Supplementary data

Safety and efficacy of four drug regimens versus standard-of-care for the treatment of symptomatic outpatients with COVID-19: a randomised, open-label, multi-arm, phase 2 clinical trial

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Table S1 Post-screening schedule of patient assessments.

Procedure	Enrolment Day 1[a]	Treatment and follow-up period — days										EOS Day 28 (±2)
		2	3 (+1)	4–6	7 (±1)	8–9	10 (±1)	11–13	14 (±2)	15–20	21 (±2)	
Study therapy[b]	●	●	●	●	●							
Pharmacokinetic sampling[b]			●		●							
Mid-nasal swab and saliva specimen			●		●		●		●		●	●
Blood for serology	●											●
Participant reported vital signs	●	●	●	●	●	●	●	●	●		●	●
Participant reported SpO_2	●	●	●	●	●	●	●	●	●			
Completion of daily survey	●	●	●	●	●	●	●	●	●		●	●
Completion of FLU-PRO Plus questionnaire	●	●	●	●	●	●	●	●	●		●	●
WHO Ordinal Scale for Clinical Improvement[c]	●				●				●		●	●
Adverse event review and clinician contact	●	●	●	●	●	●	●	●	●	●	●	●

EOS, end of study; WHO, World Health Organization.

[a] Additional assessments that were conducted on day 1 and not during follow-up were: confirmation of inclusion and exclusion criteria, completion of the consent process, assessment of past and current medical conditions and concomitant medications, physical examination, vital signs, and an electrocardiograph.

[b] The duration of treatment and pharmacokinetic sampling were dependent upon the treatment arm.

[c] By 9-point Scale; 0-uninfected, 1-no limitation of activities, 2-limitation of activities, 3-hospitalized but no oxygen therapy, 4-oxygen by mask or nasal prongs, 5-non-invasive ventilation or high-flow oxygen, 6-intubation and mechanical ventilation, 7-ventilation with additional organ support, 8-death.

Table S2 Bioanalytical methods to determine drug concentrations.

Analyte	Calibration range	Matrix	Internal standard
Amodiaquine	0·156–10·0 ng/mL	Plasma	Amodiaquine-d10
N-desethyl amodiaquine	1·56–100 ng/mL	Plasma	N-desethyl amodiaquine-d5
Favipiravir	0·391–25·0 µg/mL	Plasma	Favipiravir Impurity 3
Sofosbuvir	2·50–160 ng/mL	Plasma	$[2H_6]$-Sofosbuvir
Artesunate	1·56–200 ng/mL	Plasma	Artesunate-d4
Dihydroartemisinin	3·91–500 ng/mL	Plasma	Dihydroartemisinin-d4
Daclatasavir	15·6–1000 ng/mL	Plasma	Daclatasavir-d6
Nitazoxanide	100–15,000 ng/mL	Plasma	Nitazoxanide
Pyronaridine	0·977–500 ng/mL	Whole blood	Pyronaridine $^{13}C_2$-d4
Tizoxanide	100–15,000 ng/mL	Plasma	Tizoxanide-d4

Extraction from the biological matrix used a solid phase extraction technique, with analysis by liquid chromatography with tandem mass spectrometry detection (LC-MS-MS).

Target limits for evaluable calibration standards were ±15% bias of each calibration standard point (±20% at the lower limit of quantification) and ±15% bias for each quality control sample.

Table S3 Sensitivity analysis of the primary endpoint: incidence of SARS-CoV-2 clearance on day 7 based on qualitative RT-PCR.

mITT population missing = failure	**SOC (n=39)**	**ASAQ (n=39)**	**PA (n=36)**	**FPV+NTZ (n=37)**	**SOF-DCV (n=35)**
Covariate adjusted analysis[a]					
Incidence, n/N (%)[b]	13/39 (33·3)	15/39 (38·5)	10/35 (28·6)	10/37 (27·0)	8/35 (22·9)
Risk ratio (95% CI)	Reference	0·96 (0·55, 1·67)	0·70 (0·36, 1·34)	0·72 (0·38, 1·34)	0·55 (0·27, 1·12)
P value	Reference	0·87	0·28	0·30	0·099
Crude analysis					
Incidence, n/N (%)[a]	13/39 (33·3)	15/39 (38·5)	10/36 (27·8)	10/37 (27·0)	8/35 (22·9)
Risk ratio (95% CI)	Reference	1·15 (0·64, 2·09)	0·86 (0·43, 1·7)	0·81 (0·41, 1·62)	0·69 (0·32, 1·46)
P value	Reference	0·64	0·66	0·55	0·33
As-treated population	**SOC (n=38)**	**ASAQ (n=38)**	**PA (n=34)**	**FPV+NTZ (n=35)**	**SOF-DCV (n=33)**
Covariate adjusted analysis[a]					
Incidence, n/N (%)[b]	13/38 (34·2)	15/38 (39·5)	11/33 (33·3)	9/35 (25·7)	8/33 (24·2)
Risk ratio (95% CI)	Reference	0·87 (0·46, 1·63)	0·72 (0·40, 1·03)	0·55 (0·27, 1·11)	0·47 (0·22, 1·01)
P value	Reference	0·66	0·66	0·093	0·054
Crude analysis					
Incidence, n/N (%)[a]	13/38 (34·2)	15/38 (39·5)	11/34 (32·4)	9/35 (25·7)	8/33 (24·2)
Risk ratio (95% CI)	Reference	1·15 (0·64, 2·08)	0·97 (0·51, 1·87)	0·75 (0·37, 1·54)	0·71 (0·34, 1·5)
P value	Reference	0·64	0·94	0·43	0·37

[a] The covariate adjusted regression model contained treatment arm, age at baseline (years), sex, baseline BMI, baseline comorbidities, baseline viral load category and days of symptoms at time of enrolment as covariates. The crude analysis repeated the regression model without any covariate adjustment.

[b] n/N is number of patients with clearance / number of patients evaluable at day 7.

mITT, modified intention-to-treat; SOC, standard-of-care; ASAQ, artesunate-amodiaquine; PA, pyronaridine-artesunate; FPV+NTZ, favipiravir plus nitazoxanide; SOF-DCV, sofosbuvir-daclatasvir.

Table S4 Primary analysis of the incidence of SARS-CoV-2 clearance on day 7 based on RT-PCR by subgroup (mITT population). See also Figure S1.

Subgroup	Category	Treatment arm	N	n/N (%)[a]	Comparison	Risk ratio (95%CI)	*P* value
Age	Low (≤33 years)	SOC	22	8/21 (38·1)			
		ASAQ	19	5/19 (26·3)	ASAQ / SOC	0·754 (0·245, 2·324)	0·6235
		PA	18	5/18 (27·8)	PA / SOC	0·739 (0·230, 2·382)	0·6131
		FPV+NTZ	19	7/19 (36·8)	FPV+NTZ / SOC	0·953 (0·327, 2·780)	0·9302
		SOF-DCV	18	3/18 (16·7)	SOF-DCV / SOC	0·387 (0·100, 1·504)	0·1706
	High (>33 years)	SOC	17	5/17 (29·4)			
		ASAQ	20	10/20 (50·0)	ASAQ / SOC	1·362 (0·458, 4·049)	0·5779
		PA	18	5/15 (33·3)	PA / SOC	0·760 (0·216, 2·674)	0·6686
		FPV+NTZ	18	3/18 (16·7)	FPV+NTZ / SOC	0·419 (0·097, 1·811)	0·2444
		SOF-DCV	17	5/16 (31·3)	SOF-DCV / SOC	0·885 (0·245, 3·202)	0·8526
Sex	Male	SOC	15	5/14 (35·7)			
		ASAQ	14	5/14 (35·7)	ASAQ / SOC	0·661 (0·186, 2·344)	0·5218
		PA	16	7/14 (50·0)	PA / SOC	0·804 (0·244, 2·649)	0·7201
		FPV+NTZ	22	5/22 (22·7)	FPV+NTZ / SOC	0·374 (0·102, 1·365)	0·1365
		SOF-DCV	20	4/20 (20·0)	SOF-DCV / SOC	0·300 (0·078, 1·160)	0·0811
	Female	SOC	24	8/24 (33·3)			
		ASAQ	25	10/25 (40·0)	ASAQ / SOC	1·283 (0·501, 3·289)	0·6035
		PA	20	3/19 (15·8)	PA / SOC	0·421 (0·108, 1·643)	0·2132
		FPV+NTZ	15	5/15 (33·3)	FPV+NTZ / SOC	1·057 (0·342, 3·272)	0·9228
		SOF-DCV	15	4/14 (28·6)	SOF-DCV / SOC	1·035 (0·296, 3·615)	0·9567
BMI	Low (≤30 kg/m^2)	SOC	28	10/27 (37·0)			
		ASAQ	24	10/24 (41·7)	ASAQ / SOC	0·902 (0·372, 2·192)	0·8205
		PA	21	7/19 (36·8)	PA / SOC	0·706 (0·259, 1·926)	0·4963
		FPV+NTZ	24	8/24 (33·3)	FPV+NTZ / SOC	0·645 (0·243, 1·713)	0·3787
		SOF-DCV	20	4/19 (21·1)	SOF-DCV / SOC	0·360 (0·108, 1·203)	0·0970
	High (>30 kg/m^2)	SOC	11	3/11 (27·3)			
		ASAQ	15	5/15 (33·3)	ASAQ / SOC	1·431 (0·339, 6·036)	0·6258
		PA	15	3/14 (21·4)	PA / SOC	0·758 (0·150, 3·835)	0·7376
		FPV+NTZ	13	2/13 (15·4)	FPV+NTZ / SOC	0·742 (0·119, 4·617)	0·7489
		SOF-DCV	15	4/15 (26·7)	SOF-DCV / SOC	1·219 (0·264, 5·639)	0·7998

