4C-CMV Report February 2015

The first patient was randomised on the 2nd February 2012. In total, 124 patients have been randomised to the trial, with the last patient randomised on the 13th January 2014.

Baseline Characteristics

Table 1: Baseline Characteristics for all Patients (Treatment Arms Combined)

		Control	Combined Treatments
	N	44	80
Age	Mean (SD)	55 (17.0)	58 (16.8)
BMI	Median (IQR)	27 (23.9-31.2)ǂ	26 (22.9-29.1)
Sex	Male (%)	23 (52)	55 (69)
APACHE II Score	N	41	75
	Mean (SD)	17.5 (7.0)	17.7 (5.6)
SOFA Score	Median (IQR)	8.5 (6.5-13.0)	8.0 (5.0-11.5)
	Range	2 – 18	2 – 20
White Cell Count	Mean (SD)	12.5 (6.1)	11.9 (6.5)
	Range	5.1 – 28.9	2.8 – 44.4
Neutrophilia Count	Mean (SD)	9.5 (4.9)	9.9 (6.0)
	Range	2.6 – 25.3	1.5 – 37.7
Length of Stay Prior to	Median (IQR)	5 (3-7)	5 (3-6)
Randomisation*	Range	1 – 9	1 – 21
Duration of Mechanical	Median (IQR)	3 (2-5.5)	3 (2-5)
Ventilation**	Range	1 – 7	0 – 8

ǂ One missing observation: N=43

* Time from hospital admission to date of randomisation

** Time from tracheal insertion to date of randomisation

Table 2: Baseline Characteristics for All Patients (By Treatment Group)

		Control	Valaciclovir/acyclovir	Valganciclovir/ganciclovir
	N	44	34	46
Age	Mean (SD)	55 (17.0)	58 (16.6)	57 (17.2)
BMI	Median (IQR)	27 (23.9-31.2)ǂ	26 (22.2-28.4)	27.0 (24.2-29.4)
Sex	Male (%)	23 (52)	24 (71)	31 (67)
APACHE II Score	N	41	32	43
	Mean (SD)	17.5 (7.0)	17.9 (4.6)	17.4 (6.3)
	Range	3 – 42	9 – 26	6 – 34
SOFA Score	Median (IQR)	8.5 (6.5-13.0)	8.5 (5.0-12.0)	8.0 (5.0-11.0)
	Range	2 – 18	3 – 18	2 – 20
White Cell Count	Mean (SD)	12.5 (6.1)	12.7 (5.5)	11.3 (7.2)
	Range	5.1 – 28.9	4.3 – 25.5	2.8 – 44.4
Lowest Neutrophilia	Mean (SD)	9.5 (4.9)	10.5 (5.2)	9.4 (6.6)
	Range	2.6 – 25.3	3.3 – 24.0	1.5 – 37.7
Length of Stay Prior to	Median (IQR)	5 (3-7)	5 (2-6)	5 (3-6)
Randomisation*	Range	1 – 9	1 – 21	2 – 8
Duration of Mechanical	Median (IQR)	3 (2-5.5)	4 (2-5)	3 (2-5)
Ventilation**	Range	1 – 7	1 – 7	0 – 8

ǂ One observation missing: N=43
* Time from hospital admission to date of randomisation
** Time from tracheal insertion to date of randomisation

Follow Up

Table 3: Time to Sample Assay Data Collection

	N	Median Time (Range)
Day 1	123	0 (0 – 1)
Day 6	111	5 (3 – 7)
Day 11	100	10 (6 – 12)
Day 16	89	15 (14 – 19)
Day 21	80	20 (15 – 24)
Day 26	67	25 (21 – 27)

Primary Outcome: Time To CMV Reactivation in Blood

14 have been excluded from the primary analyses due to baseline reactivation. This leaves us with 40 in the control arm

Blood CMV PCR Peak Viral Load: 1382
This is the only measurement greater than 1000 copies.

