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Title

Analytical Test Report for the assessment of neutralizing antibodies in clinical trial CMC11 (DMID 04-107)

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ARPE-19	human adult retinal pigment epithelial cells
CI	Confidence interval
CMV	Cytomegalovirus
ELN	Electronic Lab Notebook
gB	Glycoprotein B
GFP	Green fluorescent protein
GM	Geometric mean
Ig	Immunoglobulin
MRC-5	Cell line developed by "Medical Research Council"
NCPP	Non-clinical Product Performance
ORF	Open reading frame
w/ C'	with complement

1 Summary

The present report describes analysis of neutralizing antibodies in the sera of samples collected form CMC11 (DMID 04-107) clinical study. This study was a randomized, blind-observer, placebo-controlled, Phase II study designed to determine the safety and immunogenicity of the experimental CMV gB/MF59 vaccine administered to patients awaiting solid organ transplantation (SOT). In addition to the previous immunomonitoring performed by the Sponsor under the Primary Clinical Trial, Sanofi Pasteur evaluated the neutralizing activities from a subset of serum samples provided by the Sponsor. A specific study agreement (AC/ac/SP/UCLH/RFH JRO agreement amendment 2) for complementary laboratory service assay performance was established on December 2013 to support this additional testing.

In the present analysis, CMV neutralizing antibody titers were measured with CMV BADrUL131-Y4 strain (GFP marker virus) and human epithelial target cells in serum samples from 63 subjects (either CMV seronegative or seropositive at D0) who received the CMV gB/MF59 vaccine at 4 scheduled visits (D0, D28 (one month after the first dose), D56 (one month after the second dose) and D208 (one month after the third dose)). Serum samples from the placebo recipients were not tested as part of this evaluation in Sanofi Pasteur.

The neutralizing antibody titers produced against the glycoprotein-B protein contained in the vaccine were significantly increased after gB/MF59 vaccination, as soon as 28 days after the first vaccine dose, in both patients who were immunologically naive to cytomegalovirus and in those with naturally acquired immunity (paired Wilcoxon test, all p-values≤0.0453 whatever the time-point within the vaccination schedule).

In CMV seronegative vaccine recipients the neutralizing antibody titers increased after each vaccine dose administration for most of the tested subjects and peaked one month after the third vaccine dose administration (Neut Ab titers median = 80 at day 208). However, the vaccine induced immunity in CMV seronegative vaccine recipients was not able to reach the neutralizing antibody titers induced by natural infection in the same demographic and clinical population (Wilcoxon test, p<0.0001).

In CMV seropositive vaccine recipients, the first gB/MF59 vaccine dose administration was able to boost the pre-existing immunity (Neut Ab titers median = 8160 at D28, paired Wilcoxon test, p-values<0.0001) and neutralizing antibody titer medians were maintained at a plateau but no more boosted beyond the first vaccination.

2 Introduction

CMC11(DMID 04-107) clinical study was a randomized, blind-observer, placebo-controlled, Phase II study designed to determine the safety and immunogenicity of the experimental CMV gB/MF59 vaccine administered to patients awaiting solid organ transplantation (SOT). 140 eligible patients (70 CMV seronegative, 70 CMV seropositive) currently on the transplant waiting

or work-up lists for a renal or a liver transplant at Royal Free Hospital, London, UK (ClinicalTrials.gov, NCT00299260) were to receive 3 doses of 20µg of the CMV gB vaccine adjuvanted with MF59 or 3 doses of placebo administered by intramuscular (IM) injection in the deltoid muscle on a 0-, 1, and 6-month schedule. If a patient was transplanted during the participation in the trial, no further vaccinations were given and serial blood samples were tested for cytomegalovirus DNA by real-time quantitative PCR (rtqPCR). Any patient with one blood sample containing more than 3000 cytomegalovirus genomes per mL received ganciclovir until two consecutive undetectable cytomegalovirus DNA measurements. Safety and immunogenicity were co-primary endpoints and were assessed by intention to treat in patients who received at least one dose of vaccine or placebo.

For immunomonotoring, serum samples were requested at the time of first injection and 28, 56, 180, and 208 days later in those who received all three injections. In the subset of patients who received transplants, additional samples were requested at time of transplantation and 7, 35, 63, and 90 days later. The geometric mean titre and 95% CI of IgG ELISA antibodies measured against glycoprotein B was calculated at each timepoint and plotted according to patient cytomegalovirus serostatus and randomization group. Neutralizing antibodies were measured with Towne RC256 (β-galactosidase marker virus) and human fibroblast target cells. As described in the published results (1), the antibody titre (ELISA IgG) produced against the glycoprotein-B protein contained in the vaccine was significantly increased 1 month after the second injection in patients given the vaccine compared with those given placebo, both in patients who were immunologically naive to cytomegalovirus and in those with naturally acquired immunity. However, the geometric mean titre of neutralizing antibodies was not significantly increased at day 56 in seronegative patients, but was significantly increased in the seropositive patients in whom the neutralizing antibody titres correlated with glycoprotein-B antibody titres.

3 General Information

3.1 Documentation

ID number	Title	Nature
RED_00087996	Analytical Test Plan for the assessment of neutralizing antibodies in clinical trial CMC11	Protocol
RED_00089640	Amendment N°1 to ATP RED_00087996: assessment of neutralizing antibodies in clinical trial CMC11 (DMID 04-107)	Amendment
RED_00067042	Utilisation et entretien du Viruscope Microvision dans le bâtiment X Nord *version applicable*	Instruction

ID number	Title	Nature
RED_00065951	Entretien, vérification et utilisation des lecteurs ELISPOT Microvision *version applicable*	Instruction
RED_00086341	Détermination du titre en anticorps neutralisants anti-CMV dans des sérums humains par µPRNT (Plaque Reduction Neutralization Test) sur cellules épithéliales (ARPE-19) avec le virus GFP BADrUL131-Y4 *version applicable*	Instruction
RED_00084396	FDT_Séroneutralisation par fluorescence de sera humains CMV sur cellules ARPE-19 par µPRNT *version applicable*	Form
RED_00087520	Processus d'analyse pour les données de séroneutralisation_Etude clinique CMC02 *version applicable*	Instruction
RED_00078364	Report of characterization of the cytomegalovirus (CMV) Micro Plaque Reduction Neutralization Test (µPRNT) using the GFP BADrUL131-Y4 virus on epithelial cells_RED_00067121	Rapport

3.2 Seroneutralisation assay schedule

N° test	Date from	Test Number	Operators	Number of plates of ARPE-19 SN assay per test / plates ID
Test N°1	11 March 2016	20160311_AMA_SN_01	Audrey Mamessier Sandrine Painchaud	12 Plates PL1 to PL12
Test N°2	06 April 2016	20160406_AMA_SN_02	Audrey Mamessier Sandrine Painchaud	17 Plates PL13 to PL29
Test N°3 (re-test)	14 April 2016	20160414_AMA_SN_03	Audrey Mamessier	4 Plates PL30 to PL33

3.3 Responsibilities

3.3.1 Manager/Supervisor

The Manager/Supervisor was responsible for ensuring that all staff performing work related to this Analytical Test Plan (ATP) was properly trained in all relevant procedures.

The part described in the ATP was realized under the supervision of the Analytical Project Manager Catherine Caillet within the Human Immunology Unit of the Microbio-Immunology 2 (MIM2) platform as part of the PTR/R&NCS department of Sanofi Pasteur, 1541 avenue Marcel Mérieux, 69280 Marcy l'Etoile.

3.3.2 Laboratory Analysts

The analyst was responsible for executing the procedures described in the ATP and all relevant instructions as well as maintaining the associated training records in the corresponding binder.

3.3.3 Statistical Analysts

Neutralizing antibody titers were analyzed with the support of Sanofi Pasteur System Biology and Statistics platform (R&NCS-ESBD department).

Table 1: Responsibilities

Responsibilities	Title	Name	Address
Sponsor	University College London (UCL) Biomedicine Research & Development Unit	ND	Joint Research Office Gower Street London WC1E 6BT, UK
Sanofi Pasteur Representative	Clinical Team Leader	Sylvie Pichon	sanofi pasteur Campus Mérieux - Bat X Ouest 1541, Avenue Marcel Mérieux 69280 Marcy l'Etoile, France Tel : 33 00 04 37 37 08 03 Email : Sylvie.Pichon@sanofipasteur.com
Oversight of the clinical trial	Principal Investigator	Pr Paul D Griffiths	Royal Free Hospital Department of Virology Pond St London NW3 2QG, UK Tel : 44 20 7830 2997 Email : p.griffiths@medsch.ucl.ac.uk
Sample preparation	Laboratory Manager	ND	Royal Free Virology laboratory Pond St London NW3 2QG
Seroneutralization assessment	Analytical Project Manager	Catherine Caillet	Sanofi Pasteur R&NCS/PTR Immunology-Microbiology 2 platform sanofi pasteur 1541, avenue Marcel Mérieux 69280 Marcy l'Etoile, France Tel (C.Caillet) : 33 00 04 37 37 36 92 Email : Cattherine.Caillet@sanofipasteur.com
	Responsible scientist	Fabienne Piras-Douce	
	Analysts	Audrey Mamessier, Sandrine Painchaud	

Responsibilities	Title	Name	Address
Analysis	Statisticians	Catherine Hessler	Sanofi Pasteur R&NCS/ESBD System Biology and Statistics platform sanofi pasteur 1541, avenue Marcel Mérieux 69280 MARCY L'ETOILE, FRANCE
	Analysts	Sylviane Gautheron Joseline Dubayle	

3.4 Lab-book references

Responsible scientist	Manipulators	Electronic Laboratory Notebook (ELN) references
Fabienne Piras-Douce	Audrey Mamessier Sandrine Painchaud Sarah Begue	MLE-SBE-000090 MLE-AMA-000081 MLE-AMA-000085 to MLE-AMA-000094 MLE-AMA-000098 to MLE-AMA-000099

All the raw data and the preliminary analyzed data are stored in Nugenesis with the following references (Table 2).

