Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: The PREVAIL II Writing Group. A randomized, controlled trial of ZMapp for Ebola virus infection. N Engl J Med 2016;375:1448-56. DOI: 10.1056/NEJMoa1604330

Table of Contents: Supplementary Materials

Supplemental Appendix:

Members of the Multi-National PREVAIL II Study Team

The PREVAIL II trial was conducted by the National Institute of Allergy and Infectious Diseases (NIAID) of the U.S. National Institutes of Health in close partnership with the Ministries of Health of the three affected West African countries, the Institut national de la santé et de la recherche médicale (INSERM), the Republic of Sierra Leone Armed Forces, and other governmental and non-governmental agencies within the region.

In addition to the core writing group representing these partners, the following study team members also contributed substantively to the conduct of the PREVAIL II trial:

Liberia:

Jerry F. Brown

Stephen B. Kennedy

Gertrude Mulbah

Courtney Renken

PHS Officers and affiliated Staff of the Monrovia Medical Unit

Sierra Leone:

Herbert Kallon

Reginald Cole

Komba Songu M'Briwa

Sekou Kanneh

Thomas Tucker

Adam Levine

Gino Strada

Oliver Morgan

Other Groups:

The CDC and the CDC foundation

Medical, nursing, study coordinator, and other support staff of the Police Training School 1/2 ETUs, the International Medical Corps ETUs, the Emergency ETU, the China Friendship Hospital, the Adventist Development and Relief Agency ETU, and the Aspen ETU

Nigerian-European Mobil Lab in Kambia, Sierra Leone

Public Health England Lab in Port Loko, Sierra Leone

European mobile lab in Freetown, Sierra Leone

Guinea and France:

INSERM 1219, University of Bordeaux, Bordeaux, France

Daouda Sissoko

Géraldine Colin

Sylvain Juchet

Xavier Anglaret

EM Lab consortium, Bernhard-Nocht Institute for tropical medicine, Hamburg, Germany

Joseph Akoi Bore

Raymond Koundouno

Sophie Duraffour

Stephan Gunther

Centre de recherche en santé rurale, Maferyniah, Guinea

Abdoul-Habib Beavogui

Alseny-Modet Camara

Jacques Kolie

INSERM HQ, Clinical Research Department, Paris, France

Cecile Etienne

Claire Levy-Marchal

French Red Cross

Yannick Ruaux-Morison

Keira Camara

Aguibou Barry

Abdoulaye Soumah

The combined Medical, nursing, study coordinator, and other support staff of the French Red Cross, Ebola Treatment Center, Forecariah

Canada:

Andrea K. Boggild

United States:

David R. Boulware

Christopher J Kratochvil

Andre C. Kalil

Philip Smith

Angela L. Hewlett

Mark Kortepeter

Timothy Burgess

Scott Miller

Nahid Bhadelia

Colleen Kraft

Bruce Ribner

G. Marshall Lyon III

Aneesh Mehta

Jay Varkey

Mark Mulligan

Susan Rogers

Cynthia Carpentieri

Elizabeth Higgs

Jamila Aboulhab

Jerome Pierson

Risa Eckes

Betsy Herpin

Susan Vogel

Laura McNay

Mary Smolskis

Lisa Hensley

Peter Jahrling

Nikki Gettinger

Kevin Barrett

Theresa Engel

Quy Ton

Matthew Kirchoff

Hope Pogemiller

Deborah Wentworth

Grace Kelly

Judith Zuckerman

Katherine Cone

Anthony Suffredini

Daniel Chertow

Tara Palmore

Mark Miller

Benjamin Bishop

Cynthia K Osborne,

Laurie Lambert

Tara Perti

Liza Lindenberg

Jim Remington

Alejandra Miranda

Michelle Holshue

Travis Ready

Claire Gustin

Mona Patel

Catherine Groden

Susan Orsega

Jaewon Hong

Yiying Tsai

Ann Peterson

Meghan Schlosser

Jennifer Shepherd

Judith Brooks

Jerry Burge

Nancy Goldspiel

Lisa Tung

Maximilian Muenke

Tim Uyeki

Michael Montello

Lisa Cordes

Stacey McAdams

Vanessa Eccard

Molly Buehn

Leah McDonald

The combined Medical, Nursing, and support staff of the Special Clinical Studies Unit, NIH Clinical Center