Combined treatments vs control:

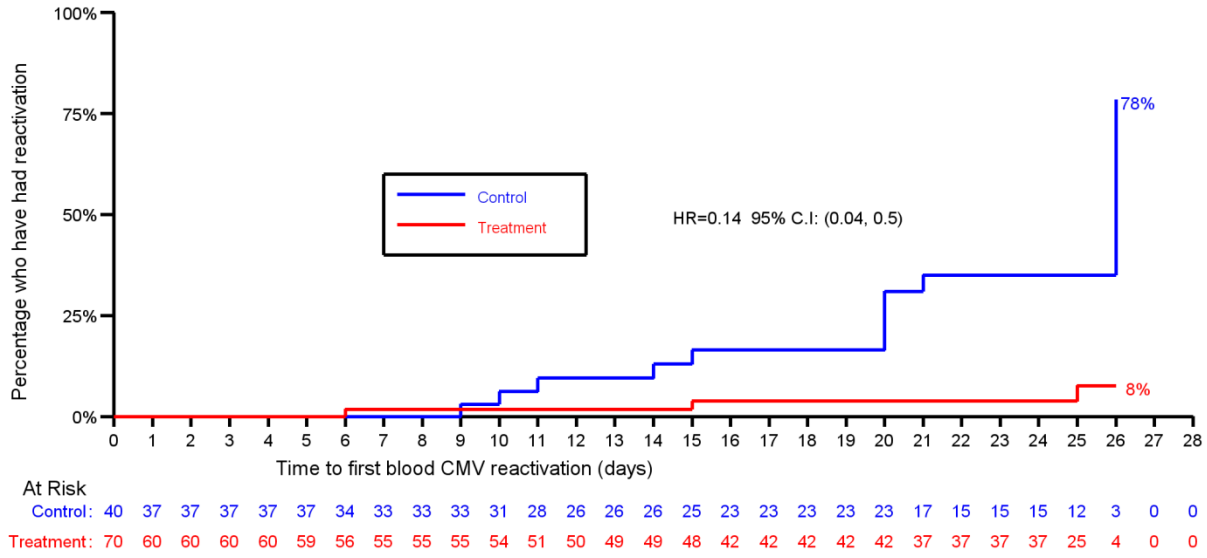
4% (3/70) reactivated in the combined treatment arm compared to 30% (12/40) who reactivated in the control arm.

RR: 0.1 (95% C.I: 0.04 to 0.5). Those in the combined treatment arms are at 90% less risk of reactivation than those in the control arm.

HR: 0.1 (95% C.I: 0.04 to 0.5). The risk of reactivation in the combined treatment arm at any given time point over 26 days is 90% less than that in the control arm.

Adjusted HR: 0.2 (95% C.I. 0.04 to 0.6). The risk of reactivation in the combined treatment arm at any given time point over 26 days is 80% less than that in the control arm, after adjusting for gender, age and SOFA Score.

Figure 1: Time to Blood CMV Reactivation (Control vs Treatments combined)



Low dose vs control:

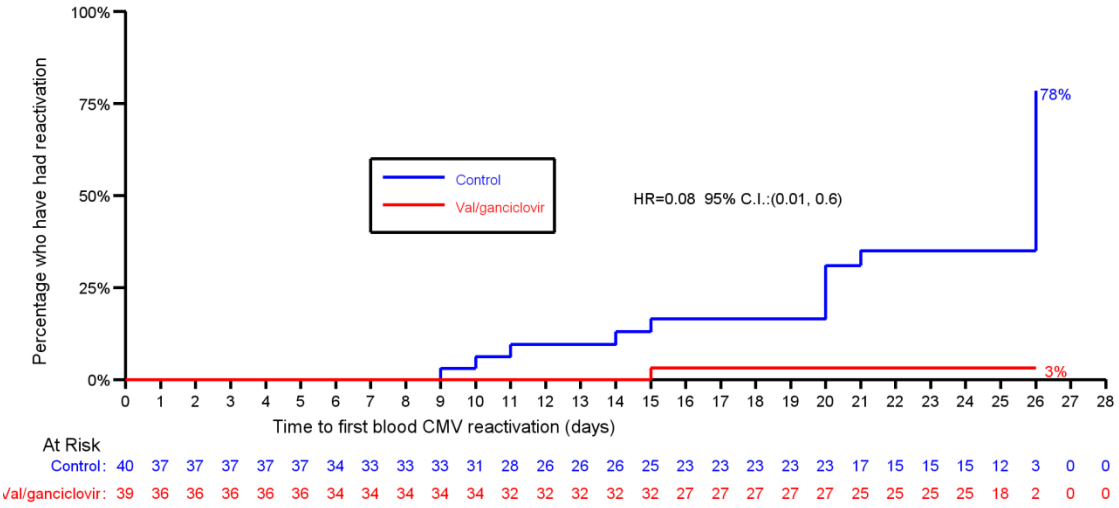
3% (1/39) reactivated in the ganciclovir arm compared to 30% (12/40) who reactivated in the control arm.

