SYNOPSIS

Name of Sponsor/ Company Sanofi Pasteur MSD S.N.C.	**Individual Study Table referring to part of the dossier** **Volume** **Page**	*(For National Authority use only)*
Name of Finished Products: M-M-R™II manufactured with rHA and VARIVAX®		
Name of Active Ingredients: **M-M-R™II manufactured with rHA**: measles, mumps, and rubella vaccine (live) **VARIVAX®**: varicella vaccine (live)		

Title of the study	An open, randomised, comparative, multicentre study of the immunogenicity and safety of M-M-R™II manufactured with recombinant Human Albumin (rHA) and VARIVAX® when administered concomitantly by intramuscular (IM) route or subcutaneous (SC) route at two separate injection sites in healthy subjects 12 to 18 months of age. Study Identification Number: **X04-MMRr-301** EudraCT number: **2004_002586_21**	
Principal investigators	**France**: Yves GILLET, MD **Germany**: Pirmin HABERMEHL, MD	
Study centres	Seventy-two (72) active centres, in France and Germany	
Publication	None	
Study period (years)	First Visit First Subject: 20-January-2005 First Visit Last Subject: 03-August-2005 Last Visit Last Subject: 05-September-2005	**Phase of development** Phase IIIb

Objectives

Primary objective

To demonstrate that, when given concomitantly with VARIVAX® by the same route at 12-18 months of age at separate injection sites, a single dose of M-M-R™II rHA administered by IM route is as immunogenic as a single dose of M-M-R™II rHA administered by SC route in terms of response rates to measles, mumps and rubella as measured by enzyme linked immunosorbent assay (ELISA) at 42 days following vaccination,

and/ or:

To demonstrate that, when given concomitantly with M-M-R™II rHA by the same route at 12-18 months of age at separate injection sites, a single dose of VARIVAX® administered by IM route is as immunogenic as a single dose of VARIVAX® administered by SC route in terms of response rate to varicella as measured by glycoprotein ELISA (gpELISA) at 42 days following vaccination.

The primary hypotheses were that the IM route would be non-inferior to the SC route for both vaccines.

Secondary objectives

- To summarise the antibody titres to measles, mumps, rubella and varicella at 42 days following vaccination in subjects 12 to 18 months of age immunised with M-M-R™II rHA and VARIVAX® administered concomitantly at two separate injection sites by the same route IM or SC.
- To evaluate the safety profiles of M-M-R™II rHA and VARIVAX® administered concomitantly at two separate injection sites by the same route IM or SC.

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Methodology Open-label randomised, comparative, multicentre study with 2 parallel groups.
Seven hundred (700) subjects planned to be randomised (1:1) to receive a single dose of M-M-R™II rHA + a single dose of VARIVAX®:
Group 1: both vaccines by IM route; **Group 2:** both vaccines by SC route

Number of subjects (planned and analysed)

Planned: 700 subjects (350 per group)

Randomised: 752 subjects

Table 1: Disposition of Subjects

	Group 1 – IM	Group 2 – SC
	n (%)	n (%)
n randomised [1]	374	378
n vaccinated [2]	374 (100%)	378 (100%)
n completed	373 (99.7%)	377 (99.7%)
n withdrawn	1 (0.3%) [3]	1 (0.3%) [4]
n withdrawn due to an adverse event	0	0

[1] 24 additional subjects were screened and not randomised
[2] Who received at least one study vaccine
[3] Withdrawal for personal reason
[4] Lost to follow-up

Analysed:

