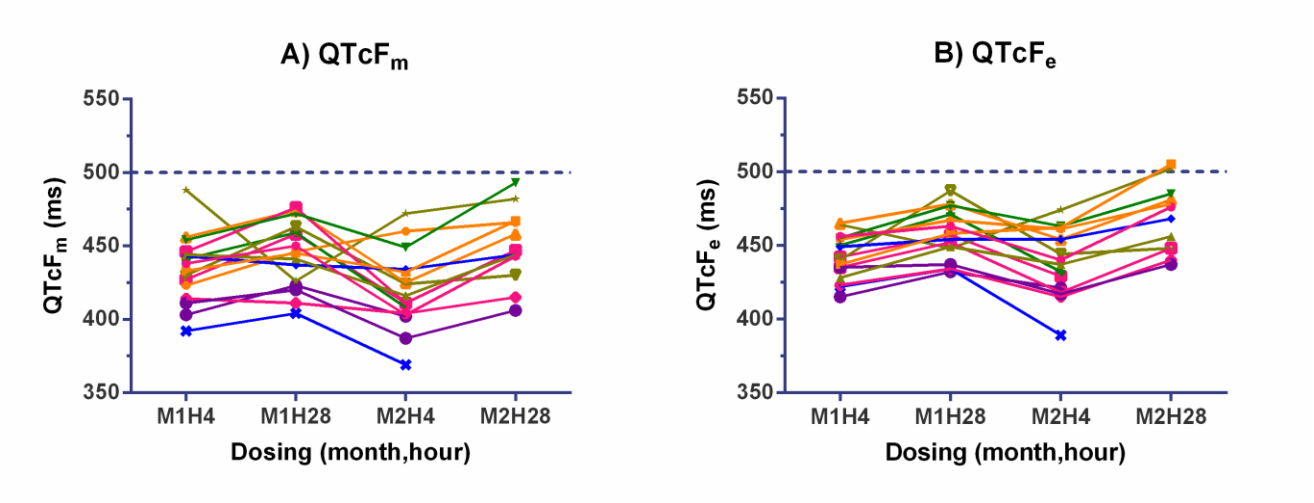
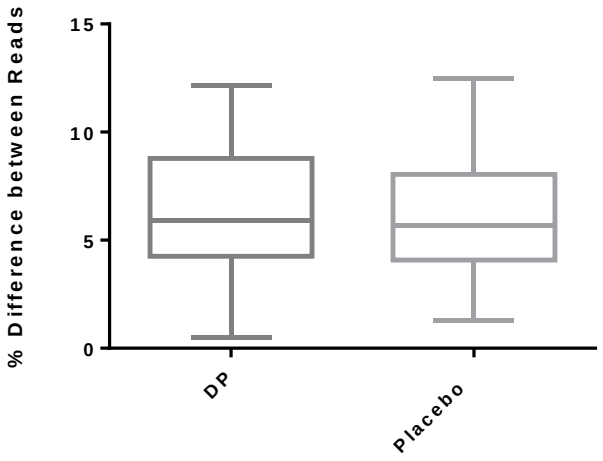


Figure S1. QTcFm (A) and QTcFe (B) measurements at the following timepoints: 4 hours after the first daily dose during Month 1 (Month 1, Hour 4 [M1H4]), 4 hours after the second daily dose during Month 1 (Month 1, Hour 28 [M1H28]), 4 hours after the first daily dose during Month 2 (Month 2, Hour 4 [M1H4]), 4 hours after the second daily dose during Month 2 (Month 2, Hour 28 [M1H28])