RR: 0.09 (95% C.I: 0.01 to 0.6). Those in the low dose arm are at 91% less risk of reactivation than those in the control arm.

HR: 0.08 (95% C.I: 0.01 to 0.6). The risk of reactivation in the low dose arm at any given time point over 26 days is 92% less than that in the control arm.

Adjusted HR: 0.07 (95% C.I. 0.01 to 0.6). The risk of reactivation in the low dose arm at any given time point over 26 days is 93% less than that in the control arm, after adjusting for gender, age and SOFA Score.

Figure 2: Time to Blood CMV Reactivation (Control vs Low Dose)



Secondary Outcome Measures

Reactivation in Blood, Urine, Throat or NDBL

NDBL

Peak Viral Load: 13647
Only 3 measurements are greater than 1000 copies (1 of these was at baseline) and 1 measurement greater than 10000 copies (this was at baseline).

Combined Treatment Arms:

6 patients had a baseline reactivation in NDBL CMV PCR. Excluding these patients, we only have 4 reactivations. 2/75 (3%) in the combined treatment arm reactivated compared with 2/43 (5%) in the control arm.

RR: 0.6 (95% C.I: 0.08 to 3.9). The event rate is low. The risk of reactivation in the combined treatment arm is 0.6 times that in the control arm.

HR: 0.6 (95% C.I: 0.09 to 4.3). The risk of reactivation at any given time point over 26 days in the low dose arm is 0.6 times that in the control arm.

Low Dose:

2/43 (5%) in the lose dose reactivated compared with 2/43 (5%) in the control arm.

RR: 1.0 (95% C.I: 0.1 to 6.8). The event rate is low. The risk of reactivation is the same in both arms.

HR: 0.9 (95% C.I: 0.1 to 6.6). The risk of reactivation at any given time point over 26 days in the low dose arm is 0.9 times that in the control arm.

Throat

Peak Viral Load: 403

Combined Treatment Arms:

6 patients had a baseline reactivation in Throat CMV PCR. Excluding these patients, we only have 7 reactivations. 3/75 (4%) in the combined treatment arm reactivated compared with 4/43 (9%) in the control arm.

RR: 0.4 (95% C.I: 0.1 to 1.8). The risk of reactivation in the combined treatment arm is 0.3 times that in the control arm.

HR: 0.5 (95% C.I: 0.1 to 2.4). The risk of reactivation at any given time point over 26 days in the low dose arm is 0.6 times that in the control arm.

Low Dose:

1/42 (2%) in the lose dose reactivated compared with 4/43 (9%) in the control arm.

RR: 0.3 (95% C.I: 0.03 to 2.2). The risk of reactivation in the low dose arm is 0.3 times that in the control arm.

HR: 0.3 (95% C.I: 0.03 to 2.5). The risk of reactivation at any given time point over 26 days in the low dose arm is 0.3 times that in the control arm.