Subgroup	Category	Treatment arm	N	n/N (%)[a]	Comparison	Risk ratio (95%CI)	*P* value
Comorbidities	None	SOC	28	11/27 (40·7)			
		ASAQ	22	9/22 (40·9)	ASAQ / SOC	0·769 (0·312, 1·893)	0·5674
		PA	21	7/19 (36·8)	PA / SOC	0·704 (0·262, 1·894)	0·4869
		FPV+NTZ	21	7/21 (33·3)	FPV+NTZ / SOC	0·615 (0·229, 1·652)	0·3347
		SOF-DCV	19	4/18 (22·2)	SOF-DCV / SOC	0·371 (0·112, 1·228)	0·1045
	≥1 comorbidity	SOC	11	2/11 (18·2)			
		ASAQ	17	6/17 (35·3)	ASAQ / SOC	2·395 (0·478, 11·988)	0·2879
		PA	15	3/14 (21·4)	PA / SOC	0·914 (0·150, 5·560)	0·9225
		FPV+NTZ	16	3/16 (18·8)	FPV+NTZ / SOC	0·991 (0·157, 6·263)	0·9923
		SOF-DCV	16	4/16 (25·0)	SOF-DCV / SOC	1·417 (0·253, 7·945)	0·6919
Viral load	Low (<176,145 copies/mL)	SOC	17	10/16 (62·5)			
		ASAQ	18	11/18 (61·1)	ASAQ / SOC	0·666 (0·327, 1·355)	0·2623
		PA	20	9/19 (47·4)	PA / SOC	0·666 (0·349, 1·269)	0·2162
		FPV+NTZ	18	9/18 (50·0)	FPV+NTZ / SOC	0·560 (0·268, 1·169)	0·1226
		SOF-DCV	19	6/18 (33·3)	SOF-DCV / SOC	0·379 (0·160, 0·901)	0·0280
	High (≥175,145 copies/mL)	SOC	22	3/22 (13·6)			
		ASAQ	21	4/21 (19·0)	ASAQ / SOC	1·672 (0·421, 6·632)	0·4648
		PA	15	1/14 (7·1)	PA / SOC	0·558 (0·065, 4·814)	0·5957
		FPV+NTZ	19	1/19 (5·3)	FPV+NTZ / SOC	0·429 (0·048, 3·805)	0·4475
		SOF-DCV	16	2/16 (12·5)	SOF-DCV / SOC	1·005 (0·190, 5·314)	0·9949
Days of symptoms	Low (≤ 3 days)	SOC	39	13/38 (34·2)			
		ASAQ	37	15/37 (40·5)	ASAQ / SOC	1·071 (0·502, 2·285)	0·8600
		PA	34	9/31 (29·0)	PA / SOC	0·718 (0·300, 1·719)	0·4568
		FPV+NTZ	34	9/34 (26·5)	FPV+NTZ / SOC	0·647 (0·264, 1·582)	0·3393
		SOF-DCV	35	8/34 (23·5)	SOF-DCV / SOC	0·571 (0·225, 1·452)	0·2395
	High (> days)	SOC	0	0			
		ASAQ	2	0/ 2 (0·0)	ASAQ / SOC	NE (NE, NE)	NE
		PA	2	1/ 2 (50·0)	PA / SOC	NE (NE, NE)	NE
		FPV+NTZ	3	1/ 3 (33·3)	FPV+NTZ / SOC	NE (NE, NE)	NE
		SOF-DCV	0	0	SOF-DCV / SOC		
Risk[b]	Low risk	SOC	27	10/26 (38·5)			
		ASAQ	21	8/21 (38·1)	ASAQ / SOC	0·750 (0·289, 1·945)	0·5541

Subgroup	Category	Treatment arm	N	n/N (%)[a]	Comparison	Risk ratio (95%CI)	*P* value
		PA	20	7/18 (38·9)	PA / SOC	0·733 (0·268, 2·006)	0·5451
		FPV+NTZ	21	7/21 (33·3)	FPV+NTZ / SOC	0·638 (0·234, 1·743)	0·3810
		SOF-DCV	19	4/18 (22·2)	SOF-DCV / SOC	0·381 (0·113, 1·281)	0·1188
	High risk	SOC	12	3/12 (25·0)			
		ASAQ	18	7/18 (38·9)	ASAQ / SOC	1·971 (0·504, 7·699)	0·3292
		PA	16	3/15 (20·0)	PA / SOC	0·773 (0·149, 4·013)	0·7593
		FPV+NTZ	16	3/16 (18·8)	FPV+NTZ / SOC	0·817 (0·148, 4·496)	0·8163
		SOF-DCV	16	4/16 (25·0)	SOF-DCV / SOC	1·189 (0·251, 5·629)	0·8271

[a] Values are n/N (%) where n/N is number of patients with clearance / number of patients evaluable at day 7.

[b] High risk was defined as age >60 years or body mass index >30 kg/m^2 plus the presence of at least one comorbidity for progression to severe disease.

mITT, modified intention-to-treat; SOC, standard-of-care; ASAQ, artesunate-amodiaquine; PA, pyronaridine-artesunate; FPV+NTZ, favipiravir plus nitazoxanide; SOF-DCV, sofosbuvir-daclatasvir; NE, non-evaluable.

Table S5 Incidence of SARS-CoV-2 clearance on day 7 based on viral culture (mITT population).

Treatment arm	N	n/N (%)[a]	Comparison	Risk ratio (95%CI)	*P* value
SOC	39	6/6 (100)			
ASAQ	39	4/4 (100)	ASAQ / SOC	1·021 (0·269, 3·875)	0·9759
PA	36	3/3 (100)	PA / SOC	1·068 (0·238, 4·801)	0·9317
FPV+NTZ	37	10/11 (90.9)	FPV+NTZ / SOC	0·855 (0·297, 2·459)	0·7713
SOF-DCV	35	5/6 (83.3)	SOF-DCV / SOC	0·772 (0·224, 2·663)	0·6816

[a] Number of patients with outcome/number of patients evaluable at day 7.

The regression model contains treatment arm, age at baseline (years), sex, baseline body mass index, baseline comorbidities, baseline viral load category and days of symptoms at time of enrolment as covariates.

mITT, modified intention-to-treat; SOC, standard-of-care; ASAQ, artesunate-amodiaquine; PA, pyronaridine-artesunate; FPV+NTZ, favipiravir plus nitazoxanide; SOF-DCV, sofosbuvir-daclatasvir.

Table S6 Incidence of SARS-CoV-2 clearance on days 3, 10, 14, 21, and 28 based on RT-PCR (mITT population). See also Figure S1.

Day	Treatment arm	N	n/N (%)[a]	Comparison	Risk ratio (95%CI)	*P* value
3[b]	SOC	39	11/39 (28·2)			
	ASAQ	39	7/39 (17·9)	ASAQ / SOC	0·468 (0·172, 1·26)	0·1354
	PA	36	6/35 (17·1)	PA / SOC	0·335 (0·114, 0·98)	0·0462
	FPV+NTZ	37	9/37 (24·3)	FPV+NTZ / SOC	0·570 (0·218, 1·49)	0·2517
	SOF-DCV	35	5/35 (14·3)	SOF-DCV / SOC	0·315 (0·101, 0·98)	0·0470
10[c]	SOC	39	13/39 (33·3)			
	ASAQ	39	13/39 (33·3)	ASAQ / SOC	0·930 (0·507, 1·70)	0·8158
	PA	36	14/35 (40·0)	PA / SOC	0·904 (0·511, 1·59)	0·7279
	FPV+NTZ	37	11/37 (29·7)	FPV+NTZ / SOC	0·857 (0·475, 1·54)	0·6104
	SOF-DCV	35	12/35 (34·3)	SOF-DCV / SOC	1·001 (0·568, 1·76)	0·9983
14[c]	SOC	39	22/39 (56·4)			
	ASAQ	39	20/39 (51·3)	ASAQ / SOC	0·979 (0·644, 1·49)	0·9227
	PA	36	16/35 (45·7)	PA / SOC	0·792 (0·513, 1·22)	0·2940
	FPV+NTZ	37	19/37 (51·4)	FPV+NTZ / SOC	0·954 (0·626, 1·45)	0·8258
	SOF-DCV	35	18/35 (51·4)	SOF-DCV / SOC	0·909 (0·580, 1·42)	0·6760
21[b]	SOC	39	26/39 (66·7)			
	ASAQ	39	21/39 (53·8)	ASAQ / SOC	0·775 (0·434, 1·38)	0·3888
	PA	36	24/35 (68·6)	PA / SOC	0·973 (0·548, 1·72)	0·9259
	FPV+NTZ	37	24/37 (64·9)	FPV+NTZ / SOC	0·948 (0·533, 1·68)	0·8549
	SOF-DCV	35	24/35 (68·6)	SOF-DCV / SOC	0·952 (0·535, 1·69)	0·8679
28[c]	SOC	39	28/39 (71·8)			
	ASAQ	39	26/39 (66·7)	ASAQ / SOC	0·963 (0·704, 1·31)	0·8134
	PA	36	24/35 (68·6)	PA / SOC	1·018 (0·726, 1·42)	0·9188
	FPV+NTZ	37	27/37 (73·0)	FPV+NTZ / SOC	1·150 (0·838, 1·57)	0·3863
	SOF-DCV	35	24/35 (68·6)	SOF-DCV / SOC	0·989 (0·724, 1·35)	0·9459

[a] Number of patients with outcome/number of patients evaluable at each time point.

