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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Supplementary Material

Anti-influenza immune plasma for the treatment of patients with severe influenza A: a randomised, double-blind, phase 3 trial

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The following sites collected the high titer anti-influenza immune plasma that was used in the IRC005 study:
Mississippi Valley Regional Blood Center
Memorial Blood Centers
Gulf Coast Regional Blood Center

In addition to writing group, the following study team members contributed significantly to the conduct of the IRC005 trial:
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Supplemental methods:

Sample Size and Power Considerations

The planned sample size for the trial was 150 subjects, randomized in an approximately 2:1 ratio to high-titer versus low-titer anti-influenza plasma. To evaluate the power of the study, the following assumptions were made:

a. The primary analysis would compare the high-titer and low-titer plasmas using a proportional odds model and a two-sided Type I error rate of 0.05.

b. It was anticipated that very few of these subjects would be randomized and not start study plasma infusion (and so be excluded from the primary analysis) or be lost to follow-up prior to Day 7 (and so have missing data for the primary endpoint). In addition, power is reduced slightly and hence the effective sample size is reduced by interim analyses reviewed by the DSMB. Conservatively, a 10% reduction in the total sample size from 150 to 135 subjects was made to allow for these issues.

c. Data from the control arm of IRC002(1) for adults with influenza A infection, NEW score ≥3, and duration of time from onset of symptoms of influenza to randomization ≤6 days, suggested the distribution of subjects in the low-titer arm for the primary endpoint shown in the following table:

Anticipated Distribution of Subjects in the Ordinal Scale

	Low-Titer Arm	High-Titer Arm	
	(Based on IRC 002)	80% Power	90% Power
Died	10%	4.3%	3.7%
In ICU	35%	20.4%	18.4%
Non-ICU hospitalization, requiring supplemental oxygen	25%	23.6%	22.6%
Non-ICU hospitalization, not requiring supplemental oxygen	10%	13.3%	13.4%
Not hospitalized, but unable to resume normal activities	5%	7.9%	8.2%
Not hospitalized, but with full resumption of normal activities	15%	30.6%	33.7%
Proportional odds ratio comparing high titer to low titer		2.50	2.88

Based on the above assumptions, the table also shows the type of true difference (assuming proportional odds) that would be detected with 80% or 90% power. These powers were obtained using the PASS software (NCSS, Kaysville, Utah). For example,

the study would have 80% power to detect a proportional odds ratio of 2.50. This is the odds ratio that arises when comparing the proportion not hospitalized and able to resume normal activities in the high-titer arm (30.6%) to that in the low-titer arm (15%). The proportional odds model assumes that the same odds ratio applies to the cumulative proportions moving up the ordinal scale: for example, for the proportion not hospitalized in the high-titer arm (30.6+7.9=38.5%) to that in the low-titer arm (15+5=20%); or for the proportion alive and not in an ICU in the high-titer arm (30.6+7.9+13.3+23.6=75.4%) to that in the low-titer arm (15+5+10+25=55%).

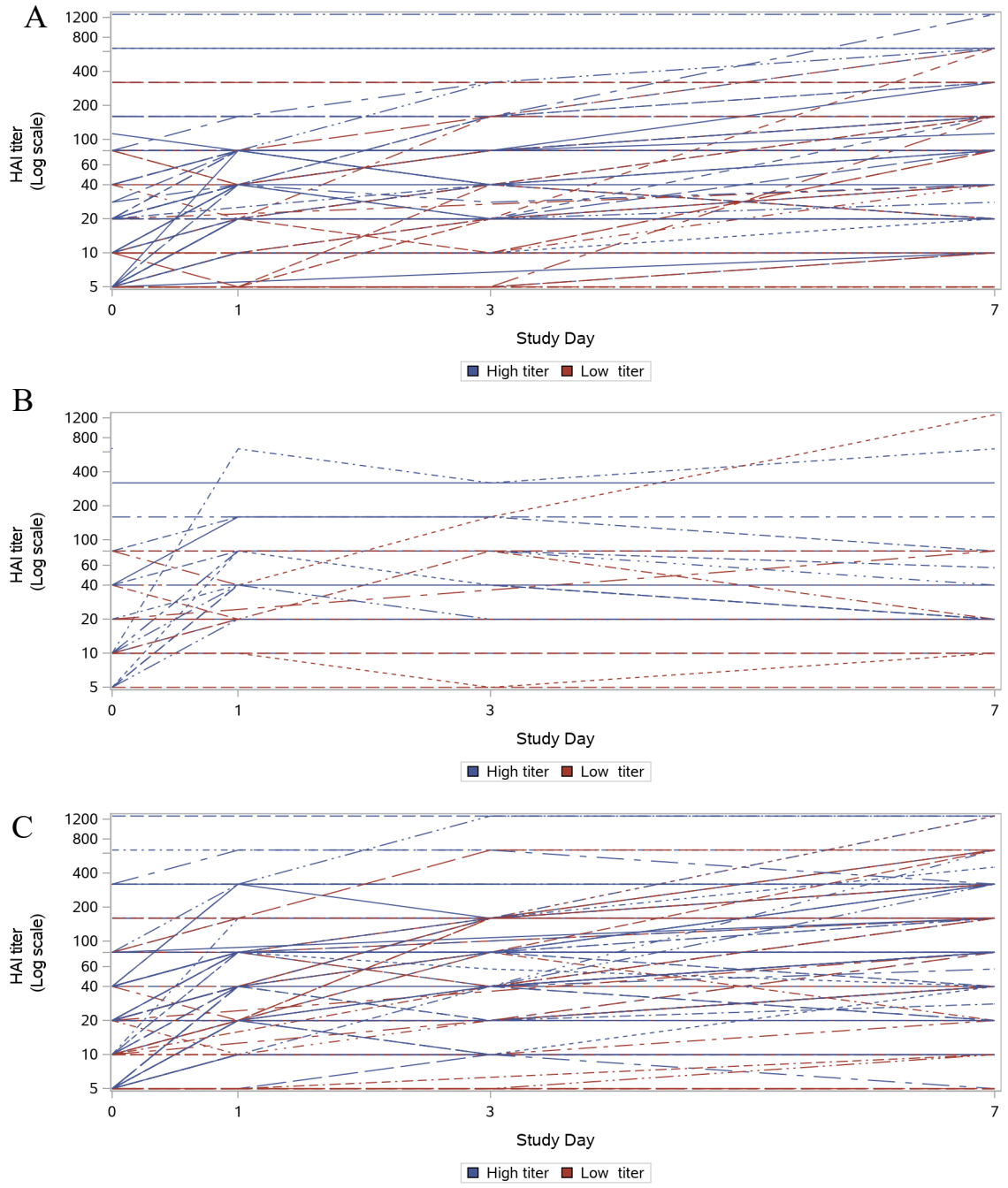
Supplemental Tables and Figures:

Supplemental Figure 1. HAI titres over time by subjects and randomized treatments. (boxes span from the lower limit of the 95% CI to upper limit of the 95% CI)

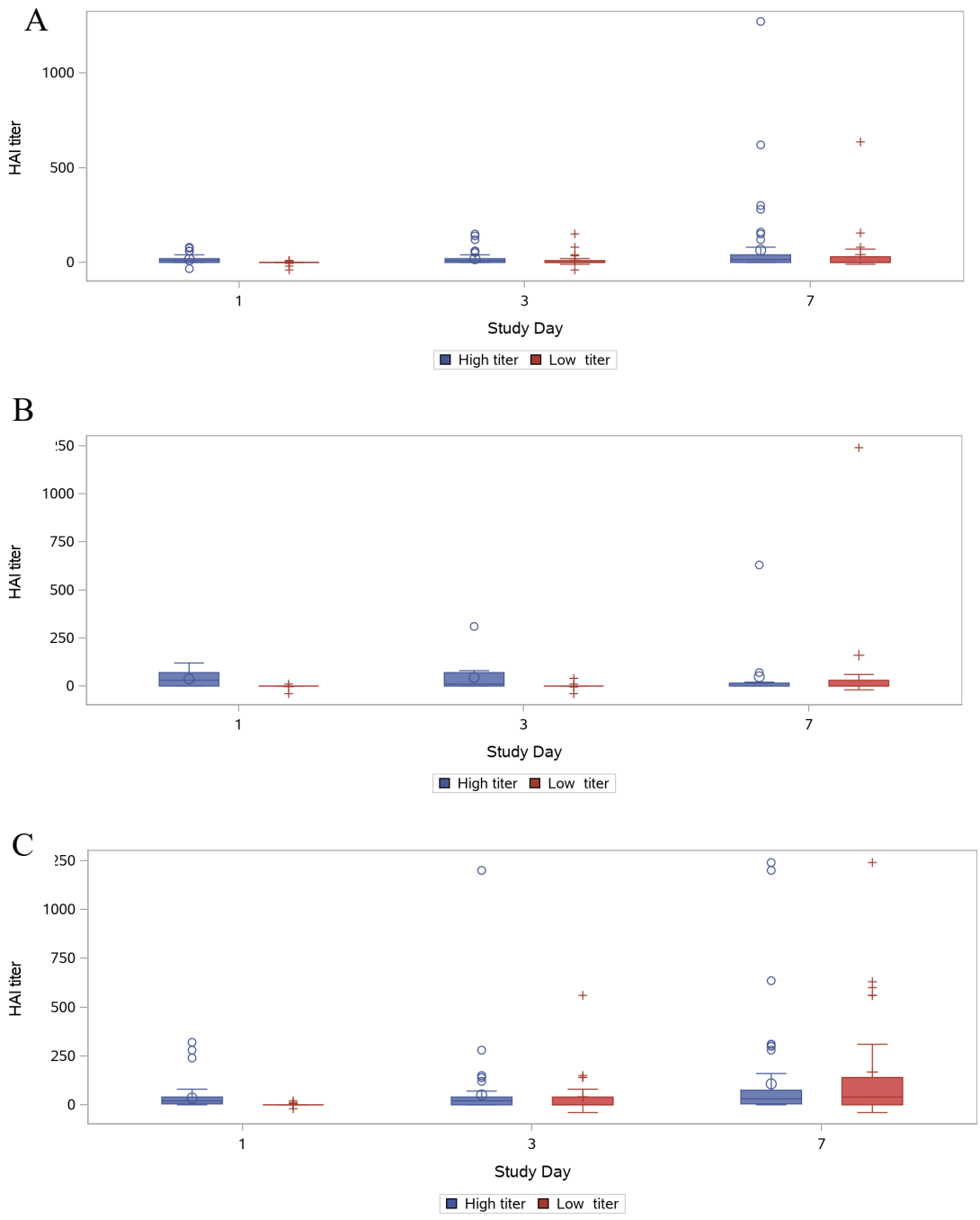
A) influenza A/California/7/2009 H1N1

B) influenza A/Switzerland/9715293/2013 H3N2

C) influenza A/Hong Kong/4801/2014 H3N2



Supplemental Figure 2. HAI titres changes over time by randomized treatments. (boxes span from the lower limit of the 95% CI to upper limit of the 95% CI)
A) influenza A/California/7/2009 H1N1
B) influenza A/Switzerland/9715293/2013 H3N2
C) influenza A/Hong Kong/4801/2014 H3N2