Urine

Peak Viral Load: 278

Combined Treatment Arms:

2 patients had a baseline reactivation in Urine CMV PCR. Excluding these patients, we only have 4 reactivations. 0/79 (0%) in the combined treatment arm reactivated compared with 4/43 (9%) in the control arm.

Unable to compute ratios due to no events in the treatment arm.

Low Dose:

0/45 (0%) in the lose dose reactivated compared with 4/43 (9%) in the control arm.

Unable to compute ratios due to no events in the treatment arm.

Blood, NDBL, Throat or Urine Reactivation

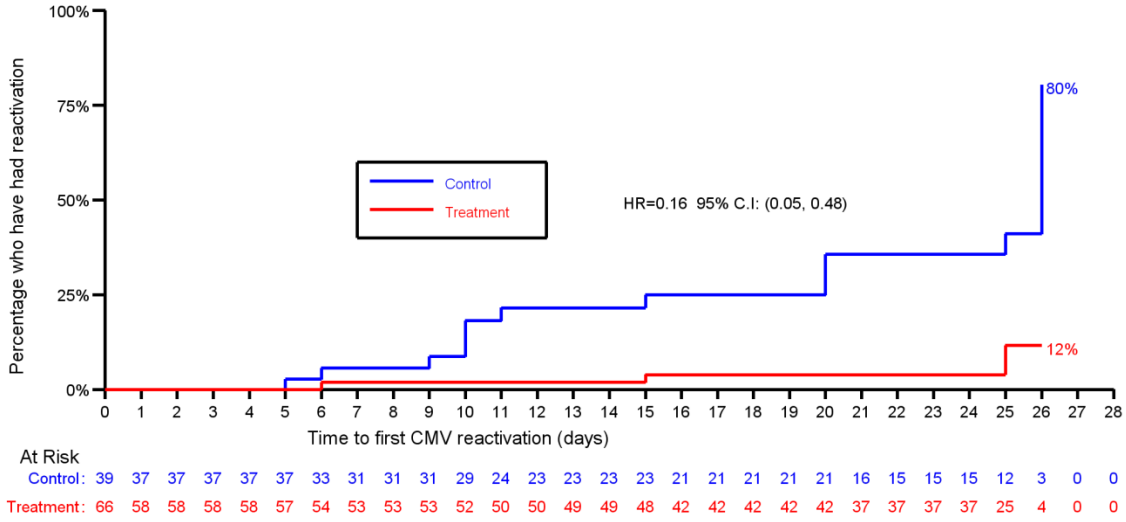
Combined Treatment Arms:

19 patients had a baseline reactivation in any CMV PCR. Excluding these patients, we have 18 reactivations. 4/66 (6%) in the combined treatment arm reactivated compared with 14/39 (36%) in the control arm.

RR: 0.2 (95% C.I: 0.06 to 0.5). The risk of reactivation in the combined treatment arm is 0.2 times that in the control arm.

HR: 0.2 (95% C.I: 0.05 to 0.5). The risk of reactivation at any given time point over 26 days in the low dose arm is 0.2 times that in the control arm.

Figure 3: Time To (Any) CMV Reactivation (Control vs Treatment Combined)



Low Dose:

2/38 (5%) in the lose dose reactivated compared with 14/39 (36%) in the control arm.

RR: 0.1 (95% C.I: 0.04 to 0.6). The risk of reactivation in the low dose arm is 0.1 times that in the control arm.

HR: 0.1 (95% C.I: 0.03 to 0.5). The risk of reactivation at any given time point over 26 days in the low dose arm is 0.1 times that in the control arm.

