow-up were included in the safety analysis. The objective defined for the study was to describe the safety profile of a refrigerator-stable formulation of VARIVAX®. First, the carry-over effect and the period effect were tested for overall injection site reactions and for vaccine-related and unrelated systemic adverse events. If no carry-over or period effects were seen then the safety data following the two VARIVAX® injections were pooled (Group 1 at Period 1 and Group 2 at Period 2). If carry-over and/ or period effects existed, the data following the two VARIVAX® injections were not to be pooled but only described by period. Descriptive statistics (including two-sided exact 95% confidence intervals) were provided for all safety criteria by period and for the pooled data, depending on the former analysis results. In order to use M-M-R™II as an active control, the descriptive analysis defined for VARIVAX® was also to be performed for the safety data following M-M-R™II vaccination. Additionally, country-country differences were investigated.

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SUMMARY – CONCLUSIONS	**M-M-R™II SAFETY RESULTS** During the safety follow-up periods following M-M-R™II administration, 378/502 (75.3%) subjects in the safety set reported at least one adverse event following M-M-R™II injection, and 225/502 (44.8%) subjects reported at least one vaccine-related adverse event. More injection site reactions were seen following M-M-R™II injection given at the first visit (38/251 (15.1%) subjects) than when M-M-R™II was given at the second visit (18/251 (7.2%) subjects). A maximum rectal or rectal equivalent temperature ≥39.4°C was reported by 64/485 (13.2%) subjects when examined from Day 5 to Day 12 following injection and by 121/497 (24.3%) subjects throughout the 42 day follow-up period. A total of 8/502 (1.6%) subjects reported measles/ measles-like rashes and 12/502 (2.4%) subjects reported rubella/ rubella-like rashes. No cases of mumps-like illness were observed. The four (4) serious adverse events reported following M-M-R™II administration were hospitalisations for an infectious disease or injury and were all assessed as unrelated to the study vaccine. **VARIVAX® SAFETY RESULTS** During the safety follow-up periods following VARIVAX® administration, 360/501 (71.9%) subjects in the safety set reported at least one adverse event and 239/501 (47.7%) subjects reported at least one vaccine-related adverse event. Injection site reactions were reported by 142/501 (28.3%) subjects and they were predominantly of small size (≤2.5cm) or of mild intensity. Two types of injection site reactions were observed following VARIVAX® administration: • injection site reactions with onset on the day following vaccination (incidence ≥1% for erythema, pain and swelling) and mean duration of 1 to 3 days, • injection site reactions with onset 1 to 2 weeks post-vaccination (incidence ≥10% for erythema; ≥1% for swelling, pain and rash) and mean duration of 1 week. Systemic adverse events were reported by 326/501 (65.1%) subjects and only 152/501 (30.3%) subjects reported vaccine-related systemic adverse events. Pyrexia was the most common systemic adverse event reported by 227/501 (45.3%) subjects; only 127/501 (25.3%) subjects reported vaccine-related pyrexia. A maximum rectal or rectal equivalent temperature ≥39.4°C was reported by 84/493 (17.0%) subjects distributed across the 42-day safety period. A total of 16/501 (3.2%) subjects reported varicella/ varicella-like rashes. All laboratory-tested samples (from 3 out of the 9 non-injection site rashes) were wild type varicella strain. Varicella/ varicella-like rashes were mainly of mild intensity and with a maximum rectal or rectal equivalent temperature less than 39.4°C or normal. Injection site rashes started between Day 3 and Day 9 post-vaccination whereas non-injection site rashes were distributed across the 42-day safety period. Of the four (4) serious adverse events reported following VARIVAX® administration, one was assessed as vaccine-related (an idiopathic thrombocytopenic purpura that occurred 24 days post-vaccination; the subject was successfully treated with immunoglobulins and recovered promptly). The other serious adverse events were hospitalisations for an infectious disease.
SUMMARY – CONCLUSIONS	**CONCLUSION** M-M-R™II was generally safe and well tolerated and its safety profile was comparable with that seen in previous studies. The safety profile of the refrigerator-stable formulation of VARIVAX® in healthy 12 to 15 month-old children was acceptable.
Date of the report	07-December-2006