A. Pre-dose (0 hours)



B. Post-dose (28 hours)

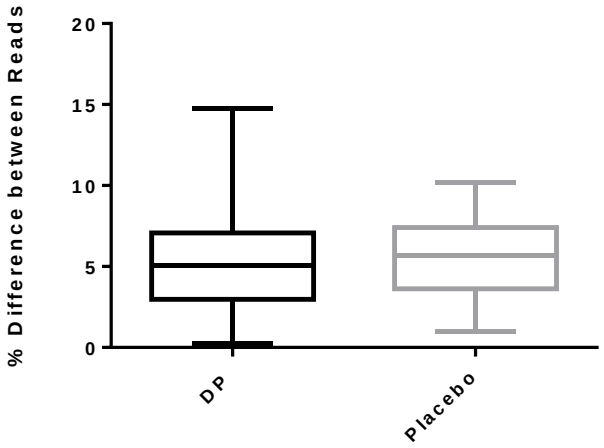
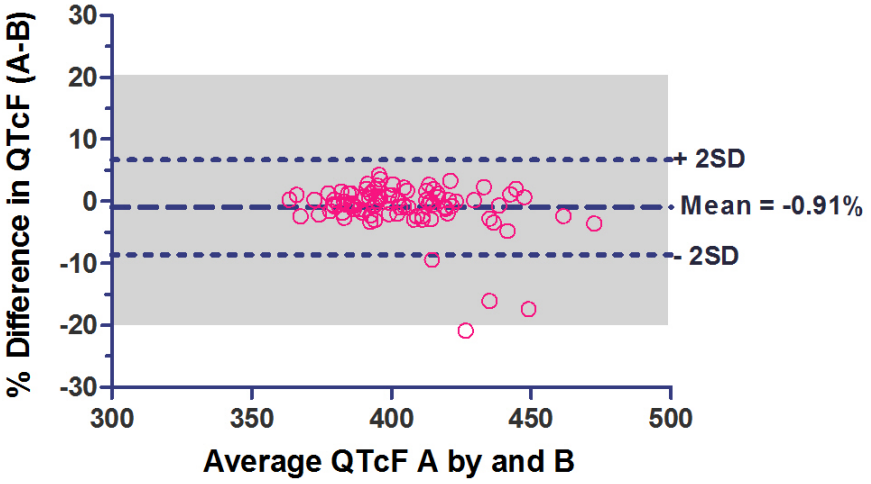
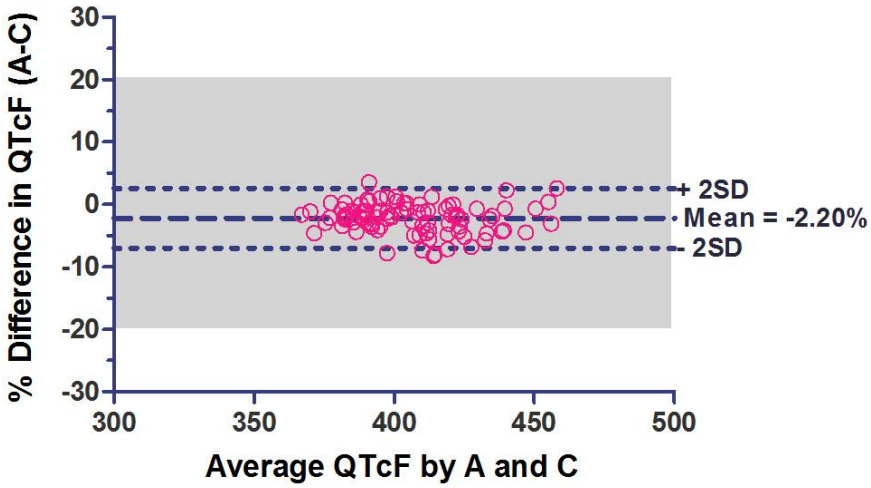


Figure S2. Differences between manual and electronic reads of the QTc interval were not significantly different between treatment groups at (A) before the first dose of dihydroartemisinin-piperaquine on Day 1 (p=0.96) or (B) after the second dose of dihydroartemisinin-piperaquine on Day 2 (p=0.60).





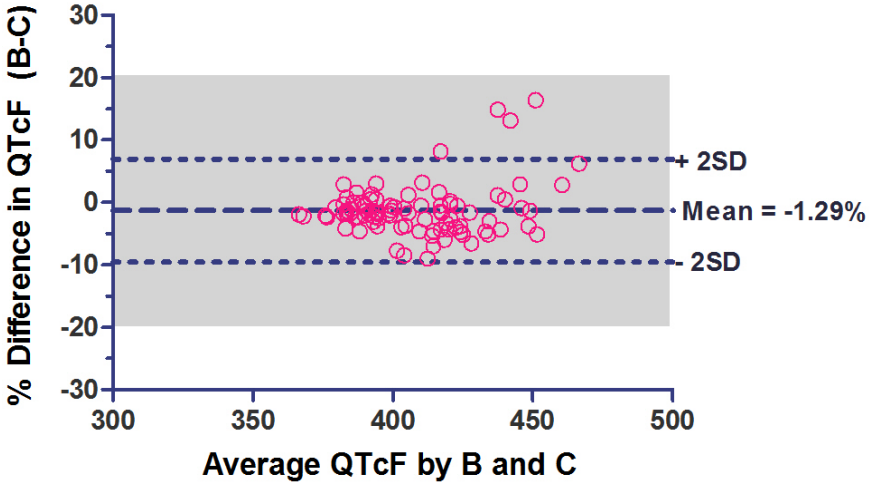


Figure S3. There was no significant interreader variability between three blinded ECG readers.