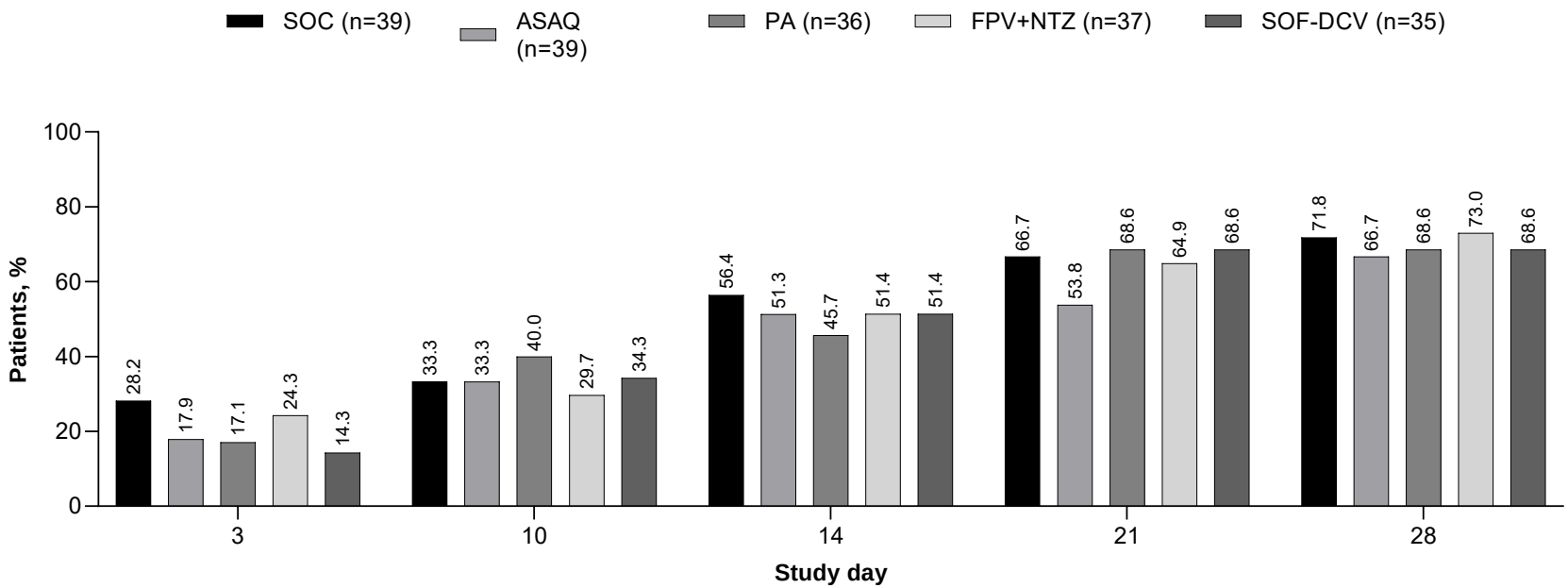
[b] Log link and Poisson distribution.

[c] Log link and binomial distribution.

mITT, modified intention-to-treat; SOC, standard-of-care; ASAQ, artesunate-amodiaquine; PA, pyronaridine-artesunate; FPV+NTZ, favipiravir plus nitazoxanide; SOF-DCV, sofosbuvir-daclatasvir.

The logistic regression model contained treatment arm, age at baseline (years), sex, baseline body mass index, baseline comorbidities, baseline viral load category and days of symptoms at time of enrolment as covariates.

Figure S1 Incidence of SARS-CoV-2 clearance on days 3, 10, 14, 21, and 28 based on RT-PCR (mITT population). See also Table S6.



mITT, modified intention-to-treat; SOC, standard-of-care; ASAQ, artesunate-amodiaquine; PA, pyronaridine-artesunate; FPV+NTZ, favipiravir plus nitazoxanide; SOF-DCV, sofosbuvir-daclatasvir.

Table S7 Repeated measure analysis of log_{10} viral load of SARS-CoV-2 change from baseline (mITT population).

Treatment arm	Day	N[a]	LSmean change (SE)	95%CI	Difference test–reference (SE)	95%CI	2-sided *P* value
SOC (N=39)	3	37	−1·33 (0·32)	−1·96, −0·69	Reference		
	7	38	−2·53 (0·28)	−3·09, −1·97			
	10	36	−2·99 (0·26)	−3·50, −2·48			
	14	37	−3·40 (0·27)	−3·94, −2·86			
ASAQ (N=39)	3	38	−1·31 (0·31)	−1·92, −0·69	0·02 (0·44)	−0·85, 0·89	0·9642
	7	37	−2·57 (0·28)	−3·12, −2·02	−0·04 (0·39)	−0·81, 0·73	0·9248
	10	38	−2·71 (0·25)	−3·20, −2·22	0·28 (0·35)	−0·42, 0·97	0·4293
	14	38	−3·25 (0·26)	−3·76, −2·73	0·15 (0·37)	−0·58, 0·89	0·6773
PA (N=36)	3	32	−1·48 (0·34)	−2·15, −0·81	−0·16 (0·46)	−1·07, 0·76	0·7374
	7	31	−2·42 (0·30)	−3·02, −1·82	0·11 (0·41)	−0·70, 0·93	0·7852
	10	31	−3·01 (0·27)	−3·55, −2·47	−0·02 (0·37)	−0·76, 0·72	0·9574
	14	31	−3·48 (0·29)	−4·05, −2·91	−0·08 (0·39)	−0·86, 0·70	0·8405
FPV+NTZ (N=37)	3	37	−0·98 (0·31)	−1·60, −0·36	0·35 (0·45)	−0·54, 1·24	0·4393
	7	35	−2·43 (0·28)	−2·99, −1·87	0·10 (0·40)	−0·69, 0·90	0·7947
	10	35	−2·90 (0·25)	−3·40, −2·40	0·09 (0·36)	−0·63, 0·81	0·7981
	14	35	−3·46 (0·27)	−3·99, −2·93	−0·06 (0·38)	−0·82, 0·70	0·8709
SOF-DCV (N=35)	3	33	−0·90 (0·33)	−1·56, −0·24	0·43 (0·46)	−0·48, 1·34	0·3546
	7	33	−2·35 (0·30)	−2·94, −1·76	0·18 (0·41)	−0·63, 0·99	0·6576
	10	34	−2·92 (0·27)	−3·44, −2·40	0·07 (0·37)	−0·66, 0·80	0·8526
	14	34	−3·14 (0·28)	−3·69, −2·58	0·26 (0·39)	−0·51, 1·03	0·5006

[a] Number of patients with available data at the respective time point. mITT, modified intention-to-treat; SOC, standard-of-care; ASAQ, artesunate-amodiaquine; PA, pyronaridine-artesunate; FPV+NTZ, favipiravir plus nitazoxanide; SOF-DCV, sofosbuvir-daclatasvir. The mixed-effect linear model for repeated measures includes treatment, age at baseline (years), sex, body mass index at baseline, baseline comorbidities, baseline viral load category, days of symptoms at time of enrolment and treatment-by-visit interaction as fixed effects.

Table S8 Repeated measure analysis of log_{10} viral load of SARS-CoV-2 change from baseline in high-risk patients (mITT population).

Treatment arm	Day	N[a]	LSmean change (SE)	95%CI	Difference test–reference (SE)	95%CI	2-sided *P* value
SOC (N=39)	3	12	−1·44 (0·68)	−2·79, −0·09	Reference		
	7	12	−3·12 (0·61)	−4·33, −1·92			
	10	12	−3·43 (0·59)	−4·60, −2·26			
	14	11	−3·76 (0·60)	−4·96, −2·56			
ASAQ (N=39)	3	17	−1·40 (0·62)	−2·63, −0·18	0·04 (0·74)	−1·43, 1·51	0·9583
	7	16	−3·02 (0·57)	−4·15, −1·89	0·10 (0·63)	−1·15, 1·35	0·8729
	10	18	−3·39 (0·54)	−4·47, −2·31	0·03 (0·58)	−1·13, 1·20	0·9559
	14	17	−3·94 (0·55)	−5·04, −2·84	−0·18 (0·61)	−1·39, 1·03	0·7658
PA (N=36)	3	15	−1·81 (0·64)	−3·08, −0·54	−0·37 (0·76)	−1·89, 1·15	0·6316
	7	14	−3·02 (0·59)	−4·18, −1·85	0·11 (0·65)	−1·19, 1·41	0·8705
	10	13	−3·62 (0·57)	−4·76, −2·47	−0·19 (0·62)	−1·43, 1·05	0·7617
	14	14	−4·20 (0·57)	−5·34, −3·06	−0·44 (0·64)	−1·71, 0·83	0·4925
FPV+NTZ (N=37)	3	16	−1·16 (0·64)	−2·43, 0·10	0·28 (0·77)	−1·27, 1·82	0·7206
	7	16	−3·44 (0·58)	−4·60, −2·29	−0·32 (0·66)	−1·64, 1·00	0·6327
	10	16	−3·07 (0·56)	−4·19, −1·95	0·36 (0·63)	−0·90, 1·62	0·5726
	14	14	−4·08 (0·58)	−5·23, −2·92	−0·31 (0·66)	−1·63, 1·00	0·6339
SOF-DCV (N=35)	3	16	−1·30 (0·63)	−2·55, −0·04	0·14 (0·75)	−1·36, 1·65	0·8488
	7	15	−3·19 (0·58)	−4·35, −2·03	−0·06 (0·65)	−1·35, 1·23	0·9212
	10	16	−3·64 (0·56)	−4·76, −2·52	−0·21 (0·61)	−1·43, 1·00	0·7280
	14	16	−4·30 (0·56)	−5·42, −3·17	−0·54 (0·63)	−1·79, 0·71	0·3948

[a] Number of patients with available data at the respective time point.

mITT, modified intention-to-treat; SOC, standard-of-care; ASAQ, artesunate-amodiaquine; PA, pyronaridine-artesunate; FPV+NTZ, favipiravir plus nitazoxanide; SOF-DCV, sofosbuvir-daclatasvir. The mixed-effect linear model for repeated measures includes treatment, age at baseline (years), sex, body mass index at baseline, baseline comorbidities, baseline viral load category, days of symptoms at time of enrolment and treatment-by-visit interaction as fixed effects.

High risk was defined as age >60 years or body mass index >30 kg/m^2 plus the presence of at least one comorbidity for progression to severe disease.

Table S9 Proportional odds model for disease progression for day 7, 14, 21, and 28 (mITT population).

Day	Treatment arm	N	Comparison	Adjusted odds ratio (95%CI)	*P* value
7	SOC	39			
	ASAQ	39	ASAQ / SOC	0·41 (0·13, 1·31)	0·1317
	PA	36	PA / SOC	0·71 (0·22, 2·36)	0·5803
	FPV+NTZ	37	FPV+NTZ / SOC	1·12 (0·35, 3·61)	0·8480
	SOF-DCV	35	SOF-DCV / SOC	1·59 (0·48, 5·27)	0·4447
14	SOC	39			
	ASAQ	39	ASAQ / SOC	0·46 (0·11, 1·93)	0·2906
	PA	36	PA / SOC	0·33 (0·07, 1·56)	0·1613
	FPV+NTZ	37	FPV+NTZ / SOC	1·04 (0·28, 3·90)	0·9528
	SOF-DCV	35	SOF-DCV / SOC	1·87 (0·49, 7·13)	0·3577
21	SOC	39			
	ASAQ	39	ASAQ / SOC	1·88 (0·26,>9·99)	0·5292
	PA	36	PA / SOC	0·90 (0·10, 8·36)	0·9266
	FPV+NTZ	37	FPV+NTZ / SOC	3·18 (0·47,>9·99)	0·2354
	SOF-DCV	35	SOF-DCV / SOC	2·48 (0·33,>9·99)	0·3742
28	SOC	39			
	ASAQ	39	ASAQ / SOC	1·31 (0·29, 5·93)	0·7285
	PA	36	PA / SOC	0·29 (0·04, 2·06)	0·2172
	FPV+NTZ	37	FPV+NTZ / SOC	1·13 (0·23, 5·46)	0·8792
	SOF-DCV	35	SOF-DCV / SOC	1·43 (0·29, 6·94)	0·6597

WHO, world health organization; mITT, modified intention-to-treat; SOC, standard-of-care; ASAQ, artesunate-amodiaquine; PA, pyronaridine-artesunate; FPV+NTZ, favipiravir plus nitazoxanide; SOF-DCV, sofosbuvir-daclatasvir.

