Table S1: Compartmental Model Fits for Ivermectin and Piperaquine

	Ivermectin		Piperaquine	
	One compartment	**Two compartment**	**Two compartment**	**Three compartment**
-2 log likelihood	6528.440	6202.912	17608.90	16375.37
AIC	6538.519	6217.061	17620.95	16391.45
BIC	6561.626	6249.373	17653.27	16434.52

Table S2: Number of observed concentrations and outcomes (ivermectin and piperaquine)

Time (days)	plasma samples venous	plasma samples capillary	ivermectin venous	ivermectin capillary	mortality rate	ivermectin venous + mortality rate	ivermectin: venous + capillary	piperaquine venous	piperaquine capillary	QTcF	piperaquine venous + QTcF	piperaquine: venous + capillary
0	141	-	0	-	141	-	-	1	-	141	1	-
2	-	-	-	-	-	-	-	-	-	132	-	-
2+4h	133	86	88	58	128	86	58	133	87	133	133	87
7	128	85	70	30	128	70	29	128	85	-	-	85
10	118	-	52	-	112	52	-	118	-	-	-	-
14	122	-	29	-	119	28	-	122	-	-	-	-
21	117	-	8	-	111	7	-	115	-	-	-	-
28	118	-	3	-	111	3	-	117	-	118	117	-
Pop PK	516	162	284	93	-	-	90	512	161	-	-	160
Total	1,393	335	534	181	850	246	177	1,246	333	524	251	332

Pop PK= population pharmacokinetic samples which were drawn between days 0 to 28 and did not coincide with other outcomes.

Ivermectin observations for days 21 and 28 are mostly absent as they are below the limit of quantitation.

Table S3: Ivermectin LC$_{50}$'s by assay duration, and versus previous studies

Duration of mosquito follow-up post-feeding (days):	A. LC$_{50}$ unadjusted to baseline mortality (CI95%) (ng/mL):	B. LC$_{50}$ adjusted to baseline mortality (CI95%) (ng/mL):	C. Comparator in vivo study[15] LC$_{50}$ adjusted to baseline mortality (CI95%) (ng/mL):	D. Comparator in vitro studies LC$_{50}$ adjusted to baseline mortality (CI95%) (ng/mL):	Relative Difference:
1	1656 (1281-2287)	3883 (2378-9552)	1172 (499-N/A)		
2	19.71(17.5-22.3)	26.79 (22.64-31.93)	43.95 (36.30-54.87)		
3	7.89 (7.13-8.73)	10.29 (8.96-11.86)	20.94 (17.73-25.15)	6.1 (3.4-11.0)[15]	D vs B: 0.6
4	5.07 (4.57-5.61)	6.92 (6.02-7.98)	15.40 (13.04-18.44)		
5	3.61 (3.24-4.01)	5.26 (4.56-6.09)	13.39 (11.24-16.18)	22.4 (18.0-26.9)[16]	D vs B: 4.3
6	2.68 (2.39-32.99)	4.13 (3.57-4.79)	8.59 (7.09-10.52)		
7	2.08 (1.85-2.33)	3.35 (2.89-3.89)	7.92 (6.49-9.77)	15.9 (14.6-17.3)[17]	D vs B: 4.7
8	1.74 (1.55-1.96)	2.97 (2.56-3.46)	7.43 (6.03-9.25)		
9	1.50 (1.32-1.70)	2.78 (2.38-3.25)	7.06 (5.69-8.86)	19.8 (14.3-25.3)[18]	D vs B: 7.1
10	1.24 (1.08-1.41)	2.55 (2.17-3.01)	6.52 (5.22-8.23)		C vs B: 2.6
11	1.15 (0.99-1.32)	2.62 (2.22-3.11)			
12	0.97 (0.83-1.13)	2.60 (2.18-3.10)			
13	0.80 (0.67-0.95)	2.56 (2.13-3.08)			
14	0.62 (0.51-0.74)	2.53 (2.09-3.07)			
15	0.45 (0.36-0.56)	2.50 (2.04-3.07)			
16	0.31 (0.23-0.40)	2.45 (1.98-3.06)			
17	0.17 (0.11-0.25)	2.43 (1.95-3.06)			
18	0.012 (0.0054-0.027)	2.34 (1.85-2.98)			
19	<0.01	2.44 (1.90-3.16)			
20	<0.01	2.42 (1.85-3.18)			
21	<0.01	2.32 (1.74-3.12)			
22	<0.01	2.31 (1.69-3.18)			
23	<0.01	2.21 (1.58-3.13)			
24	<0.01	2.19 (1.52-3.20)			
25	<0.01	2.08 (1.40-3.14)			
26	<0.01	1.92 (1.23-3.06)			
27	<0.01	1.87 (1.14-3.12)			
28	<0.01	1.97 (1.15-3.44)			