Note: As log scale y-axis cannot support zero or negative change values, the axis are presented as linear

Supplemental Table 1. HAI in plasma infusion (all seasons, tested to vaccine strain for a given year)

			Randomized treatment	
		Total	High	Low
First Unit			titer	titer
		(N=138)	(N=91)	(N=47)
A/California/7/2009 (H1N1)	N	80	53	27
	Median (Q1, Q3)	160 (10, 320)	320 (160, 453)	5 (5, 10)
A/Michigan/45/2015 (H1N1)	N	58	38	20
	Median (Q1, Q3)	160 (5, 320)	240 (160, 320)	5 (5, 5)
A/Switzerland/9715293/2013 (H3N2)	N	35	23	12
	Median (Q1, Q3)	160 (5, 320)	160 (160, 453)	5 (5, 8)
A/HongKong/4801/2014 (H3N2)	N	103	68	35
	Median (Q1, Q3)	160 (10, 320)	320 (160, 547)	5 (5, 10)
Second Unit				
A/California/7/2009 (H1N1)	N	71	48	23
	Median (Q1, Q3)	160 (10, 320)	320 (160, 320)	5 (5, 10)
A/Michigan/45/2015 (H1N1)	N	58	38	20
	Median (Q1, Q3)	160 (5, 320)	160 (160, 320)	5 (5, 5)
A/Switzerland/9715293/2013 (H3N2)	N	31	21	10
	Median (Q1, Q3)	160 (10, 640)	640 (160, 905)	5 (5, 10)
A/HongKong/4801/2014 (H3N2)	N	98	65	33
	Median (Q1, Q3)	160 (5, 320)	320 (160, 320)	5 (5, 5)

Supplemental Table 2. Influenza Viral Shedding by Treatment Arm

	Randomized treatment				Exact logistic regression High titer vs. Low titer		
Influenza virus in OP sample at Day 3	Total (N=138)	High titer (N=91)	Low titer (N=47)	p-value*	Odds ratio	95% CI	p-value
Detectable	100 (80%)	65 (76%)	35 (88%)	0.23	0.47	[0.13, 1.43]	0.23
Undetectable	25 (20%)	20 (24%)	5 (13%)				
Died prior to Day 3	1	1	0				
Lost to follow-up prior to Day 3	1	0	1				
In follow-up but no result	11	5	6				

**Fisher's exact test (detectable vs. undetectable)*
The category 'Detectable' includes results reported as '<75 copies/mL'

Table 3. Disposition following initial hospitalization

			Randomized treatment			Proportional odds model High titer vs. Low titer		
		Total (N=138)	High titer (N=91)	Low titer (N=47)	p-value*	Odds ratio	95% CI	p-value
Disposition following initial hospitalization	N	138	91	47	0.12	1.73	[0.87, 3.44]	0.12
	Death	8 (6%)	4 (4%)	4 (9%)				
	Ongoing at 28 days	6 (4%)	3 (3%)	3 (6%)				
	Long-term care / Chronic Nursing Facility	11 (8%)	7 (8%)	4 (9%)				
	Transferred to rehabilitation	7 (5%)	4 (4%)	3 (6%)				
	Home with home health / other assistance	21 (15%)	13 (14%)	8 (17%)				
	Home without assistance	85 (62%)	60 (66%)	25 (53%)				

**Exact Wilcoxon test*
Test of proportional odds assumption: p-value = 0.99

NOTE: an odds ratio of greater than one is indicative of better disposition for the high titer group versus the low titer group

Table 4: PEW Score at Days 0, 3 and 7

			Randomized treatment	
		Total (N=13)	**High titer (N=8)**	**Low titer (N=5)**
PEW Score at Day 0	Median (Q1, Q3)	8 (5, 12)	9.0 (5.0, 11.5)	8 (4, 13)
	Min, Max	3, 16	3, 13	3, 16
	> 0	13 (100%)	8 (100%)	5 (100%)
	N with imputed Score	0	0	0
PEW Score at Day 3	Median (Q1, Q3)	5 (3, 9)	6.5 (5.0, 10.5)	3 (2, 4)
	Min, Max	2, 98	3, 98	2, 12
	> 0	13 (100%)	8 (100%)	5 (100%)
	N with imputed Score	2	2	0
PEW Score at Day 7	Median (Q1, Q3)	3 (1, 5)	3.5 (1.0, 5.5)	2 (1, 3)
	Min, Max	0, 98	1, 98	0, 8
	> 0	12 (92%)	8 (100%)	4 (80%)
	N with imputed Score	1	1	0

For subjects who died before the evaluation day (and so are assumed to have a worse outcome than other surviving subjects) a Score of 99 is imputed
For subjects who were on ECMO on the evaluation day (and so are assumed to have a worse outcome than other surviving subjects but better outcome than non-surviving subjects) a Score of 98 is imputed
For other surviving subjects with a missing Score, the Score was imputed with the last available Score carried forward