Table 2: ID numbers of raw data files in NuGenesis AvP_FR_Research database

Data ID	Data Name	Department & Platform	Analyst	Project Name	Instrument ID	Software Name	Test Numb	Date/Time of Capture
CCD126956	TXT CMC11 TEST3	PTR- Microbio Immunology Franchise 2	Mamessier Audrey	CMV	PM0181 - Elispot 1 Microvision	Spot v3.3.1	CMC11	20/04/2016 12:45
CCD126957	SPT CMC11 TEST3	PTR- Microbio Immunology Franchise 2	Mamessier Audrey	CMV	PM0181 - Elispot 1 Microvision	Spot v3.3.1	CMC11	20/04/2016 12:45
CCD126952	20160414 CMC11 TEST3	PTR- Microbio Immunology Franchise 2	Mamessier Audrey	CMV	PM0627 - Viruscope Microvision 2	Viruscope v2.0.4	CMC11	20/04/2016 11:12
CCD123813	TXT	PTR- Microbio Immunology Franchise 2	Mamessier Audrey	CMV	PM0181 - Elispot 1 Microvision	Spot v3.3.1	CMC11	12/04/2016 20:41
CCD123820	SPT	PTR- Microbio Immunology Franchise 2	Mamessier Audrey	CMV	PM0181 - Elispot 1 Microvision	Spot v3.3.1	CMC11	12/04/2016 20:41
CCD123788	20160408 CMC11 TEST2	PTR- Microbio Immunology Franchise 2	Mamessier Audrey	CMV	PM0627 - Viruscope Microvision 2	Viruscope v2.0.4	CMC11	12/04/2016 12:40
CCD111171	20160311 CMC11 TEST1	PTR- Microbio Immunology Franchise 2	Mamessier Audrey	CMV	PM0627 - Viruscope Microvision 2	Viruscope v2.0.4	CMC11	22/03/2016 12:10
CCD074906	SPT	PTR- Microbio Immunology Franchise 2	Mamessier Audrey	CMV	PM0181 - Elispot 1 Microvision	Spot v3.3.1	CMC11	16/03/2016 13:16
CCD074306	TXT	PTR- Microbio Immunology Franchise 2	Mamessier Audrey	CMV	PM0181 - Elispot 1 Microvision	Spot v3.3.1	CMC11	16/03/2016 13:16

4 Material and methods

4.1 Material

4.1.1 Serum samples

A total of 198 sequential serum samples (approximatively 1 mL each, stored at ≤-70°C) from 63 CMV gB/MF59 vaccine recipients as described in Table 3, collected at baseline (D0), D28, D56 and D208, were analyzed.

The serum samples were heat inactivated (+56°C, 30min) in Sanofi Pasteur laboratory, before performing the neutralizing assay (no heat inactivation performed by the Royal Free Virology laboratory during the sample preparation).

The serum sample ID and their allocation per seroneutralization (SN) assay and per SN plates are described in Table 4. The experiments were performed under blinded conditions using the sample ID provided by the sponsor. Each groups were tested independently either in test 1 or test 2. The test 3 was dedicated to re-test some out-of range samples.

Table 3: Number of Tested Samples per Group and Visits

	Transplant group	CMV status	V01(N) D0	V02(N) D28	V03(N) D56	V05(N) D208	**Total**
Group 1	Renal	Positive	18*	19	18	13	**68**
Group 2	Renal	Negative	20	20	16	11	**67**
Group 3	Liver	Positive	10	10	5	1	**26**
Group 4	Liver	Negative	14	14	7	2	**37**
Total			**62**	**63**	**46**	**27**	**198**

1 Sample 001-00028-V01 was missing

Table 4: List of CMC11 clinical trial samples by groups

#Group	Sample ID	Visit for sampling	Sampling date	#TEST for SN CMC11	SN assay plate ref
001	001-00001 V#1	V1	14/09/2006	1	PL1
001	001-00001 V#2	V2	13/10/2006	1	PL1
001	001-00001 V#3	V3	10/11/2006	1	PL1
001	001-00001 V#5	V5	16/04/2007	1	PL1
001	001-00006 V#1	V1	21/09/2006	2	PL13
001	001-00006 V#2	V2	25/10/2006	2	PL13
001	001-00006 V#3	V3	29/11/2006	2	PL13
001	001-00006 V#5	V5	25/05/2007	2	PL13
001	001-00013 V#1	V1	13/11/2006	1	PL1
001	001-00013 V#2	V2	18/12/2006	1	PL1
001	001-00016 V#1	V1	24/11/2006	1	PL2
001	001-00016 V#2	V2	22/12/2006	1	PL2
001	001-00016 V#3	V3	26/01/2007	1	PL2
001	001-00016 V#5	V5	16/08/2007	1	PL2
001	001-00021 V#1	V1	01/12/2006	1	PL2
001	001-00021 V#2	V2	21/12/2006	1	PL2
001	001-00021 V#3	V3	23/01/2007	1	PL2
001	001-00021 V#5	V5	28/06/2007	1	PL2
001	001-00022 V#1	V1	15/12/2006	2	PL13
001	001-00022 V#2	V2	16/01/2007	2	PL13
001	001-00022 V#3	V3	13/02/2007	2	PL13
001	001-00022 V#5	V5	16/07/2007	2	PL13
001	001-00024 V#1	V1	22/02/2007	2	PL14
001	001-00024 V#2	V2	15/03/2007	2	PL14
001	001-00024 V#3	V3	21/05/2007	2	PL14
001	001-00024 V#5	V5	14/01/2009	2	PL14
001	001-00025 V#1	V1	08/03/2007	2	PL15
001	001-00025 V#2	V2	03/04/2007	2	PL15
001	001-00025 V#3	V3	21/05/2007	2	PL15
001	001-00025 V#5	V5	19/01/2009	2	PL15
001	001-00028 V#1	V1	16/04/2007	missing sample	N/A
001	001-00028 V#2	V2	18/05/2007	2	PL14
001	001-00028 V#3	V3	26/07/2007	2	PL14
001	001-00035 V#1	V1	04/02/2008	1	PL3
001	001-00035 V#2	V2	05/03/2008	1	PL3
001	001-00035 V#3	V3	04/04/2008	1	PL3
001	001-00035 V#5	V5	18/09/2008	1	PL3
001	001-00036 V#1	V1	21/02/2008	1	PL3
001	001-00036 V#2	V2	18/06/2008	1	PL3
001	001-00038 V#1	V1	11/04/2008	2	PL15
001	001-00038 V#2	V2	08/05/2008	2	PL15
001	001-00038 V#3	V3	03/07/2008	2	PL15
001	001-00036 V#3	V3	17/07/2008	1	PL3
001	001-00038 V#5	V5	21/01/2009	2	PL15
001	001-00041 V#1	V1	22/05/2008	2	PL16
001	001-00041 V#2	V2	22/07/2008	2	PL16
001	001-00041 V#3	V3	12/08/2008	2	PL16
001	001-00041 V#5	V5	23/02/2009	2	PL16
001	001-00042 V#1	V1	27/05/2008	2	PL16
001	001-00042 V#2	V2	25/06/2008	2	PL16
001	001-00042 V#3	V3	04/08/2008	2	PL16
001	001-00042 V#5	V5	26/01/2009	2	PL16
001	001-00045 V#1	V1	30/05/2008	2	PL17
001	001-00045 V#2	V2	07/07/2008	2	PL17
001	001-00045 V#3	V3	31/07/2008	2	PL17
001	001-00045 V#5	V5	16/01/2009	2	PL17
001	001-00046 V#1	V1	09/06/2008	2	PL17
001	001-00046 V#2	V2	08/07/2008	2	PL17
001	001-00046 V#3	V3	11/08/2008	2	PL17
001	001-00047 V#1	V1	12/06/2008	2	PL18
001	001-00047 V#2	V2	17/07/2008	2	PL18
001	001-00047 V#3	V3	14/08/2008	2	PL18
001	001-00049 V#1	V1	04/07/2008	2	PL18
001	001-00049 V#2	V2	19/08/2008	2	PL18
001	001-00049 V#3	V3	16/09/2008	2	PL18
001	001-00053 V#1	V1	19/08/2008	2	PL19
001	001-00053 V#2	V2	18/09/2008	2	PL19
001	001-00053 V#3	V3	05/01/2009	2	PL19
001	001-00053 V#5	V5	25/03/2009	2	PL19

