Multimedia Appendix 1: Summary of Study Design and Schedule of Assessment (SPIRIT Flow Diagram)

Phase	Recruitment Phase	Enrolment	Treatment Phase			Post-treatment Follow-up phase					
Location	OPD	OPD	OPD	OPD[b]	OPD[b]	OPD visits					
Visit number	#1	#2	#2	#3	#4	#5	#6	#7	#8	#9	#10
Study Time Hour	-1h [a]	-0.5h	0h	24h	48h	52h	168h	240h	336h	504h	672h
Day	D00	D00	D00	D01	D02	D02+4h ±2h[c]	D07 ±3d[c]	D10 ±3d[c]	D14 ±3d[c]	D21 ±3d[c]	D28 ±3d[c]
Recruitment											
Pre-screening	X										
Enrolment											
Eligibility screen		X									
Informed Consent		X									
Study code issued		X									
Allocation		X									
Interventions											
IVM-0 arm			X[i]	X[i]	X[i]						
IVM-300 arm			X[i]	X[i]	X[i]						
IVM-600 arm			X[i]	X[i]	X[i]						
Clinical assessments		D00			D02	D02+4h	D07	D10	D14	D21	D28
Copy Clinic/Lab data from hospital records											
Physical Exam.		X				X	X	X	X	X	X
Pupillometry		X				X	X	X	X	X	X
ECG		X			X[j]	X					X
Questionnaire AE		X				X	X	X	X	X	X
Blood sample[d,e,h]		V 5.4ml				V+C 5.9ml	V+C 5.9ml	V 5.4ml	V 5.4ml	V 5.4ml	V 5.4ml
Unscheduled sick-patient clinic visits						Passive surveillance for 28 days (clinical malaria and other acute illnesses)[k]					
Entomological assessments		D00				D02+4h	D07	D10	D14	D21	D28
Membrane feeding[f]		X				X	X	X	X	X	X
Direct feeding							X[g]				

Visit 1: Pre-Screening interview
Visit 2: Consent, Screening, & Enrolment. First treatment dose given under direct observation.
Visits 3 and 4: Treatment visits. 2nd and 3rd treatment doses given under direct observation. In exceptional cases doses of day 1 and 2 can be taken at home.
Visits 5 to 10: Scheduled follow-up visits for assessment of efficacy parameters

a. Patients can be pre-study screened any time from visiting the OPD. The figure of -1 hour is provided for illustration purposes only.
b. The day of enrolment is always considered as Day-0. Doses given under direct observation. In exceptional cases doses of day 1 and 2 can be taken at home.
c. Visit window= number of days an actual subject visit may fall outside of the planned protocol schedule visit to still meet protocol requirements. It is preferential to stick to the scheduled days of visit. However, if this is not feasible (e.g. due to other commitments of the patient) then it preferable to allow flexibility in the schedule. The date of actual visit will always need to be recorded in the CRF.
d. Enrolment & baseline blood sample (~5.4 mL) by venepuncture: haemoglobin (0.01 mL), malaria smear / RDT (0.01 mL), dried blood spots (DBS) for PCR (0.3 mL) will be stored for parasite genetics to differentiate reinfection from recrudescence in case of treatment failure, membrane feeding (~1 mL), pharmacology (~4 mL: ~2mL plasma for drug levels, 2mL pellet for host metabolism genetics).
e. Follow-up blood sample (~5.4 mL) by venepuncture: haemoglobin (0.01 mL), malaria smear (0.01 mL), malaria RDT (0.005 mL), dried blood spots for PCR (0.3 mL), membrane feeding (~1 mL), pharmacology (~4mL: ~2mL plasma for drug levels).
f. Membrane feeding will be used to assess: Mosquito survival (daily up to 21 to 28 days after feed; Oocyst prevalence at day 10 after feeding).
g. Direct skin feeding in a sub-sample only.
h. Finger prick (capillary) blood sample on Day 2+4h and Day 7: drug levels (~0.5ml to obtain ~0.25ml plasma).
i. Each treatment visit: IVM-0 (DP, placebo 600 mcg/kg), IVM-300 (DP, ivermectin 300 mcg/kg/day, placebo 300 mcg/kg/day), IVM-600 (DP, ivermectin 600 mcg/kg/day)
j. Before 3rd dose.
k. RDT/smear, Hb, dried blood spots for parasite genetics.

V=venepuncture. C=capillary, DP=dihydroartemisinin-piperaquine, IVM=ivermectin, Hb=haemoglobin, MS=malaria smear, Pf=Plasmodium falciparum