Figure 4: Time To (Any) CMV Reactivation (Control vs Low Dose)

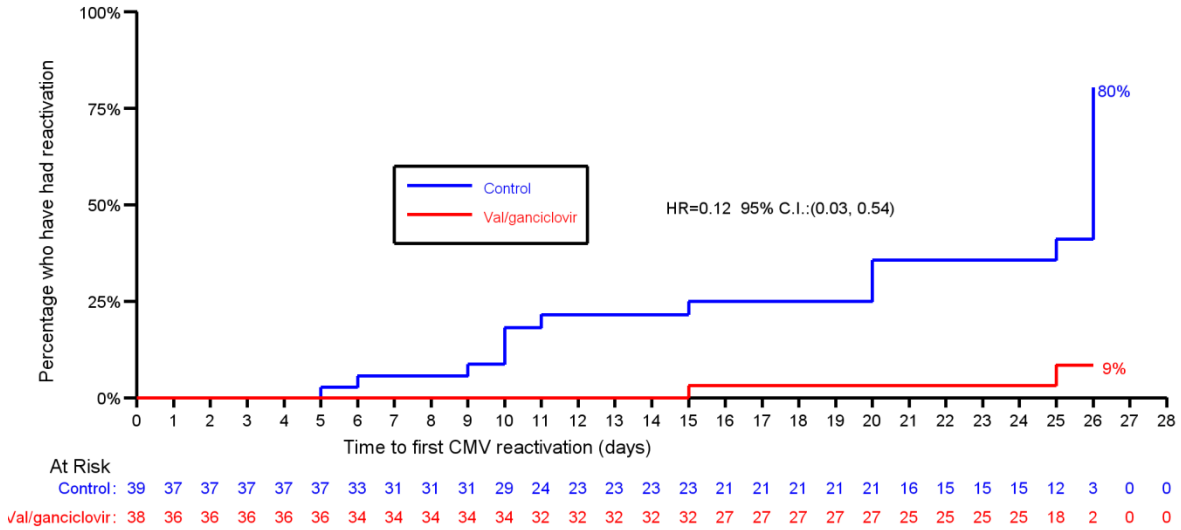


Table 4: Peak Viral Load by Treatment Arm

	Control	Valacicloivr/acyclovir	Valganciclovir/ganciclovir
Blood CMV Level	1382	113	836
NDBL CMV Level	1664	13647	822
Throat CMV Level	269	403	190
Urine CMV Level	278	<20	213

Area Under The Curve

Area under the curve is calculated excluding baseline reactivations, so our result isn't biased.

Table 5: AUC Comparing the Combined Treatment Arm with the Control Arm

		Control	Treatment Combined
Blood CMV PCR Levels	N	12	3
	Mean (SD)	577.8 (1111.8)	91.3 (18.8)
	Range	17.0 – 3720.0	80.0 – 113.0
Throat CMV PCR Levels	N	4	3
	Mean (SD)	192.1 (185.2)	786.2 (473.2)
	Range	41.0 – 462.0	275.0 – 1209.0
NDBL CMV PCR Levels	N	2	2
	Mean (SD)	4188.0 (5844.2)	1059.0 (1408.9)
	Range	55.0 – 8320.0	63.0 – 2055.0
Urine CMV PCR Levels	N	4	0
	Mean (SD)	329.6 (350.8)	-
	Range	84.0 – 834.0	-

Table 6: AUC Comparing the Low Dose Arm with the Control Arm

		Control	Valganciclovir/ ganciclovir
Blood CMV PCR Levels	N	12	1
	Mean (SD)	577.8 (1111.8)	113.0 (-)
	Range	17.0 – 3720.0	113.0
Throat CMV PCR Levels	N	4	1
	Mean (SD)	192.1 (185.2)	874.5 (-)
	Range	41.0 – 462.0	875.0
NDBL CMV PCR Levels	N	2	2
	Mean (SD)	4188.0 (5844.2)	1059.0 (1408.9)
	Range	55.0 – 8320.0	63.0 – 2055.0
Urine CMV PCR Levels	N	4	0
	Mean (SD)	329.6 (350.8)	-
	Range	84.0 – 834.0	-

Organ Failure

Note: For the Number of Organ Free Failure Days and Organ Moderate Dysfunction Free Days I used a negative binomial model rather than a poisson model (which was suggested in the SAP) due to overdispersion of the data. This is the suggested model for such count data.