#Group	Sample ID	Visit for sampling	Sampling date	#TEST for SN CMC1	SN assay plate ref
002	002-00001 V#1	V1	21/09/2006	1	PL4
002	002-00001 V#2	V2	30/10/2006	1	PL4
002	002-00001 V#3	V3	04/12/2006	1	PL4
002	002-00003 V#1	V1	15/11/2006	1	PL4
002	002-00003 V#2	V2	20/12/2006	1	PL4
002	002-00003 V#3	V3	25/01/2007	1	PL4
002	002-00005 V#1	V1	22/02/2007	1	PL5
002	002-00005 V#2	V2	03/09/2007	1	PL5
002	002-00005 V#3	V3	29/09/2007	1	PL5
002	002-00005 V#5	V5	20/11/2007	1	PL5
002	002-00007 V#1	V1	26/03/2007	2	PL21
002	002-00007 V#2	V2	19/04/2007	2	PL21
002	002-00007 V#3	V3	18/05/2007	2	PL21
002	002-00008 V#1	V1	24/05/2007	2	PL21
002	002-00008 V#2	V2	28/06/2007	2	PL21
002	002-00008 V#3	V3	27/07/2007	2	PL21
002	002-00012 V#1	V1	04/07/2007	1	PL5
002	002-00012 V#2	V2	27/07/2007	1	PL5
002	002-00012 V#3	V3	23/08/2007	1	PL5
002	002-00012 V#5	V5	20/02/2008	1	PL5
002	002-00014 V#1	V1	06/09/2007	1	PL6
002	002-00014 V#2	V2	29/09/2007	1	PL6
002	002-00014 V#3	V3	08/11/2007	1	PL6
002	002-00014 V#5	V5	01/05/2008	1	PL6
002	002-00016 V#1	V1	06/11/2007	1	PL6
002	002-00016 V#2	V2	03/12/2007	1	PL6
002	002-00016 V#3	V3	23/01/2008	1	PL6
002	002-00016 V#5	V5	03/07/2008	1	PL6
002	002-00018 V#1	V1	28/11/2007	2	PL22
002	002-00018 V#2	V2	24/01/2008	2	PL22
002	002-00018 V#3	V3	13/02/2008	2	PL22
002	002-00021 V#1	V1	30/01/2008	2	PL22
002	002-00021 V#2	V2	05/03/2008	2	PL22
002	002-00021 V#5	V5	08/09/2008	2	PL22
002	002-00022 V#1	V1	04/04/2008	2	PL23
002	002-00022 V#2	V2	29/04/2008	2	PL23
002	002-00022 V#3	V3	09/06/2008	2	PL23
002	002-00022 V#5	V5	27/10/2009	2	PL23
002	002-00024 V#1	V1	25/04/2008	2	PL21
002	002-00024 V#2	V2	09/06/2008	2	PL21
002	002-00025 V#1	V1	02/05/2008	2	PL24
002	002-00025 V#2	V2	06/06/2008	2	PL24
002	002-00025 V#5	V5	17/12/2008	2	PL24
002	002-00028 V#1	V1	08/05/2008	2	PL24
002	002-00028 V#2	V2	23/10/2008	2	PL24
002	002-00028 V#5	V5	07/01/2009	2	PL24
002	002-00029 V#1	V1	15/05/2008	2	PL23
002	002-00029 V#2	V2	16/06/2008	2	PL23
002	002-00029 V#3	V3	23/07/2008	2	PL23
002	002-00029 V#5	V5	17/12/2008	2	PL23
002	002-00031 V#1	V1	21/05/2008	2	PL25
002	002-00031 V#2	V2	02/07/2008	2	PL25
002	002-00031 V#3	V3	05/08/2008	2	PL25
002	002-00035 V#1	V1	06/06/2008	2	PL25
002	002-00035 V#2	V2	25/07/2008	2	PL25
002	002-00035 V#3	V3	05/09/2008	2	PL25
002	002-00036 V#1	V1	12/06/2008	2	PL26
002	002-00036 V#2	V2	10/07/2008	2	PL26
002	002-00036 V#3	V3	18/08/2008	2	PL26
002	002-00037 V#1	V1	16/06/2008	2	PL26
002	002-00037 V#2	V2	21/07/2008	2	PL26
002	002-00037 V#3	V3	18/08/2008	2	PL26
002	002-00037 V#5	V5	26/01/2009	2	PL26
002	002-00040 V#1	V1	04/08/2008	2	PL27
002	002-00040 V#2	V2	01/09/2008	2	PL27
002	002-00040 V#3	V3	29/09/2008	2	PL27
002	002-00040 V#5	V5	05/02/2009	2	PL27

#Group	Sample ID	Visit for sampling	Sampling date	#TEST for SN CMC1	SN assay plate ref
003	003-00001 V#1	V1	03/08/2006	1	PL8
003	003-00001 V#2	V2	07/09/2006	1	PL8
003	003-00004 V#1	V1	10/08/2006	1	PL7
003	003-00004 V#2	V2	14/09/2006	1	PL7
003	003-00004 V#3	V3	26/10/2006	1	PL7
003	003-00006 V#1	V1	15/08/2006	1	PL7
003	003-00006 V#2	V2	14/09/2006	1	PL7
003	003-00006 V#5	V5	15/03/2007	1	PL7
003	003-00007 V#1	V1	05/10/2006	1	PL8
003	003-00007 V#2	V2	30/11/2006	1	PL8
003	003-00007 V#3	V3	01/02/2007	1	PL8
003	003-00009 V#1	V1	21/11/2006	1	PL8
003	003-00009 V#2	V2	11/01/2007	1	PL8
003	003-00011 V#1	V1	21/02/2007	1	PL9
003	003-00011 V#2	V2	15/03/2007	1	PL9
003	003-00011 V#3	V3	23/04/2007	1	PL9
003	003-00015 V#1	V1	21/06/2007	1	PL9
003	003-00015 V#2	V2	26/07/2007	1	PL9
003	003-00022 V#1	V1	03/12/2007	1	PL9
003	003-00022 V#2	V2	11/01/2008	1	PL9
003	003-00023 V#1	V1	07/02/2008	2	PL20
003	003-00023 V#2	V2	06/03/2008	2	PL20
003	003-00023 V#3	V3	03/04/2008	2	PL20
003	003-00024 V#1	V1	17/04/2008	2	PL20
003	003-00024 V#2	V2	22/05/2008	2	PL20
003	003-00024 V#3	V3	26/06/2008	2	PL20

#Group	Sample ID	Visit for sampling	Sampling date	#TEST for SN CMC1	SN assay plate ref
004	004-00001 V#1	V1	03/07/2006	1	PL10
004	004-00001V#2	V2	13/09/2006	1	PL10
004	004-00003 V#1	V1	03/08/2006	1	PL10
004	004-00003 V#2	V2	31/08/2006	1	PL10
004	004-00006 V#1	V1	10/08/2006	1	PL10
004	004-00006 V#2	V2	26/10/2006	1	PL10
004	004-00006 V#3	V3	10/01/2007	1	PL10
004	004-00006 V#5	V5	01/03/2007	1	PL10
004	004-00008 V#1	V1	02/11/2006	1	PL11
004	004-00008 V#2	V2	08/03/2007	1	PL11
004	004-00008 V#3	V3	19/04/2007	1	PL11
004	004-00008 V#5	V5	02/08/2007	1	PL11
004	004-00009 V#1	V1	02/11/2006	1	PL11
004	004-00009 V#2	V2	30/11/2006	1	PL11
004	004-00009 V#3	V3	11/01/2007	1	PL11
004	004-00012 V#1	V1	06/02/2007	1	PL12
004	004-00012 V#2	V2	08/03/2007	1	PL12
004	004-00016 V#1	V1	14/06/2007	2	PL27
004	004-00016 V#2	V2	12/07/2007	2	PL27
004	004-00016 V#3	V3	04/09/2007	2	PL27
004	004-00017 V#1	V1	14/06/2007	1	PL12
004	004-00017 V#2	V2	12/07/2007	1	PL12
004	004-00021 V#1	V1	16/08/2007	1	PL12
004	004-00021 V#2	V2	26/10/2007	1	PL12
004	004-00022 V#1	V1	01/11/2007	2	PL28
004	004-00022 V#2	V2	29/11/2007	2	PL28
004	004-00022 V#3	V3	03/01/2008	2	PL28
004	004-00024 V#1	V1	12/11/2007	2	PL28
004	004-00024 V#2	V2	13/12/2007	2	PL28
004	004-00024 V#3	V3	07/02/2008	2	PL28
004	004-00025 V#1	V1	15/11/2007	2	PL29
004	004-00025 V#2	V2	12/12/2007	2	PL29
004	004-00025 V#3	V3	10/01/2008	2	PL29
004	004-00028 V#1	V1	23/01/2008	2	PL24
004	004-00028 V#2	V2	23/10/2008	2	PL24
004	004-00030 V#1	V1	10/06/2008	2	PL25
004	004-00030 V#2	V2	21/08/2008	2	PL25

4.1.2 Cells

ARPE-19 (ATCC CRL-2302) is a spontaneously arising retinal pigment epithelia (RPE) cell line derived in 1986 by Amy Aotaki-Keen from the normal eyes of a 19-year-old male (2).

The cell line obtained from ATCC was passaged 9 times and a working cell bank was established and stored in liquid nitrogen at passage 10 (RED_00079455). ARPE-19 cells were cultured in F175cm² flask with DMEM/F12 10% FCS and usually split twice a week. Cells were used for seroneutralization tests until passage 30

4.1.3 Virus

Virus BADrUL131-Y4 (from Thomas Shenk, Princeton University, Princeton, NJ) was derived from a BAC clone of the CMV strain AD169 genome that was modified to express GFP and repaired for the UL131 mutation to express a functional UL131 protein (3) (4).

Virus (batch # 1305) was titered on ARPE-19 cells by limiting dilution in 96-well plates and calculated at 5.8log10 FFU/ml (ELN MLE-AMA-000014).

4.1.4 Reagents

Table 5: List of Reagents

Name	Supplier	Reference number	Batch number	Storage temperature
DMEM/F12+Glutamax	Gibco	31331	1685776	+5°C ± 3°C
PBS 1X (steril)	Gibco	141-94855A	1678538	+5°C ± 3°C
Antibiotic/Antimycotic (100X)	Gibco	15240-096	1705700	≤-20°C
Fetal calf serum (FCS) *	Hyclone	SH30084-04	GYE0113	≤-20°C
Guinea pig complement (2 x 3.5mL)*	Biomérieux	72122	1004110180	+5°C ± 3°C
Virus BADrUL131-Y4-GFP*	Sanofi Pasteur	ND	1305	≤-70°C
0.25% Trypsin EDTA(1X), Phenol Red	Gibco	25200	1648607	≤-20°C
Trypan Blue Stain	Gibco	15250	1665084	+20°C±5°C
Formaldehyde 36% w/v (39% w/w)	GRP Rectapur	20910294	15B120518	+20°C±5°C
CytoTect® (positive control)	Biotest	PZN-6939178	B797045	+5°C ± 3°C

*Critical reagents**

4.1.5 Equipment

Table 6: List of Equipment

Equipment	Manufacturer	Reference	Immo #	Location
Laminar Flow cabinet with chemical filter	Faster	Safe Fast TOP 128D	123083	XN203
Laminar Flow cabinet	steril Compact	VBHC2 72	25846	XN203
Incubator CO_2	Binder	CB150	25804	XN203
Incubator CO_2	Binder	CB150	25805	XN203
Centrifuge	Heraeus	Multifuge	25865	XN203
Refrigerator +5°C±3°C	Liebherr	UKS 3600 352L	995053	XN203
Chemical fume hood	Elvetec	NA	26140	XN208
Ultrafreezer ≤–70°C	Jouan	VXE490	25800	XN203
Microscope inverse	Olympus	CKX51	25798	XN203
Viruscope (Software Viruscope 2.0.4)	Microvision	SCAN	PM0627 GILES000443421	XN222
Water bath	Memmert	WNE14	994408	XN203
ELISPOT Reader (Spot 3.3.1 for analysis)	Microvision	19943/19944	PM0181 GILES000441974	XN209

4.2 Methods

4.2.1 Seroneutralization Assay

The seroneutralization was performed according instruction RED_00086341 (Détermination du titre en anticorps neutralisants anti-CMV dans des sérums humains par µPRNT (Plaque Reduction Neutralization Test) sur cellules épithéliales (ARPE-19) avec le virus GFP BADrUL131-Y4) and described in appendix Section 8.1.