Disease severity was measured by WHO Ordinal Scale score for Clinical Improvement (ordered from 0<1<2<...<8). The longitudinal proportional odds model includes time point, treatment and treatment-by-time point interaction as fixed-effect factors. Baseline age (in years), sex, baseline BMI, baseline WHO Ordinal Scale score, baseline comorbidities, baseline viral load category and days of symptoms at time of enrolment are included as covariates. Participant-specific intercepts were included as random effects.

An adjusted odds ratio > 1 suggests a higher chance of more severe disease at the corresponding time point in the experimental treatment arm versus SOC.

Table S10 Cox regression analysis of time to first zero WHO Ordinal Scale score for Clinical Improvement (mITT population).

Treatment arm	N	n/M (%)	Comparison	Hazard ratio (95%CI)	*P* value
SOC	39	31/37 (83·8)			
ASAQ	39	32/39 (82·1)	ASAQ / SOC	1·29 (0·77, 2·16)	0·3270
PA	36	31/35 (88·6)	PA / SOC	1·45 (0·85, 2·46)	0·1712
FPV+NTZ	37	31/36 (86·1)	FPV+NTZ / SOC	0·81 (0·48, 1·37)	0·4220
SOF-DCV	35	28/35 (80·0)	SOF-DCV / SOC	0·77 (0·44, 1·34)	0·3515

WHO, world health organization; mITT, modified intention-to-treat; SOC, standard-of-care; ASAQ, artesunate-amodiaquine; PA, pyronaridine-artesunate; FPV+NTZ, favipiravir plus nitazoxanide; SOF-DCV, sofosbuvir-daclatasvir; n, number of participants with WHO Ordinal Scale for Clinical Improvement; M, number of evaluable participants.

The cox regression model includes treatment arm, age at baseline (years), sex, baseline BMI, baseline comorbidities, baseline viral load category and days of symptoms at time of enrolment as covariates. A hazard ratio > 1 favors the treatment arm in the numerator of the ratio (= higher probability of having zero WHO Ordinal Scale score).

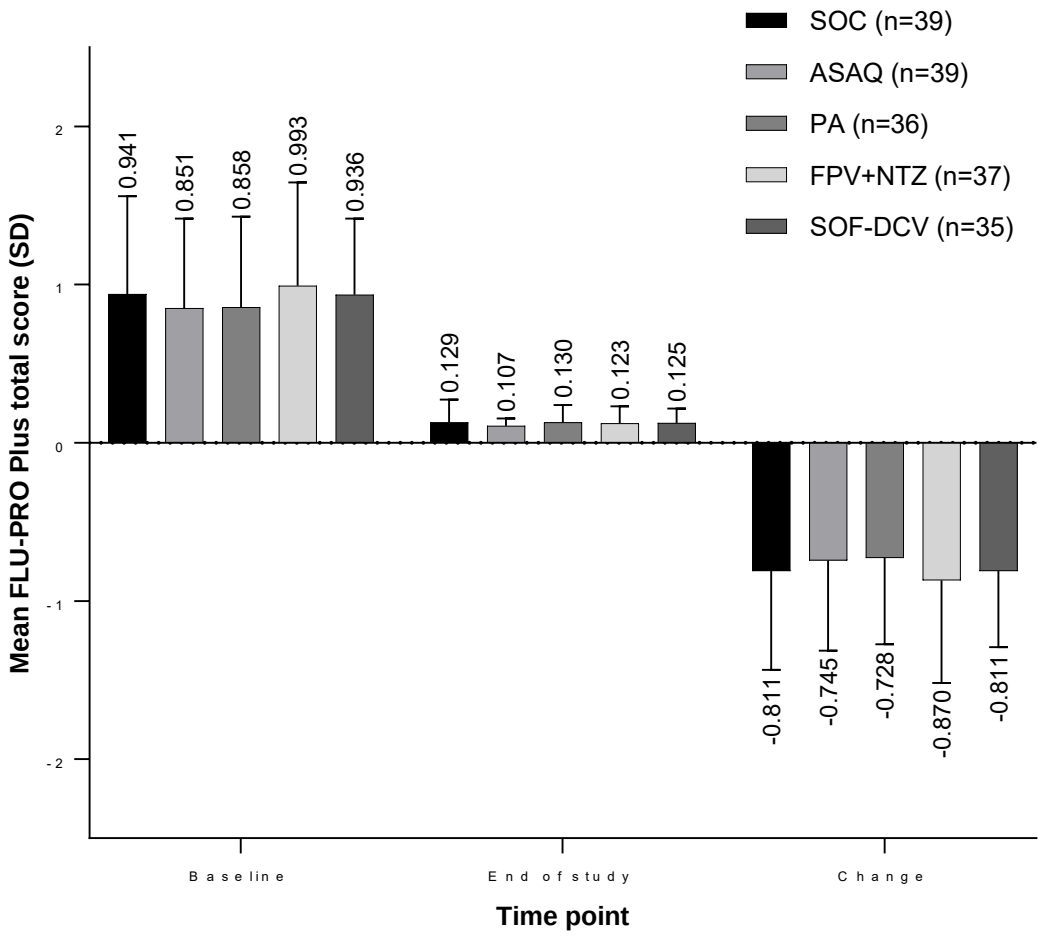
Table S11 Poisson regression analysis for the proportion of days with fever, SpO_2 values <93%, or respiratory symptoms after randomisation (mITT population).

Treatment arm	N	N days with symptoms	N days of observation	Raw rate	Rate estimate (95%CI)	Comparison	Rate ratio (95%CI)	*P* value
Days with fever								
SOC	39	3	503	0·596	0·248 (0·060, 1·028)			
ASAQ	39	0	552	0·000	<0·001 (<0·001, INFTY)	ASAQ / SOC	<0·001 (<0·001, INFTY)	0·9999
PA	36	8	462	1·732	0·695 (0·235, 2·052)	PA / SOC	2·805 (0·718, 10·951)	0·1379
FPV+NTZ	37	3	501	0·599	0·220 (0·055, 0·889)	FPV+NTZ / SOC	0·890 (0·166, 4·766)	0·8918
SOF-DCV	35	4	479	0·835	0·417 (0·114, 1·523)	SOF-DCV / SOC	1·685 (0·340, 8·342)	0·5226
SpO_2 <93%								
SOC	39	2	502	0·398	0·237 (0·040, 1·412)			
ASAQ	39	0	535	0·000	<0·001 (<0·001, INFTY)	ASAQ / SOC	<0·001 (<0·001, INFTY)	0·9999
PA	36	3	448	0·670	0·284 (0·048, 1·677)	PA / SOC	1·198 (0·175, 8·190)	0·8539
FPV+NTZ	37	1	500	0·200	0·129 (0·015, 1·070)	FPV+NTZ / SOC	0·543 (0·044, 6·767)	0·6353
SOF-DCV	35	1	480	0·208	0·116 (0·012, 1·108	SOF-DCV / SOC	0·491 (0·042, 5·718)	0·5702
Days with respiratory symptoms								
SOC	39	189	530	35·660	32·959 (28·252, 38·450)			
ASAQ	39	164	585	28·034	25·934 (22·134, 30·386)	ASAQ / SOC	0·787 (0·637, 0·972)	0·0262
PA	36	164	490	33·469	31·037 (26·451, 36·416)	PA / SOC	0·942 (0·759, 1·168)	0·5838
FPV+NTZ	37	156	527	29·602	28·085 (23·947, 32·937)	FPV+NTZ / SOC	0·852 (0·685, 1·061)	0·1519
SOF-DCV	35	179	507	35·306	35·005 (30·099, 40·711)	SOF-DCV / SOC	1·062 (0·858, 1·315)	0·5807

mITT, modified intention-to-treat; SOC, standard-of-care; ASAQ, artesunate-amodiaquine; PA, pyronaridine-artesunate; FPV+NTZ, favipiravir plus nitazoxanide; SOF-DCV, sofosbuvir-daclatasvir.

Raw rate was calculated as the number of days with fever / number of days of observation x 100. Rate estimate was derived by means of a Poisson regression model, adjusted to a 100 day period. The Poisson regression model contained treatment arm, age at baseline (years), sex, baseline body mass index, baseline comorbidities, baseline viral load category and days of symptoms at time of enrolment as covariates. For each participant the number of days of observation (i.e. days where temperature is non-missing) was used as offset. INFTY=estimated as positive infinity.

Figure S2 FLU-PRO Plus questionnaire scores and changes from baseline (mITT population).



mITT, modified intention-to-treat; SOC, standard-of-care; ASAQ, artesunate-amodiaquine; PA, pyronaridine-artesunate; FPV+NTZ, favipiravir plus nitazoxanide; SOF-DCV, sofosbuvir-daclatasvir.

Table S12 Investigational drug blood or plasma concentrations (pharmacokinetic population).