Table 5: PELOD Score at Days 0, 3 and 7

			Randomized treatment	
		Total (N=12)	**High titer (N=8)**	**Low titer (N=4)**
PELOD Score at Day 0	Median (Q1, Q3)	0.5 (0.0, 3.0)	0 (0, 1)	3.0 (1.5, 12.0)
	Min, Max	0, 32	0, 32	0, 21
	> 0	6 (50%)	3 (38%)	3 (75%)
	N with imputed Score	0	0	0
PELOD Score at Day 3	Median (Q1, Q3)	0.0 (0.0, 20.5)	0 (0, 10)	17.0 (6.5, 26.0)
	Min, Max	0, 98	0, 98	0, 31
	> 0	5 (42%)	2 (25%)	3 (75%)
	N with imputed Score	3	3	0
PELOD Score at Day 7	Median (Q1, Q3)	0.0 (0.0, 6.5)	0.0 (0.0, 5.5)	1.5 (0.0, 12.0)
	Min, Max	0, 98	0, 98	0, 21
	> 0	5 (42%)	3 (38%)	2 (50%)
	N with imputed Score	1	1	0

For subjects who died before the evaluation day (and so are assumed to have a worse outcome than other surviving subjects) a Score of 99 is imputed
For subjects who were on ECMO on the evaluation day (and so are assumed to have a worse outcome than other surviving subjects but better outcome than non-surviving subjects) a Score of 98 is imputed
For other surviving subjects with a missing Score, the Score was imputed with the last available Score carried forward

Supplemental Table 6: Concomittant antiviral use

		Randomized treatment	
Antiviral	**Total (N=138)**	**High titer (N=91)**	**Low titer (N=47)**
Oseltamivir	123 (89%)	81 (89%)	42 (89%)
Oseltamivir + Peramivir	3 (2%)	2 (2%)	1 (2%)
Oseltamivir + Rimantadine	1 (1%)	0 (0%)	1 (2%)
Peramivir	2 (1%)	1 (1%)	1 (2%)
None	9 (7%)	7 (8%)	2 (4%)

Supplemental Table 7: Total number of Serious Adverse Events (SAEs) by MedDRA System Organ Class (SOC) and Preferred Term (PT) after randomization, including SAEs reported after the Day 28 visit.