<u>Mapp Biopharmaceutical, Inc.</u>

Tara Nyhuis

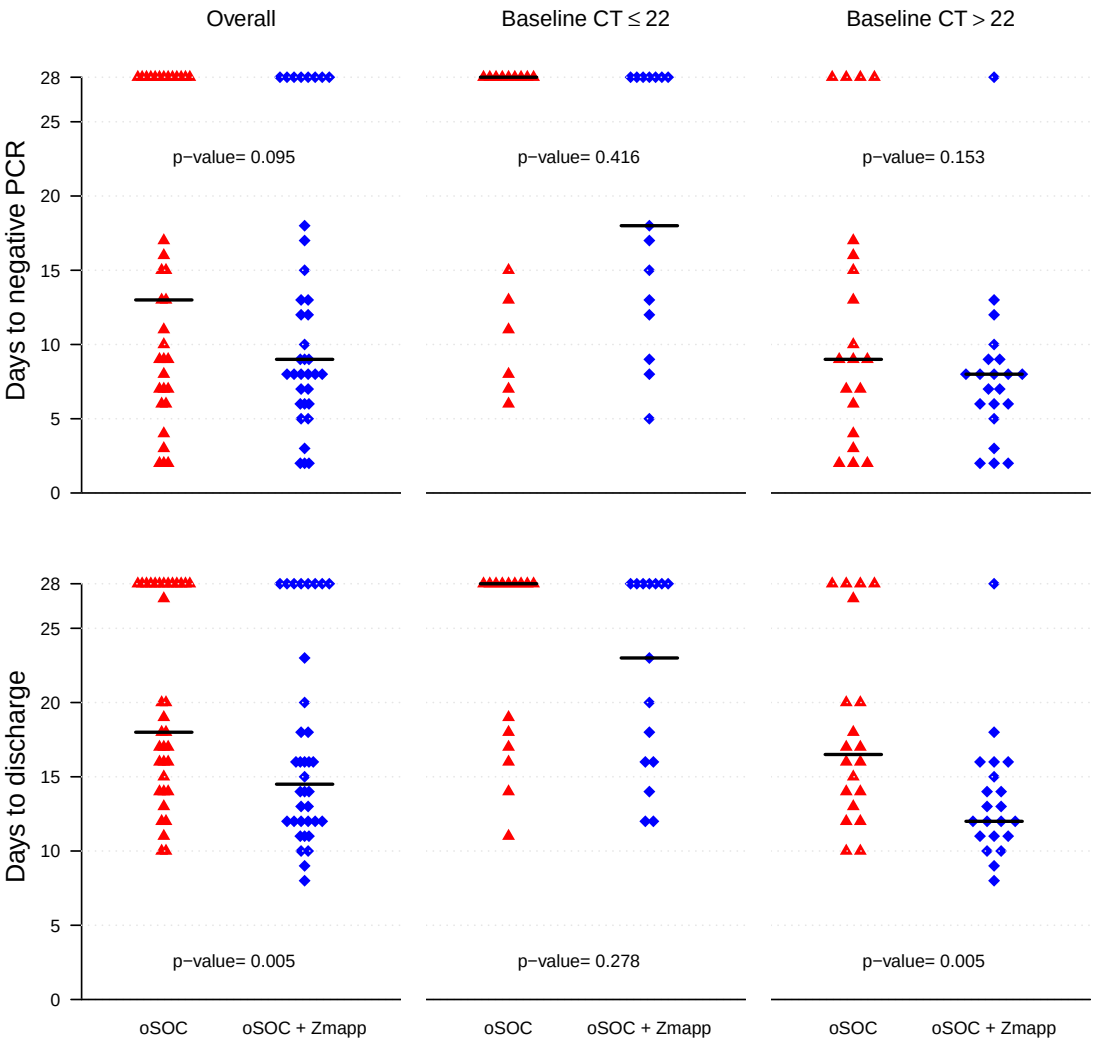
Larry Zeitlin

Miles Brennan

Kevin Whaley

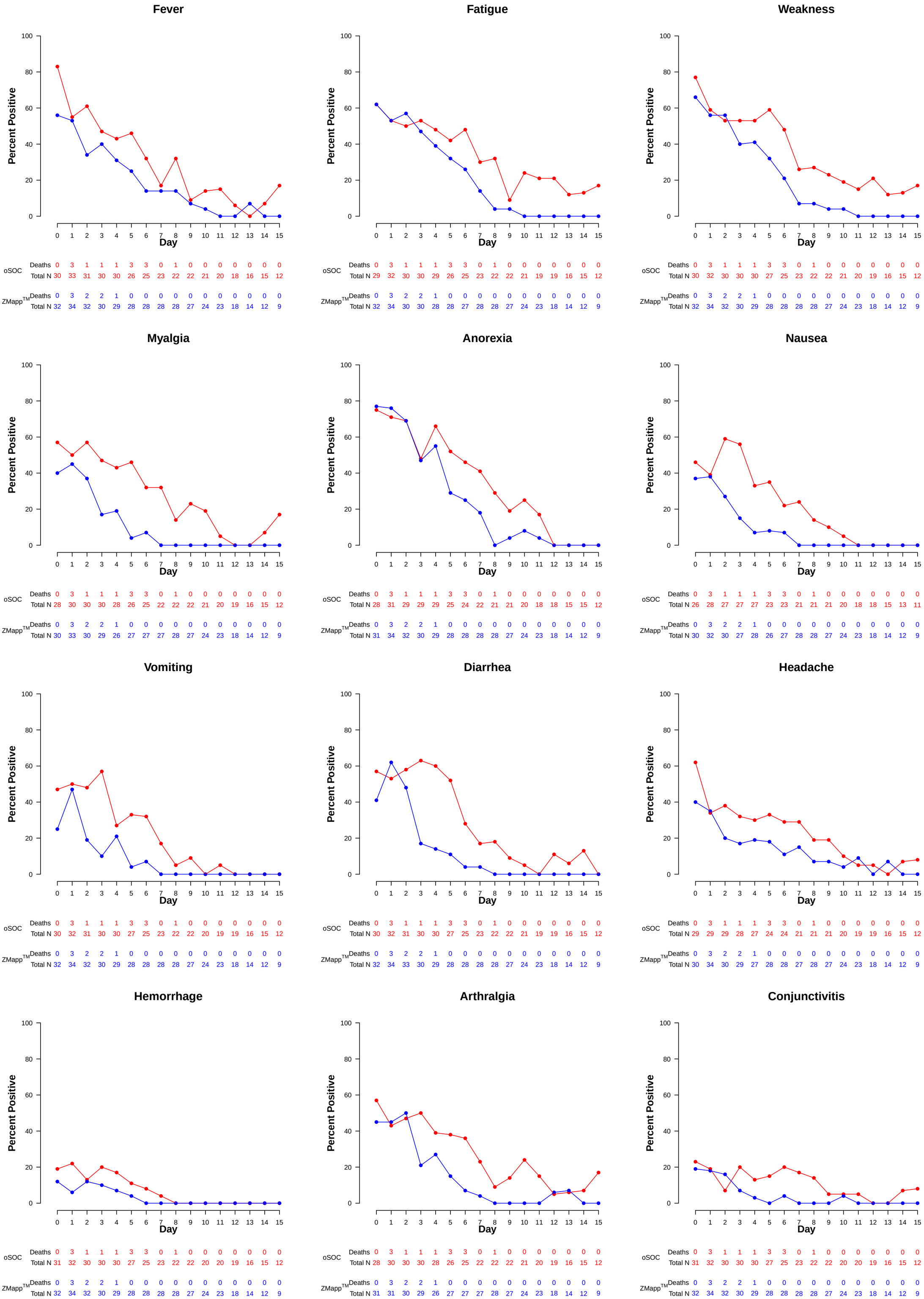
Thomas Moench

Figure S1: Viral Load Clearance and ETU Discharge Day



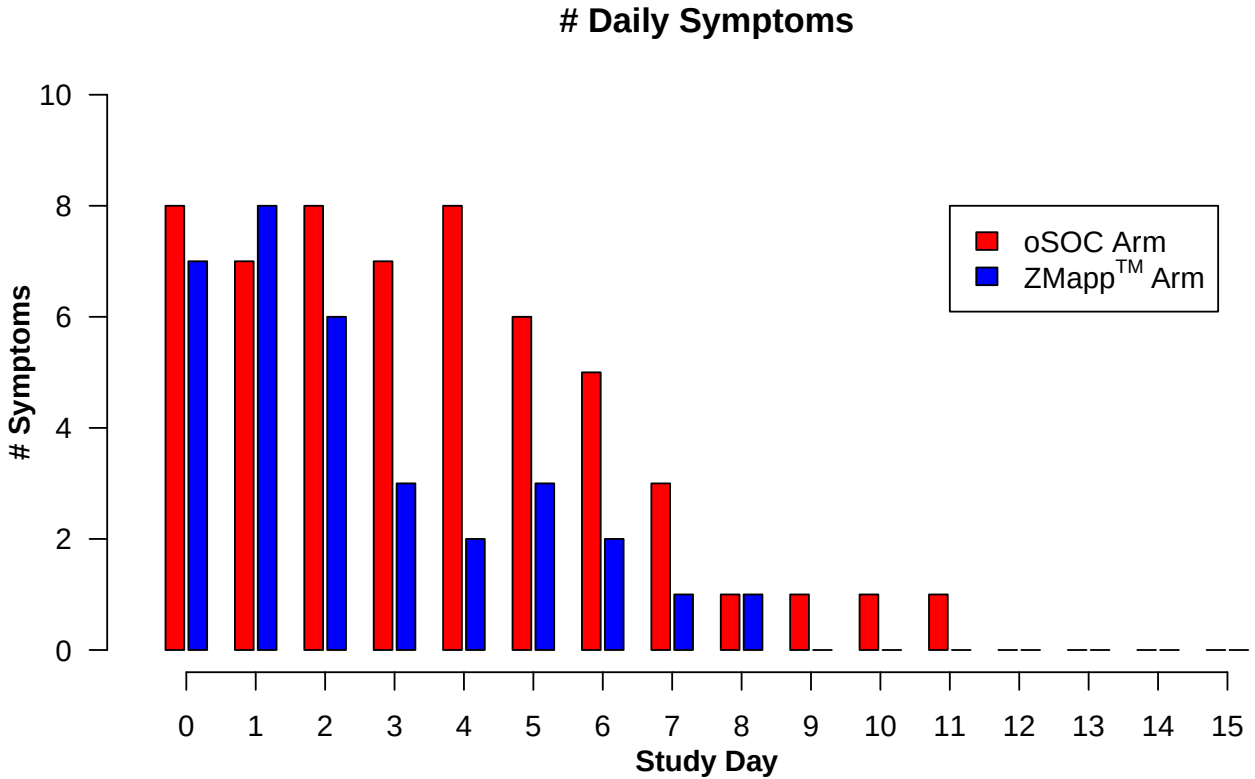
Legend: The median number of days to viral load clearance (top panel) and to discharge from the ETU (bottom panel) for patients in the oSOC arm (red) and in the ZMapp-containing arm (blue).

Figure S2: The Mean Percentage of Patients with Specific EVD Symptoms



Legend: The mean percentage of patients in the oSOC alone arm (red line) and in the ZMapp-containing arm (blue line) reported to have specific symptoms commonly associated with EVD are shown from baseline through Day 14 of the study.