Briefly, two-fold serial dilutions of heat-inactivated (+56°C, 30 min) human sera are mixed with a fixed amount of GFP BADrUL131-Y4 virus and guinea pig complement. This mixture is transferred to 96-well plates containing confluent ARPE-19 cells. After an incubation period of 4 days, the number of infected cells detected as green spots due to the expression of GFP are counted by a fluorescent ELISPOT reader. Fifty percent inhibitory concentration (IC50) values are calculated by plotting the number of spots against the serum dilution and a best fit 4-parameter curve is drawn to interpolate the serum dilution at the point of the curve corresponding to the number of spots obtained using half the amount of the virus without serum.

4.3 Statistical analysis

As data in the CMV seronegative (CMV-) group were not normally distributed, non-parametric statistics were used. For the same reason, neutralizing antibody titers medians, but no geometric mean titers were calculated for each group at each visit.

For comparison between pre (V01) and post-vaccination results (for each visit V02, V03, V05), an unilateral Wilcoxon test on paired data was used (test the hypothesis that titers are higher after vaccination).

For comparisons between the CMV seronegative (CMV-) and CMV seropositive (CMV+) populations, bilateral Wilcoxon test was used (test the difference between the 2 groups at each visit).

Analyses were performed using JMP®10.0.1 and SAS®v9.2 softwares.

5 Results

5.1 CMV-Specific Neutralizing Antibody Titers in CMV Seropositive and Seronegative Vaccine Recipient

The neutralizing activity against the BADrUL131-Y4 CMV virus strain on epithelial cells (ARPE-19) was monitored by seroneutralization assays in individual serum samples collected from 63 gB/MF59 vaccinated subjects (either CMV seronegative or seropositive at D0 baseline) at D0 (V01), D28 (V02 one month after the first dose), D56 (V03 one month after the second dose) and D208 (V05 one month after the third dose).

The seroneutralization technique is detailed in Section 8.1 and raw data are shown in Section 8.2. Groups 1 and 3 were analyzed together as a CMV seropositive group (CMV+ at baseline) as well as groups 2 and 4 were analyzed together as a CMV seronegative group (CMV- at baseline). Neutralizing antibody titer Medians were calculated for both groups, i.e. CMV+ and CMV-, for each visit time point and are summarized in Table 7. Individual neutralizing antibody titers for each group at each time-point are depicted in Figure 1.

As expected, at baseline (V01/D0) the CMV seronegative groups did not exhibit CMV specific neutralizing antibody titers (Neut Ab titers $\leq$ 10), whereas high neutralizing antibody titers were recorded in the CMV seropositive group (Neut Ab titers median = 4174).

gB/MF59 vaccine administration to CMV seronegative subjects induced an increase of CMV neutralizing antibody titers with a peak of response monitored at D208, i.e. one month after the third vaccine dose administration (Neut Ab titers median = 80).

In CMV seropositive subjects, the first gB/MF59 vaccine dose administration induced an increase of neutralizing antibody titers (Neut Ab titers median = 8160). Neutralizing antibody titer medians were no more boosted beyond the first vaccination, however one month after the final vaccine

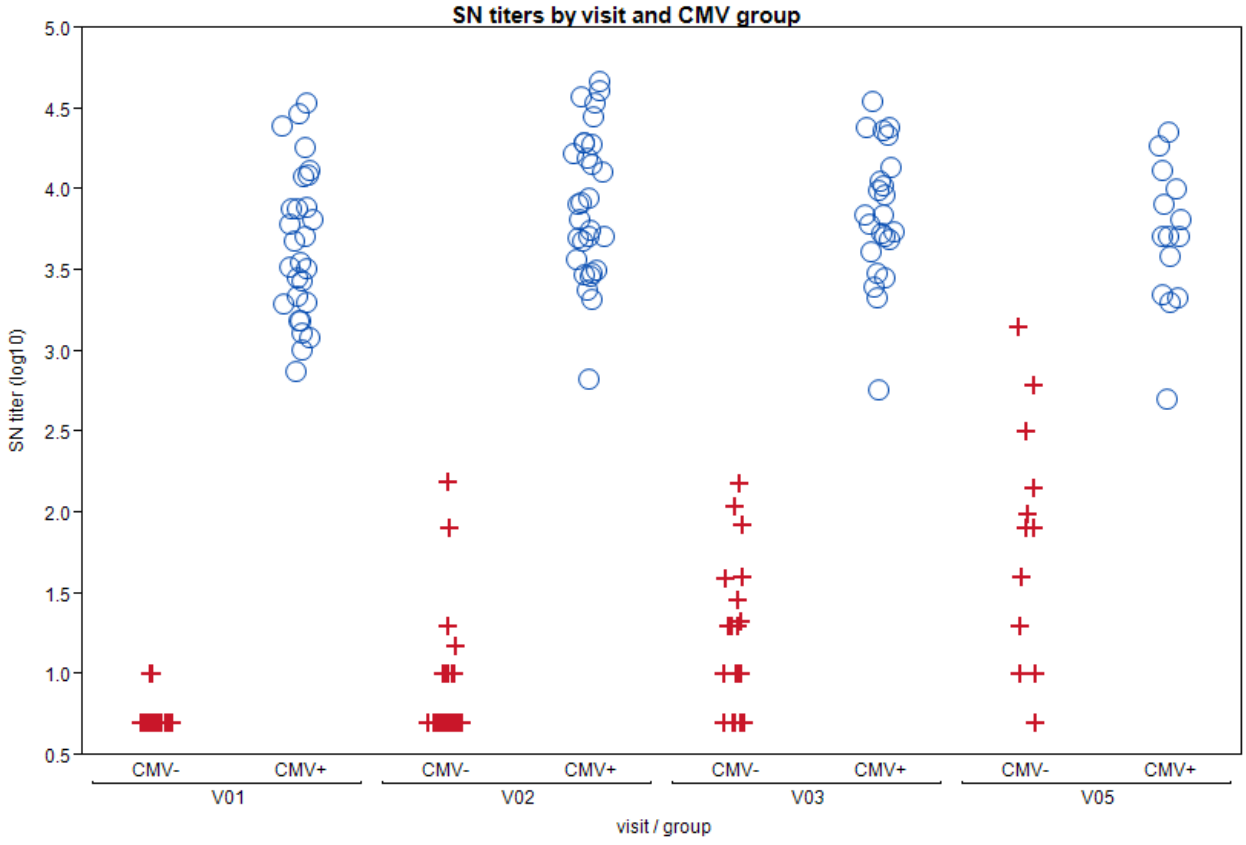
dose (D208, Neut Ab titers = 5120) neutralizing antibody titer medians remained higher than the antibody titer median at day 0.

Table 7: Descriptive Analysis of CMV-Specific Neutralizing Antibody Titers in CMV Seropositive and Seronegative Vaccine Recipient

	CMV seronegative at baseline (groups 2 and 4)				**CMV seropositive at baseline (groups 1 and 3)**			
Visit (Day)	N*	Median	Min-Max	25^{th}-75^{th} percentiles	N*	Median	Min-Max	25^{th}-75^{th} percentiles
V01 (D0)	34	5	5-10	5-5	28	4174	749-34273	1965-9810
V02 (D28)	34	5	5-156	5-10	29	8160	667-46191	3725-18973
V03 (D56)	23	10	5-153	5-29	23	6894	574-35193	4081-13711
V05 (D208)	13	80	5-1412	20-143	14	5120	507-22388	2251-10124

*N=number of vaccinated subjects with a serum samples available for measurement of neutralizing antibody titers

Figure 1: Individual Neutralizing Antibody Titers for CMV Seropositive and Seronegative Vaccine Recipient at each Time-point



5.2 CMV-Specific Neutralizing Antibody Titers were either Induced or Boosted by gB/MF59 Vaccine

In CMV Seronegative and Seropositive vaccine recipients, pre- and post-vaccination neutralizing antibody titers were compared to determine whether the vaccine regimen was capable of inducing or boosting, respectively, CMV-Specific Neutralizing Antibody Titers.

As presented in Table 8, whatever the CMV group (seropositive or seronegative), a significant increase of neutralizing antibody titers was observed after vaccination whatever the analyzed time-point (paired Wilcoxon test, all p-values≤0.0453).

The evolution of individual neutralizing titers by subject is depicted in Figure 2 for both CMV seronegative and seropositive groups.