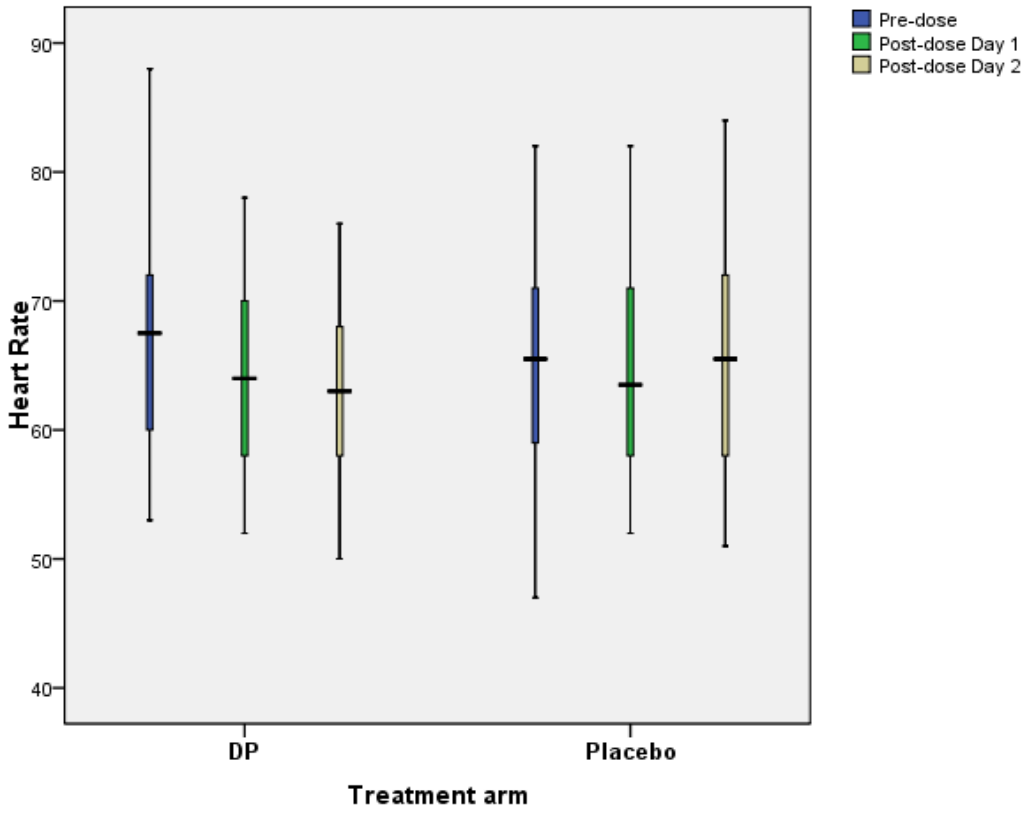


Figure S4. Heart rate did not change significantly pre-dose, after the first dose or after the second dose of study drug. It was also not significantly different between groups.

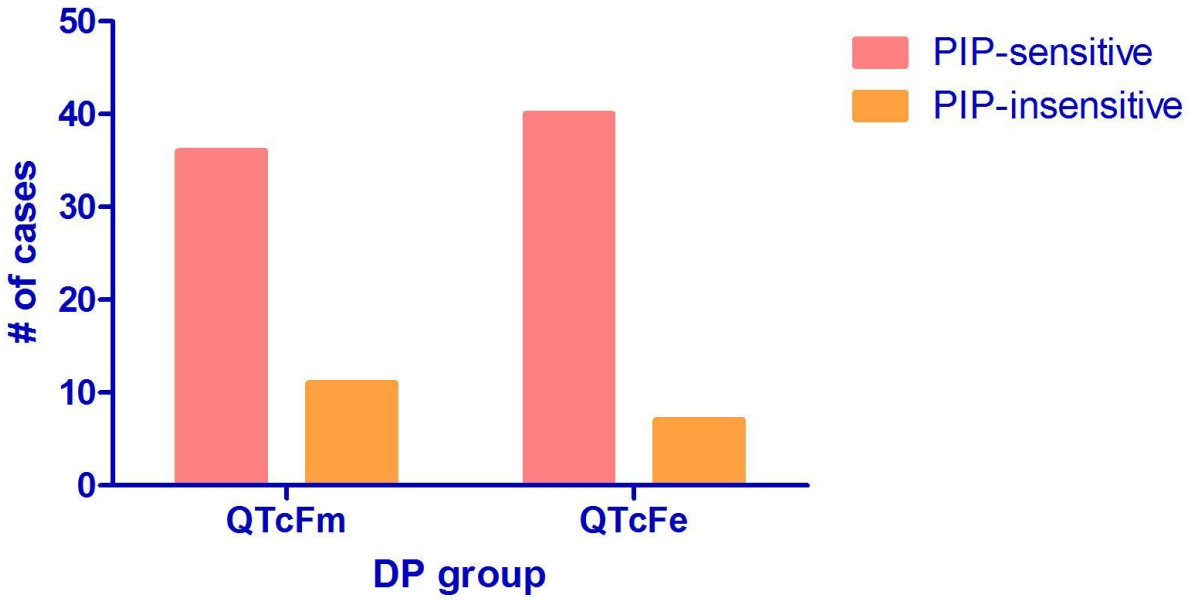


Figure S5. Plasma piperaquine significantly correlated to QTcF interval change from baseline in 36/47 individuals who received dihydroartemisinin-piperaquine based on QTcFm and 40/47 based on QTcFe (R2 with value for $P<0.05$). Contingency test demonstrated significant effect of piperaquine effect on QTc ($P<0.0001$).

Table S1. ECG findings before and after dosing of dihydroartemisinin-piperaquine in halted subjects.