LC$_{50}$'s using predicted concentrations and 3-parameter method; Hill's coefficient was fixed to 1. LC$_{50}$'s adjusted to baseline mortality are the concentrations required to kill 50% of mosquitoes that would have otherwise survived the assay without ivermectin exposure. Adjusted LC$_{50}$'s are more consistent during follow-up than unadjusted LC$_{50}$'s. Additionally, unadjusted LC$_{50}$'s cannot be determined over longer follow-up periods due to high baseline mortality. Comparator *in vivo* values were calculated using author's dataset.[15] Comparator *in vitro* values as reported,[16, 17] except for one study that was converted from mol/L to ng/mL,[15] and another study for which the SE was converted to CI95%.[18] One study did not report whether it was adjusted to baseline, however probit analysis with control population was used, so baseline adjustment is assumed.[18]

Table S4: Piperaquine concentration and QTcF interval (observed data)

Outcome	IVM-3x600 (N=47)	IVM-3x300 (N=48)	Placebo (N=46)	Mean[†Δ] or Risk[‡] difference (95% CI), p-value		
				IVM-3x600 vs Placebo	IVM-3x300 vs Placebo	IVM-3x600 vs IVM-3x300
QTcF interval (Day 2+4h), change from baseline (ms)	27 (17) (n=42)	33 (17) (n=45)	29 (18) (n=44)	-0.8 (-8.0, 6.5), 0.84[†]	4.7 (-2.6, 11.9), 0.21[†]	-5.4 (-12.3, 1.5), 0.13[†]
QTcF interval (Day 2+4h), ≥500 ms	0/42 (0%)	1/45 (2.2%)	0/44 (0%)	0.0% (-0.4%, 3.7%), 1.00[‡]	2.2% (-1.4%, 5.8%), 0.23[‡]	-2.2% (-5.9%, 1.5%), 0.24[‡]
Piperaquine plasma concentration (Day 2+4h) (ng/mL)	313 (208-586) (n=43)	327 (179-545) (n=45)	269 (169-399) (n=45)	35.8 (-107.2, 178.7), 0.62[Δ]	28.9 (-108.1, 165.9), 0.68[Δ]	6.9 (-126.3, 140.0), 0.92[Δ]

Data are mean (SD), median (IQR), or n/N (%), unless otherwise specified. IVM-3x600=ivermectin 600 mcg/kg/day for 3 days. IVM-3x300=ivermectin 300 mcg/kg/day for 3 days. QTcF=electrocardiogram QT interval, corrected for heart rate using Fredericia's formula.

Δ Mean difference (95% CI), p-value: obtained from GLM models.

† Mean difference (95% CI), p-value: obtained from GEE models adjusted for baseline measurement and repeated measures.

‡ Risk Difference (95% CI), p-value: obtained from GLM models.

Table S5: Piperaquine concentration and QTcF interval (population fitted data)

Parameter	All Patients (N=141) [p5-p95]	IVM-3x600 (N=47) [p5-p95]	IVM-3x300 (N=48) [p5-p95]	Placebo (N=46) [p5-p95]
QTcF, baseline (E_{min}) (ms)	399.3 [377.5-416.3]	398.7 [371.9-413.2]	399.1 [379.5-415]	399.5 [379.8-416.5]
ΔQTcF, maximum possible change from baseline (E_{max}) (ms)	53.5 [31.1-122.9]	51.2 [32.2-119.6]	49.7 [31.2-123.3]	66.3 [27.2-118.3]
QTcF, maximum possible effect (E_{max}+E_{min}) (ms)	449.8 [415.1-520.0]*	445.2 [421.3-520.0]	447.8 [417.2-520.0]	464.1 [415.4-520.0]
Piperaquine concentration achieving half-maximal effect on QTcF (EC_{50}) (ng/mL)	181.7 [16.0-1200.0]	169.2 [16.0-1200.0]	199.0 [16.1-1200.0]	218.2 [15.9-1200.0]

Data are median [p5-p95]. IVM-3x600=ivermectin 600 mcg/kg/day for 3 days. IVM-3x300=ivermectin 300 mcg/kg/day for 3 days. QTcF=electrocardiogram QT interval, corrected for heart rate using Fredericia's formula.

* 18 subjects did not display a concentration-effect relationship for piperaquine and QT interval and their EC_{50} was estimated at the upper limit of the prediction, 1200 ng/mL. Upper limit for maximum possible effect (E_{max}+E_{min}) was set to be 520 ms which is 10 ms higher than the highest QT interval observed amongst all the patients.