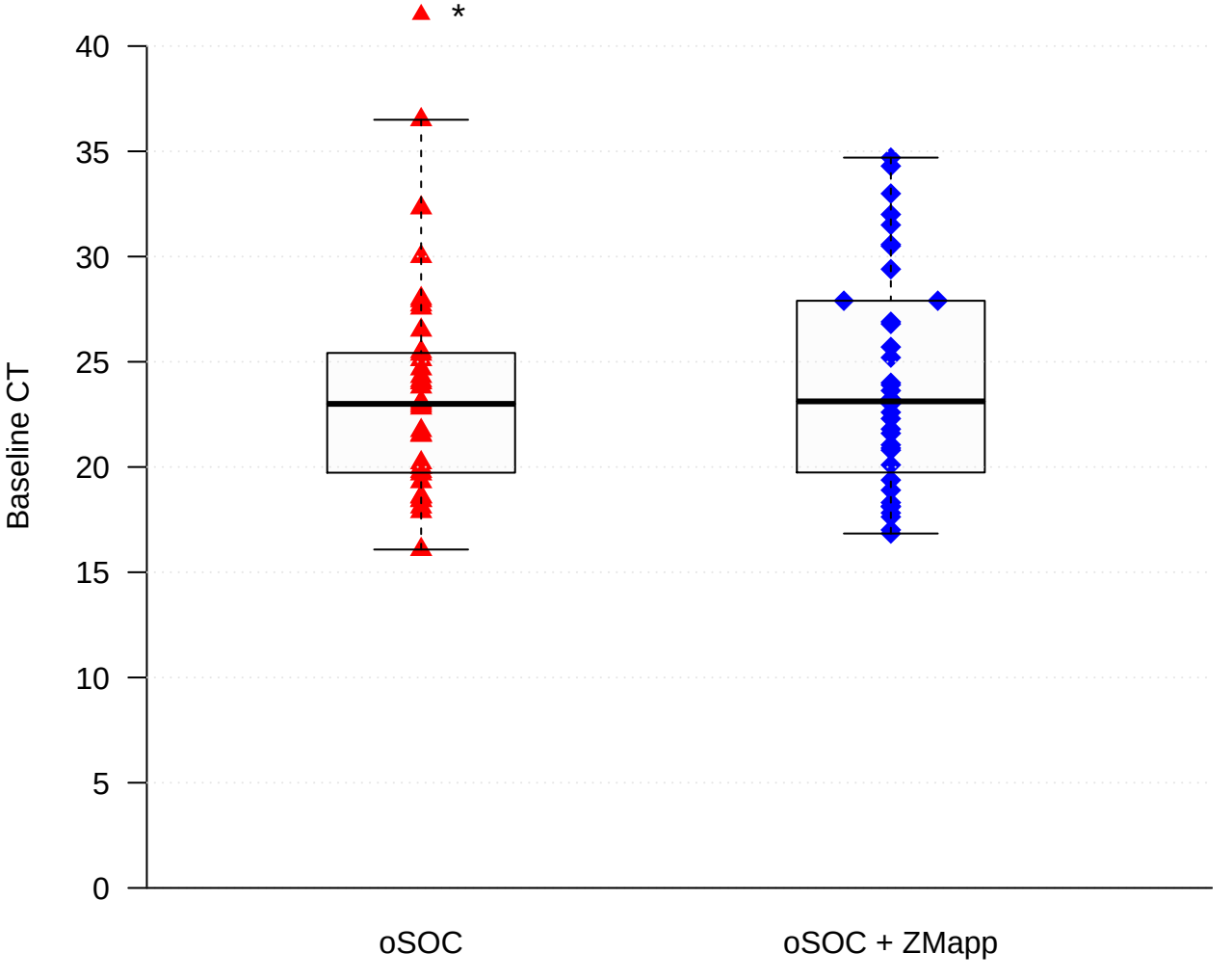
Figure S3: Daily EVD Symptoms



		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
oSOC	Deaths	0	3	1	1	1	3	3	0	1	0	0	0	0	0	0	0
	Total N	31	33	31	30	30	27	25	23	22	22	21	20	19	16	15	12
ZMapp™	Deaths	0	3	2	2	1	0	0	0	0	0	0	0	0	0	0	0
	Total N	32	34	33	30	29	28	28	28	28	27	24	23	18	14	12	9

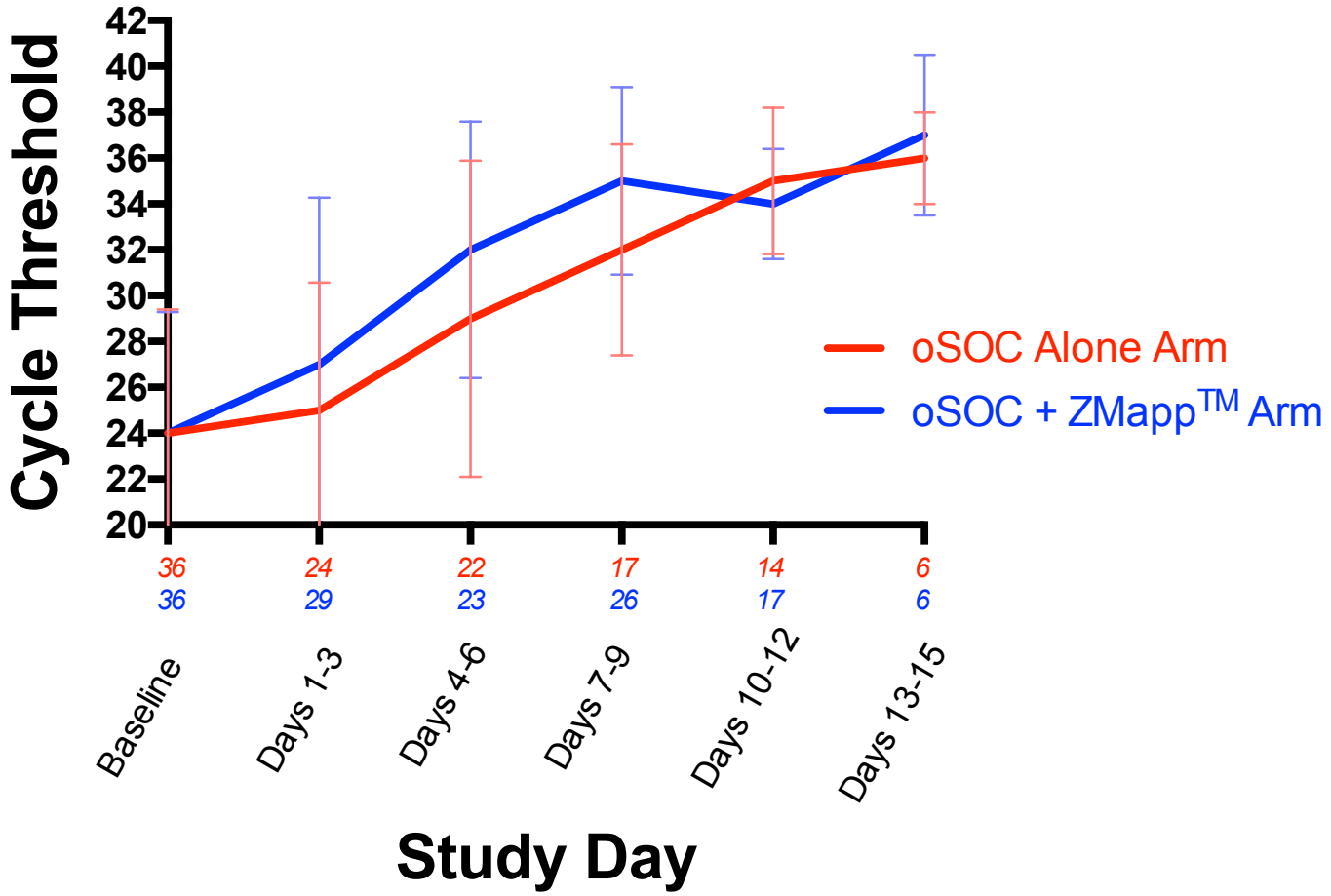
Legend: The median number of symptoms reported daily by patients in the two treatment arms (oSOC alone arm - red, the ZMapp-containing arm -blue) through Day 14 of the trial.

Figure S4: Baseline Cycle Threshold Values of Enrolled Patients



Legend: A dot blot of the baseline CT values of patients in the two treatment arms showing the median values (dark horizontal bar), 25th-75th IQR (box), and range (upper and lower horizontal bars). The asterisk depicts one patient in the oSOC who was LTFU on the day of randomization and whose data are excluded from this analysis.

Figure S5: Viral Load over Time



Legend: The kinetics of the EBOV viral load (CT values ± S.D.) over time in patients in the two treatment arms. PCR tests were performed every 1-3 days in survivors. Shown along the x-axis are the numbers of patients (red = oSOC arm, blue = oSOC + ZMapptm arm) who contributed to each time point.