Table 7: Organ Failure/Moderate Dysfunction Free Days Compared Between the Low Dose Arm and Control Arm

		Control	Valganciclovir/ ganciclovir	Rate Ratio (95% CI)
Organ Failure Free Days	N	44	46	
	Median (IQR)	3.5 (0.0-18.0)	2.0 (0.0-11.0)	0.7 (0.3 to 1.6)
	Range	0 – 31	0 – 36	
Organ Moderate Dysfunction Free Days	Median (IQR)	18.0 (2.0-24.0)	16.5 (4.0-21.0)	1.0 (0.6 to 1.7)
	Range	0 - 41	0 - 44	

The incident rate of organ failure free days (days where SOFA<2) in the low dose arm is 0.7 times that in the control arm. The incident rate of moderate dysfunction free days (days where SOFA<5) in the low dose arm is the same as the rate in the control arm.

Table 8: Organ Failure/Moderate Dysfunction Free Days Compared Between the Combined Treatment Arm and Control Arm

		Control	Treatment Combined	Rate Ratio (95% CI)
Organ Failure Free Days	N	44	80	
	Median (IQR)	3.5 (0.0-18.0)	2 (0.0-12.0)	0.7 (0.4 to 1.5)
	Range	0 – 31	0 – 36	
Organ Moderate Dysfunction Free Days	Median (IQR)	18.0 (2.0-24.0)	15.0 (2.0-22.0)	0.9 (0.6 to 1.4)
	Range	0 - 41	0-44	

The incident rate of organ failure free days in the combined treatment arm is 0.7 times that in the control arm. The incident rate of moderate dysfunction free days in the combined treatment arm is 0.9 times that in the control arm.

Time to ITU and Hospital Discharge (by 3 months)

ITU Discharge

By 3 months, 34/46 (74%) in the low dose arm had been discharged from the ITU by 3 months and in the control group 36/44 (82%) had been discharged.

HR: 0.7 (95% C.I: 0.4 to 1.1)

By 3 months, 55/80 (69%) had been discharged from the ITU in the combined treatment arm.

HR:0.6 (95% C.I: 0.4 to 1.0)

Hospital Discharge

By 3 months, 28/46 (61%) in the low dose arm had been discharged from the hospital compared to 30/44 (68%) in the control arm.

HR: 0.8 (95% C.I: 0.5 to 1.3)

By 3 months, 45/80 (56%) in the combined treatment arm had been discharged from the hospital.

HR: 0.7 (95% C.I: 0.4 to 1.1)

Time to Renal Insufficiency

Defined as Creatinine Clearance < 60ml/min:

24/46 (52%) had renal insufficiency in the low dose arm compared to 23/44 (52%) who had renal insufficiency in the control arm. 46/80 (58%) had renal insufficiency in the combined treatment arm.

The risk of renal insufficiency was the same (RR: 1.0 (95% C.I: 0.7 to 1.5)) in the low dose arm compared to the control arm and, in the combined treatment arm, was 1.1 times (RR: 1.1 (95% C.I: 0.8 to 1.5)) that in the control arm. The risk of renal insufficiency at any given time point over the 28 days was the same in the lose dose arm as the control arm (HR: 1.0 (95% C.I: 0.6 to 1.8)). The risk at any given time point in the combined treatment arm was 1.2 times that in the control arm (HR: 1.2 (95% C.I: 0.7 to 2.0))

Defined as Creatinine Clearance < 30ml/min or having haemodialysis/haemofiltration:

8/46 (17%) had renal insufficiency in the low dose arm compared to 11/44 (25%) who had renal insufficiency in the control arm. 11/80 (14%) had renal insufficiency in the combined treatment arm.