Table 2: Analysis Sets of Subjects

	Group 1 – IM	Group 2 – SC	All
	n (%)	n (%)	n (%)
Randomised Set	374	378	752
Full Analysis Set (FAS) [1]	370 (98.9%)	375 (99.2%)	745 (99.1%)
FAS – Measles	369 (98.7%)	374 (98.9%)	743 (98.8%)
FAS – Mumps	370 (98.9%)	375 (99.2%)	745 (99.1%)
FAS – Rubella	369 (98.7%)	374 (98.9%)	743 (98.8%)
FAS – Varicella	369 (98.7%)	375 (99.2%)	744 (98.9%)
Per Protocol Sets (PPS)			
PPS initially seronegative to Measles [2]	349 (93.3%)	363 (96.0%)	712 (94.7%)
PPS initially seronegative to Mumps [3]	349 (93.3%)	363 (96.0%)	712 (94.7%)
PPS initially seronegative to Rubella [4]	321 (85.8%)	318 (84.1%)	639 (85.0%)
PPS initially seronegative to Varicella [5]	336 (89.8%)	345 (91.3%)	681 (90.6%)
PPS initially seronegative to Measles + Mumps + Rubella [2+3+4]	316 (84.5%)	316 (83.6%)	632 (84.0%)
PPS initially seronegative to Measles + Mumps + Rubella + Varicella [2+3+4+5]	298 (79.7%)	300 (79.4%)	598 (79.5%)
Safety Set [6]	375	377	752

[1] All subjects with post-vaccination serology results irrespective of baseline antibody titres and according to the route as issued from the randomisation
[2] Baseline antibody titres < 255 mIU/mL, [3] < 10 ELISA Ab units/mL, [4] < 10 IU/mL, [5] < 1.25 gpELISA units/mL
[6] Actual route. Subject 13601 randomised in the SC group (Group 2) received both vaccines by IM route thus was analysed for safety in the IM group (Group 1)

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Name of Active Ingredients: **M-M-R™II manufactured with rHA**: measles, mumps, and rubella vaccine (live) **VARIVAX®**: varicella vaccine (live)		

Diagnosis and main criteria for inclusion	Healthy infants aged 12-18 months; consent form signed by both parents/ legal representative; no previous vaccination history and/ or suspected clinical history and/ or exposure in the past 30 days to measles, mumps, rubella and/ or varicella; no known sensitivity/ allergy to any component of the study vaccines and/ or anaphylactic/ anaphylactoid reaction to egg proteins; no impairment of the immune system (including use of corticosteroids); no receipt of any inactivated vaccines in the past 14 days or any live vaccines in the past 30 days.
Test/ reference vaccines, dose and mode of administration, batch numbers	**M-M-R™II rHA**: lyophilised preparation of combined live attenuated measles virus (more attenuated Enders' Edmonston strain), live attenuated mumps virus (Jeryl Lynn™ [Level B] strain) and live attenuated rubella virus (Wistar RA 27/3 strain). **Presentation**: Powder and solvent for suspension for injection. **Dose**: Single (entire volume of the reconstituted vaccine). **On site storage**: +2°C to +8°C **Batch numbers**: Powder 0644172 (expiry 05-July-2005)/ Diluent 1032L (expiry 30-April-2006). **VARIVAX®**: lyophilised preparation with ≥ 1350 plaque-forming units (PFU) of a live attenuated varicella virus (Oka/ Merck strain). **Presentation**: Powder and solvent for suspension for injection. **Dose**: Single (entire amount of the reconstituted vaccine). **On site storage**:+2°C to +8°C **Batch number**: HV20550 (expiry 12-August-2005).
Vaccination schedule	**Group 1:** received M-M-R™II rHA and VARIVAX® both by IM route at two separate injection sites at Day 0. **Group 2:** received M-M-R™II rHA and VARIVAX® both by SC route at two separate injection sites at Day 0.
Follow-up duration	First blood sample taken before vaccination and second blood sample taken at Day 42 (+14 days) post-vaccination. Safety follow-up for 42 days post-vaccination.
Criteria for evaluation	**Immunogenicity** **Primary**: Response rates to measles, mumps, rubella and varicella 42 days following vaccination. **Secondary:** Geometric mean of antibody titres to measles, mumps, rubella and varicella 42 days following vaccination. **Safety: Table 3: Safety Criteria**