Table S1: Participating Study sites

Country	Site Name	No. enrolled	Last Enrollment Date	IV Fluids	IV Medications	Serum Chemistries	Hemodynamic Monitoring	ICU Level Care[1]	Favipiravir
Guinea	French Red Cross	12	24-Oct-15	X	X	X	X		X
Liberia	ELWA-3 ETU	4	21-Nov-15	X	X	X	X		
	Monrovia Medical Unit ETU	1	22-Mar-15	X	X	X	X	X	
Sierra Leone	Police Training School #1	20	14-Jul-15	X	X	X	X		
	Police Training School #2	3	7-Apr-15	X	X	X	X		
	Emergency	5	17-May-15	X	X	X	X	X	
	China Friendship Hospital	1	13-Apr-15	X	X	X	X		
	Adventist Development & Relief	1	28-Apr-15	X	X	X	X		
	IMC Lunsar	14	14-Jul-15	X	X	X	X		
	IMC Kambia	10	10-Sep-15	X	X	X	X		
USA	NIH Clinical Center	1	13-Mar-15	X	X	X	X	X	
Total		72	21-Nov-15						

[1] includes mechanical ventilation, vasopressor medications, renal dialysis, and other modern ICU-level support functions

Supplemental Table S2: Baseline Symptoms Reports by Treatment Arm

Symptom	Baseline: All Patients	Baseline: oSOC Arm	Baseline: oSOC + ZMapp™ Arm
Fever (%)	43 (68.3)	25 (80.6)	18 (56.3)
Sore throat (%)	11 (17.2)	8 (25.0)	3 (9.4)
Cough (%)	23 (35.9)	13 (40.6)	10 (31.3)
Fatigue (%)	38 (59.4)	18 (56.3)	20 (62.5)
Weakness (%)	44 (68.8)	23 (71.9)	21 (65.6)
Dizziness (%)	19 (30.2)	7 (22.6)	12 (37.5)
Confusion (%)	3 (4.8)	0 (0.0)	3 (9.4)
Hearing loss (%)	1 (1.6)	1 (3.1)	0 (0.0)
Headache (%)	31 (49.2)	19 (61.3)	12 (37.5)
Myalgia (%)	28 (45.2)	16 (51.6)	12 (38.7)
Arthralgia (%)	30 (46.9)	16 (50.0)	14 (43.8)
Anorexia (%)	46 (71.9)	22 (68.8)	24 (75.0)
Nausea (%)	23 (39.0)	12 (41.4)	11 (36.7)
Vomiting (%)	22 (34.4)	14 (43.8)	8 (25.0)
Diarrhea (%)	30 (46.9)	17 (53.1)	13 (40.6)
Abd. pain (%)	32 (50.0)	17 (53.1)	15 (46.9)
Trouble urinating (%)	3 (4.7)	1 (3.1)	2 (6.3)
Chest pain (%)	14 (21.9)	10 (31.3)	4 (12.5)
Breathing difficulties (%)	7 (10.9)	4 (12.5)	3 (9.4)
Hiccups (%)	8 (12.5)	5 (15.6)	3 (9.4)
Rash (%)	5 (7.8)	3 (9.4)	2 (6.3)
Edema (%)	2 (3.1)	1 (3.1)	1 (3.1)
Conjunctivitis (%)	13 (20.3)	7 (21.9)	6 (18.8)
Oral ulcers/thrush (%)	9 (14.1)	4 (12.5)	5 (15.6)
Hemorrhage (%)	10 (15.6)	6 (18.8)	4 (12.5)

Multi-organ failure (%)	1 (1.6)	0 (0.0)	1 (3.1)
Convulsions (%)	1 (1.6)	0 (0.0)	1 (3.1)

Supplemental Table S3: Optimized Supportive Care Measures Provided in the Treatment Arms

	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day7	
	oOSC alone	ZMapp +oOSC	oOSC alone	ZMapp +oOSC	oOSC alone	ZMapp +oOSC	oOSC alone	ZMapp +oOSC	oOSC alone	ZMapp +oOSC	oOSC alone	ZMapp +oOSC	oOSC alone	ZMapp +oOSC
No. alive in ETU	35	36	31	33	30	30	30	29	28	28	25	28	23	28
No. (%) normal saline (NS)	5 (14)	4 (11)	5 (16)	4 (12)	7 (23)	5 (17)	6 (20)	3 (10)	4 (14)	2 (7)	2 (8)	1 (4)	2 (9)	2 (7)
No. (%) lactated Ringers (LR)	15 (43)	8 (22)	13 (42)	13 (39)	12 (40)	5 (17)	12 (40)	4 (14)	7 (25)	7 (25)	3 (12)	3 (11)	6 (26)	3 (11)
No. (%) NS + dextrose	6 (17)	6 (17)	4 (13)	5 (15)	4 (13)	4 (13)	3 (10)	5 (17)	3 (11)	1 (4)	2 (8)	0 (0)	1 (4)	1 (4)
No. (%) LR + dextrose	10 (29)	10 (28)	8 (26)	7 (21)	8 (27)	8 (27)	5 (17)	5 (17)	7 (25)	5 (18)	7 (28)	5 (18)	7 (30)	5 (18)
No. (%) Hartmann's	1 (3)	0 (0)	1 (3)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
No. (%) Hartmann's+dextrose	1 (3)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	1 (4)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)
No. (%) with any of above	22 (63)	22 (61)	21 (68)	21 (64)	21 (70)	14 (47)	19 (63)	10 (34)	13 (46)	9 (32)	13 (52)	6 (21)	12 (52)	6 (21)
<u>All Patients</u>														
Total median (25^{th}, 75^{th}) iv volume in liters for those receiving any of above	2.2 (1.5,4.0)	1.3 (0.5,2.0)	2.0 (1.0,3.3)	1.6 (1.0,2.5)	2.3 (1.5,3.3)	1.5 (1.0,3.0)	2.5 (1.0,3.0)	2.2 (1.4,3.0)	2.0 (1.5,2.7)	1.5 (1.0,3.0)	1.4 (1.0,2.5)	1.5 (1.0,3.1)	1.7 (0.8,2.7)	2.6 (2.0,3.0)
Total median (25^{th}, 75^{th}) iv volume in liters assuming zero for those not receiving any of above	1.5 (0.0,2.8)	0.5 (0.0,1.5)	1.0 (0.0,3.0)	1.0 (0.0,2.0)	1.5 (0.0,3.0)	0.0 (0.0,1.5)	1.0 (0.0,2.6)	0.0 (0.0,1.4)	0.0 (0.0,2.0)	0.0 (0.0,0.8)	0.4 (0.0,1.4)	0.0 (0.0,0.0)	0.5 (0.0,2.0)	0.0 (0.0,0.0)
<u>Pediatric Patients only</u>														
Total median (25^{th}, 75^{th}) iv volume in liters for those receiving any of above	1.2 (0.8,3.2)	0.5 (0.5,1.0)	2.8 (0.3,3.5)	1.0 (1.0,1.5)	2.3 (0.5,6.5)	1.4 (0.5,3.2)	2.3 (0.5,4.0)	1.4 (0.9,2.4)	1.12 (0.5,2.3)	1.0 (0.5,2.5)	0.8 (0.5,1.0)	1.5 (1.5,3.1)	0.8 (0.5,1.0)	2.0 (1.5,
Total median (25^{th}, 75^{th}) iv volume in liters assuming zero for those not receiving any of above	0.3 (0.0,1.2)	0.3 (0.0,0.8)	0.0 (0.0,1.5)	0.8 (0.0,1.0)	0.0 (0.0,2.3)	0.4 (0.0,1.4)	0.0 (0.0,0.5)	0.0 (0.0,0.9)	0.0 (0.0,5.0)	0.0 (0.0,0.5)	0.0 (0.0,0.5)	0.0 (0.0,0.8)	0.3 (0.0,0.8)	0.0 (0.0,0.8)
<u>Adult Patients only</u>														
Total median (25^{th}, 75^{th}) iv volume in liters for those receiving any of above	2.4 (2.0,4.0)	2.0 (1.0,3.0)	1.8 (1.0,3.3)	2.5 (1.5,2.7)	2.3 (1.5,3.3)	2.0 (1.5,3.0)	2.5 (2.0,3.0)	2.7 (2.0,3.0)	2.0 (1.5,2.1)	1.5 (1.0,3.0)	1.5 (1.0,3.0)	1.0 (1.0,4.0)	2.3 (1.0,3.0)	3.0 (3.0,3.1)
Total median (25^{th}, 75^{th}) iv volume in liters assuming zero for those not receiving any of above	2.0 (0.0,3.0)	1.0 (0.0,2.0)	1.5 (0.6,3.0)	1.5 (0.0,2.5)	2.0 (0.8,3.2)	0.0 (0.0,1.5)	2.0 (0.0,3.0)	0.0 (0.0,2.0)	0.4 (0.0,2.0)	0.0 (0.0,1.0)	0.5 (0.0,1.9)	0.0 (0.0,0.0)	0.5 (0.0,2.5)	0.0 (0.0,0.0)