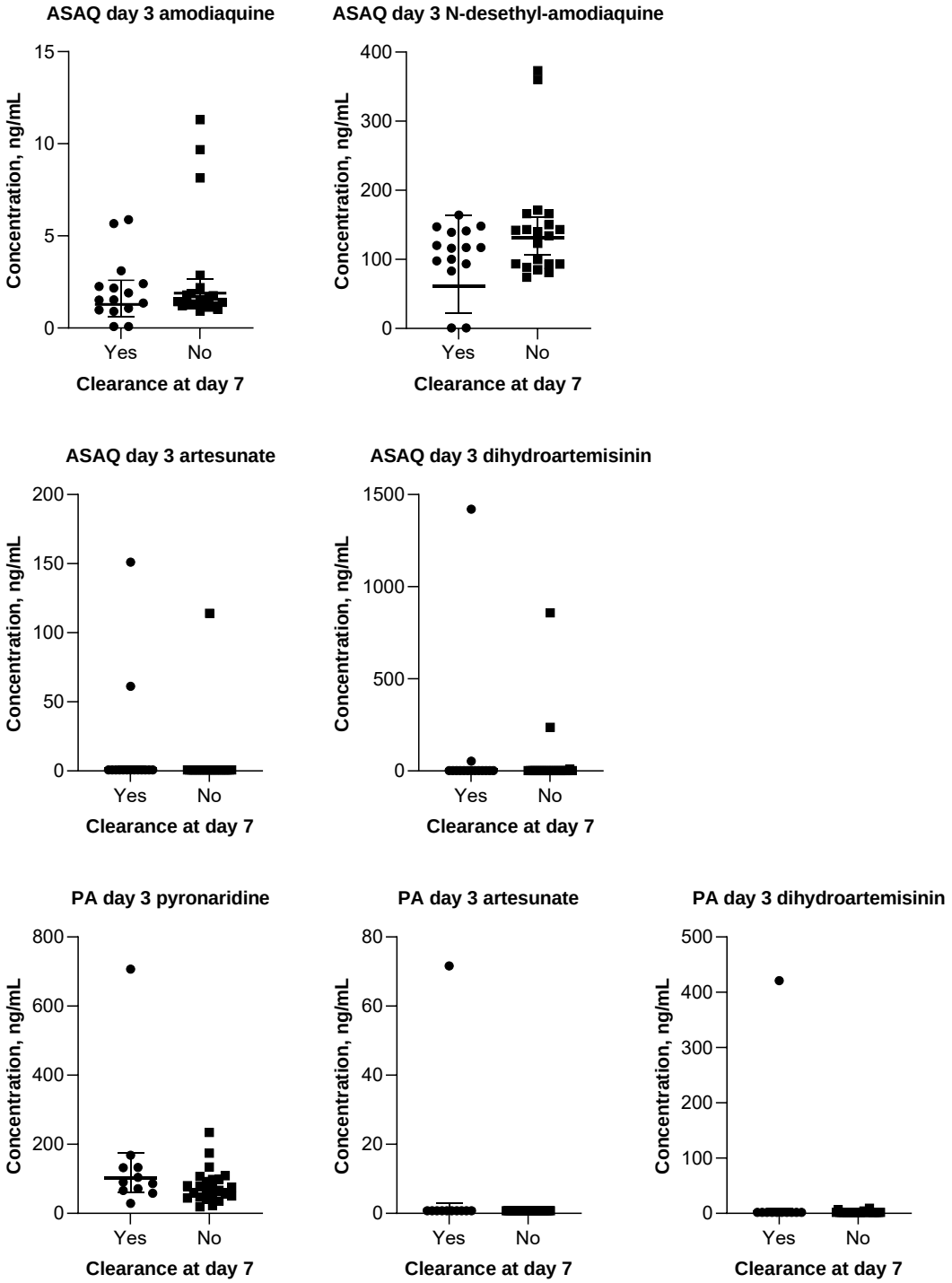
ASAQ (n=39) Day 3	n (%)	Mean	Geometric mean	SD	Minimum	Q1	Median	Q3	Maximum
Artesunate, ng/mL	37 (94·9)	9·533	1·158	31·7108	0·78	0·78	0·78	0·78	151
Dihydroartemisinin, ng/mL	37 (94·9)	71·369	3·586	269·9415	1·96	1·955	1·955	1·955	1420
Amodiaquine, ng/mL	36 (92·3)	2·4211	1·6137	2·54236	0·078	1·21	1·525	2·225	11·3
N-desethylamodiaquine, ng/mL	35 (89·7)	128·7	94·61	71·309	0·8	93·1	120	147	373
ASAQ (n=39) Day 7	**n (%)**	**Mean**	**Geometric mean**	**SD**	**Minimum**	**Q1**	**Median**	**Q3**	**Maximum**
Artesunate, ng/mL	38 (97·4)	0·78	0·78	0	0·78	0·78	0·78	0·78	0·78
Dihydroartemisinin, ng/mL	38 (97·4)	1·955	1·955	0	1·96	1·955	1·955	1·955	1·96
Amodiaquine, ng/mL	38 (97·4)	0·2104	0·1826	0·10385	0·078	0·078	0·215	0·266	0·44
N-desethylamodiaquine, ng/mL	38 (97·4)	67·24	53·21	27·734	0·8	52·00	69·10	87·20	142·0
PA (n=36) Day 3	**n (%)**	**Mean**	**Geometric mean**	**SD**	**Minimum**	**Q1**	**Median**	**Q3**	**Maximum**
Pyronaridine, ng/mL	35 (97·2)	101·67	77·34	114·817	19·2	50·6	76·6	107	707
Artesunate, ng/mL	36 (100)	2·747	0·884	11·8033	0·78	0·78	0·78	0·78	71·6
Dihydroartemisinin, ng/mL	36 (100)	13·996	2·508	69·7875	1·96	1·955	1·955	1·955	421
PA (n=36) Day 7	**n (%)**	**Mean**	**Geometric mean**	**SD**	**Minimum**	**Q1**	**Median**	**Q3**	**Maximum**
Pyronaridine, ng/mL	35 (97·2)	52·95	46·99	25·498	10·9	38	49·7	65·7	134
Artesunate, ng/mL	35 (97·2)	0·78	0·78	0	0·78	0·78	0·78	0·78	0·78
Dihydroartemisinin, ng/mL	35 (97·2)	1·955	1·955	0	1·96	1·955	1·955	1·955	1·96
FPV+NTZ (n=38) Day 7	**n (%)**	**Mean**	**Geometric mean**	**SD**	**Minimum**	**Q1**	**Median**	**Q3**	**Maximum**
Favipiravir, µg/mL	38 (100)	9639·2	1593·2	14658·34	196	195·5	439·8	15000	61800
Nitazoxanide, ng/mL	38 (100)	50	50	0	50	50	50	50	50
Tizoxanide, ng/mL	38 (100)	2118·1	472·8	3708·66	50	50	610	2260	17400
SOF-DCV (n=33) Day 7	**n (%)**	**Mean**	**Geometric mean**	**SD**	**Minimum**	**Q1**	**Median**	**Q3**	**Maximum**
Sofosbuvir, ng/mL	33 (100)	90·61	1·58	513·311	1·3	1·25	1·25	1·25	2950
Daclatasvir, ng/mL	33 (100)	590·88	316·04	679·044	7·8	208	452	674	3510

ASAQ, artesunate-amodiaquine; PA, pyronaridine-artesunate; FPV+NTZ, favipiravir plus nitazoxanide; SOF-DCV, sofosbuvir-daclatasvir. Drug plasma or blood levels in these samples were determined at a central site (FARMOVS, Bloemfontein, South Africa) using validated protocols (Supplementary appendix Table S2).

Figure S3 Drug plasma or blood concentrations at day 3 and day 7 in patients with or without SARS-CoV-2 clearance based on RT-PCR at day 7 (pharmacokinetic population).

Concentrations below the lower limit of quantification (LLOQ) were imputed with LLOQ/2.

mITT, modified intention-to-treat; SOC, standard-of-care; ASAQ, artesunate-amodiaquine; PA, pyronaridine-artesunate; FPV+NTZ, favipiravir plus nitazoxanide; SOF-DCV, sofosbuvir-daclatasvir.