Visit 1 Day 0				**Day 4**		**Visit 2 Day 42**
Solicited injection-site adverse reactions[1]						
Other[2] injection-site adverse reactions Temperature[3] Measles-, rubella- and varicella-like rashes (injection-site or non-injection-site) and mumps-like symptoms Other[2] systemic[4] adverse events						
Serious adverse events						

[1] Injection site erythema, injection site swelling and injection site pain
[2] Spontaneously reported
[3] Temperatures were measured daily axillary and additionally rectally if axillary temperature ≥ 37.1°C. Analysis was made on rectal equivalent temperatures (rectal temperatures or temperatures converted to rectal equivalent by adding 0.9°C to axillary temperatures)
[4] Adverse events not at the injection-site

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Statistical methods

Immunogenicity

Primary: the statistical analysis was based on two-sided 95% (adjusted for multiplicity) confidence interval (CI) stratified by regions (i.e. centres or pooled centres based on geographic location) around the difference in response rates [Group 1 (IM) – Group 2 (SC)] for each valence (i.e. 3 valences for M-M-R™II rHA, 1 valence for VARIVAX®). The non-inferiority criterion was achieved if the lower bound of the 95% CI was > -10% and was met for one or both vaccines. Hochberg adjustment was applied for multiplicity. Immunogenicity was evaluated on the PPS with supportive analysis on the FAS.

Secondary: a descriptive analysis was performed for measles, mumps, rubella and varicella including geometric mean of antibody titres (GMT) and 95% CI.

Safety

A descriptive analysis was performed for adverse events with separate summaries of injection-site adverse reactions and systemic adverse events.

SUMMARY – CONCLUSIONS

DEMOGRAPHY

Table 4: Demographic and Other Baseline Characteristics – Randomised set

		Group 1– IM (N=374)	Group 2 – SC (N=378)
Age at vaccination (months)	Mean (SD) Median Minimum - Maximum	13.79 (1.72) 13.19 12.02 ; 18.96	13.69 (1.59) 13.14 11.96 [1] ; 18.86
Gender	Male Female	206 (55.1%) 168 (44.9%)	210 (55.6%) 168 (44.4%)
Body mass index (kg/m^2)	Mean (SD) Median Minimum - Maximum	16.92 (1.60) 16.87 12.44 ; 22.68	16.92 (1.46) 16.87 12.78 ; 24.65

[1] Subject 13401 in the SC group had 12 months minus 2 days at inclusion; this subject was not excluded from the PPS.
SD: Standard deviation

The two groups were comparable with respect to these characteristics. The results on the FAS, PPS and Safety Set were comparable to those on the Randomised Set.

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IMMUNOGENICITY RESULTS

Table 5: Summary of Antibody Responses (Response Rates and GMT) to Measles, Mumps, Rubella and Varicella at 6 Weeks Post-vaccination for Subjects Initially Seronegative to Measles, Mumps, Rubella or Varicella (< 1.25 gpELISA units/mL) – Antigen specific PPS

		Group 1 – IM (N[1]=374)			Group 2 – SC (N[1]=378)		
		n[2]	Antibody response	[95% CI]	n[2]	Antibody response	[95% CI]
Measles	n (%) ≥255 mIU/mL	349	329/349 (94.3%)	[91.3 ; 96.5]	363	349/363 (96.1%)	[93.6 ; 97.9]
	GMT		2396.43	[2117.72 ; 2711.82]		2560.64	[2278.50 ; 2877.71]
Mumps	n (%) ≥10 ELISA Ab units/mL	349	341/349 (97.7%)	[95.5 ; 99.0]	363	356/363 (98.1%)	[96.1 ; 99.2]
	GMT		86.42	[78.66 ; 94.95]		89.77	[82.57 ; 97.61]
Rubella	n (%) ≥10 IU/mL	321	315/321 (98.1%)	[96.0 ; 99.3]	318	312/318 (98.1%)	[95.9 ; 99.3]
	GMT		97.22	[88.55 ; 106.73]		94.37	[85.67 ; 103.95]
Varicella	n (%) ≥5 gpELISA units/mL	336	297/336 (88.4%)	[84.5 ; 91.6]	345	295/345 (85.5%)	[81.3 ; 89.0]
	GMT		9.83	[9.20 ; 10.50]		9.21	[8.62 ; 9.84]