No. (%) Albumin	1 (3)	0 (0)	1 (3)	0 (0)	1 (3)	0 (0)	1 (3)	0 (0)	1 (4)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)
No. (%) Potassium	7 (20)	8 (22)	9 (29)	10 (30)	7 (23)	7 (23)	7 (23)	4 (14)	6 (21)	4 (14)	2 (8)	3 (11)	2 (9)	2 (7)
No. (%) Calcium	2 (6)	0 (0)	1 (3)	0 (0)	2 (7)	0 (0)	3 (10)	0 (0)	1 (4)	0 (0)	2 (8)	0 (0)	2 (9)	0 (0)
No. (%) Magnesium	2 (6)	2 (6)	1 (3)	1 (3)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)	1 (4)
Favipiravir	5 (14)	7 (19)	5 (16)	7 (21)	5 (17)	6 (20)	5 (17)	6 (21)	4 (14)	6 (21)	3 (12)	6 (21)	3 (13)	6 (21)
Invasive mechanical vent	0 (0)	0 (0)	1 (3)	1 (3)	1 (3)	0 (0)	1 (3)	0 (0)	1 (4)	0 (0)	1 (4)	0 (0)	1 (4)	0 (0)
Other supplemental oxygen	1 (3)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Vasopressor or inotrope	1 (3)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Antiemetics	14 (40)	7 (19)	11 (35)	7 (21)	16 (53)	5 (17)	14 (47)	5 (17)	10 (36)	3 (11)	6 (24)	1 (4)	4 (17)	1 (4)
Loperamide	6 (17)	5 (14)	6 (19)	9 (27)	6 (20)	4 (13)	6 (20)	3 (10)	5 (18)	3 (11)	2 (8)	1 (4)	3 (13)	0 (0)
Antidiarrheal	2 (6)	2 (6)	2 (6)	3 (9)	2 (7)	2 (7)	4 (13)	1 (3)	3 (11)	1 (4)	3 (12)	1 (4)	1 (4)	0 (0)
Gastric acid inhibitors	14 (40)	9 (25)	14 (45)	11 (33)	11 (37)	12 (40)	11 (37)	9 (31)	13 (46)	8 (29)	8 (32)	8 (29)	9 (39)	8 (29)
Anticonvulsants	0 (0)	1 (3)	1 (3)	0 (0)	1 (3)	0 (0)	1 (3)	0 (0)	1 (4)	1 (4)	1 (4)	0 (0)	1 (4)	0 (0)
Anxiolytics	1 (3)	1 (3)	1 (3)	2 (6)	1 (3)	0 (0)	1 (3)	0 (0)	1 (4)	0 (0)	1 (4)	0 (0)	1 (4)	0 (0)
Antibiotics	26 (74)	28 (78)	26 (84)	28 (85)	23 (77)	24 (80)	20 (67)	21 (72)	21 (75)	18 (64)	12 (48)	15 (54)	9 (39)	13 (46)
Antimalarials	7 (20)*	20 (56)*	5 (16)	16 (48)	5 (17)	10 (33)	3 (10)	7 (24)	6 (21)	5 (18)	4 (16)	3 (11)	3 (13)	1 (4)
Fresh frozen plasma	1 (3)	1 (3)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other blood products	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Antipyretics	27 (77)	31 (86)	23 (74)	24 (73)	21 (70)	20 (67)	20 (67)	19 (66)	19 (68)	13 (46)	13 (52)	12 (43)	13 (57)	10 (36)
Corticosteroids	0 (0)	0 (0)	1 (3)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)	1 (4)	0 (0)
Multivitamin	12 (34)	14 (39)	16 (52)	17 (52)	14 (47)	18 (60)	17 (57)	15 (52)	11 (39)	15 (54)	9 (36)	15 (54)	9 (39)	13 (46)

* While the numbers listed here conform to the official Day 1 reports of empiric antimalarial use, review of Day 0 and Day 1 case report forms in Sierra Leone gives a revised estimate of at least 14 of 35 (40.0%) oSOC patients having received antimalarials within a day of study entry versus 23 of 36 (63.9%) ZMapp™ recipients in this same category ($p = 0.04$ for difference). A subset analysis, adjusted for this presumably chance difference in use of antimalarial drugs at entry, was performed and showed no significant effect on the primary endpoint: i.e. both the absolute and relative risk differences were similar to the unadjusted differences cited in the primary outcome.

Supplemental Table S4: Summary of ZMapp™ Infusion Events

	ZMapp			
	Dose 1	Dose 2	Dose 3	All Doses
Doses administered	36	29	28	93
No. alive in ETU	36	29	28	93
Pre-treatments administered				
None (%)	2 (5.9)	0 (0.0)	3 (11.1)	5 (5.7)
Antihistamine (%)	32 (94.1)	26 (96.3)	24 (88.9)	82 (93.2)
Antipyretic (%)	22 (64.7)	18 (66.7)	18 (66.7)	58 (65.9)
Antiemetic (%)	2 (5.9)	1 (3.7)	1 (3.7)	4 (4.5)
Other (%)	0 (0.0)	1 (3.7)	1 (3.7)	2 (2.3)
Infusion time				
Median hours (25^{th}, 75^{th})	5.0 (3.6, 7.0)	2.9 (2.3, 4.8)	3.4 (2.6, 4.2)	3.8 (2.6, 3.8)
Range	0.4-19.1	0.8-11.6	1.1-7.4	0.4-19.1
Mean hours (SD)	6.2 (4.5)	3.8 (2.4)	2.8 (4.1)	4.4 (4.1)
Infusion volumes				
Median ml (25^{th}, 75^{th})	588 (363,719)	588 (375,713)	607 (363,719)	
Percent of prepared dose administered				
Mean (SD)	95.0 (17.5)	97.2 (9.7)	96.5 (18.3)	96.1 (15.6)
<50%	2 (5.6)	0 (0)	1 (3.6)	3 (3.2)
50-74%	0 (0)	2 (6.9)	0 (0)	2 (2.2)
>75%	34 (94.4)	27 (93.1)	27 (96.4)	88 (94.6)
Adverse events				
AE during infusion (%)	9 (25.0)	4 (13.8)	3 (10.7)	16 (17.2)
AE leading to intervention (%)	8 (22.2)	4 (13.8)	2 (7.1)	14 (15.1)

Type of AE				
Elevation in fever (%)	5 (13.9)	2 (6.9)	1 (3.6)	8 (8.6)
Hypotension (%)	4 (11.1)	2 (6.9)	1 (3.6)	7 (7.5)
Tachycardia (%)	2 (5.6)	1 (3.4)	1 (3.6)	4 (4.3)
Tachypnea (%)	2 (5.6)	1 (3.4)	0 (0.0)	3 (3.2)
Hypertension (%)	1 (2.8)	1 (3.4)	1 (3.6)	3 (3.2)
Confusion (%)	1 (2.8)	1 (3.4)	0 (0.0)	2 (2.2)
Seizure (%)	1 (2.8)	0 (0.0)	0 (0.0)	1 (1.1)
Difficulty breathing (%)	1 (2.8)	0 (0.0)	0 (0.0)	1 (1.1)
Chills (%)	1 (2.8)	0 (0.0)	0 (0.0)	1 (1.1)
Vomiting (%)	1 (2.8)	0 (0.0)	0 (0.0)	1 (1.1)
Agitation (%)	0 (0.0)	1 (3.4)	0 (0.0)	1 (1.1)
Interventions taken during infusion				
Infusion slowed (%)	5 (13.9)	3 (10.3)	3 (10.7)	11 (11.8)
Infusion stopped (%)	6 (16.7)	4 (13.8)	1 (3.6)	11 (11.8)
Medication administered (%)	5 (13.9)	1 (3.4)	1 (3.6)	7 (7.5)