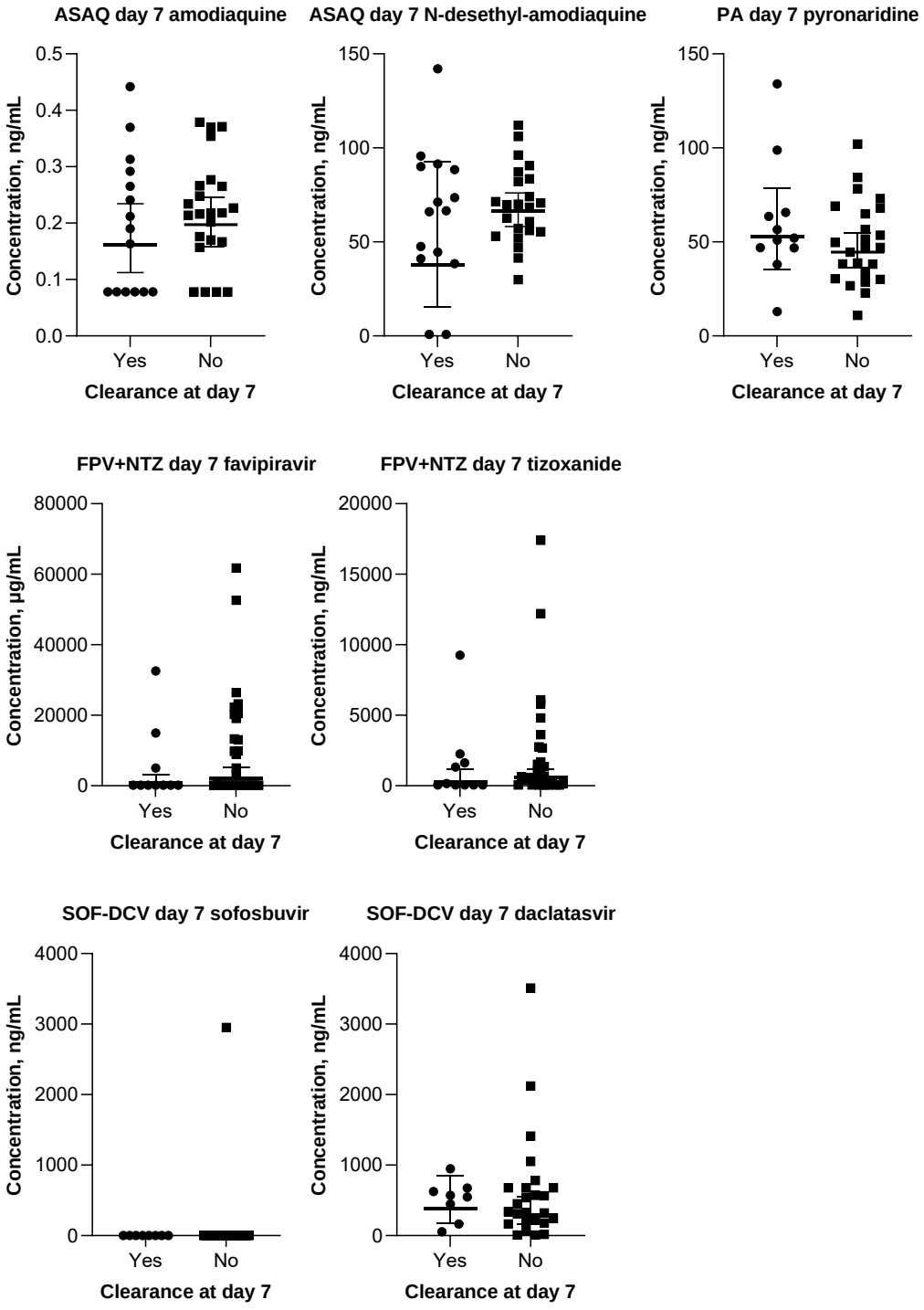

ASAQ day 7 amodiaquine
Concentration, ng/mL
0.5
0.4
0.3
0.2
0.1
0.0
Yes
No
Clearance at day 7
ASAQ day 7 N-desethyl-amodiaquine
Concentration, ng/mL
150
100
50
0
Yes
No
Clearance at day 7
PA day 7 pyronaridine
Concentration, ng/mL
150
100
50
0
Yes
No
Clearance at day 7
FPV+NTZ day 7 favipiravir
Concentration, µg/mL
80000
60000
40000
20000
0
Yes
No
Clearance at day 7
FPV+NTZ day 7 tizoxanide
Concentration, ng/mL
20000
15000
10000
5000
0
Yes
No
Clearance at day 7
SOF-DCV day 7 sofosbuvir
Concentration, ng/mL
4000
3000
2000
1000
0
Yes
No
Clearance at day 7
SOF-DCV day 7 daclatasvir
Concentration, ng/mL
4000
3000
2000
1000
0
Yes
No
Clearance at day 7

Table S13 Treatment emergent adverse events of any cause and maximum severity (safety population).

Primary system organ class Preferred term, n patients (%)	Severity grade	SOC (n=39)		ASAQ (n=39)		PA (n=38)		FPV+NTZ (n=38)		SOF-DCV (n=36)	
		Patients n (%)	Events	Patients n (%)	Events	Patients n (%)	Events	Patients n (%)	Events	Patients n (%)	Events
Any adverse event	Any	14 (35·9)	32	18 (46·2)	46	21 (55·3)	48	31 (81·6)	77	21 (58·3)	35
Patients may have had more than	Grade 1	13 (33·3)	28	18 (46·2)	39	20 (52·6)	44	31 (81·6)	67	18 (50·0)	30
one adverse event, worst adverse	Grade 2	1 (2·6)	2	4 (10·3)	7	3 (7·9)	3	6 (15·8)	9	4 (11·1)	4
event was counted in any category	Grade 3	2 (5·1)	2	0	0	1 (2·6)	1	0	0	1 (2·8)	1
	Grade 4	0	0	0	0	0	0	1 (2·6)	1	0	0
	Grade 5	0	0	0	0	0	0	0	0	0	0
Blood and lymphatic system disorders	Any	0	0	0	0	0	0	1 (2·6)	1	0	0
	Grade 4	0	0	0	0	0	0	1 (2·6)	1	0	0
Pancytopenia	Grade 4	0	0	0	0	0	0	1 (2·6)	1	0	0
Cardiac disorders	Any	0	0	0	0	1 (2·6)	1	0	0	0	0
	Grade 1	0	0	0	0	1 (2·6)	1	0	0	0	0
Sinus tachycardia	Grade 1	0	0	0	0	1 (2·6)	1	0	0	0	0
Ear and labyrinth disorders	Any	0	0	1 (2·6)	1	0	0	0	0	0	0
	Grade 1	0	0	1 (2·6)	1	0	0	0	0	0	0
Tinnitus	Grade 1	0	0	1 (2·6)	1	0	0	0	0	0	0
Eye disorders	Any	1 (2·6)	1	2 (5·1)	2	2 (5·3)	4	3 (7·9)	3	4 (11·1)	4
	Grade 1	1 (2·6)	1	2 (5·1)	2	2 (5·3)	4	3 (7·9)	3	4 (11·1)	4
Photophobia	Grade 1	1 (2·6)	1	0	0	1 (2·6)	1	0	0	0	0
Xerophthalmia	Grade 1	0	0	1 (2·6)	1	1 (2·6)	1	0	0	0	0
Conjunctival discoloration	Grade 1	0	0	0	0	0	0	1 (2·6)	1	0	0
Conjunctivitis allergic	Grade 1	0	0	0	0	0	0	0	0	1 (2·8)	1
Eye pain	Grade 1	0	0	0	0	0	0	1 (2·6)	1	0	0
Eye pruritus	Grade 1	0	0	0	0	1 (2·6)	1	0	0	0	0
Eye swelling	Grade 1	0	0	0	0	0	0	0	0	1 (2·8)	1
Iris discoloration	Grade 1	0	0	0	0	0	0	1 (2·6)	1	0	0
Ocular hyperaemia	Grade 1	0	0	0	0	0	0	0	0	1 (2·8)	1
Orbital oedema	Grade 1	0	0	0	0	1 (2·6)	1	0	0	0	0

Primary system organ class Preferred term, n patients (%)	Severity grade	SOC (n=39)		ASAQ (n=39)		PA (n=38)		FPV+NTZ (n=38)		SOF-DCV (n=36)	
		Patients n (%)	Events	Patients n (%)	Events	Patients n (%)	Events	Patients n (%)	Events	Patients n (%)	Events
Periorbital swelling	Grade 1	0	0	1 (2·6)	1	0	0	0	0	0	0
Vision blurred	Grade 1	0	0	0	0	0	0	0	0	1 (2·8)	1
Gastrointestinal disorders	Any	11 (28·2)	17	12 (30·8)	18	13 (34·2)	19	22 (57·9)	31	9 (25·0)	12
	Grade 1	10 (25·6)	16	12 (30·8)	17	13 (34·2)	18	21 (55·3)	29	8 (22·2)	11
	Grade 2	0	0	1 (2·6)	1	1 (2·6)	1	2 (5·3)	2	1 (2·8)	1
	Grade 3	1 (2·6)	1	0	0	0	0	0	0	0	0
Nausea	Any	2 (5·1)	2	6 (15·4)	6	4 (10·5)	4	8 (21·1)	8	4 (11·1)	4
	Grade 1	2 (5·1)	2	6 (15·4)	6	3 (7·9)	3	8 (21·1)	8	4 (11·1)	4
	Grade 2	0	0	0	0	1 (2·6)	1	0	0	0	0
Diarrhoea	Any	5 (12·8)	5	3 (7·7)	3	3 (7·9)	3	7 (18·4)	7	4 (11·1)	4
	Grade 1	4 (10·3)	4	3 (7·7)	3	3 (7·9)	3	6 (15·8)	6	3 (8·3)	3
	Grade 2	0	0	0	0	0	0	1 (2·6)	1	1 (2·8)	1
	Grade 3	1 (2·6)	1	0	0	0	0	0	0	0	0
Abdominal pain	Any	2 (5·1)	2	2 (5·1)	2	4 (10·5)	4	8 (21·1)	8	2 (5·6)	2
	Grade 1	2 (5·1)	2	2 (5·1)	2	4 (10·5)	4	7 (18·4)	7	2 (5·6)	2
	Grade 2	0	0	0	0	0	0	1 (2·6)	1	0	0
Vomiting	Any	4 (10·3)	4	5 (12·8)	5	5 (13·2)	5	2 (5·3)	2	1 (2·8)	1
	Grade 1	4 (10·3)	4	4 (10·3)	4	5 (13·2)	5	2 (5·3)	2	1 (2·8)	1
	Grade 2	0	0	1 (2·6)	1	0	0	0	0	0	0
Constipation	Grade 1	2 (5·1)	2	0	0	0	0	1 (2·6)	1	0	0
Mouth ulceration	Grade 1	1 (2·6)	1	0	0	2 (5·3)	2	0	0	0	0
Dyspepsia	Grade 1	1 (2·6)	1	0	0	1 (2·6)	1	0	0	0	0
Haemorrhoids	Grade 1	0	0	0	0	0	0	2 (5·3)	2	0	0
Abdominal distension	Grade 1	0	0	0	0	0	0	0	0	1 (2·8)	1
Abdominal pain upper	Grade 1	0	0	1 (2·6)	1	0	0	0	0	0	0
Dry mouth	Grade 1	0	0	1 (2·6)	1	0	0	0	0	0	0
Flatulence	Grade 1	0	0	0	0	0	0	1 (2·6)	1	0	0
Gastrooesophageal reflux disease	Grade 1	0	0	0	0	0	0	1 (2·6)	1	0	0
Mouth swelling	Grade 1	0	0	0	0	0	0	1 (2·6)	1	0	0