Table 8: Statistical Analysis of Pre- and Post-Vaccination Neutralizing Antibody Titers

CMV-

Wilcoxon test (based on the rank)

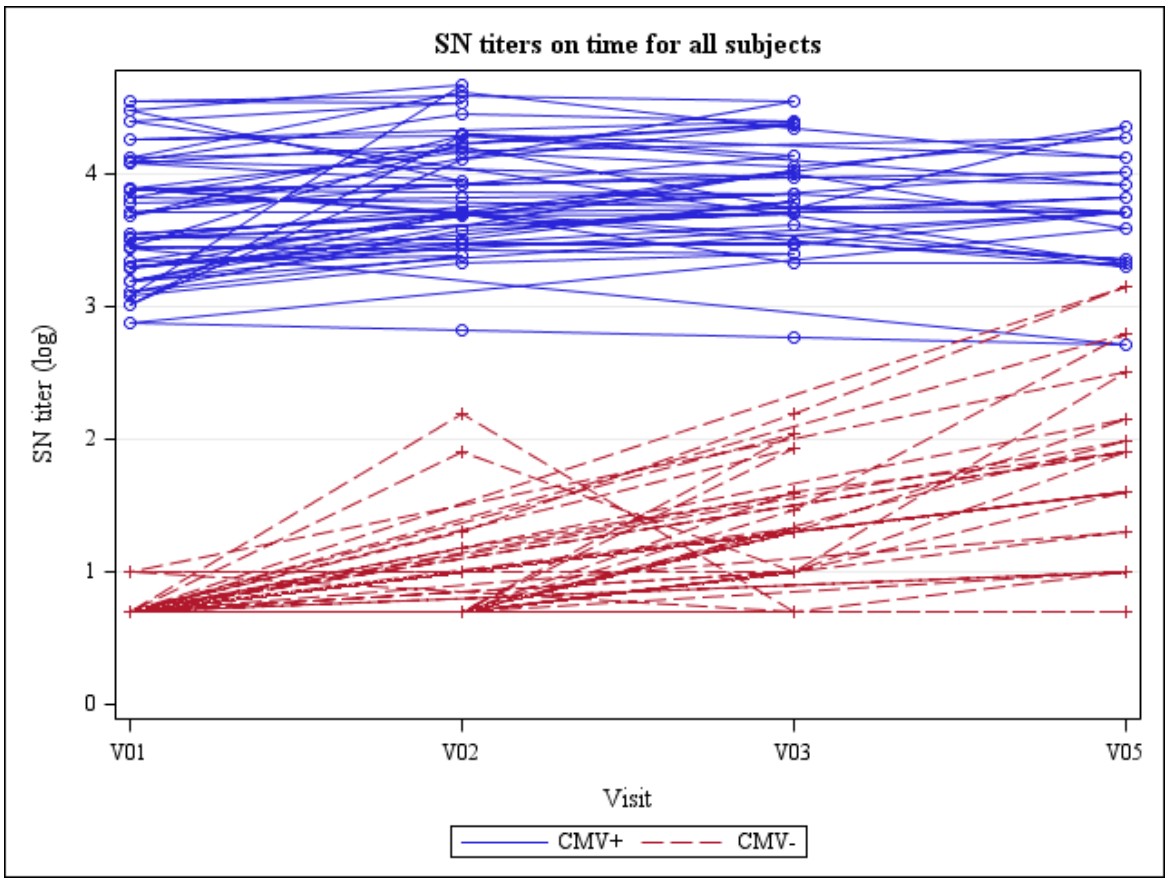
	log_SN_V02-log_SN_V01	log_SN_V03-log_SN_V01	log_SN_V05-log_SN_V01
Test statistic S	14.000	68.000	39.000
Unilateral p-value	0.0078*	<.0001*	0.0002*

CMV+

Wilcoxon test (based on the rank)

	log_SN_V02-log_SN_V01	log_SN_V03-log_SN_V01	log_SN_V05-log_SN_V01
Test statistic S	168.000	116.500	27.500
Unilateral p-value	<.0001*	<.0001*	0.0453*

Figure 2: Evolution of Individual Neutralizing antibody Titers in Subjects from CMV Seropositive and Seronegative Vaccine Recipient Groups



5.3 CMV-Specific Neutralizing Antibody Titers in CMV Seronegative Vaccine Recipient Remained Lower than those Induced by Natural Infection

The neutralizing antibody titers obtained one month after the third vaccine dose in CMV seronegative vaccine recipient (Neut Ab titers median = 80 at day 208) were compared to neutralizing antibody titers induced by natural infection in the same demographic and clinical population, i.e V01 from CMV seropositive subjects at baseline enrolled in CMC11 study (Neut Ab titers median = 4174).

The neutralizing antibody titers obtained at the last visit after vaccination (V05) in the CMV- group were significantly different from those obtained in the CMV+ group before vaccination (Wilcoxon test, $p<0.0001$, Table 9, titers higher in the CMV+ group). Therefore, the vaccine-induced titer increase in the seronegative group was not able to reach the level of naturally acquired immunity. Whatever the visit time, SN titers obtained in the seronegative group were

significantly different from those obtained in the seropositive group (Wilcoxon test, all p-values≤0.0002, titers higher in the seropositive group).

Table 9: Comparison of CMV- and CMV+ group by visit

Comparison	visit	test	p-value
CMV+ V01 vs CMV- V05		Two-Sided Pr > |Z|	<.0001
CMV+ vs CMV-	V01	Two-Sided Pr > |Z|	<.0001
CMV+ vs CMV-	V02	Two-Sided Pr > |Z|	<.0001
CMV+ vs CMV-	V03	Two-Sided Pr > |Z|	<.0001
CMV+ vs CMV-	V05	Two-Sided Pr > |Z|	0.0002

6 Discussion / Conclusion

The aim of the present study was to measure CMV neutralizing antibody titers with CMV BADrUL131-Y4 strain and human epithelial target cells in serum samples from 63 subjects (either CMV seronegative or seropositive at D0) who received the CMV gB/MF59 vaccine.

The neutralizing antibody titers produced against the glycoprotein-B protein contained in the vaccine were significantly increased after vaccination, as soon as day 28 after the first vaccine dose, in both patients who were immunologically naive to cytomegalovirus and in those with naturally acquired immunity (paired Wilcoxon test, all p-values≤0.0453 whatever the time-point within the vaccination schedule).

In CMV seronegative vaccine recipients the neutralizing antibody titers increased after each vaccine dose administration for most of the tested subjects and peaked one month after the third vaccine dose administration (Neut Ab titers median = 80 at day 208). However, the vaccine induced immunity in CMV seronegative vaccine recipients was not able to reach the neutralizing antibody titers induced by natural infection in the same demographic and clinical population (Wilcoxon test, p<0.0001).

In CMV seropositive vaccine recipients, the first gB/MF59 vaccine dose administration was able to boost the pre-existing immunity (Neut Ab titers median = 8160 at D28, paired Wilcoxon test, p-values<0.0001) and neutralizing antibody titer medians were maintained at a plateau but no more boosted beyond the first vaccination.

This additional immunomonitoring performed by Sanofi Pasteur to evaluate the neutralizing activities from a subset of serum samples provided by the Sponsor, presented some discrepancies with the previous analyses performed by the Sponsor and described in the published results (1). In the primary clinical trial analysis, neutralizing antibodies were measured with Towne RC256 (β-galactosidase marker virus) and human fibroblast target cells. The geometric mean titer of neutralizing antibodies was not significantly increased at day 56 in seronegative patients, but was significantly increased in the seropositive patients in whom the neutralizing antibody titers correlated with glycoprotein-B antibody titers. These discrepancies might be due to the different neutralizing assays and thus different neutralizing activities on ARPE-19 epithelial cells versus

MRC-5 fibroblasts cells or a lack of sensitivity of a β -galactosidase versus GFP-fluorescent marker virus (Towne RC256 versus BADrUL131-Y4).

Results will be shared with the sponsor to evaluate if further analyses are needed.

7 Bibliographie / References List

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3 Wang D, Shenk T (2005) Human cytomegalovirus UL131 open reading frame is required for epithelial cell tropism. J Virol 79: 10330-10338

4 Yu D, Smith GA, Enquist LW, Shenk T (2002) Construction of a self-excisable bacterial artificial chromosome containing the human cytomegalovirus genome and mutagenesis of the diploid TRL/IRL13 gene. J Virol 76: 2316-2328

8 Appendices

8.1 Seroneutralization assay method

The method is detailed in instruction RED_00086341 and briefly described hereafter and an outline is shown in Figure 5.

8.1.1 Plating of ARPE-19 cells on Day -1

The epithelial cells ARPE-19 are cultured in the 96-well optical bottom plates one day in advance (D-1) to allow them to attach to the plate and form a confluent cell monolayer. The cells are plated at a concentration of 25 000 cells/well and are and incubated at +37°C ± 1°C with 5% CO2 until next day.

8.1.2 Set up of seroneutralization reaction on Day 1

- Serum dilutions

One test will be performed with each serum sample with a starting dilution of 1/10.Hundred µL of serial diluted serum is needed for each test, therefore a total volume of 150 µL serial diluted serum will be prepared which corresponds at 15 µL undiluted serum.

- Preparation of virus solution

Prepare the virus solution by diluting the virus in culture medium supplemented with 5%-10% guinea pig complement (as determined for each lot) so that 50 µL will contain 800 FFU (16000 FFU/mL = 4.2log FFU/mL) of the GFP BADrUL131-Y4 strain and 5%-10% of guinea pig complement.

- Serum / Virus incubation

Add the virus solution to the appropriate wells and incubate at +37°C ± 1°C with 5% CO2 for 1 hr.

- Transfer of serum/virus mix to pre-plated cells

Take out the plates containing the cells prepared the day before, eliminate supernatant and add 100 µL of infection medium DMEM/F12 1% FCS to each well. Transfer 100 µL of each well of the serum/virus mix plate to each well of 96-well plates containing the cell monolayer using a multichannel pipette and incubate plates at +37°C ± 1°C with 5% CO2 for 4 days for ARPE-19 cells.

8.1.3 Fixation of ARPE-19 cells at Day 4

Fix the ARPE-19 cells using 1% formaldehyde to each well and incubate plates at room temperature for 1 h. After 3 washing steps eliminate supernatant and let the plates dry under the chemical fume hood, protected from light. Read the plates on ELISPOT-plate reader

8.1.4 Acquisition

The plates are read with an automatic VIRUSCOPE -15 plates reader equipped with a fluorescent FITC UV filter (Plate reader Microvision) according to Instruction RED_00067042 Utilisation et entretien du VIRUSCOPE Microvision dans le bâtiment XNord *version applicable.* The spots are counted using the cartography files (.mcv) of each plate using the Spot II (Microvision) software following the instruction RED_00065951 using a template which was generated during the development of the method.