	Electronic QTcF					Manual QTcF				
Subject	Predose	Post Dose 1	Post Dose 2	Maximum QT increase	Max %Increase	Predose	Post Dose 1	Post Dose 2	Maximum QT increase	Max %Increase
14	417	536		119	29%	401	466		65	16%
15	420	489	544	124	30%	410	457	482	72	18%
55	436	479	505	69	16%	409	464	486	77	19%
68	435	469	515	80	18%	415	440	489	74	18%
Avg. DP	413	439	456	43	10%	390	420	441	51	13%
Avg. Placebo	415	418	414	3	1%	391	396	396	5	1%

Table S2. Adverse Events Rates per treatment arm

Preferred Term	Response	DHA_piperaquine (N= 47)	Placebo (N= 22)	P value
Abdominal discomfort	Yes	1(2.13)	0(0.00)	1.0000
	No	46(97.87)	22(100.0)	
Abdominal pain	Yes	1(2.13)	1(4.55)	0.5392
	No	46(97.87)	21(95.45)	
Abdominal pain upper	Yes	1(2.13)	0(0.00)	1.0000
	No	46(97.87)	22(100.0)	
Arthralgia	Yes	1(2.13)	1(4.55)	0.5392
	No	46(97.87)	21(95.45)	
Body tinea	Yes	1(2.13)	0(0.00)	1.0000
	No	46(97.87)	22(100.0)	
Chest discomfort	Yes	2(4.26)	0(0.00)	1.0000
	No	45(95.74)	22(100.0)	
Cough	Yes	3(6.38)	0(0.00)	0.5461
	No	44(93.62)	22(100.0)	
Dermatitis atopic	Yes	1(2.13)	0(0.00)	1.0000
	No	46(97.87)	22(100.0)	
Diarrhoea	Yes	1(2.13)	0(0.00)	1.0000
	No	46(97.87)	22(100.0)	
Dizziness	Yes	14(29.79)	2(9.09)	0.0713
	No	33(70.21)	20(90.91)	
Electrocardiogram QT prolonged	Yes	26(55.32)	0(0.00)	<0.0001
	No	21(44.68)	22(100.0)	
Eye irritation	Yes	1(2.13)	0(0.00)	1.0000
	No	46(97.87)	22(100.0)	
Fatigue	Yes	3(6.38)	0(0.00)	0.5461
	No	44(93.62)	22(100.0)	
Gastritis	Yes	0(0.00)	3(13.64)	0.0294
	No	47(100.0)	19(86.36)	
Headache	Yes	9(19.15)	2(9.09)	0.4822
	No	38(80.85)	20(90.91)	
Helminthic infection	Yes	2(4.26)	1(4.55)	1.0000
	No	45(95.74)	21(95.45)	
Herpes zoster	Yes	1(2.13)	0(0.00)	1.0000
	No	46(97.87)	22(100.0)	
Hypomagnesaemia	Yes	1(2.13)	0(0.00)	1.0000
	No	46(97.87)	22(100.0)	
Influenza like illness	Yes	0(0.00)	1(4.55)	0.3188

	No	47(100.0)	21(95.45)	
Leptospirosis	Yes	1(2.13)	0(0.00)	1.0000
	No	46(97.87)	22(100.0)	
Malaise	Yes	1(2.13)	0(0.00)	1.0000
	No	46(97.87)	22(100.0)	
Malaria	Yes	10(21.28)	13(59.09)	0.0028
	No	37(78.72)	9(40.91)	
Musculoskeletal chest pain	Yes	1(2.13)	0(0.00)	1.0000
	No	46(97.87)	22(100.0)	
Musculoskeletal pain	Yes	1(2.13)	1(4.55)	0.5392
	No	46(97.87)	21(95.45)	
Myalgia	Yes	1(2.13)	0(0.00)	1.0000
	No	46(97.87)	22(100.0)	
Nail infection	Yes	0(0.00)	1(4.55)	0.3188
	No	47(100.0)	21(95.45)	
Nasopharyngitis	Yes	6(12.77)	2(9.09)	1.0000
	No	41(87.23)	20(90.91)	
Nausea	Yes	11(23.40)	2(9.09)	0.2001
	No	36(76.60)	20(90.91)	
Neck pain	Yes	1(2.13)	0(0.00)	1.0000
	No	46(97.87)	22(100.0)	
Oral herpes	Yes	1(2.13)	0(0.00)	1.0000
	No	46(97.87)	22(100.0)	
Oropharyngeal pain	Yes	2(4.26)	0(0.00)	1.0000
	No	45(95.74)	22(100.0)	
Pyrexia	Yes	2(4.26)	0(0.00)	1.0000
	No	45(95.74)	22(100.0)	
Rash	Yes	0(0.00)	1(4.55)	0.3188
	No	47(100.0)	21(95.45)	
Rash generalised	Yes	0(0.00)	1(4.55)	0.3188
	No	47(100.0)	21(95.45)	
Scrub typhus	Yes	1(2.13)	0(0.00)	1.0000
	No	46(97.87)	22(100.0)	
Seasonal allergy	Yes	1(2.13)	0(0.00)	1.0000
	No	46(97.87)	22(100.0)	
Skin wound	Yes	4(8.51)	0(0.00)	0.2985
	No	43(91.49)	22(100.0)	
Tinea cruris	Yes	0(0.00)	1(4.55)	0.3188
	No	47(100.0)	21(95.45)	
Tinea infection	Yes	0(0.00)	1(4.55)	0.3188
	No	47(100.0)	21(95.45)	

Toothache	Yes	1(2.13)	0(0.00)	1.0000
	No	46(97.87)	22(100.0)	
Vertigo	Yes	2(4.26)	0(0.00)	1.0000
	No	45(95.74)	22(100.0)	
Vessel puncture site haematoma	Yes	0(0.00)	1(4.55)	0.3188
	No	47(100.0)	21(95.45)	
Vomiting	Yes	2(4.26)	1(4.55)	1.0000
	No	45(95.74)	21(95.45)	
Wound infection	Yes	0(0.00)	1(4.55)	0.3188
	No	47(100.0)	21(95.45)	

Table S3. Clinical Vignettes of Halted Participants

Box 1.