The risk of renal insufficiency in the low dose arm was 0.7 times that in the control arm (RR: 0.7 (95% C.I: 0.3 to 1.6)). In the combined treatment arm, was 0.6 times (RR: 0.6 (95% C.I: 0.3 to 1.2)) that in the control arm. The risk of renal insufficiency at any given time point over the 28 days in the low dose arm was 0.6 times that in the control arm (HR: 0.6 (95% C.I: 0.3 to 1.6)). The risk at any given time point in the combined treatment arm was 0.5 times that in the control arm (HR: 0.5 (95% C.I: 0.2 to 1.2))

Time To Neutropenia – no neutropenia

Time to Thrombocytopenia

10/46 (22%) had thrombocytopenia in the low dose arm, 10/44 (23%) had thrombocytopenia in the control arm.

RR: 1.0 (95% C.I: 0.4 to 2.1). The risk of thrombocytopenia was the same in the low dose arm as the control arm.

HR: 0.9 (95% C.I: 0.4 to 2.2). The risk of thrombocytopenia in the low dose arm, at any given time point over 28 days, was 0.9 times the risk in the control arm.

19/80 (24%) had thrombocytopenia in the combined treatment arm.

RR: 1.0 (95% C.I: 0.5 to 2.0). The risk of thrombocytopenia was the same in the combined treatment arm as the control arm.

HR: 1.0 (95% C.I: 0.5 to 2.2). The risk of thrombocytopenia at any given time point over the 28 days was the same in the combined treatment arm as the control arm.

Number of Platelet Transfusions

The number of platelet transfusions was inflated with zeros. The assumption was for missing forms was that these patients didn't have any platelet transfusions (these forms would be missing due to discharge or death so it is a sound assumption). Where the entry was missing (so we have a form but the number of platelet transfusions has not been added) we have left this as missing.

Table 9: Frequency of Platelet Transfusions by Arm

Number of Platelet Transfusions	Control Arm Frequency	Valaciclovir/acyclovir Frequency	Valganciclovir/ganciclovir Frequency	Total Frequency
Missing	0	2	4	6
0	34	24	31	89
1	2	3	1	6
2	3	2	3	8
3	0	0	2	2
4	2	1	0	3
5	1	0	2	3
7	0	0	1	1
8	0	0	1	1
10	0	1	1	2
12	1	1	0	2
18	1	0	0	1

Given the count frequency, I'm not sure that we have enough data to calculate whether there are differences between the arms.

Mortality Data

Table 10: Mortality by Combined Treatment Arm

		Control	Treatment Combined	Relative Risk	95% CI
	N	44	80		
AliveAt28days	No (%)	7 (16%)	24 (30%)	1.9	0.9 - 4.0
HasDied	Yes (%)	9 (20%)	27 (34%)	1.7	0.9 – 3.2

Table 11: Mortality by Treatment Arm

		Control	Valaciclovir/ acyclovir	Valganciclovir/ ganciclovir	Relative Risk*	95% C.I.	Relative Risk	95% C.I.
	N	44	34	46				
AliveAt28days	No (%)	7 (16%)	14 (41%)	10 (22%)	2.6	1.2 – 5.7	1.4	0.6 - 3.3
HasDied	Yes (%)	9 (20%)	15 (44%)	12 (26%)	2.2	1.1 – 4.3	1.3	0.6 – 2.7

* Relative risk comparing valganciclovir/ganciclovir to control

Serious Adverse Events

There have been 37/124 (30%) SAEs reported in 33 patients.

Table 12: Proportion of Patients who had an SAE by Treatment Arm

Control	Valaciclovir/acyclovir	Valganciclovir/ganciclovir
7/44 (16%)	10/34 (29%)	16/46 (35%)

Premature Cessation

9/80 (11%) of patients in the treatment arms prematurely stopped taking the study drug. 4 patients stopped due to an SAE (patients 030, 052, 078 and 118). See list of SAEs for further details. In three cases, the supervising clinician withdrew for other reason (other reasons were: withdrawal of care, missed one dose; terminal care, missed one dose; and low platelet count). One patient had an allergic reaction to the study drug; and the family of the other patient requested the study drug to stop due to the patient being in an acute confused state/delirium.