	Randomized treatment																															
	Total (N=88)										High titer (N=60)										Low titer (N=28)									
Event	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Number events		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Number events		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Number events	
Overall	**1**	**1%**	**2**	**2%**	**34**	**39%**	**38**	**43%**	**13**	**15%**	**88**	**100%**	**0**	**0%**	**0**	**0%**	**27**	**45%**	**25**	**42%**	**8**	**13%**	**60**	**100%**	**1**	**4%**	**2**	**7%**	**7**	**25%**	**13**	**46%**	**5**	**18%**	**28**	**100%**
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**0**	**0%**	**0**	**0%**	**7**	**8%**	**11**	**13%**	**5**	**6%**	**23**	**26%**	**0**	**0%**	**0**	**0%**	**6**	**10%**	**8**	**13%**	**2**	**3%**	**16**	**27%**	**0**	**0%**	**0**	**0%**	**1**	**4%**	**3**	**11%**	**3**	**11%**	**7**	**25%**
ACUTE RESPIRATORY DISTRESS SYNDROME	0	0%	0	0%	1	1%	3	3%	2	2%	6	7%	0	0%	0	0%	1	2%	3	5%	0	0%	4	7%	0	0%	0	0%	0	0%	0	0%	2	7%	2	7%
RESPIRATORY DISTRESS	0	0%	0	0%	1	1%	2	2%	0	0%	3	3%	0	0%	0	0%	1	2%	2	3%	0	0%	3	5%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
HAEMOTHORAX	0	0%	0	0%	0	0%	2	2%	0	0%	2	2%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%	0	0%	0	0%	0	0%	1	4%	0	0%	1	4%
PNEUMONIA ASPIRATION	0	0%	0	0%	1	1%	0	0%	1	1%	2	2%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	1	4%	1	4%
RESPIRATORY FAILURE	0	0%	0	0%	0	0%	1	1%	1	1%	2	2%	0	0%	0	0%	0	0%	0	0%	1	2%	1	2%	0	0%	0	0%	0	0%	1	4%	0	0%	1	4%
HYPOXIA	0	0%	0	0%	1	1%	1	1%	0	0%	2	2%	0	0%	0	0%	1	2%	1	2%	0	0%	2	3%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
DYSPNOEA	0	0%	0	0%	1	1%	1	1%	0	0%	2	2%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%	0	0%	0	0%	0	0%	1	4%	0	0%	1	4%
PNEUMOTHORAX	0	0%	0	0%	1	1%	1	1%	0	0%	2	2%	0	0%	0	0%	1	2%	1	2%	0	0%	2	3%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
ACUTE RESPIRATORY FAILURE	0	0%	0	0%	0	0%	0	0%	1	1%	1	1%	0	0%	0	0%	0	0%	0	0%	1	2%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	4%	0	0%	0	0%	1	4%
CARDIAC DISORDERS	**0**	**0%**	**0**	**0%**	**5**	**6%**	**5**	**6%**	**2**	**2%**	**12**	**14%**	**0**	**0%**	**0**	**0%**	**5**	**8%**	**3**	**5%**	**2**	**3%**	**10**	**17%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**2**	**7%**	**0**	**0%**	**2**	**7%**
CARDIOMYOPATHY	0	0%	0	0%	1	1%	1	1%	0	0%	2	2%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%	0	0%	0	0%	0	0%	1	4%	0	0%	1	4%
ATRIAL FIBRILLATION	0	0%	0	0%	1	1%	1	1%	0	0%	2	2%	0	0%	0	0%	1	2%	1	2%	0	0%	2	3%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
PERICARDIAL HAEMORRHAGE	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	4%	0	0%	1	4%
CARDIOPULMONARY FAILURE	0	0%	0	0%	0	0%	0	0%	1	1%	1	1%	0	0%	0	0%	0	0%	0	0%	1	2%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
CARDIAC ARREST	0	0%	0	0%	0	0%	0	0%	1	1%	1	1%	0	0%	0	0%	0	0%	0	0%	1	2%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
CARDIAC FAILURE	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
ATRIAL FLUTTER	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
SUPRAVENTRICULAR TACHYCARDIA	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
PERICARDIAL EFFUSION	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
VENTRICULAR TACHYCARDIA	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
INFECTIONS AND INFESTATIONS	**1**	**1%**	**0**	**0%**	**4**	**5%**	**2**	**2%**	**1**	**1%**	**8**	**9%**	**0**	**0%**	**0**	**0%**	**4**	**7%**	**0**	**0%**	**1**	**2%**	**5**	**8%**	**1**	**4%**	**0**	**0%**	**0**	**0%**	**2**	**7%**	**0**	**0%**	**3**	**11%**
UROSEPSIS	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
SINUSITIS	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
GASTROENTERITIS NOROVIRUS	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
TRACHEITIS	1	1%	0	0%	0	0%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	4%	0	0%	0	0%	0	0%	0	0%	1	4%
SYSTEMIC CANDIDA	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	4%	0	0%	1	4%
SEPTIC SHOCK	0	0%	0	0%	0	0%	0	0%	1	1%	1	1%	0	0%	0	0%	0	0%	0	0%	1	2%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
PNEUMONIA	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
SEPSIS	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	4%	0	0%	1	4%
INVESTIGATIONS	**0**	**0%**	**0**	**0%**	**2**	**2%**	**6**	**7%**	**0**	**0%**	**8**	**9%**	**0**	**0%**	**0**	**0%**	**1**	**2%**	**4**	**7%**	**0**	**0%**	**5**	**8%**	**0**	**0%**	**0**	**0%**	**1**	**4%**	**2**	**7%**	**0**	**0%**	**3**	**11%**
HAEMOGLOBIN DECREASED	0	0%	0	0%	1	1%	1	1%	0	0%	2	2%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%	0	0%	0	0%	1	4%	0	0%	0	0%	1	4%
BLOOD CREATININE INCREASED	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
CREATININE RENAL CLEARANCE DECREASED	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
LIVER FUNCTION TEST ABNORMAL	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
WHITE BLOOD CELL COUNT DECREASED	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	4%	0	0%	1	4%
PLATELET COUNT DECREASED	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	4%	0	0%	1	4%
BLOOD POTASSIUM DECREASED	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**0**	**0%**	**2**	**2%**	**3**	**3%**	**2**	**2%**	**0**	**0%**	**7**	**8%**	**0**	**0%**	**0**	**0%**	**3**	**5%**	**1**	**2%**	**0**	**0%**	**4**	**7%**	**0**	**0%**	**2**	**7%**	**0**	**0%**	**1**	**4%**	**0**	**0%**	**3**	**11%**