8.1.5 Validation criteria

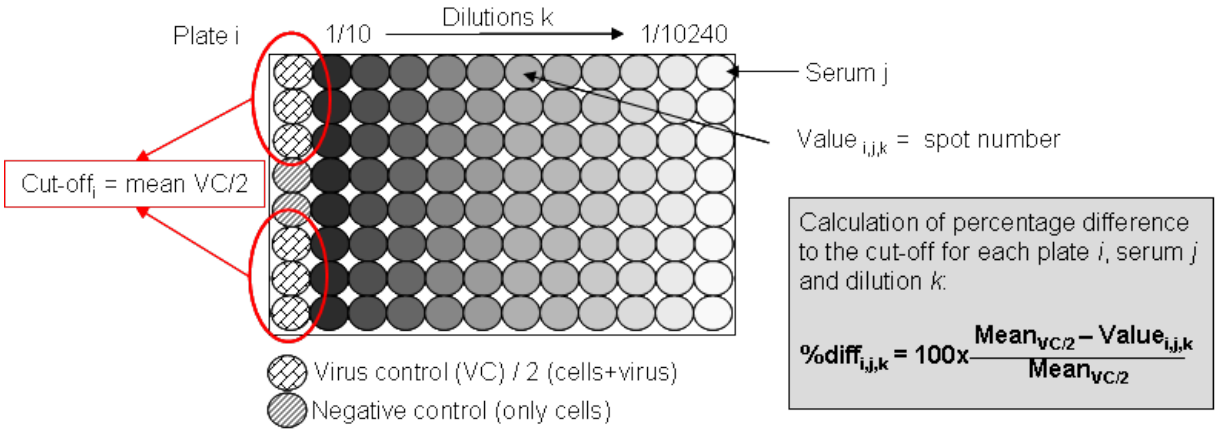
-The cell control wells contain < 5 spot
-The mean number of spots in VC/2 wells has a spot count mean > 150 spots
-The negative control serum has a titer < first dilution

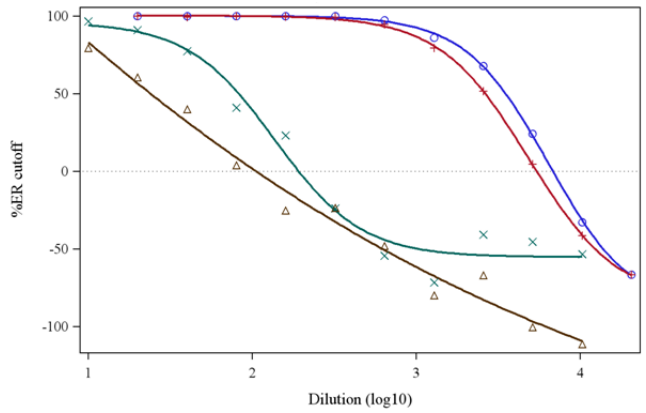
8.1.6 Titer calculation

After reading plates, Instruction RED_00087520 Processus d'analyse pour les données de séroneutalisation –etude Clinique CMC02 are applied and PRNT50 values are calculated by plotting the number of spots against the serum dilution and a best fit 4-parameter curve is drawn to interpolate the serum dilution at the point of the curve corresponding to the number of spots obtained using half the amount of the virus without serum (mean of 6 replicates). The Titer are calculated with STACS TitresSN-Pasteur 1.0.0 GxP
https://partners.sanofi.com/sites/Biostats/services/Pages/webpage_titer_sn.aspx

All samples with titers < first dilution (e.g. <10), the titer of first dilution /2 (e.g 5) will be attributed. All samples with titers >highest dilution (e.g 10 240) will be retested with a higher starting dilution.

Figure 3: Plate layout





For one serum, the %diff from cut-off are plotted against serum dilutions and a best fit 4-parameter curve was drawn to interpolate the serum dilution at the 0% difference to the cut-off. This inverse dilution is considered as the PRNT50 value.

8.1.7 Titer attribution

The Titer are calculated with STACS TitresSN-Pasteur 1.0.0 GxP
https://partners.sanofi.com/sites/Biostats/services/Pages/webpage_titer_sn.aspx

2 folders are generated by this service:

- One excel folder where calculated results are resumed.
- One pdf folder described results and associated graphics.

Figure 4: Sections in report pdf

Results for seroneutralization titers computed with a four parameter model

7. Appendix - Explanation of the different sections

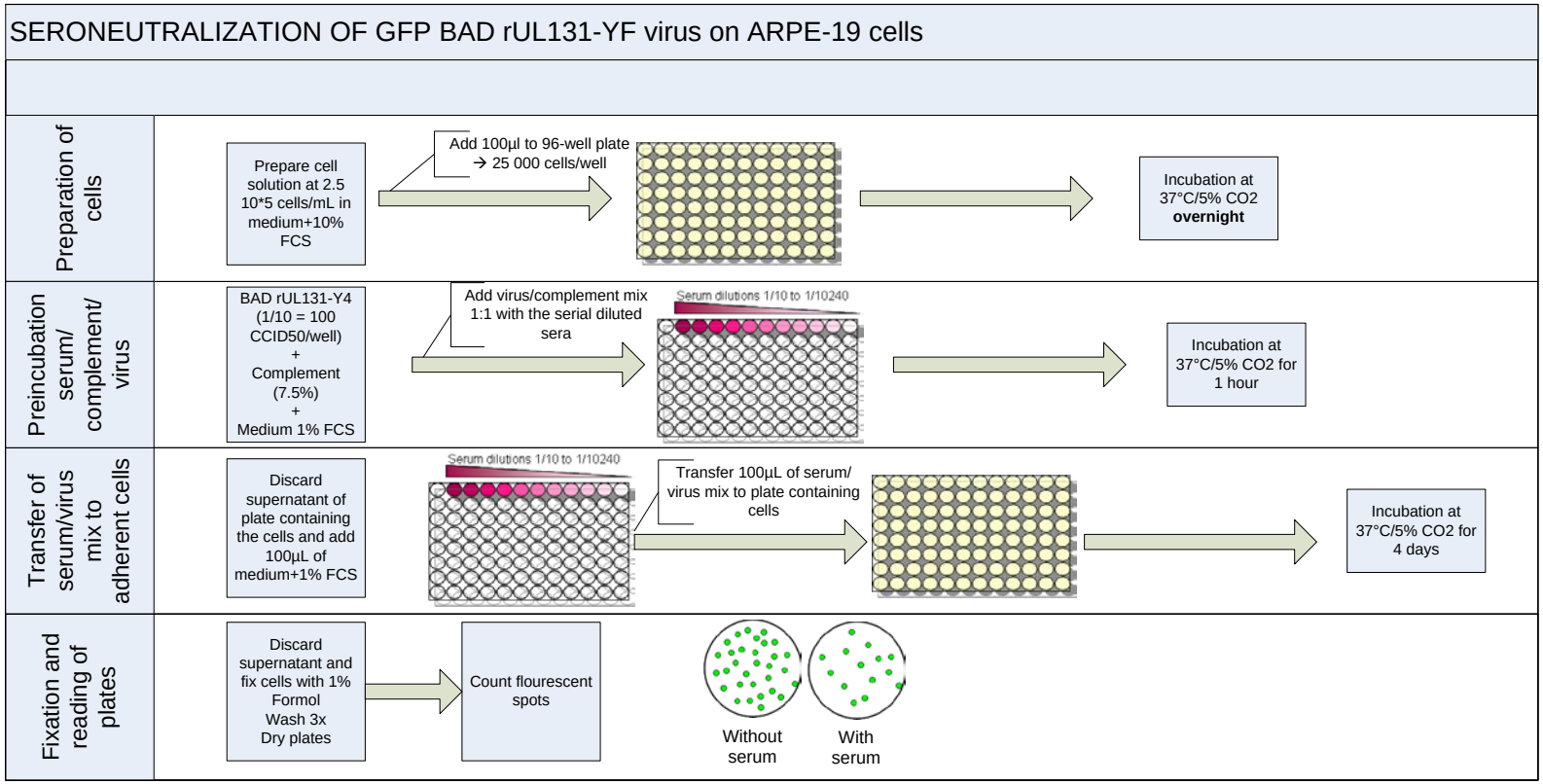
- Section 1) Seroneutralization titers are computed with a four parameter model in log10 and in natural values.
- Section 2) A problem occurs in the modeling or the r-square is not sufficiently high (R^2<0.85): Titers has to be checked with the graphical representation.
- Section 3) Seroneutralization titers are not computed with a four parameter model. The titer is equal to the latest dilution which gives a result below the cutoff.
- Section 4) Data are always below or above the cutoff. The given titer is below first dilution or above last dilution.
- Section 5) Aberrant samples. The curve crosses more than once the axis y=cutoff.
- Section 6) Aberrant samples. The model converges but the modelization curve does not cross the axis %diff=0.

Table 10: Example of report table xls

Plate	Line	Different dilution	Mouse	Test	4P Estimated titer	Biologist titer	Section	First dilution	Dilution step	Rsquare
PL1	A		1	A4	226	/	1	10	2	0,98
PL1	B		2	A8	NC	/	5	10	2	/
PL1	C	25	3	A6	14	10	2	10	2	0,9
PL1	D		4	A3	<10	<10	4	10	2	/
PL1	E		5	A5	<10	10	2	10	2	0,71
PL1	F		6	A7	NC	/	6	10	2	0,91
PL1	G		7	A2	<10	<10	4	10	2	/
PL1	H		8	A1	NC	/	6	10	2	0,91
PL2	A		9	A4	227	/	1	10	2	0,98
PL2	B		10	A8	NC	/	5	10	2	/
PL2	C		11	A6	14	10	2	10	2	0,9
PL2	D		12	A3	<10	<10	4	10	2	/
PL2	E	40	13	A5	<10	10	2	10	2	0,71
PL2	F		14	A7	NC	/	6	10	2	0,91
PL2	G		15	A2	<10	<10	4	10	2	/
PL2	H		16	A1	NC	/	6	10	2	0,91

For a result in section 2 or 3, the titer will be equal to the lastest dilution (inverse dilution) which give a result below the cut-off (i.e. biologist titer).