Primary system organ class Preferred term, n patients (%)	Severity grade	SOC (n=39)		ASAQ (n=39)		PA (n=38)		FPV+NTZ (n=38)		SOF-DCV (n=36)	
		Patients n (%)	Events	Patients n (%)	Events	Patients n (%)	Events	Patients n (%)	Events	Patients n (%)	Events
General disorders and administration site conditions	Any	2 (5·1)	2	4 (10·3)	4	1 (2·6)	1	0	0	1 (2·8)	1
	Grade 1	2 (5·1)	2	4 (10·3)	4	1 (2·6)	1	0	0	1 (2·8)	1
Chest discomfort	Grade 1	0	0	2 (5·1)	2	0	0	0	0	0	0
Chest pain	Grade 1	2 (5·1)	2	0	0	0	0	0	0	0	0
Axillary pain	Grade 1	0	0	0	0	0	0	0	0	1 (2·8)	1
Chills	Grade 1	0	0	1 (2·6)	1	0	0	0	0	0	0
Vessel puncture site haematoma	Grade 1	0	0	0	0	1 (2·6)	1	0	0	0	0
Vessel puncture site pain	Grade 1	0	0	1 (2·6)	1	0	0	0	0	0	0
Immune system disorders	Any	0	0	0	0	1 (2·6)	1	0	0	0	0
	Grade 1	0	0	0	0	1 (2·6)	1	0	0	0	0
Seasonal allergy	Grade 1	0	0	0	0	1 (2·6)	1	0	0	0	0
Infections and infestations	Any	1 (2·6)	1	2 (5·1)	2	3 (7·9)	4	5 (13·2)	5	3 (8·3)	3
	Grade 1	1 (2·6)	1	1 (2·6)	1	3 (7·9)	3	4 (10·5)	4	2 (5·6)	2
	Grade 2	0	0	1 (2·6)	1	1 (2·6)	1	1 (2·6)	1	1 (2·8)	1
Upper respiratory tract infection	Grade 1	0	0	0	0	3 (7·9)	3	0	0	1 (2·8)	1
Lower respiratory tract infection	Grade 2	0	0	1 (2·6)	1	1 (2·6)	1	0	0	0	0
Vulvovaginal candidiasis	Grade 1	0	0	0	0	0	0	2 (5·3)	2	0	0
COVID-19 pneumonia	Grade 2	0	0	0	0	0	0	0	0	1 (2·8)	1
Conjunctivitis	Grade 1	0	0	0	0	0	0	1 (2·6)	1	0	0
Ear infection	Grade 1	1 (2·6)	1	0	0	0	0	0	0	0	0
Furuncle	Grade 1	0	0	0	0	0	0	1 (2·6)	1	0	0
Gingivitis	Grade 1	0	0	0	0	0	0	0	0	1 (2·8)	1
HIV infection	Grade 2	0	0	0	0	0	0	1 (2·6)	1	0	0
Periodontitis	Grade 1	0	0	1 (2·6)	1	0	0	0	0	0	0
Injury, poisoning and procedural complications	Any	0	0	1 (2·6)	1	0	0	0	0	1 (2·8)	1
	Grade 1	0	0	1 (2·6)	1	0	0	0	0	1 (2·8)	1
Procedural dizziness	Grade 1	0	0	1 (2·6)	1	0	0	0	0	0	0
Soft tissue injury	Grade 1	0	0	0	0	0	0	0	0	1 (2·8)	1
Metabolism and nutrition disorders	Any	0	0	1 (2·6)	1	0	0	1 (2·6)	1	0	0

Primary system organ class Preferred term, n patients (%)	Severity grade	SOC (n=39)		ASAQ (n=39)		PA (n=38)		FPV+NTZ (n=38)		SOF-DCV (n=36)	
		Patients n (%)	Events	Patients n (%)	Events	Patients n (%)	Events	Patients n (%)	Events	Patients n (%)	Events
	Grade 1	0	0	1 (2·6)	1	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0	1 (2·6)	1	0	0
Decreased appetite	Grade 1	0	0	1 (2·6)	1	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0	1 (2·6)	1	0	0
Musculoskeletal and connective tissue disorders	Any	0	0	3 (7·7)	3	0	0	5 (13·2)	5	0	0
	Grade 1	0	0	2 (5·1)	2	0	0	5 (13·2)	5	0	0
	Grade 2	0	0	1 (2·6)	1	0	0	0	0	0	0
Back pain	Any	0	0	3 (7·7)	3	0	0	2 (5·3)	2	0	0
	Grade 1	0	0	2 (5·1)	2	0	0	2 (5·3)	2	0	0
	Grade 2	0	0	1 (2·6)	1	0	0	0	0	0	0
Muscle spasms	Grade 1	0	0	0	0	0	0	2 (5·3)	2	0	0
Pain in jaw	Grade 1	0	0	0	0	0	0	1 (2·6)	1	0	0
Nervous system disorders	Any	4 (10·3)	5	4 (10·3)	6	12 (31·6)	12	7 (18·4)	9	5 (13·9)	8
	Grade 1	4 (10·3)	5	4 (10·3)	5	11 (28·9)	11	6 (15·8)	8	4 (11·1)	6
	Grade 2	0	0	1 (2·6)	1	1 (2·6)	1	1 (2·6)	1	2 (5·6)	2
Dizziness	Any	4 (10·3)	4	2 (5·1)	2	9 (23·7)	9	4 (10·5)	4	3 (8·3)	4
	Grade 1	4 (10·3)	4	2 (5·1)	2	8 (21·1)	8	3 (7·9)	3	3 (8·3)	3
	Grade 2	0	0	0	0	1 (2·6)	1	1 (2·3)	1	1 (2·8)	1
Headache	Any	0	0	3 (7·7)	3	2 (5·3)	2	3 (7·9)	3	3 (8·3)	3
	Grade 1	0	0	2 (5·1)	2	2 (5·3)	2	3 (7·9)	3	3 (8·3)	3
	Grade 2	0	0	1 (2·6)	1	0	0	0	0	0	0
Paraesthesia	Grade 1	1 (2·6)	1	0	0	1 (2·6)	1	1 (2·6)	1	0	0
Somnolence	Grade 1	0	0	0	0	0	0	1 (2·6)	1	0	0
Syncope	Grade 2	0	0	0	0	0	0	0	0	1 (2·8)	1
Tremor	Grade 1	0	0	1 (2·6)	1	0	0	0	0	0	0
Psychiatric disorders	Any	1 (2·6)	2	4 (10·3)	4	1 (2·6)	2	1 (2·6)	2	0	0
	Grade 1	0	0	2 (5·1)	2	1 (2·6)	2	0	0	0	0
	Grade 2	1 (2·6)	1	2 (5·1)	2	0	0	1 (2·6)	2	0	2
	Grade 3	1 (2·6)	1	0	0	0	0	0	0	0	0

Primary system organ class Preferred term, n patients (%)	Severity grade	SOC (n=39)		ASAQ (n=39)		PA (n=38)		FPV+NTZ (n=38)		SOF-DCV (n=36)	
		Patients n (%)	Events	Patients n (%)	Events	Patients n (%)	Events	Patients n (%)	Events	Patients n (%)	Events
Insomnia	Any	0	0	3 (7·7)	3	1 (2·6)	1	0	0	0	0
	Grade 1	0	0	2 (5·1)	2	1 (2·6)	1	0	0	0	0
	Grade 2	0	0	1 (2·6)	1	0	0	0	0	0	0
Anxiety	Grade 1	0	0	0	0	1 (2·6)	1	0	0	0	0
	Grade 2	0	0	0	0	0	0	1 (2·6)	1	0	0
Panic attack	Grade 2	0	0	1 (2·6)	1	0	0	1 (2·6)	1	0	0
Depression	Grade 2	1 (2·6)	1	0	0	0	0	0	0	0	0
Suicidal ideation	Grade 3	1 (2·6)	1	0	0	0	0	0	0	0	0
Renal and urinary disorders	Any	0	0	0	0	1 (2·6)	1	11 (28·9)	12	0	0
	Grade 1	0	0	0	0	1 (2·6)	1	11 (28·9)	12	0	0
Chromaturia	Grade 1	0	0	0	0	1 (2·6)	1	11 (28·9)	12	0	0
Reproductive system and breast disorders	Any	1 (2·6)	1	0	0	0	0	3 (7·9)	4	0	0
	Grade 1	1 (2·6)	1	0	0	0	0	1 (2·6)	2	0	0
	Grade 2	0	0	0	0	0	0	2 (5·3)	2	0	0
Breast discoloration	Grade 2	0	0	0	0	0	0	1 (2·6)	1	0	0
Breast pain	Grade 1	1 (2·6)	1	0	0	0	0	0	0	0	0
Prostatitis	Grade 1	0	0	0	0	0	0	1 (2·6)	1	0	0
Semen discoloration	Grade 1	0	0	0	0	0	0	1 (2·6)	1	0	0
Uterine haemorrhage	Grade 2	0	0	0	0	0	0	1 (2·6)	1	0	0
Respiratory, thoracic and mediastinal disorders	Any	2 (5·1)	2	2 (5·1)	3	3 (7·9)	3	3 (7·9)	4	4 (11·1)	4
	Grade 1	2 (5·1)	2	2 (5·1)	2	2 (5·3)	2	3 (7·9)	4	3 (8·3)	3
	Grade 2	0	0	1 (2·6)	1	0	0	0	0	0	0
	Grade 3	0	0	0	0	1 (2·6)	1	0	0	1 (2·8)	1
Oropharyngeal pain	Grade 1	1 (2·6)	1	0	0	0	0	2 (5·3)	2	0	0
Respiratory distress	Any	0	0	1 (2·6)	1	1 (2·6)	1	0	0	1 (2·8)	1
	Grade 2	0	0	1 (2·6)	1	0	0	0	0	0	0
	Grade 3	0	0	0	0	1 (2·6)	1	0	0	1 (2·8)	1
Epistaxis	Grade 1	0	0	0	0	0	0	1 (2·6)	1	1 (2·8)	1
Nasal congestion	Grade 1	0	0	1 (2·6)	1	0	0	1 (2·6)	1	0	0

Primary system organ class Preferred term, n patients (%)	Severity grade	SOC (n=39)		ASAQ (n=39)		PA (n=38)		FPV+NTZ (n=38)		SOF-DCV (n=36)	
		Patients n (%)	Events	Patients n (%)	Events	Patients n (%)	Events	Patients n (%)	Events	Patients n (%)	Events
Rhinitis allergic	Grade 1	0	0	0	0	1 (2·6)	1	0	0	1 (2·8)	1
Dyspnoea	Grade 1	0	0	0	0	0	0	0	0	1 (2·8)	1
Hiccups	Grade 1	0	0	0	0	1 (2·6)	1	0	0	0	0
Rhinorrhoea	Grade 1	1 (2·6)	1	0	0	0	0	0	0	0	0
Throat irritation	Grade 1	0	0	1 (2·6)	1	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	Any	0	0	1 (2·6)	1	0	0	0	0	1 (2·8)	1
	Grade 1	0	0	1 (2·6)	1	0	0	0	0	1 (2·8)	1
Ecchymosis	Grade 1	0	0	1 (2·6)	1	0	0	0	0	0	0
Rash vesicular	Grade 1	0	0	0	0	0	0	0	0	1 (2·8)	1
Vascular disorders	Any	1 (2·6)	1	0	0	0	0	0	0	1 (2·8)	1
	Grade 1	0	0	0	0	0	0	0	0	1 (2·8)	1
	Grade 2	1 (2·6)	1	0	0	0	0	0	0	0	0
Hot flush	Grade 1	0	0	0	0	0	0	0	0	1 (2·8)	1
Hypertension	Grade 2	1 (2·6)	1	0	0	0	0	0	0	0	0

SOC, standard-of-care; ASAQ, artesunate-amodiaquine; PA, pyronaridine-artesunate; FPV+NTZ, favipiravir plus nitazoxanide; SOF-DCV, sofosbuvir-daclatasvir.