ALLERGIC TRANSFUSION REACTION	0	0%	1	1%	2	2%	1	1%	0	0%	4	5%	0	0%	0	0%	2	3%	0	0%	0	0%	2	3%	0	0%	1	4%	0	0%	1	4%	0	0%	2	7%
TOXICITY TO VARIOUS AGENTS	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
TRAUMATIC LIVER INJURY	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
TRANSFUSION-RELATED CIRCULATORY OVERLOAD	0	0%	1	1%	0	0%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	4%	0	0%	0	0%	0	0%	1	4%
VASCULAR DISORDERS	**0**	**0%**	**0**	**0%**	**4**	**5%**	**1**	**1%**	**0**	**0%**	**5**	**6%**	**0**	**0%**	**0**	**0%**	**1**	**2%**	**1**	**2%**	**0**	**0%**	**2**	**3%**	**0**	**0%**	**0**	**0%**	**3**	**11%**	**0**	**0%**	**0**	**0%**	**3**	**11%**
EXTREMITY NECROSIS	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	4%	0	0%	0	0%	1	4%
HYPOTENSION	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	4%	0	0%	0	0%	1	4%
HAEMORRHAGE	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	4%	0	0%	0	0%	1	4%
PERIPHERAL ISCHAEMIA	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
SHOCK HAEMORRHAGIC	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
RENAL AND URINARY DISORDERS	**0**	**0%**	**0**	**0%**	**2**	**2%**	**2**	**2%**	**0**	**0%**	**4**	**5%**	**0**	**0%**	**0**	**0%**	**1**	**2%**	**1**	**2%**	**0**	**0%**	**2**	**3%**	**0**	**0%**	**0**	**0%**	**1**	**4%**	**1**	**4%**	**0**	**0%**	**2**	**7%**
RENAL FAILURE	0	0%	0	0%	1	1%	1	1%	0	0%	2	2%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%	0	0%	0	0%	0	0%	1	4%	0	0%	1	4%
ACUTE KIDNEY INJURY	0	0%	0	0%	1	1%	1	1%	0	0%	2	2%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%	0	0%	0	0%	1	4%	0	0%	0	0%	1	4%
NERVOUS SYSTEM DISORDERS	**0**	**0%**	**0**	**0%**	**0**	**0%**	**3**	**3%**	**1**	**1%**	**4**	**5%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**2**	**3%**	**0**	**0%**	**2**	**3%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**1**	**4%**	**1**	**4%**	**2**	**7%**
CEREBRAL HAEMORRHAGE	0	0%	0	0%	0	0%	0	0%	1	1%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	4%	1	4%
ISCHAEMIC STROKE	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
ENCEPHALOPATHY	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	4%	0	0%	1	4%
HYPOXIC-ISCHAEMIC ENCEPHALOPATHY	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**0**	**0%**	**0**	**0%**	**2**	**2%**	**0**	**0%**	**2**	**2%**	**4**	**5%**	**0**	**0%**	**0**	**0%**	**1**	**2%**	**0**	**0%**	**1**	**2%**	**2**	**3%**	**0**	**0%**	**0**	**0%**	**1**	**4%**	**0**	**0%**	**1**	**4%**	**2**	**7%**
GENERALISED OEDEMA	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
MULTI-ORGAN FAILURE	0	0%	0	0%	0	0%	0	0%	1	1%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	4%	1	4%
ASTHENIA	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	4%	0	0%	0	0%	1	4%
DEATH	0	0%	0	0%	0	0%	0	0%	1	1%	1	1%	0	0%	0	0%	0	0%	0	0%	1	2%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
METABOLISM AND NUTRITION DISORDERS	**0**	**0%**	**0**	**0%**	**2**	**2%**	**2**	**2%**	**0**	**0%**	**4**	**5%**	**0**	**0%**	**0**	**0%**	**2**	**3%**	**1**	**2%**	**0**	**0%**	**3**	**5%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**1**	**4%**	**0**	**0%**	**1**	**4%**
FLUID OVERLOAD	0	0%	0	0%	2	2%	0	0%	0	0%	2	2%	0	0%	0	0%	2	3%	0	0%	0	0%	2	3%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
METABOLIC ACIDOSIS	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	4%	0	0%	1	4%
LACTIC ACIDOSIS	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
GASTROINTESTINAL DISORDERS	**0**	**0%**	**0**	**0%**	**2**	**2%**	**1**	**1%**	**0**	**0%**	**3**	**3%**	**0**	**0%**	**0**	**0%**	**2**	**3%**	**1**	**2%**	**0**	**0%**	**3**	**5%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**
GASTROINTESTINAL HAEMORRHAGE	0	0%	0	0%	1	1%	1	1%	0	0%	2	2%	0	0%	0	0%	1	2%	1	2%	0	0%	2	3%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
ABDOMINAL PAIN	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
PSYCHIATRIC DISORDERS	**0**	**0%**	**0**	**0%**	**1**	**1%**	**1**	**1%**	**0**	**0%**	**2**	**2%**	**0**	**0%**	**0**	**0%**	**1**	**2%**	**1**	**2%**	**0**	**0%**	**2**	**3%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**
DELIRIUM	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
MENTAL STATUS CHANGES	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**2**	**2%**	**2**	**2%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**2**	**3%**	**2**	**3%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**
MANTLE CELL LYMPHOMA REFRACTORY	0	0%	0	0%	0	0%	0	0%	1	1%	1	1%	0	0%	0	0%	0	0%	0	0%	1	2%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
LUNG CARCINOMA CELL TYPE UNSPECIFIED STAGE IV	0	0%	0	0%	0	0%	0	0%	1	1%	1	1%	0	0%	0	0%	0	0%	0	0%	1	2%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**0**	**0%**	**0**	**0%**	**0**	**0%**	**2**	**2%**	**0**	**0%**	**2**	**2%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**2**	**3%**	**0**	**0%**	**2**	**3%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**
THROMBOTIC THROMBOCYTOPENIC PURPURA	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
THROMBOCYTOPENIA	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%