Figure 5: Seroneutralization method



8.2 Seroneutralization Data

Appendix 1: Group#1 Raw Data

Name of current study	Subject identifier	Centre identification	Patient Identifier	Visit	Page	Primary Biological Sample Type	Derived Biological Sample Type	CMI Assay	Type of cell	Type of Cytokine measured	Cell Stimulation Reagent	Replicate	Original test value	Test unit
STUDY	SUB_ID	CEN_ID	PAT_ID	VISIT_IE	PAGE_IE	CMITY_C	CMITE_C	CMITEST	CMICEL	CMICYT	CMISTIM	CMIREP	CMIVAL	CMIUNI
CMC11	001-00001 V#1	1	00001	RES_V01	14-Sep-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	6038	1/dil
CMC11	001-00001 V#2	1	00001	RES_V02	13-Oct-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	6563	1/dil
CMC11	001-00001 V#3	1	00001	RES_V03	10-Nov-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	6967	1/dil
CMC11	001-00001 V#5	1	00001	RES_V05	16-Apr-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5120	1/dil
CMC11	001-00006 V#1	1	00006	RES_V01	21-Sep-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	6482	1/dil
CMC11	001-00006 V#2	1	00006	RES_V02	25-Oct-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	15665	1/dil
CMC11	001-00006 V#3	1	00006	RES_V03	29-Nov-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5490	1/dil
CMC11	001-00006 V#5	1	00006	RES_V05	25-May-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	22388	1/dil
CMC11	001-00013 V#1	1	00013	RES_V01	13-Nov-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	2161	1/dil
CMC11	001-00013 V#2	1	00013	RES_V02	18-Dec-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	2372	1/dil
CMC11	001-00016 V#1	1	00016	RES_V01	24-Nov-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	1280	1/dil
CMC11	001-00016 V#2	1	00016	RES_V02	22-Dec-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	3725	1/dil
CMC11	001-00016 V#3	1	00016	RES_V03	26-Jan-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5120	1/dil
CMC11	001-00016 V#5	1	00016	RES_V05	16-Aug-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5120	1/dil
CMC11	001-00021 V#1	1	00021	RES_V01	1-Dec-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	1984	1/dil
CMC11	001-00021 V#2	1	00021	RES_V02	21-Dec-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	2956	1/dil
CMC11	001-00021 V#3	1	00021	RES_V03	23-Jan-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	2861	1/dil
CMC11	001-00021 V#5	1	00021	RES_V05	28-Jun-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5120	1/dil
CMC11	001-00022 V#1	1	00022	RES_V01	15-Dec-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	1549	1/dil
CMC11	001-00022 V#2	1	00022	RES_V02	16-Jan-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	2867	1/dil
CMC11	001-00022 V#3	1	00022	RES_V03	13-Feb-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	3013	1/dil
CMC11	001-00022 V#5	1	00022	RES_V05	16-Jul-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	2251	1/dil
CMC11	001-00024 V#1	1	00024	RES_V01	22-Feb-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	7650	1/dil
CMC11	001-00024 V#2	1	00024	RES_V02	15-Mar-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	14322	1/dil
CMC11	001-00024 V#3	1	00024	RES_V03	21-May-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	11132	1/dil
CMC11	001-00024 V#5	1	00024	RES_V05	14-Jan-09	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	18472	1/dil
CMC11	001-00025 V#1	1	00025	RES_V01	8-Mar-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	12999	1/dil
CMC11	001-00025 V#2	1	00025	RES_V02	3-Apr-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	40960	1/dil
CMC11	001-00025 V#3	1	00025	RES_V03	21-May-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	21684	1/dil
CMC11	001-00025 V#5	1	00025	RES_V05	19-Jan-09	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	13142	1/dil
CMC11	001-00028 V#2	1	00028	RES_V02	18-May-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	19533	1/dil
CMC11	001-00028 V#3	1	00028	RES_V03	26-Jul-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	13711	1/dil
CMC11	001-00035 V#1	1	00035	RES_V01	4-Feb-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5120	1/dil
CMC11	001-00035 V#2	1	00035	RES_V02	5-Mar-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5120	1/dil
CMC11	001-00035 V#3	1	00035	RES_V03	4-Apr-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5400	1/dil
CMC11	001-00035 V#5	1	00035	RES_V05	18-Sep-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	6512	1/dil
CMC11	001-00036 V#1	1	00036	RES_V01	21-Feb-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	3202	1/dil
CMC11	001-00036 V#2	1	00036	RES_V02	18-Jun-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5579	1/dil
CMC11	001-00036 V#3	1	00036	RES_V03	17-Jul-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	6894	1/dil
CMC11	001-00038 V#1	1	00038	RES_V01	11-Apr-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	7520	1/dil
CMC11	001-00038 V#2	1	00038	RES_V02	8-May-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	8209	1/dil
CMC11	001-00038 V#3	1	00038	RES_V03	3-Jul-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	9887	1/dil
CMC11	001-00038 V#5	1	00038	RES_V05	21-Jan-09	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	3890	1/dil
CMC11	001-00041 V#1	1	00041	RES_V01	22-May-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	749	1/dil
CMC11	001-00041 V#2	1	00041	RES_V02	22-Jul-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	667	1/dil
CMC11	001-00041 V#3	1	00041	RES_V03	12-Aug-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	574	1/dil
CMC11	001-00041 V#5	1	00041	RES_V05	23-Feb-09	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	507	1/dil
CMC11	001-00042 V#1	1	00042	RES_V01	27-May-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	2712	1/dil
CMC11	001-00042 V#2	1	00042	RES_V02	25-Jun-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	3010	1/dil
CMC11	001-00042 V#3	1	00042	RES_V03	4-Aug-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	4081	1/dil
CMC11	001-00042 V#5	1	00042	RES_V05	26-Jan-09	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	1977	1/dil
CMC11	001-00045 V#1	1	00045	RES_V01	30-May-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	7672	1/dil
CMC11	001-00045 V#2	1	00045	RES_V02	7-Jul-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	8160	1/dil
CMC11	001-00045 V#3	1	00045	RES_V03	31-Jul-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	9308	1/dil
CMC11	001-00045 V#5	1	00045	RES_V05	16-Jan-09	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	10124	1/dil
CMC11	001-00046 V#1	1	00046	RES_V01	9-Jun-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	3517	1/dil
CMC11	001-00046 V#2	1	00046	RES_V02	8-Jul-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	4765	1/dil
CMC11	001-00046 V#3	1	00046	RES_V03	11-Aug-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	4908	1/dil
CMC11	001-00047 V#1	1	00047	RES_V01	12-Jun-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	3290	1/dil
CMC11	001-00047 V#2	1	00047	RES_V02	17-Jul-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	3154	1/dil
CMC11	001-00047 V#3	1	00047	RES_V03	14-Aug-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	6062	1/dil
CMC11	001-00049 V#1	1	00049	RES_V01	4-Jul-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	1945	1/dil
CMC11	001-00049 V#2	1	00049	RES_V02	19-Aug-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5114	1/dil
CMC11	001-00049 V#3	1	00049	RES_V03	16-Sep-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	10625	1/dil
CMC11	001-00053 V#1	1	00053	RES_V01	19-Aug-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	1554	1/dil
CMC11	001-00053 V#2	1	00053	RES_V02	18-Sep-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	4999	1/dil
CMC11	001-00053 V#3	1	00053	RES_V03	5-Jan-09	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	2141	1/dil
CMC11	001-00053 V#5	1	00053	RES_V05	25-Mar-09	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	2140	1/dil