Supplemental Table S5: Serious Adverse Events (SAE) by Study Arm

SAE #	Study Arm	Patient Identifier	Study Day of SAE	Event Description	Assessed as Possibly Treatment-related?	Study Day of Death
1	oSOC	A	2	Worsened renal insufficiency	No	
2		A	2	Syncope		
3		A	5	Death due to hypotensive shock		5
4	oSOC	B	8	Multi-organ failure secondary to EVD	No	8
5	oSOC	C	3	Death due to EVD	No	3
6	oSOC	D	1	Head injury	No	
7		D	2	Death due to EVD		2
8	oSOC	E	4	Death due to EVD	No	4
9	oSOC	F	6	Death due to EVD	No	6
10	oSOC	G	1	Multi-organ failure due to EVD	No	1
11	oSOC	H	6	Death due to EVD	No	6
12	oSOC	I	6	Death due to EVD with respiratory complications	No	6
13	oSOC	J	1	Death due to EVD	No	1
14	oSOC	K	1	Death due to EVD	No	1
15	oSOC	L	5	Death due to EVD	No	5
16	oSOC	M	5	Death due to EVD	No	5
17	oSOC + ZMapp^{tm}	N	2	Death due to sepsis	No	2
18	oSOC + ZMapp^{tm}	O	5	Generalized seizure	No	
19	oSOC + ZMapp^{tm}	P	1	Multi-organ failure due to EVD	No	1
20	oSOC + ZMapp^{tm}	Q	1	Death due to EVD	No	1
21	oSOC + ZMapp^{tm}	R	3	Hypovolemic shock due to acute hemorrhage	No	3
22	oSOC + ZMapp^{tm}	S	1	Multi-organ failure due to EVD	No	1

23	oSOC + ZMapp^{tm}	T	2	Severe diarrhea	No	2
24	oSOC + ZMapp^{tm}	U	0	Arterial Hypertension	Yes	
25	oSOC + ZMapp^{tm}	V	4	Multi-organ failure due to EVD	No	4
26	oSOC + ZMapp^{tm}	W	55	Hospitalization with febrile illness (malaria)	No	
27	oSOC + ZMapp^{tm}	X	3	Death due to EVD	No	3

Supplemental Table S6: Daily Status of Patients by Treatment Group*

	oOSC alone			ZMapp^{tm} + oOSC		
Day	Died	Alive in ETU	Alive Discharged	Died	Alive in ETU	Alive Discharged
1	3	32	0	3	33	0
2	4	31	0	5	31	0
3	5	30	0	7	29	0
4	6	29	0	8	28	0
5	9	26	0	8	28	0
6	12	23	0	8	28	0
7	12	23	0	8	28	0
8	13	22	0	8	27	1
9	13	22	0	8	26	2
10	13	20	2	8	24	4
11	13	19	3	8	21	7
12	13	17	5	8	15	13
13	13	16	6	8	13	15
14	13	13	9	8	10	18
15	13	12	10	8	9	19
16	13	9	13	8	4	24
17	13	6	16	8	4	24
18	13	4	18	8	2	26
19	13	3	19	8	2	26
20	13	1	21	8	1	27
21	13	1	21	8	1	27
22	13	1	21	8	1	27
23	13	1	21	8	0	28
24	13	1	21	8	0	28
25	13	1	21	8	0	28
26	13	1	21	8	0	28
27	13	0	22	8	0	28

* excluding 1 oSOC patient LTFU

Supplemental Table S7: Number of Patients and Mortality Percentage by Age

Age	oOSC alone	ZMapp + oOSC
< 5	5 (80.0%)	4 (25.0%)
5 -17	3 (0.0%)	11 (18.1%)
18-39	21 (19.0%)	14 (21.4%)
> 40	7 (71.4%)	7 (28.6%)
Total	36 (36.1%)	36 (22.2%)

DRUG STORAGE AND PREPARATION INFORMATION

STORAGE AND HANDLING

Long term storage requirements: Store ZMapp vials at -20 ± 5 ºC until time of use.

Special requirements for safe handling: None

DOSE PREPARATION

Doses of ZMapp^{tm} should be prepared in infusion bags containing normal saline to a concentration of approximately 4 mg/mL. Preparation of multiple infusion bags at one time is recommended according to the number of bags anticipated to be used in 6 hours.

The infusion kit for administration to the patient should include a low-protein binding in-line filter.

INFUSION RATE

The infusion rate of ZMapp^{tm} may range from 50 mg/hr (12.5 mL/hr) up to 800 mg/hr (200 mL/hr) see Table 1. ZMapp^{tm} infusion bags should be prepared to accommodate the anticipated rate of administration. When possible, prepare infusion bags at volumes that minimize residual volume in the partially used ZMapp^{tm} vials. The height of the infusion bag may be increased as needed if the infusion rate slows below the target.

Table 1: Infusion rates for 4mg/mL solution using an infusion set delivering 1 mL per 16 drops.

Infusion Rate	mL/hour	Drops/Min
50 mg/hr	12.5	3
100 mg/hr	25	7

200 mg/hr	50	13
300 mg/hr	75	20
400 mg/hr	100	27
500 mg/hr	125	33
600 mg/hr	150	40
700 mg/hr	175	47
800 mg/hr	200	53

General Guidance for Infusions:

First Infusion:

The initial intravenous infusion rate should begin at 50 mg/hour (12.5 mL/hr) for the first 30 minutes. Increase the dose rate by 50 mg/hr every 15-30 minutes to a maximum of 600 mg/hour (150 mL/hr). The infusion should be maintained at this rate (600 mg/hour) until the total study drug dose is met, or until the infusion must be stopped due to persistent infusion reactions of CTCAE grade 2 or above. For severe infusion reactions, stop the infusion until reaction symptoms subside to CTCAE grade 1 levels. Restart the infusion at 50% of the rate at which the reaction was observed. If the reaction does not re-occur, proceed to increase the rate as before at the discretion of the treating physician. Mild or moderate infusion reactions should be treated by reducing the rate by 50% until symptoms subside to grade 1 levels, and then resume the rate increases as before at the discretion of the treating physician.
For a patient weighing 70 kg, the total recommended dose (at 50 mg/kg) would be 3500 mg, in 875 mL (4 mg/mL solution).

Second and Third Infusions:

In the absence of toxicity during the most recent prior infusion, initiate the infusion at

200 mg/hr (50 mL/hr), and increase the rate by 200 mg increments every 15-30 minutes to a maximum of 800 mg/hr.

Patient Monitoring and Assessment:

Patients should be monitored closely during each ZMapp^{tm} infusion.
When available, the following parameters for patient monitoring should be recorded:

- Vital signs and nursing observation every 15 minutes during first 2 hours of infusion. Subsequent frequency of monitoring should be subject to individual patient response.
- Oximetry monitoring, with supplemental nasal oxygen in the event of drop in percent oxygenation.
- Parenteral glucocorticoids and epinephrine should be available at beside at all times.
- Acetaminophen and antihistamines may be repeated every 4 hours as needed.
- Bronchodilators may be used as needed. Medical and radiological pulmonary assessment, if available and as needed for shortness of breath.
- Patients with preexisting cardiac or pulmonary pathology should be monitored carefully.

Statistical Supplement

Bayesian and Frequentist Analysis of 28-Day Mortality Overall and by Subgroup

In Tables S1-S18, the Bayesian test, estimate, and 95% credible interval is contrasted with two frequentist tests, estimates, and 95% confidence intervals. To facilitate comparison, we report one minus the probability that ZMapp™ is superior for the Bayesian test. This is analogous to a 1-sided p-value. Note that Fisher's exact test estimates an odds ratio rather than a relative risk, so it is not directly comparable to the other two methods in terms of estimation.

Overall

Table S1. Deaths by treatment arm overall.

	Dead	Alive
oSOC	13	22
ZMapp™	8	28

Table S2. Bayesian and frequentist results for overall death.