note: Table shows counts of SAEs, not counts of subjects (i.e., multiple events from the same subject are counted in each row)

Supplemental Table 8: Total number of Adverse Events (AEs) by MedDRA System Organ Class (SOC) and Preferred Term (PT) after randomization *

	High titer (N=126)												Low titer (N=57)											
Event	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Number events		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Number events	
Overall	**3**	**2%**	**0**	**0%**	**85**	**67%**	**32**	**25%**	**6**	**5%**	**126**	**100%**	**1**	**2%**	**7**	**12%**	**28**	**49%**	**16**	**28%**	**5**	**9%**	**57**	**100%**
INVESTIGATIONS	**0**	**0%**	**0**	**0%**	**23**	**18%**	**8**	**6%**	**0**	**0%**	**31**	**25%**	**0**	**0%**	**0**	**0%**	**6**	**11%**	**3**	**5%**	**0**	**0%**	**9**	**16%**
HAEMOGLOBIN DECREASED	0	0%	0	0%	4	3%	1	1%	0	0%	5	4%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%
ASPARTATE AMINOTRANSFERASE INCREASED	0	0%	0	0%	1	1%	1	1%	0	0%	2	2%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%
BLOOD GLUCOSE INCREASED	0	0%	0	0%	2	2%	0	0%	0	0%	2	2%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%
WHITE BLOOD CELL COUNT INCREASED	0	0%	0	0%	2	2%	1	1%	0	0%	3	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
BLOOD CREATININE INCREASED	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%
BLOOD POTASSIUM DECREASED	0	0%	0	0%	2	2%	0	0%	0	0%	2	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
HAEMATOCRIT DECREASED	0	0%	0	0%	2	2%	0	0%	0	0%	2	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
LYMPHOCYTE COUNT DECREASED	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%
CREATININE RENAL CLEARANCE DECREASED	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
BLOOD TRIGLYCERIDES INCREASED	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
BLOOD CALCIUM DECREASED	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
TROPONIN INCREASED	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%
BLOOD BILIRUBIN INCREASED	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%
ANION GAP INCREASED	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
LIVER FUNCTION TEST ABNORMAL	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
BLOOD BICARBONATE DECREASED	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
TROPONIN T INCREASED	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
PROTHROMBIN TIME PROLONGED	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
EPIDERMAL GROWTH FACTOR RECEPTOR DECREASED	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
BLOOD ALBUMIN DECREASED	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
BLOOD PHOSPHORUS DECREASED	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
WHITE BLOOD CELL COUNT DECREASED	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%
PLATELET COUNT DECREASED	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%
ALANINE AMINOTRANSFERASE INCREASED	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
NEUTROPHIL COUNT INCREASED	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**0**	**0%**	**0**	**0%**	**8**	**6%**	**8**	**6%**	**2**	**2%**	**18**	**14%**	**0**	**0%**	**1**	**2%**	**4**	**7%**	**3**	**5%**	**3**	**5%**	**11**	**19%**
ACUTE RESPIRATORY DISTRESS SYNDROME	0	0%	0	0%	1	1%	3	2%	0	0%	4	3%	0	0%	0	0%	1	2%	0	0%	2	4%	3	5%
RESPIRATORY FAILURE	0	0%	0	0%	0	0%	0	0%	1	1%	1	1%	0	0%	0	0%	1	2%	1	2%	0	0%	2	4%
RESPIRATORY DISTRESS	0	0%	0	0%	1	1%	2	2%	0	0%	3	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
HYPOXIA	0	0%	0	0%	2	2%	1	1%	0	0%	3	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
HAEMOTHORAX	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%
PNEUMONIA ASPIRATION	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	1	2%	1	2%
DYSPNOEA	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%
PNEUMOTHORAX	0	0%	0	0%	1	1%	1	1%	0	0%	2	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
WHEEZING	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
EPISTAXIS	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	0	0%	0	0%	1	2%
ACUTE RESPIRATORY FAILURE	0	0%	0	0%	0	0%	0	0%	1	1%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%
PLEURAL EFFUSION	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%
METABOLISM AND NUTRITION DISORDERS	**1**	**1%**	**0**	**0%**	**13**	**10%**	**2**	**2%**	**0**	**0%**	**16**	**13%**	**0**	**0%**	**0**	**0%**	**3**	**5%**	**2**	**4%**	**0**	**0%**	**5**	**9%**
HYPOKALAEMIA	1	1%	0	0%	4	3%	0	0%	0	0%	5	4%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
FLUID OVERLOAD	0	0%	0	0%	3	2%	0	0%	0	0%	3	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
HYPOGLYCAEMIA	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%
METABOLIC ACIDOSIS	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%
HYPOPHOSPHATAEMIA	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%
VITAMIN D DEFICIENCY	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
HYPERGLYCAEMIA	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
HYPERKALAEMIA	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
ACIDOSIS	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%
HYPERTRIGLYCERIDAEMIA	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%
LACTIC ACIDOSIS	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
HYPERNATRAEMIA	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
CARDIAC DISORDERS	**0**	**0%**	**0**	**0%**	**9**	**7%**	**3**	**2%**	**1**	**1%**	**13**	**10%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**2**	**4%**	**0**	**0%**	**2**	**4%**
CARDIOMYOPATHY	0	0%	0	0%	2	2%	0	0%	0	0%	2	2%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%
ATRIAL FIBRILLATION	0	0%	0	0%	2	2%	1	1%	0	0%	3	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
PERICARDIAL HAEMORRHAGE	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%
TACHYCARDIA	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
CARDIAC ARREST	0	0%	0	0%	0	0%	0	0%	1	1%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
CARDIAC FAILURE	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
ATRIAL FLUTTER	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
CARDIAC FAILURE CONGESTIVE	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
SUPRAVENTRICULAR TACHYCARDIA	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
PERICARDIAL EFFUSION	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
VENTRICULAR TACHYCARDIA	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%

**The protocol required reporting of all grade 3 or grade 4 AEs, and all SAEs, as well as any AE leading to plasma discontinuation (regardless of grade).*