[1] Number of vaccinated subjects
[2] Number of subjects initially seronegative to measles, mumps, rubella or varicella contributing to each PPS

The results on the PPS for subjects initially seronegative to all 3 antigens contained in M-M-R™II rHA and on the PPS for subjects initially seronegative to all 4 antigens, as well as results on the FAS were comparable to those on the PPS for subjects initially seronegative to each specific antigen

Table 6: Non-inferiority Analysis (Stratified by Region[1]) of Response Rates to Measles, Mumps, Rubella and Varicella at 6 weeks Post-vaccination for Subjects Initially Seronegative to Measles, Mumps, Rubella or Varicella (< 1.25 gpELISA units/mL) – Antigen specific PPS

	Estimate of the difference Group 1 (IM) – Group 2 (SC)	[95% CI] [2]	Non-inferiority
Measles	-1.89%	[-5.28 ; 1.29]	Yes
Mumps	-0.33%	[-2.67 ; 2.00]	Yes
Rubella	-0.02%	[-2.42 ; 2.43]	Yes
Varicella	2.93%	[-2.18 ; 8.06]	Yes

[1] Stratification by region (centres were pooled based on geographic location in 4 regions in France and in 5 regions in Germany due to low recruitment by centre) with a weight proportional to the number of subjects within each region
[2] The lower bound of the 95% CI on the difference >- 10% implies that the difference is statistically significantly lower than the pre-defined clinically relevant non-inferiority margin of 10%.

The non-stratified analysis and stratified by country as well as the analysis done on the FAS provided comparable results to the region-stratified analysis performed on the PPS..

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SAFETY RESULTS

The following Table 7 summarises all reported adverse events by group. Safety follow-up was obtained for all vaccinated subjects.

Table 7: Global Summary of Safety – Safety Set (N=752)

	Group 1 – IM n vaccinated =374 [1]	Group 2 – SC n vaccinated =376[1]
	n (%)[2]	n (%)[2]
Any adverse event [3] from Day 0 to Day 42	**313 (83.7%)**	**325 (86.4%)**
Any vaccine-related adverse event [3] to M-M-R™II rHA	190 (50.8%)	202 (53.7%)
Any vaccine-related adverse event [3] to VARIVAX®	173 (46.3%)	210 (55.9%)
Any injection-site adverse reaction from Day 0 to Day 42	**97 (25.9%)**	**151 (40.2%)**
Any injection-site adverse reaction to M-M-R™II rHA	59 (15.8%)	97 (25.8%)
Any injection-site adverse reaction to VARIVAX®	78 (20.9%)	129 (34.3%)
Any injection-site rash of interest [4]	0	10 (2.7%)
Any systemic adverse event from Day 0 to Day 42	**295 (78.9%)**	**295 (78.5%)**
Any vaccine-related systemic adverse event	156 (41.7%)	156 (41.5%)
Any vaccine-related systemic adverse event to M-M-R™II rHA	153 (40.9%)	149 (39.6%)
Any vaccine-related systemic adverse event to VARIVAX®	121 (32.4%)	125 (33.2%)
Any measles/ measles-like rash [5]	11 (2.9%)	10 (2.7%)
Any mumps/ mumps-like illness	0	1 (0.3%)
Any rubella/ rubella-like rash [5]	10 (2.7%)	10 (2.7%)
Any varicella/ varicella-like rash [5]	2 (0.5%)	12 (3.2%)
Any serious adverse event from Day 0 to Visit 2	**1 (0.3%)**	**4 (1.1%)**
Any death	0	0
Any vaccine-related serious adverse event	0	1 (0.3%)
Any vaccine-related serious adverse event to M-M-R™II rHA	0	1 (0.3%) [6]
Any vaccine-related serious adverse event to VARIVAX®	0	1 (0.3%) [6]
Any withdrawal due to an adverse event	**0**	**0**