	Bayesian	Barnard	Fisher
1-tailed p-value or 1-P(ZMapp™ is better)	0.088	0.114	0.132
Absolute difference and 95% confidence/credible interval	-0.142 (-0.343,0.064)	-0.149 (-0.362, 0.068)	NA
Relative risk/Odds ratio and 95% confidence/credible interval	0.619 (0.287,1.238)	0.598 (0.253, 1.274)	0.484 (0.147,1.538)

Sensitivity Analysis: Missing Patient=Survival

Table S3. Deaths by treatment arm with the missing patient counted as a survival.

	Dead	Alive
oSOC	13	23
ZMapp™	8	28

Table S4. Bayesian and frequentist results with the missing patient counted as a survival.

	Bayesian	Barnard	Fisher
1-tailed p-value or 1-P(ZMapp™ is better)	0.102	0.119	0.150
Absolute difference and 95% confidence/credible interval	-0.132 (-0.331, 0.072)	-0.139 (-0.346, 0.078)	NA
Relative risk/Odds ratio and 95% confidence/credible interval	0.636 (0.295, 1.275)	0.615 (0.259, 1.312)	0.506 (0.154, 1.600)

Sensitivity Analysis: Missing Patient=Death

Table S5. Deaths by treatment arm with the missing patient counted as a death.

	Dead	Alive
oSOC	14	22
ZMapp™	8	28

Table S6. Bayesian and frequentist results with the missing patient counted as a death.

	Bayesian	Barnard	Fisher
1-tailed p-value or 1-P(ZMapp™ is better)	0.065	0.067	0.100
Absolute difference and 95% confidence/credible interval	-0.159 (-0.359, 0.048)	-0.167 (-0.374,0.050)	NA
Relative risk/Odds ratio and 95% confidence/credible interval	0.593 (0.277,1.166)	0.571 (0.237, 1.201)	0.449 (0.138. 1.407)

Subgroup CT≤22

Table S7. Deaths by treatment arm in CT≤22 subgroup.

	Dead	Alive
oSOC	9	6
ZMapp™	7	8

Table S8. Bayesian and frequentist results in CT≤22 subgroup.

	Bayesian	Barnard	Fisher

1-tailed p-value or 1-P(ZMapp™ is better)	0.240	0.292	0.358
Absolute difference and 95% confidence/credible interval	-0.120 (-0.433, 0.210)	-0.133 (-0.491, 0.252)	NA
Relative risk/Odds ratio and 95% confidence/credible interval	0.797 (0.390, 1.520)	0.778 (0.333, 1.635)	0.583 (0.108, 3.084)

Subgroup CT>22

Table S9. Deaths by treatment arm in CT>22 subgroup.

	Dead	Alive
oSOC	4	16
ZMapp™	1	20

Table S10. Bayesian and frequentist results in CT>22 subgroup.

	Bayesian	Barnard	Fisher
1-tailed p-value or 1-P(ZMapp™ is better)	0.082	0.083	0.157
Absolute difference and 95% confidence/credible interval	-0.137 (-0.354, 0.060)	-0.152 (-0.388, 0.068)	NA
Relative risk/Odds ratio and 95% confidence/credible interval	0.346 (0.047, 1.517)	0.238 (0.009, 1.617)	0.200 (0.004, 2.370)

Subgroup USA/LIBERIA/Sierra Leone

Table S11. Deaths by treatment arm in USA/Liberia/Sierra Leone subgroup.

	Dead	Alive
oSOC	11	19
ZMapp™	7	22

Table S12. Bayesian and frequentist results in USA/Liberia/Sierra Leone subgroup.

	Bayesian	Barnard	Fisher
1-tailed p-value or 1-P(ZMapp™ is better)	0.154	0.160	0.223
Absolute difference and 95% confidence/credible interval	-0.118 (-0.338, 0.110)	-0.125 (-0.357, 0.119)	NA
Relative risk/Odds ratio and 95% confidence/credible interval	0.681 (0.301,1.424)	0.658 (0.262, 1.511)	0.550 (0.150, 1.942)

Subgroup Guinea

Table S13. Deaths by treatment arm in Guinea subgroup.

	Dead	Alive
oSOC	2	3
ZMapp™	1	6

Table S14. Bayesian and frequentist results in Guinea subgroup.

	Bayesian	Barnard	Fisher
1-tailed p-value or 1-P(ZMapp™ is better)	0.175	0.254	0.364
Absolute difference and 95% confidence/credible interval	-0.207 (-0.625, 0.227)	-0.257 (-0.744, 0.324)	NA
Relative risk/Odds ratio and 95% confidence/credible interval	0.489 (0.070, 2.337)	0.357, (0.013, 3.429)	0.250 (0.004, 7.540)

Subgroup Adult

Table S15. Deaths by treatment arm in adult subgroup.

	Dead	Alive
oSOC	9	18
ZMapp™	5	16

Table S16. Bayesian and frequentist results in adult subgroup.

	Bayesian	Barnard	Fisher
1-tailed p-value or 1-P(ZMapp™ is better)	0.248	0.318	0.347
Absolute difference and 95% confidence/credible interval	-0.086 (-0.324, 0.165)	-0.095 (-0.354, 0.179)	NA
Relative risk/Odds ratio and 95% confidence/credible interval	0.746 (0.286,1.722)	0.714 (0.225, 1.843)	0.625 (0.136, 2.643)

Subgroup Pediatric

Table S17. Deaths by treatment arm in pediatric subgroup.

	Dead	Alive
oSOC	4	4

ZMapp™	3	12

Table S18. Bayesian and frequentist analyses in pediatric subgroup.

	Bayesian	Barnard	Fisher
1-tailed p-value or 1-P(ZMapp™ is better)	0.075	0.085	0.156
Absolute difference and 95% confidence/credible interval	-0.267 (-0.607, 0.094)	-0.300 (-0.677, 0.120)	NA
Relative risk/Odds ratio and 95% confidence/credible interval	0.457 (0.134, 1.359)	0.400 (0.088, 1.578)	0.25 (0.026, 2.339)

Principal Stratification

Background: One question raised about Ebola treatments is whether some patients arrive at the clinic too sick (or too late) to receive a treatment benefit. Some studies have used this reasoning to justify eliminating early deaths from analyses. A major concern about this approach is that it is a post-randomization event and assumes treatment is not causing early deaths. A principal stratification analysis was described in the statistical analysis plan (SAP) to address this concern. In this analysis, we use baseline variables to construct a risk score that characterizes the probability of death at the time of randomization. If, in the total cohort, some patients were too sick to receive a benefit, then we would expect to see a greater treatment effect amongst patients with a lower baseline risk of death. The basic idea is: if we had used a more informed method of stratifying subjects at baseline, would we have seen a bigger treatment effect?

Using logistic regression, we define a low-risk group and evaluate the treatment effect. As described in the SAP, the complete cohort was used to evaluate risk ignoring treatment assignment. An additional potential benefit of this approach is that it may adjust for potential imbalances in baseline risk of death. We outline the basic approach and then provide results:

1) Evaluate the association of baseline symptom variables with probability of death in logistic regression models that include cycle threshold (Ct>22 vs Ct≤22). The output from these models is given in Table S19.
2) Any symptoms with a statistically significant odds ratio will be included in a final model used to compute a "risk score" or probability of death based on the relevant baseline symptom variables and cycle threshold. See tables S20 and S21.
3) Patients with a risk score less than 50% will be classified as "low risk." [The statistical analysis plan indicated that more categories would be used, but with the small number of deaths, we opted to create only high/low risk].

4) The treatment effect was evaluated in patients classified as low risk.

Results:

Table S19. Output from logistic regression models evaluating risk of death with two covariates in each model: 1) the baseline symptom and 2) cycle threshold (Ct>22 vs Ct≤22).