Halted Participant 1

A 19-year old male without significant past medical history, allergies or recent medication use was screened for the study. Screening vital signs, physical exam, and laboratory values were not clinically significant except for eosinophilia (20.8%) attributed to asymptomatic intestinal helminthiasis (a common finding in this population; please note that he did not receive any antihelminthic treatment during this study). After enrollment, his predose ECG was normal with a QTcFe of 417ms (QTcFm 401ms). He tolerated study drug administration well, but at four hours post-dose, his average QTcFe was 536ms (a grade 3 adverse event representing a 29% increase over baseline, grade 3), though significantly less following manual measurement (466ms QTcFm, grade 1, 16% increase). A pronounced sinus arrhythmia was noted that may have confounded the electronic interpretation. Repeat ECGs performed approximately 30 minutes later showed sustained prolonged QTcFe of 518ms (grade 3, 24% increase), but QTcFm of 460ms (grade 1,15% increase). Examples of the participant's pre- and post-dose ECG tracings are shown in Figure 2. The volunteer reported mild transient fatigue post-dose but otherwise had no complaints. The following day, repeat ECG had returned to normal with QTcFe of 429ms. Study drug administration was halted. Vignettes for the remaining three subjects can be found in the Supplemental Information. A summary of pre and post-dose measurements for the halted participants is shown in Supplemental Table 3.

Halted Participant 2

A 20-year old male without significant past medical history, allergies, or recent medication use was enrolled in the study. Vital signs and physical exam at screening were unremarkable. Labs included a negative malaria smear; CBC, renal and liver function tests, electrolytes and G6PD activity were normal. Predose ECG was normal with a QTcFe of 420ms (410 ms by manual read)(Figure 1A). He was randomized and administered study drug which was well-tolerated. Average QTcFe at 4 hours post-dose on ECG was 489ms (16% increase, grade 2) but only 457ms (grade 1, 12% increase) by manual read. The next day, he returned for the second dose with QTcFe on pre-dose ECG of 448ms (437ms manual) and a post-dose QTcFe on ECG at 4 hours of 544ms (grade 3, 30% increase over baseline) but only 482ms by manual (grade 2, 18% increase over baseline)(Figure 1B). It decreased to 509ms electronic (grade 3) and 468ms manual (grade 1) within 30 minutes, and then to 477ms electronic (grade 1) and 442 manual within 90 minutes. Due to flattening of T waves in lead II, lead V5 was used for manual reading. The volunteer remained asymptomatic and repeat ECG showed normal QTcFe of 444ms within 24 hours. A blinded DSMB review halted this participant for reasons of an almost undetectable T wave in lead II and a biphasic T-U wave in lead III.