Supplemental Table 8 Continued

	High titer (N=126)												Low titer (N=57)											
Event	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Number events		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Number events	
INFECTIONS AND INFESTATIONS	**1**	**1%**	**0**	**0%**	**8**	**6%**	**0**	**0%**	**1**	**1%**	**10**	**8%**	**1**	**2%**	**0**	**0%**	**2**	**4%**	**2**	**4%**	**0**	**0%**	**5**	**9%**
SEPSIS	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%
SEPTIC SHOCK	0	0%	0	0%	1	1%	0	0%	1	1%	2	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
URINARY TRACT INFECTION	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
HEPATITIS C	1	1%	0	0%	0	0%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
SINUSITIS	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
CLOSTRIDIUM DIFFICILE INFECTION	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
GASTROENTERITIS NOROVIRUS	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
TRACHEITIS	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	0	0%	0	0%	0	0%	1	2%
PNEUMONIA KLEBSIELLA	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%
SYSTEMIC CANDIDA	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%
BACTERAEMIA	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%
CATHETER SITE CELLULITIS	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
PNEUMONIA	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
VASCULAR DISORDERS	**0**	**0%**	**0**	**0%**	**5**	**4%**	**3**	**2%**	**0**	**0%**	**8**	**6%**	**0**	**0%**	**0**	**0%**	**4**	**7%**	**0**	**0%**	**0**	**0%**	**4**	**7%**
DEEP VEIN THROMBOSIS	0	0%	0	0%	3	2%	0	0%	0	0%	3	2%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%
HYPOTENSION	0	0%	0	0%	1	1%	1	1%	0	0%	2	2%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%
EXTREMITY NECROSIS	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%
HAEMORRHAGE	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%
SHOCK	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
PERIPHERAL ISCHAEMIA	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
SHOCK HAEMORRHAGIC	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**0**	**0%**	**0**	**0%**	**4**	**3%**	**2**	**2%**	**0**	**0%**	**6**	**5%**	**0**	**0%**	**0**	**0%**	**3**	**5%**	**1**	**2%**	**0**	**0%**	**4**	**7%**
ANAEMIA	0	0%	0	0%	4	3%	0	0%	0	0%	4	3%	0	0%	0	0%	2	4%	0	0%	0	0%	2	4%
THROMBOCYTOPENIA	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	1	2%	1	2%	0	0%	2	4%
THROMBOTIC THROMBOCYTOPENIC PURPURA	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
NERVOUS SYSTEM DISORDERS	**1**	**1%**	**0**	**0%**	**3**	**2%**	**2**	**2%**	**0**	**0%**	**6**	**5%**	**0**	**0%**	**1**	**2%**	**1**	**2%**	**1**	**2%**	**1**	**2%**	**4**	**7%**
ENCEPHALOPATHY	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%
CEREBRAL HAEMORRHAGE	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	1	2%
DIZZINESS	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%
HEADACHE	1	1%	0	0%	0	0%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
ISCHAEMIC STROKE	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
PARALYSIS	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
VOCAL CORD PARALYSIS	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
HYPOXICISCHAEMIC ENCEPHALOPATHY	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
CEREBRAL INFARCTION	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	0	0%	0	0%	1	2%
GASTROINTESTINAL DISORDERS	**0**	**0%**	**0**	**0%**	**4**	**3%**	**1**	**1%**	**0**	**0%**	**5**	**4%**	**0**	**0%**	**0**	**0%**	**2**	**4%**	**0**	**0%**	**0**	**0%**	**2**	**4%**
GASTROINTESTINAL HAEMORRHAGE	0	0%	0	0%	2	2%	1	1%	0	0%	3	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
CONSTIPATION	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
NAUSEA	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%
VOMITING	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%
ABDOMINAL PAIN	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**0**	**0%**	**0**	**0%**	**3**	**2%**	**1**	**1%**	**0**	**0%**	**4**	**3%**	**0**	**0%**	**2**	**4%**	**0**	**0%**	**1**	**2%**	**0**	**0%**	**3**	**5%**
ALLERGIC TRANSFUSION REACTION	0	0%	0	0%	2	2%	0	0%	0	0%	2	2%	0	0%	1	2%	0	0%	1	2%	0	0%	2	4%
TOXICITY TO VARIOUS AGENTS	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
TRAUMATIC LIVER INJURY	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
TRANSFUSIONRELATED CIRCULATORY OVERLOAD	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	0	0%	0	0%	1	2%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**0**	**0%**	**0**	**0%**	**2**	**2%**	**0**	**0%**	**0**	**0%**	**2**	**2%**	**0**	**0%**	**0**	**0%**	**2**	**4%**	**0**	**0%**	**1**	**2%**	**3**	**5%**
GENERALISED OEDEMA	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
PYREXIA	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
CHEST PAIN	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%
MULTIORGAN FAILURE	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	1	2%
ASTHENIA	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%
RENAL AND URINARY DISORDERS	**0**	**0%**	**0**	**0%**	**1**	**1%**	**1**	**1%**	**0**	**0%**	**2**	**2%**	**0**	**0%**	**0**	**0%**	**1**	**2%**	**1**	**2%**	**0**	**0%**	**2**	**4%**
RENAL FAILURE	0	0%	0	0%	1	1%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	1	2%	0	0%	1	2%
ACUTE KIDNEY INJURY	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	1	2%	0	0%	0	0%	1	2%
PSYCHIATRIC DISORDERS	**0**	**0%**	**0**	**0%**	**2**	**2%**	**1**	**1%**	**0**	**0%**	**3**	**2%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**
MENTAL STATUS CHANGES	0	0%	0	0%	2	2%	0	0%	0	0%	2	2%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
DELIRIUM	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**3**	**5%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**3**	**5%**
PRURITUS	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	0	0%	0	0%	1	2%
URTICARIA	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	0	0%	0	0%	1	2%
DERMATITIS CONTACT	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	0	0%	0	0%	1	2%
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**2**	**2%**	**2**	**2%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**
MANTLE CELL LYMPHOMA REFRACTORY	0	0%	0	0%	0	0%	0	0%	1	1%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
LUNG CARCINOMA CELL TYPE UNSPECIFIED STAGE IV	0	0%	0	0%	0	0%	0	0%	1	1%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%

References:

1. Beigel JH, Tebas P, Elie-Turenne MC, Bajwa E, Bell TE, Cairns CB, et al. Immune plasma for the treatment of severe influenza: an open-label, multicentre, phase 2 randomised study. Lancet Respir Med. 2017;5(6):500-11.
2. Shu B, Wu KH, Emery S, Villanueva J, Johnson R, Guthrie E, et al. Design and performance of the CDC real-time reverse transcriptase PCR swine flu panel for detection of 2009 A (H1N1) pandemic influenza virus. J Clin Microbiol. 2011;49(7):2614-9.
3. Centers for Disease Control - 510(k) Summary for Centers for Disease Control and Prevention human influenza virus real-time RT-PCR detection and characterization panel. 2008 [Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf8/k080570.pdf.
4. World Health Organization - Manual for the laboratory diagnosis and virological surveillance of influenza. Geneva: World Health Organization; 2011.