Baseline symptom	OR	p-value	95% CI
Conjunctivitis	11.0	0.01	(1.80, 66.8)
Hemorrhage	13.6	0.01	(1.93, 96.35)
Arthrlagia	4.8	0.05	(1.04,22.57)
Confusion	17.8	0.06	(0.90,350.25)
Appetite loss	6.9	0.09	(0.72,66.56)
Abdominal pain	4.2	0.12	(0.69,25.89)
Fever	3.7	0.13	(0.66,21.14)
Diarrhea	3.6	0.13	(0.67,18.65)
Sore throat	3.4	0.14	(0.66,17.60)
Weakness	2.8	0.21	(0.57,13.31)
Nausea	2.4	0.23	(0.57,10.15)
Headache	2.2	0.28	(0.53,8.88)
Thrush	2.3	0.34	(0.41,13.38)
Dizziness	0.6	0.47	(0.13,2.60)
Oliguira	2.5	0.58	(0.10,64.38)
Myalgia	1.5	0.59	(0.35,6.27)
Cough	1.3	0.67	(0.35,5.07)
Breathing difficulty	1.4	0.72	(0.20,9.96)
Fatigue	1.3	0.74	(0.29,5.83)
Vomiting	1.3	0.77	(0.33,4.52)
Chest pain	1.2	0.78	(0.37,5.69)
Rash	1.4	0.81	(0.08,24.7)

Hiccups	1.2	0.83	(0.21,7.10)
Female	0.9	0.84	(0.28, 2.79)
Young (<18 vs 18+)	1.2	0.76	(0.36, 4.10)

Note that hearing loss, edema, organ failure and convulsions were reported in only one subject at baseline, making estimation infeasible.

Model used to compute the risk score

Conjunctivitis, hemorrhage and arthralgia are the three baseline symptoms variables with statistically significant odds ratios after adjusting for cycle threshold. Table S20 shows the results when we include these 3 symptoms and cycle threshold in the same model.

Table S20. Multivariate logistic regression model

Baseline symptom	Odds Ratio	p-value	95% CI
Ct≤22	19.6	0.001	(3.2-117.8)
Hemorrhage	3.5	0.302	(0.3-37.9)
Arthralgia	4.9	0.066	(0.9-26.9)
Conjunctivitis	7.3	0.056	(1.0-55.3)

We create a linear combination of these variables that predicts death and then stratify by low risk versus high risk. Due to missing baseline symptoms values, 12 patients were dropped from this analysis, resulting in five fewer deaths. We note that the following model described in Table S21 produces the same risk stratification:

Table S21. Multivariate logistic regression model removing baseline hemorrhage

Baseline symptom	Odds Ratio	p-value	95% CI
Ct≤22	22.8	0.001	3.8-134.8
Arthralgia	5.3	0.051	1.0-28.0
Conjunctivitis	9.4	0.023	1.4-64.4

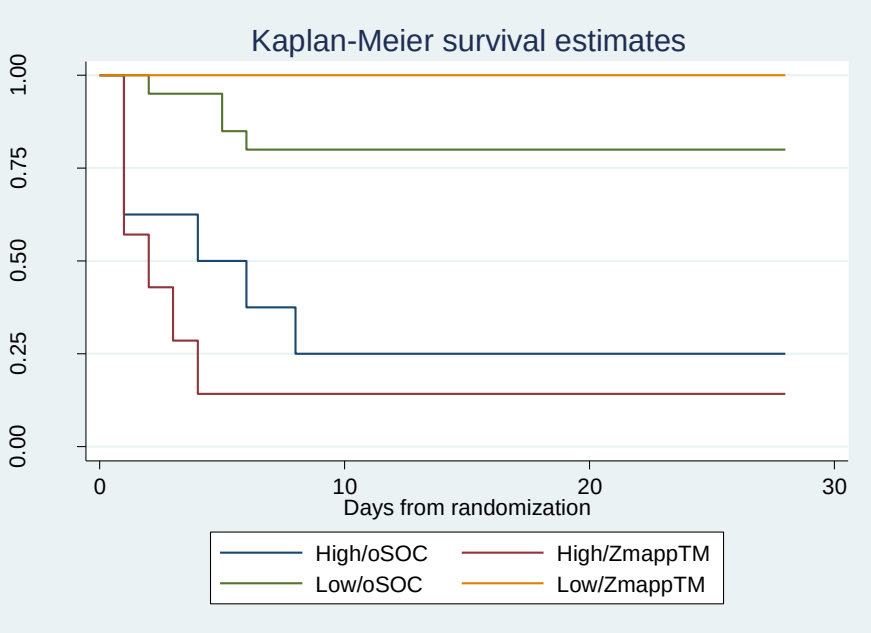
Updated analysis based on risk score

Table S22 describes the primary outcome by treatment group within the low- and high-risk groups. Within the low-risk group, the oSOC arm had 4 deaths while the ZMapp™ arm had none, a noteworthy difference using Bayesian and frequentist analyses. Figure S4 shows Kaplan-Meier curves by treatment group and risk category.

Table S22. Treatment effect within low- and high-risk strata

	Low Risk		High Risk	
	oSOC (n=20)	ZMapp™ (n=24)	oSOC (n=8)	ZMapp™ (n=7)
Days to death: Median[IQR]	5 [3.5,5.5]	NA	2.5 [1, 6]	1.5 [1,3]
Expected deaths	2.64	2.02	5.77	5.57
Observed deaths	4	0	6	6
Bayesian analyses				
Difference in mortality rates (95% credible interval)	-0.183 (-0.390, -0.019)		0.079 (-0.306, 0.449)	
Posterior probability that ZMapp™ is better	0.985		0.335	
Frequentist analyses				
Barnard's p-value	0.037		0.691	
Fisher's exact p-value	0.036		1.0	

Figure S1. Survival curves by treatment group and risk category.



Does this analysis balance baseline risk?

An important question is whether this principal stratification approach had the additional advantage of balancing baseline risk between treatment groups. Unfortunately, it did not. Amongst the low-risk group, the mean risk scores in the oSOC and the ZMapp™+oSOC arms were 0.13 and 0.08, respectively. This is further seen in Figure S2, which shows elevated baseline risk of death in oSOC (red triangles) compared to ZMapp™+oSOC (blue diamonds) in the low-risk group (those below the horizontal dashed line). Table S23 provides a breakdown of the proportion of low cycle threshold and each symptom by risk category.

Figure S2. Predicted baseline risk of death by treatment group.

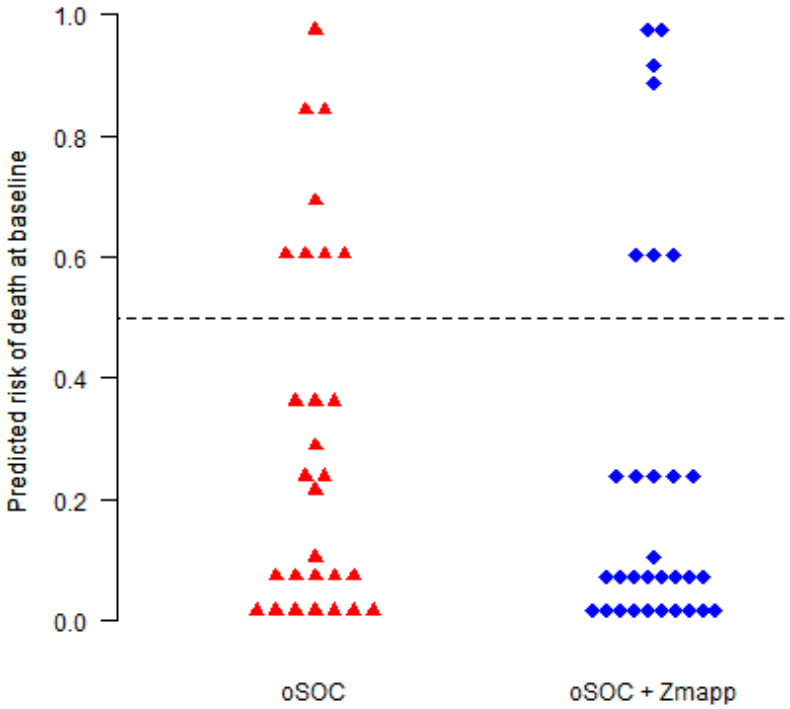


Table S23. Percent with low CT and symptoms according to baseline risk score.

	Low Risk		High Risk	
	oSOC (n=20)	ZMapp™ (n=24)	oSOC (n=8)	ZMapp™ (n=7)
CT ≤22	10%	21%	100%	100%
Conjuctivitis	25%	4%	25%	57%
Arthralgia	45%	33%	88%	8%

Hemorrhage	10%	0%	38%	43%