Figure 1A. Pre-dose EKG

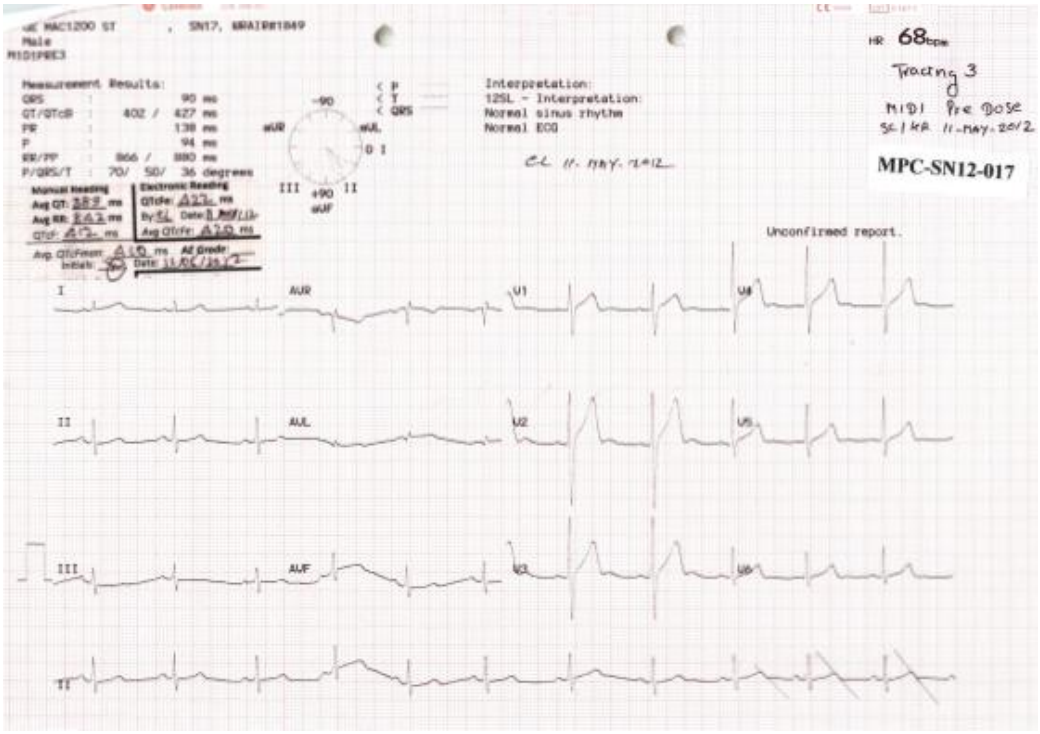
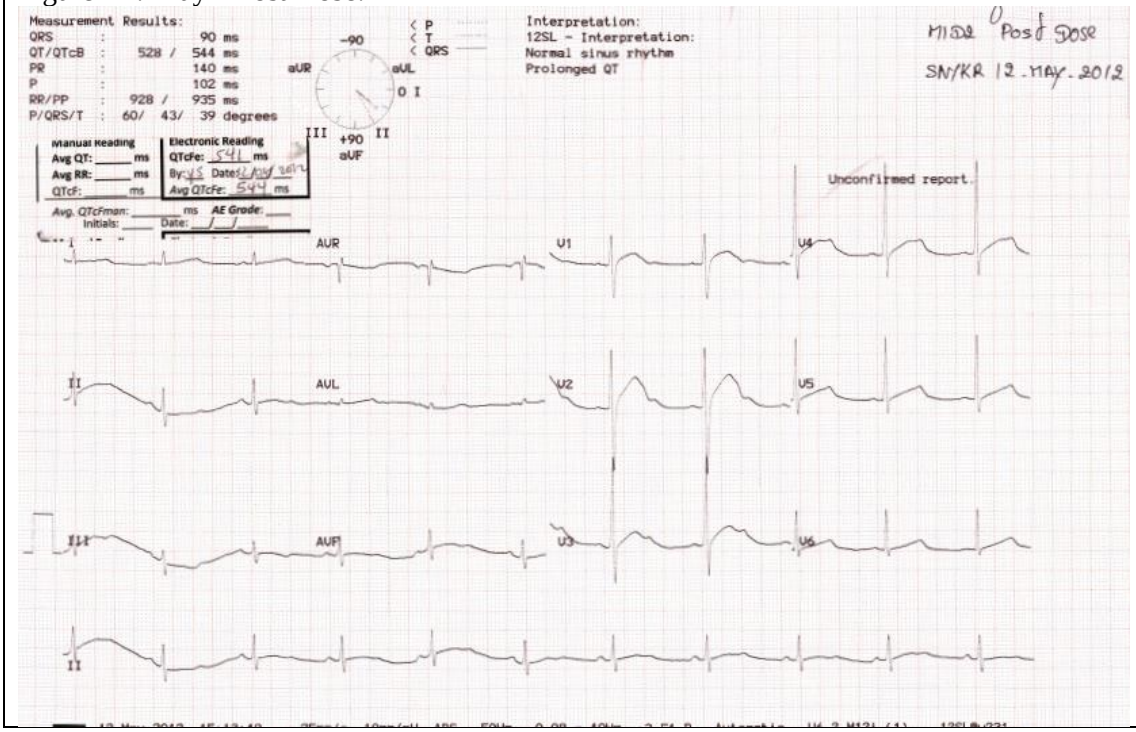


Figure 1B. Day 2 Post-Dose:



Halted Participant 3

A 32-year old male without significant past medical history was enrolled in the study. At screening, he complained of an upper respiratory infection and muscle aches in the previous week for which he had taken amoxicillin, paracetamol and one other unknown drug that had been stopped a few days prior to screening. His past medical history was significant for an episode of pneumonia with hospitalization in 2004 and appendectomy in 2005. He reported no personal or family history of cardiac disease. He had no known drug allergies, but did report an episode of 'allergy' with itching in the past after ingesting bee larvae, a local delicacy. He reported that he smoked two packs of cigarettes daily and drank alcohol three times per week. He had four episodes of malaria in 2009, but none in the past year. At screening, his vital signs and exam were unremarkable. Laboratory testing demonstrated normal electrolytes and G6PD activity. He was randomized to receive the study drug but vomited the first dose after thirty minutes had elapsed. An additional half dose of test article (2.25 tablets) was administered, per approved method of administration, and tolerated well by the participant [17]. Average QTcFe at 4 hours post-dose was 479 ms (10% increase, grade 1), and 464 ms (grade 1, 14%increase) by manual read. The following day, he returned for the second dose. His pre-dose QTcFe was 440ms (417 ms manually), and a post-dose QTcFe at 4 hours of 505ms (grade 3, 16% increase over baseline) and 486 ms by manual (grade 2, 19% increase over baseline) (Figure 2A). Approximately 1 hour later, it remained elevated to 518ms electronic (grade 3), and 515 ms manual (grade 3 or 26% increase). By 8 hours post-dose, QTcFe had decreased to 473 ms (grade 1) and (464ms manually, grade 1). There were no complaints of palpitations or other cardiac-related symptoms at any time. The subject was halted.