Appendix 2: Group#2 Raw Data

Name of current study	Subject identifier	Centre identification	Patient Identifier	Visit	Page	Primary Biological Sample Type	Derived Biological Sample Type	CMI Assay	Type of cell	Type of Cytokine measured	Cell Stimulation Reagent	Replicate	Original test value	Test unit
STUDY	SUB_ID	CEN_ID	PAT_ID	VISIT_ID	PAGE_ID	CMITY_C	CMITE_C	CMITEST	CMICEL	CMICYT	CMISTIM	CMIREP	CMIVAL	CMIUNI
CMC11	002-00001 V#1	2	00001	RES_V01	21-Sep-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00001 V#2	2	00001	RES_V02	30-Oct-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00001 V#3	2	00001	RES_V03	4-Dec-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	20	1/dil
CMC11	002-00003 V#1	2	00003	RES_V01	15-Nov-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00003 V#2	2	00003	RES_V02	20-Dec-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00003 V#3	2	00003	RES_V03	25-Jan-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	10	1/dil
CMC11	002-00005 V#1	2	00005	RES_V01	22-Feb-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00005 V#2	2	00005	RES_V02	3-Sep-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	10	1/dil
CMC11	002-00005 V#3	2	00005	RES_V03	28-Sep-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	10	1/dil
CMC11	002-00005 V#5	2	00005	RES_V05	20-Nov-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	40	1/dil
CMC11	002-00007 V#1	2	00007	RES_V01	26-Mar-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00007 V#2	2	00007	RES_V02	19-Apr-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	15	1/dil
CMC11	002-00007 V#3	2	00007	RES_V03	18-May-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	39	1/dil
CMC11	002-00008 V#1	2	00008	RES_V01	24-May-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00008 V#2	2	00008	RES_V02	28-Jun-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00008 V#3	2	00008	RES_V03	27-Jul-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00012 V#1	2	00012	RES_V01	4-Jul-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00012 V#2	2	00012	RES_V02	27-Jul-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00012 V#3	2	00012	RES_V03	23-Aug-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	20	1/dil
CMC11	002-00012 V#5	2	00012	RES_V05	20-Feb-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	143	1/dil
CMC11	002-00014 V#1	2	00014	RES_V01	6-Sep-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00014 V#2	2	00014	RES_V02	28-Sep-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00014 V#3	2	00014	RES_V03	8-Nov-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	10	1/dil
CMC11	002-00014 V#5	2	00014	RES_V05	1-May-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	320	1/dil
CMC11	002-00016 V#1	2	00016	RES_V01	6-Nov-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	10	1/dil
CMC11	002-00016 V#2	2	00016	RES_V02	3-Dec-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	10	1/dil
CMC11	002-00016 V#3	2	00016	RES_V03	23-Jan-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	20	1/dil
CMC11	002-00016 V#5	2	00016	RES_V05	3-Jul-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	40	1/dil
CMC11	002-00018 V#1	2	00018	RES_V01	28-Nov-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00018 V#2	2	00018	RES_V02	24-Jan-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00018 V#3	2	00018	RES_V03	13-Feb-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	110	1/dil
CMC11	002-00021 V#1	2	00021	RES_V01	30-Jan-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00021 V#2	2	00021	RES_V02	5-Mar-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00021 V#5	2	00021	RES_V05	8-Sep-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	10	1/dil
CMC11	002-00022 V#1	2	00022	RES_V01	4-Apr-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00022 V#2	2	00022	RES_V02	29-Apr-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00022 V#3	2	00022	RES_V03	9-Jun-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	29	1/dil
CMC11	002-00022 V#5	2	00022	RES_V05	27-Oct-09	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	610	1/dil
CMC11	002-00024 V#1	2	00024	RES_V01	25-Apr-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00024 V#2	2	00024	RES_V02	9-Jun-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00025 V#1	2	00025	RES_V01	2-May-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00025 V#2	2	00025	RES_V02	6-Jun-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00025 V#5	2	00025	RES_V05	17-Dec-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	97	1/dil
CMC11	002-00028 V#1	2	00028	RES_V01	8-May-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00028 V#2	2	00028	RES_V02	23-Oct-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00028 V#5	2	00028	RES_V05	7-Jan-09	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	20	1/dil
CMC11	002-00029 V#1	2	00029	RES_V01	15-May-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00029 V#2	2	00029	RES_V02	16-Jun-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00029 V#3	2	00029	RES_V03	23-Jul-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00029 V#5	2	00029	RES_V05	17-Dec-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	10	1/dil
CMC11	002-00031 V#1	2	00031	RES_V01	21-May-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00031 V#2	2	00031	RES_V02	2-Jul-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00031 V#3	2	00031	RES_V03	5-Aug-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	84	1/dil
CMC11	002-00035 V#2	2	00035	RES_V01	25-Jul-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00035 V#3	2	00035	RES_V02	5-Sep-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	156	1/dil
CMC11	002-00035 V#1	2	00035	RES_V03	6-Jun-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00036 V#1	2	00036	RES_V01	12-Jun-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00036 V#2	2	00036	RES_V02	10-Jul-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00036 V#3	2	00036	RES_V03	18-Aug-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00037 V#1	2	00037	RES_V01	16-Jun-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00037 V#2	2	00037	RES_V02	21-Jul-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	20	1/dil
CMC11	002-00037 V#3	2	00037	RES_V03	18-Aug-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	153	1/dil
CMC11	002-00037 V#5	2	00037	RES_V05	26-Jan-09	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	1412	1/dil
CMC11	002-00040 V#1	2	00040	RES_V01	4-Aug-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00040 V#2	2	00040	RES_V02	1-Sep-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00040 V#3	2	00040	RES_V03	29-Sep-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	002-00040 V#5	2	00040	RES_V05	5-Feb-09	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil

Appendix 3: Group#3 Raw Data

Name of current study	Subject identifier	Centre identification	Patient Identifier	Visit	Page	Primary Biological Sample Type	Derived Biological Sample Type	CMI Assay	Type of cell	Type of Cytokine measured	Cell Stimulation Reagent	Replicate	Original test value	Test unit
STUDY	SUB_ID	CEN_ID	PAT_ID	VISIT_ID	PAGE_ID	CMITY_C	CMITE_C	CMITEST	CMICEL	CMICYT	CMISTIM	CMIREP	CMIVAL	CMIUNI
CMC11	003-00001 V#1	3	00001	RES_V01	3-Aug-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	24645	1/dil
CMC11	003-00001 V#2	3	00001	RES_V02	7-Sep-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	33890	1/dil
CMC11	003-00004 V#1	3	00004	RES_V01	10-Aug-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	34273	1/dil
CMC11	003-00004 V#2	3	00004	RES_V02	14-Sep-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	37790	1/dil
CMC11	003-00004 V#3	3	00004	RES_V03	26-Oct-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	35193	1/dil
CMC11	003-00006 V#1	3	00006	RES_V01	15-Aug-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	4830	1/dil
CMC11	003-00006 V#2	3	00006	RES_V02	14-Sep-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	18973	1/dil
CMC11	003-00006 V#5	3	00006	RES_V05	15-Mar-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	8142	1/dil
CMC11	003-00007 V#1	3	00007	RES_V01	5-Oct-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	12159	1/dil
CMC11	003-00007 V#2	3	00007	RES_V02	30-Nov-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	27889	1/dil
CMC11	003-00007 V#3	3	00007	RES_V03	1-Feb-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	24224	1/dil
CMC11	003-00009 V#1	3	00009	RES_V01	21-Nov-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	18195	1/dil
CMC11	003-00009 V#2	3	00009	RES_V02	11-Jan-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	19209	1/dil
CMC11	003-00011 V#1	3	00011	RES_V01	21-Feb-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	1009	1/dil
CMC11	003-00011 V#2	3	00011	RES_V02	15-Mar-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	12780	1/dil
CMC11	003-00011 V#3	3	00011	RES_V03	23-Apr-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	23155	1/dil
CMC11	003-00015 V#1	3	00015	RES_V01	21-Jun-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	11948	1/dil
CMC11	003-00015 V#2	3	00015	RES_V02	26-Jul-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	8798	1/dil
CMC11	003-00022 V#1	3	00022	RES_V01	3-Dec-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	29458	1/dil
CMC11	003-00022 V#2	3	00022	RES_V02	11-Jan-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	46191	1/dil
CMC11	003-00023 V#1	3	00023	RES_V01	7-Feb-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	1197	1/dil
CMC11	003-00023 V#2	3	00023	RES_V02	6-Mar-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	2099	1/dil
CMC11	003-00023 V#3	3	00023	RES_V03	3-Apr-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	2480	1/dil
CMC11	003-00024 V#1	3	00024	RES_V01	17-Apr-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	2805	1/dil
CMC11	003-00024 V#2	3	00024	RES_V02	22-May-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	16747	1/dil
CMC11	003-00024 V#3	3	00024	RES_V03	26-Jun-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	23913	1/dil

Appendix 4: Group#4 Raw Data

Name of current study	Subject identifier	Centre identification	Patient Identifier	Visit	Page	Primary Biological Sample Type	Derived Biological Sample Type	CMI Assay	Type of cell	Type of Cytokine measured	Cell Stimulation Reagent	Replicate	Original test value	Test unit
STUDY	SUB_ID	CEN_ID	PAT_ID	VISIT_ID	PAGE_ID	CMITY_C	CMITE_C	CMITEST	CMICEL	CMICYT	CMISTIM	CMIREP	CMIVAL	CMIUNI
CMC11	004-00001 V#1	4	00001	RES_V01	3-Aug-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	004-00001V#2	4	00001	RES_V02	13-Sep-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	004-00003 V#1	4	00003	RES_V01	3-Aug-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	004-00003 V#2	4	00003	RES_V02	31-Aug-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	004-00006 V#1	4	00006	RES_V01	10-Aug-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	004-00006 V#2	4	00006	RES_V02	26-Oct-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	80	1/dil
CMC11	004-00006 V#3	4	00006	RES_V03	10-Jan-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	10	1/dil
CMC11	004-00006 V#5	4	00006	RES_V05	1-Mar-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	80	1/dil
CMC11	004-00008 V#1	4	00008	RES_V01	2-Nov-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	004-00008 V#2	4	00008	RES_V02	8-Mar-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	004-00008 V#3	4	00008	RES_V03	19-Apr-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	40	1/dil
CMC11	004-00008 V#5	4	00008	RES_V05	2-Aug-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	80	1/dil
CMC11	004-00009 V#1	4	00009	RES_V01	2-Nov-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	004-00009 V#2	4	00009	RES_V02	30-Nov-06	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	004-00009 V#3	4	00009	RES_V03	11-Jan-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	004-00012 V#1	4	00012	RES_V01	6-Feb-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	004-00012 V#2	4	00012	RES_V02	8-Mar-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	004-00016 V#1	4	00016	RES_V01	14-Jun-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	004-00016 V#2	4	00016	RES_V02	12-Jul-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	004-00016 V#3	4	00016	RES_V03	4-Sep-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	004-00017 V#1	4	00017	RES_V01	14-Jun-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	10	1/dil
CMC11	004-00017 V#2	4	00017	RES_V02	12-Jul-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	10	1/dil
CMC11	004-00021 V#1	4	00021	RES_V01	16-Aug-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	004-00021 V#2	4	00021	RES_V02	26-Oct-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	10	1/dil
CMC11	004-00022 V#1	4	00022	RES_V01	1-Nov-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	004-00022 V#2	4	00022	RES_V02	29-Nov-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	004-00022 V#3	4	00022	RES_V03	3-Jan-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	20	1/dil
CMC11	004-00024 V#1	4	00024	RES_V01	12-Nov-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	004-00024 V#2	4	00024	RES_V02	13-Dec-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	004-00024 V#3	4	00024	RES_V03	7-Feb-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	10	1/dil
CMC11	004-00025 V#1	4	00025	RES_V01	15-Nov-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	004-00025 V#2	4	00025	RES_V02	12-Dec-07	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	004-00025 V#3	4	00025	RES_V03	10-Jan-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	21	1/dil
CMC11	004-00028 V#1	4	00028	RES_V01	23-Jan-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	004-00028 V#2	4	00028	RES_V02	23-Oct-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	10	1/dil
CMC11	004-00030 V#1	4	00030	RES_V01	10-Jun-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil
CMC11	004-00030 V#2	4	00030	RES_V02	21-Aug-08	B	SE	SERONEUTRALIZATION	ARPE-19	NA	GFP BADrUL131-Y4	1	5	1/dil