MedDRA version 23·0 was used for coding adverse events.

Table S13 Treatment emergent adverse events considered to be study drug related (safety population).

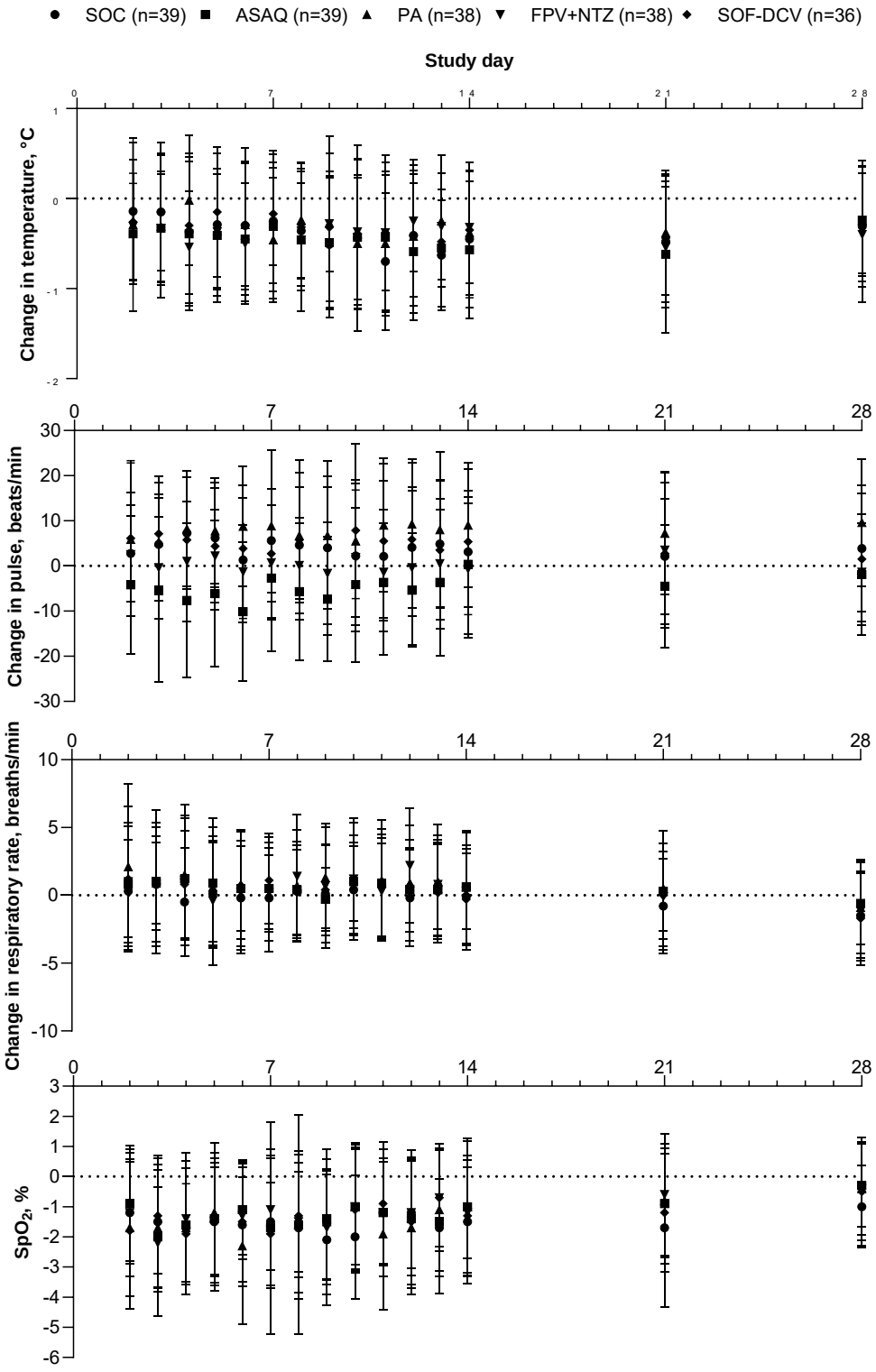
Primary system organ class Preferred term, n patients (%)	SOC (n=39)	ASAQ (n=39)	PA (n=38)	FPV+NTZ (n=38)	SOF-DCV (n=36)
Any drug-related adverse event	0	11 (28·2)	12 (31·6)	21 (55·3)	10 (27·8)
Ear and labyrinth disorders	0	1 (2·6)	0	0	0
Tinnitus	0	1 (2·6)	0	0	0
Eye disorders	0	0	0	1 (2·6)	1 (2·8)
Conjunctival discoloration	0	0	0	1 (2·6)	0
Vision blurred	0	0	0	0	1 (2·8)
Gastrointestinal disorders	0	9 (23·1)	9 (23·7)	16 (42·1)	8 (22·2)
Nausea	0	5 (12·8)	3 (7·9)	7 (18·4)	4 (11·1)
Diarrhoea	0	3 (7·7)	2 (5·3)	6 (15·8)	2 (5·6)
Abdominal pain	0	1 (2·6)	2 (5·3)	6 (15·8)	2 (5·6)
Vomiting	0	3 (7·7)	4 (10·5)	2 (5·3)	1 (2·8)
Abdominal distension	0	0	0	0	1 (2·8)
Abdominal pain upper	0	1 (2·6)	0	0	0
Gastrooesophageal reflux disease	0	0	0	1 (2·6)	0
Nervous system disorders	0	2 (5·1)	7 (18·4)	4 (10·5)	2 (5·6)
Dizziness	0	2 (5·1)	6 (15·8)	3 (7·9)	2 (5·6)
Headache	0	1 (2·6)	1 (2·6)	1 (2·6)	2 (5·6)
Psychiatric disorders	0	2 (5·1)	0	0	0
Insomnia	0	2 (5·1)	0	0	0
Renal and urinary disorders	0	0	0	11 (28·9)	0
Chromaturia	0	0	0	11 (28·9)	0
Reproductive and breast system disorders	0	0	0	1 (2·6)	0
Semen discolouration	0	0	0	1 (2·6)	0
Vascular disorders	0	0	0	0	1 (2·8)
Hot flush	0	0	0	0	1 (2·8)

Data are number of patients with an adverse event / total number of patients (%). Patients may have had more than one adverse event.

SOC, standard-of-care; ASAQ, artesunate-amodiaquine; PA, pyronaridine-artesunate; FPV+NTZ, favipiravir plus nitazoxanide; SOF-DCV, sofosbuvir-daclatasvir.

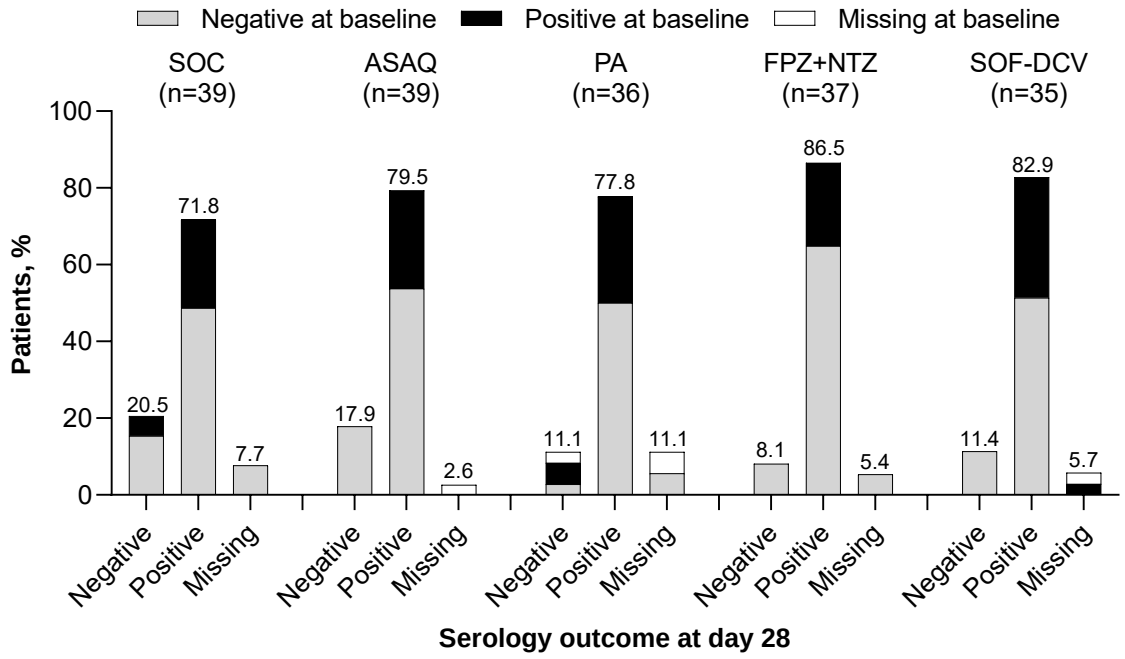
MedDRA version 23.0 was used for coding adverse events.

Figure S4 Change in vital signs from baseline (safety population).



SOC, standard-of-care; ASAQ, artesunate-amodiaquine; PA, pyronaridine-artesunate; FPV+NTZ, favipiravir plus nitazoxanide; SOF-DCV, sofosbuvir-daclatasvir.

Figure S5 Shift from baseline to day 28 in serology (mITT population).



mITT, modified intention-to-treat; SOC, standard-of-care; ASAQ, artesunate-amodiaquine; PA, pyronaridine-artesunate; FPV+NTZ, favipiravir plus nitazoxanide; SOF-DCV, sofosbuvir-daclatasvir.