Figure 2A. Pre-dose

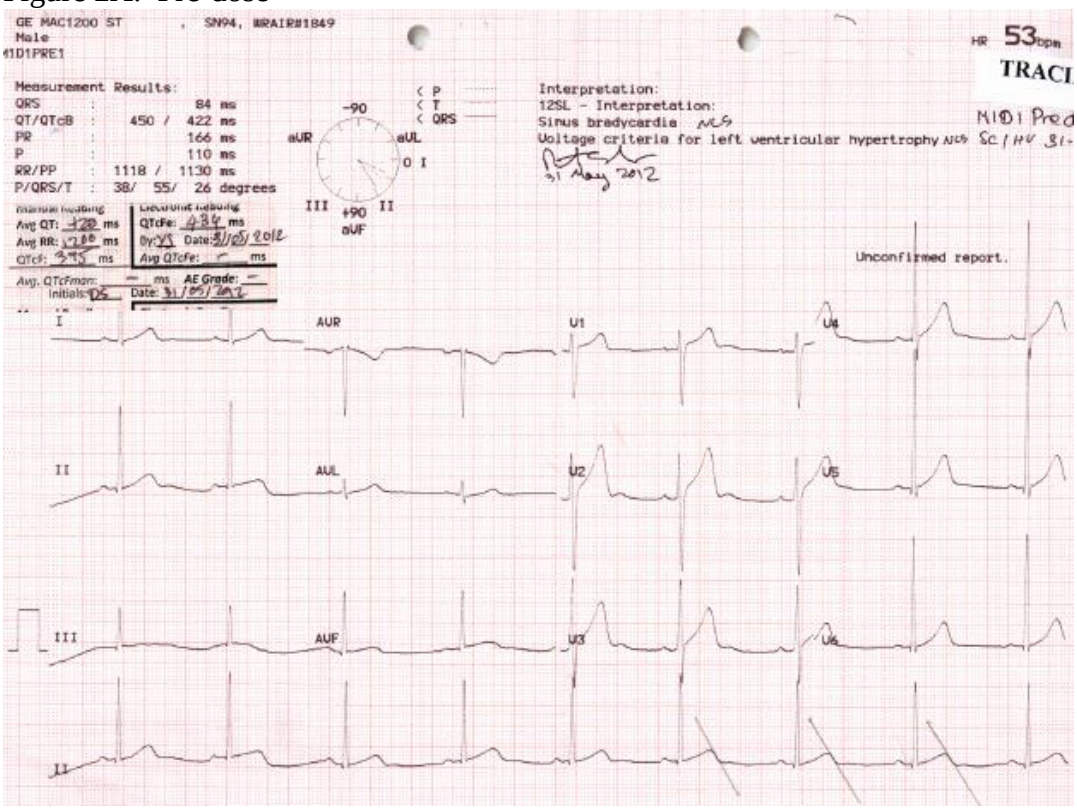
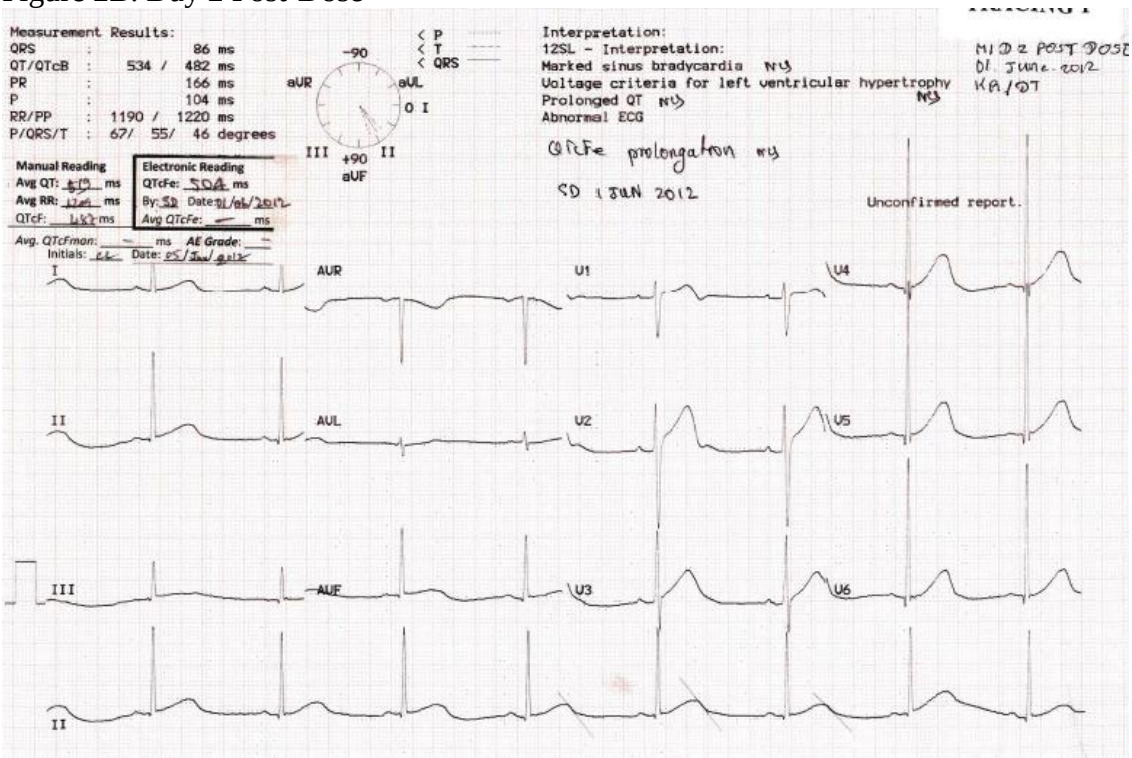


