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Supplementary webappendix

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Supplement to: Griffiths PD, Stanton A, McCarrell E, et al. Cytomegalovirus glycoprotein-B vaccine with MF59 adjuvant in transplant recipients: a phase 2 randomised placebo-controlled trial. *Lancet* 2011; **377:** 1256–63.

Cytomegalovirus glycoprotein-B vaccine with MF59 adjuvant in transplant recipients: a phase 2 randomised placebo-controlled trial: Webappendix

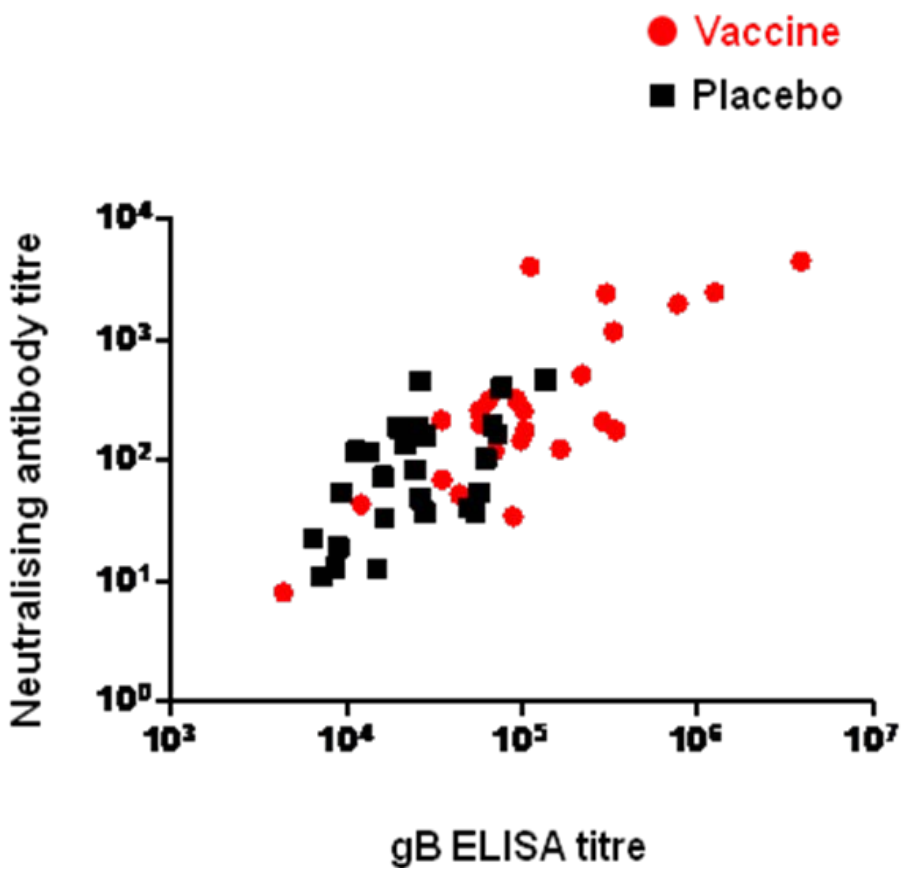
	Vaccine				Placebo			
	Cytomegalovirus positive		Cytomegalovirus negative		Cytomegalovirus positive		Cytomegalovirus negative	
	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)
	32		35		37		35	
Day 0	29	67 (40–111)	35	4 (4–4)	31	65 (40–105)	34	4 (4–4)
Day 28	29	272 (150–494)	34	4 (–)*	30	82 (54–125)	34	4 (4–4)
Day 56	24	261 (129–526)	22	5 (4–6)	27	78 (50–122)	27	4 (–)*
Day 180	19	120 (59–244)	16	4 (4–5)	22	78 (45–137)	26	4 (–)*
Day 208	16	137 (58–326)	13	17 (6–45)	18	80 (43–149)	25	4 (–)*

*Insufficient variation to compute a 95% CI. Serial dilutions of heat inactivated serum were tested. HCMV strain Towne RC256, which expresses β galacatosidase, was used and guineapig complement (5% volume/volume) was included. Target cells were human fetal foreskin fibroblasts. Infectivity was determined colourimetrically with a β-galactosidase substrate and 50% neutralising titres were calculated by graph pad prism. A dilution of 1 in 8 was the lowest used: for this analysis, negative sera were assigned a titre of 4.

Table 1: **Titre of neutralising antibody according to time from first dose of vaccine.**

Figure: Correlation of glycoprotein-B ELISA titre with neutralising antibody titre in patients seropositive for cytomegalovirus 1 month after the second dose of vaccine or placebo.

R=0·78. P<0·001.