[1] One subject in each group was not vaccinated according to protocol (subject 27601 in the IM group received the diluent of M-M-R™II rHA only and subject 11718 in the SC group received M-M-R™II rHA by deep SC); these subjects were excluded from the safety analyses.

[2] Number of subjects reporting the event at least once (percentages were calculated based on the number of subjects correctly vaccinated)

[3] Injection-site adverse reactions and systemic adverse events combined

[4] All were varicella-like injection-site rashes (2 at M-M-R™II rHA injection-site, 7 at VARIVAX® injection-site and 1 at both injection-sites)

[5] Non-injection-site measles-, rubella- or varicella-like rashes

[6] Otitis media of moderate intensity at Day 5 post-vaccination considered as a complication of a purulent rhinitis; hospitalisation for one day and discharge after recovery; the event was assessed by the investigator as possibly related to both vaccines (subject 13210).

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As shown in Table 7, the two groups were generally comparable in terms of incidence rates of systemic adverse events and measles- and rubella-like rashes and mumps-like symptoms. Varicella/ non-injection-site varicella-like rashes appeared to be less frequently reported in the IM group (0.5% in the IM group versus 3.2% in the SC group).

Injection-site adverse reactions were reported by a numerically lower number of subjects in the IM group for each vaccine (15.8% in the IM group versus 25.8% in the SC group for M-M-R™II rHA; 20.9% in the IM group versus 34.3% in the SC group for VARIVAX®). While frequencies were different, most of the injection-site adverse reactions occurred from Day 0 to Day 4 with, by decreased incidence, injection site erythema, then injection site pain, then injection site swelling, for both vaccines and for both routes.

Varicella-like injection-site rashes were reported in the SC group only (2.7% of subjects) and injection site erythema and injection site swelling occurring after Day 5 were reported by a numerically lower number of subjects in the IM group mostly following VARIVAX® injection (for injection site erythema, 0.3% in the IM group versus 4.3% in the SC group for M-M-R™II rHA, and 4.8% in the IM group versus 12.2% in the SC group for VARIVAX®; for injection site swelling, 0% in the IM group versus 1.6% in the SC group for M-M-R™II rHA, and 1.6% in the IM group versus 5.3% in the SC group for VARIVAX®).

The two groups were generally comparable with respect to the proportion of subjects who experienced a maximal rectal (or equivalent) temperature ≥ 39.4°C from Day 0 to Day 42 post-vaccination (20.9% in the IM group and 22.5% in the SC group) with about half of them from Day 5 to Day 12 post-vaccination in both groups (8.4% in the IM group and 11.7% in the SC group).

A total of 5 subjects experienced each a serious adverse event. One of these serious adverse events, an otitis media, was assessed by the investigator as possibly related to both vaccines.

No subjects were withdrawn from the study due to an adverse event.

SUMMARY – CONCLUSIONS

CONCLUSION

Immunogenicity

M-M-R™II rHA and VARIVAX® given by IM route elicited an immune response that was similar (non-inferior) to the SC administration of both vaccines as demonstrated by similar antibody response rates to measles, mumps, rubella and varicella 42 days post-vaccination. Comparable antibody titres further support this conclusion.

Safety

Overall M-M-R™II rHA and VARIVAX® given IM or SC were generally well tolerated. Overall the safety profile of M-M-R™II rHA and VARIVAX® was comparable for IM and SC administrations even if varicella-like rashes (injection-site and non-injection-site) and erythema and swelling at injection-sites appeared to be less frequently observed in the IM group than in the SC group.

Date of the report 21-December-2006