Control

Pat TNO	Date Randomised	Date Of Reaction	System	Event Severity	Related	Unexpected
005	24/02/2012	21/03/2012	Cardiovascular	Life Threatening	No	Unexpected
065	15/11/2012	16/11/2012	Respiratory	Life Threatening	No	Unexpected
087	26/03/2013	13/04/2013	Cardiovascular	Life Threatening	No	Unexpected
108	23/09/2013	28/09/2013	Neurological	Patient Died	No	Expected
114	25/10/2013	02/11/2013	Cardiovascular	Life Threatening	No	Expected
115	25/01/2013	26/10/2013	Cardiovascular	Patient Died	No	Expected
116	11/11/2013	23/11/2013	Gastrointestinal	Life Threatening	No	Expected

Valaciclovir / aciclovir

Pat TNO	Date Randomised	Date Of Reaction	System	Event Severity	Related	Unexpected
016	17/04/2012	04/05/2012	Respiratory	Life Threatening	Unlikely	Expected
020	03/05/2012	25/05/2012	Neurological	Patient Died	Unlikely	
030	13/06/2012	27/06/2012	Dermatological	Prolonged Hospitalisation	Unlikely	Expected
045	21/08/2012	29/08/2012	Lymphatic	Life Threatening	Unlikely	Expected
047	22/08/2012	04/09/2012	Dermatological	Prolonged Hospitalisation	Possibly	Expected
078	17/01/2013	26/01/2013	Renal, Dermatological, neurological	Life Threatening	Possibly	Expected
079	31/01/2013	03/02/2013	Renal, CNS	Patient Died	Possibly	Expected
089	04/04/2013	05/04/2013	Cardiovascular	Life Threatening	No	Unexpected
089	04/04/2013	05/04/2013	Cardiovascular	Patient Died	No	Unexpected
096	30/05/2013	03/06/2013	Respiratory and Cardiovascular	Life Threatening	Unlikely	Expected
096	30/05/2013	01/08/2013	Respiratory and Cardiovascular	Patient Died	Unlikely	Expected
105	05/08/2013	19/08/2013	Gastrointestinal	Prolonged Hospitalisation	Possibly	Expected

Valganciclovir / ganciclovir

Pat TNO	Date Randomised	Date Of Reaction	System	Event Severity	Related	Unexpected
001	02/02/2012	07/02/2012	Cardiovascular	Life Threatening	Possibly	Expected
014	05/04/2012	19/04/2012	Gastrointestinal	Life Threatening	No	
052	21/09/2012	28/09/2012	Haematological	Life threatening	Possibly	Expected
066	23/11/2012	06/12/2012	Gastrointestinal	Life Threatening	Possibly	Expected

091	17/04/2013	08/05/2013	Respiratory	Patient Died	Unlikely	Expected
093	30/04/2013	20/05/2013	Respiratory	Patient Died	Unlikely	Expected
095	21/05/2013	11/06/2013	Respiratory and Cardiovascular	Life threatening	Unlikely	Expected
098	07/06/2013	18/06/2013	GI/respiratory and cardiovascular	Patient Died	Unlikely	Expected
104	23/07/2013	19/08/2013	Renal	Prolonged Hospitalisation	Possibly	Expected
106	06/08/2013	13/08/2013	Cardiovascular	Life Threatening	Unlikely	Unexpected
106	06/08/2013	25/08/2013	Cardiovascular	Life Threatening	No	Unexpected
106	06/08/2013	02/09/2013	Cardiovascular	Life Threatening	No	Expected
107	19/08/2013	03/09/2013	Gastrointestinal	Prolonged Hospitalisation	No	Expected
112	16/10/2013	25/10/2013	Neurological	Life Threatening	No	Expected
118	14/11/2013	20/11/2013	Dermatological	Other	Unlikely	Expected
119	03/12/2013	07/12/2013	Haematological	Prolonged Hospitalisation	Possibly	Expected
120	05/12/2013	13/12/2013	Neurological	Other	No	Expected
121	06/12/2013	11/12/2013	Cardiovascular	Life Threatening	No	Expected