	Number of patients given vaccine with reaction (%)	Number of patients given placebo with reaction (%)
Number of available diary cards	127	150
Injection site pain		
None	61 (48%)	130 (87%)
Mild	43 (34%)	14 (9%)
Moderate	19 (15%)	5 (3%)
Severe	4 (3%)	1 (<1%)
Injection site erythema		
None	101 (80%)	135 (90%)
Mild	19 (15%)	14 (9%)
Moderate	3 (2%)	1 (<1%)
Severe	4 (3%)	0 (0%)
Injection site swelling		
None	108 (85%)	139 (93%)
Mild	7 (6%)	10 (7%)
Moderate	9 (7%)	1 (<1%)
Severe	3 (2%)	0 (0%)
Fever		
None	121 (95%)	141 (94%)
Mild	1 (<1%)	5 (3%)
Moderate	3 (2%)	4 (3%)
Severe	2 (2%)	0 (0%)
Headache		
None	97 (76%)	121 (81%)
Mild	21 (17%)	18 (12%)
Moderate	7 (6%)	10 (7%)
Severe	2 (2%)	1 (<1%)
Myalgia		
None	78 (61%)	122 (81%)
Mild	32 (25%)	18 (12%)
Moderate	12 (10%)	7 (5%)
Severe	5 (4%)	3 (2%)

Missing-equals-excluded analysis. In these calculations, the denominator was the number of available diary cards.

Table 2: **Primary safety analysis—solicited adverse events (occurring within 7 days after injection)—at any injection visit**

	Vaccine group			Placebo group		
	Number of patients	**Number of events**	**Number of events assessed as related to the injection**	**Number of patients**	**Number of events**	**Number of events assessed as related to the injection**
Serious adverse events						
Deaths†	5	5	0	8	8	0
Transplantation	10	10	0	8	8	0
Hospitalisation‡	5	7	0	11	19	0
Total	**20**	**22**	**0**	**27**	**35**	**0**
Unsolicited adverse events occurring within 28 days after injection						
Cardiac disorders	1	1	0	0	0	0
Emesis	0	0	0	1	1	0
Gastrointestinal disorder	8	12	0	7	9	0
General disorders and administration site conditions§	11	19	3	6	11	0
Infections and infestations¶	9	13	1	9	11	0
Metabolism and nutrition	2	3	0	3	3	0
Musculoskeletal, connective tissue, and bone disorders‖	7	12	4	5	8	0
Nervous system disorders	7	17	0	8	8	0
Psychiatric disorders	1	1	0	0	0	0
Renal and urinary disorders	1	1	0	0	0	0
Reproductive systems and breast disorders	2	4	0	0	0	0
Respiratory, thoracic, and mediastinal disorders	1	1	0	0	0	0
Skin and connective tissue disorders**	6	8	7	8	8	4
Blood and lymphatic	3	8	0	2	3	0
Total	**59**	**100**	**15**	**49**	**62**	**4**

Not needed now. †Causes of death in vaccine group were progression of liver disease (two patients), haemorrhage (two), and stroke (one); in placebo group they were progression of liver disease (four), haemorrhage (two), hypoxic brain injury (one), and infection (one). ‡Reasons for hospitalisation episodes in vaccine group were infection (three), hepatic decompensation (one), medical procedure (one), and other (two); in placebo group they were infection (eight), hepatic decompensation (three), medical procedure (four), metabolic (three), and other (one). §In vaccine group, pyrexia and two with pain .·¶In vaccine group, one with congested head. ||In vaccine group, two with aches, one with heavy arm, and one with heavy hand . **In vaccine group, four with itching, three with bruise; in placebo group, one with itching, one with bruise, one with scratch, and one with scab.

Table 3: **Serious adverse events occurring at any time and unsolicited adverse events occurring within 28 days of every injection**

	Median CD4 T-cell frequency (%) at day of transplant (range)	Significance (p value)
Seropositive donor, seronegative recipient		
Vaccine (n=10)	<0·01%	NA
Placebo (n=4)	<0·01%	
Seropositive donor, seropositive recipient		
Vaccine (n= 6)	0·22% (0·06–11·30)	0·63
Placebo (n=10)	0·17% (0·12–1·98)	
Seronegative donor, seropositive recipient		
Vaccine (n=10)	0·193% (<0·01–1·172)	0·59
Placebo (n=7)	0·203% (<0·01–1·69)	
Seronegative donor, seronegative recipient		
Vaccine (n=7)	<0·01%	NA
Placebo (n=7)	<0·01%	

NA=not applicable. The frequency of interferon-γ producing cells as a percentage of the total CD4 T-cell population is shown.·The cutoff of this assay was 0·01%. For comparative purposes a median frequency of 0·3% (0·1–5·1) was seen in a group of healthy cytomegalovirus seropositive volunteers (n=17) with the same assay. Significance values given for the two recipient seropositive groups were for comparisons of the indicated median CD4 T-cell frequencies in the vaccine and placebo groups with the Mann-Whitney test.·

Table 4: **CD4 T-cell responses against a cytomegalovirus whole virion lysate at day of transplantation segregated according to serostatus of donor or recipient in patients given placebo or vaccine of glycoprotein-B and MF59 adjuvant·**