Figure 2B. Day 2 Post-Dose



Halted participant 4

A 36-year old male with no drug allergies or significant cardiac history was enrolled in the study. At screening, he complained of mild abdominal pain, but did not take any medication for this sign. He reported a past medical history that was significant for a motorcycle accident with hospitalization and coma in 2004 and intermittent dyspepsia since 2007 (he takes occasional antacids for relief). He reports taking an unknown local traditional herbal tea preparation daily boiled for general health improvement since January 2012. He smoked 10 cigarettes per day and drank alcohol occasionally. He had two episodes of malaria in 2000, but most recently March 2012. Screening vital signs were normal. On physical exam, he had mild tenderness to palpation over the epigastric region, and several areas of tinea versicolor on his upper back, but otherwise normal. Laboratory evaluation included a negative malaria smear and a normal CBC with the exception of mild neutrophilia (46.2% differential), mild eosinophilia (7.2% differential) and basophilia (2.3% differential). Electrolytes, renal function, and G6PD activity were normal. Predose ECG was normal with a QTcFe of 435ms (415ms by manual read)(Figure 3A). He was randomized and administered study drug. Average QTcFe at 4 hours post-dose on ECG was 469 ms (8% increase, grade 1) and 440ms (grade 1,6% increase) by manual read. The next day, he returned for the second dose with QTcFe on pre-dose ECG of 446ms (430 ms manual), and a post-dose QTcFe on ECG at 4 hours of 515ms (grade 3, 18% increase over baseline) and 489 ms by manual (grade 2,18% increase over baseline). Repeat ECG 15 minutes later was 557 ms by electronic read and 483 ms by manual read (Figure 3B). One hour later, QTcFe remained elevated to 512ms (grade 3) versus 471 ms manual (grade 1 or14% increase over baseline). By 8 hours post-dose, QTcFe dropped to 463 ms (grade 1 or 9% increase) and 452ms manual (grade 1 or 9% increase).The volunteer remained asymptomatic but was halted from study.

Figure 3A. Day 1 Pre-dose

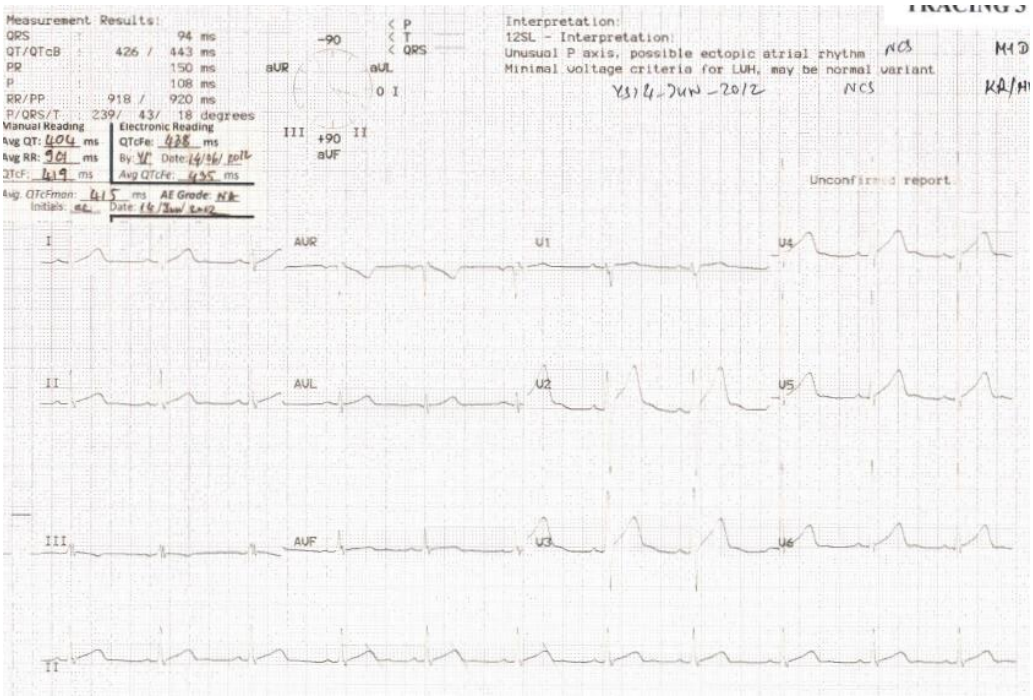


Figure 3B. Day 2 Post-dose