https://doi.org/10.1038/s41591-026-04402-w

Extended Data Table 1 | Final population pharmacokinetic model for favipiravir and ribavirin

Drug	Pharmacokinetic parameter	Estimate	95 % CI
Favipiravir	Clearance: CL = Θ_{CL} * (WT/62.5) ^{COVWT} [L/h]		
	Θ_{CL}	2.42	1.94; 2.81
	ω_{IIV} CL	40.8 %CV	24.1; 53.5
	COV_{WT}	1.18	0.170; 1.99
	Central volume of distribution: V = Θ_V [L]		
	Θ_V	41.5	35.1; 49.9
	Absorption constant: ka = Θ_{ka} [h^{-1}]		
	Θ_{ka}	1.65	1.05; 3.24
	ω_{IOV} ka	207.7 %CV	114.9; 519.0
	Absorption lag-time: ALAG = Θ_{ALAG} [h]		
	Θ_{ALAG}	0.316	0.176; 0.446
	ω_{IIV} ALAG	38.3 %CV	7.0; 92.0
	Bioavailability: F = Θ_F		
	ω_{IOV} F	32.8 %CV	22.0; 40.7
	Residual variability		
	$\sigma_{proportional}$	30.2 %CV	26.8; 33.7
Ribavirin	Clearance: CL = Θ_{CL} * (1 + COV_{SEX}) [L/h]		
	Θ_{CL}	10.9	7.06; 12.8
	ω_{IIV} CL	30.7 %CV	14.0; 49.5
	COV_{SEX} (if female) [-]	-0.366	-0.593; -0.137
	Central volume of distribution: V1 = Θ_{V1} [L]		
	Θ_{V1}	34.4	15.7; 55.1
	ω_{IIV} V1	44.1%CV	11.4; 95.7
	Peripheral volume of distribution: V2 = Θ_{V2} [L]		
	Θ_{V2}	929	560; 2194
	Peripheral volume of distribution: V3 = Θ_{V3} [L]		
	Θ_{V3}	96.8	17.1; 153
	Distribution clearance for V2: Q2 = Θ_{Q2} [L/h]		
	Θ_{Q2}	14.6	11.4; 22.0
	ω_{IIV} Q2	41.5 %CV	20.0; 60.0
	Distribution clearance for V3: Q3 = Θ_{Q3} [L/h]		
	Θ_{Q3}	23.0	7.51; 31.2
	Residual variability		
	$\sigma_{proportional}$	26.4 %CV	17.0; 32.1

Typical pharmacokinetic parameters (Θ), unexplained interindividual variability (ωIIV) of the pharmacokinetic parameters and residual variability of individually predicted vs observed favipiravir concentrations (σ). ω is calculated from the estimated variance of the log-normal distribution $\omega = \sqrt{e^{\omega^2} - 1}$.

https://doi.org/10.1038/s41591-026-04402-w

Extended Data Table 2 | Summary of treatment-emergent adverse events according to their relatedness with the study drugs

TEAEs at least possibly related	Favipiravir N=16 TEAEs	Ribavirin N=14 TEAEs
Duration in days (Median [IQR]) [1]	2 (0-10)	7 (1-10)
Severity (n [%])		
Mild (grade 1)	13 (81.3)	10 (71.2)
Moderate (grade 2)	3 (18.7)	3 (21.4)
Severe (grade 3)	0	0
Life-threatening (grade 4)	0	1 (7.1) [2]
Death (grade 5)	0	0
Seriousness (n [%])	0	1 (7.1) [2]
Relatedness with study drug (n [%])		
Certain	0	0
Probable/likely	1 (6.3)	2 (14.3)
Possible	15 (93.7)	12 (85.7)
TEAEs unlikely related	**Favipiravir N=29 TEAEs**	**Ribavirin N=27 TEAEs**
Duration in days (Median [IQR]) [1]	5.5 (2-10)	4 (1-10)
Severity (n [%])		
Mild (grade 1)	22 (75.9)	19 (70.4)
Moderate (grade 2)	7 (24.1)	8 (29.6)
Severe (grade 3)	0	0
Life-threatening (grade 4)	0	0
Death (grade 5)	0	0
Seriousness (n [%])	0	0
Relatedness with study drug (n [%])		
Unlikely	29 (100)	27 (100)

IQR, interquartile range; TEAE, treatment-emergent adverse event. [1] During active follow-up period. [2] Anemia graded as life-threatening also reported as a Serious Adverse Event. Blood transfusion required.

https://doi.org/10.1038/s41591-026-04402-w

Extended Data Table 3 | List of concomitant medications according to the WHODrug Koda[1] preferred term

WHODrug Koda preferred term	Favipiravir (N=20 participants)	Ribavirin (N=21 participants)
	n (%)	n (%)
Albumin human	4 (20.0)	2 (9.5)
Alpha-beta arteether	1 (5.0)	2 (9.5)
Amino acids and vitamins	7 (35.0)	12 (57.1)
Amlodipine	1 (5.0)	4 (19.1)
Amodiaquine	1 (5.0)	3 (14.3)
Amoxicillin	3 (15.0)	1 (4.8)
Artemether	1 (5.0)	3 (14.3)
Artesunate	3 (15.0)	1 (4.8)
Bendroflumethiazide	1 (5.0)	0
Bisacodyl	1 (5.0)	0
Bromazepam	0	1 (4.8)
Carbamazepine	0	1 (4.8)
Ceftriaxone	14 (70.0)	17 (81.0)
Dabigatran	0	1 (4.8)
Dexamethasone	1 (5.0)	2 (9.5)
Dextrose 5% + NaCl 0.9%	1 (5.0)	0
Ferrous sulfate	1 (5.0)	2 (9.5)
Folic acid	1 (5.0)	1 (4.8)
Furosemide	1 (5.0)	0
Gentamicin	1 (5.0)	0
Iron supplement with amino acids and vitamin B complex	8 (40.0)	14 (66.7)
Levofloxacin	0	1 (4.8)
Lisinopril	1 (5.0)	3 (14.3)
Metformin	1 (5.0)	2 (9.5)
Methyldopa	1 (5.0)	0
Metoclopramide	5 (25.0)	5 (23.8)
Metronidazole	7 (35.0)	8 (38.1)
Omeprazole	11 (55.0)	14 (66.7)
Ondansetron	2 (10.0)	2 (9.5)
Orphenadrine	1 (5.0)	0
Paracetamol	9 (45.0)	7 (33.3)
Potassium chloride	7 (35.0)	6 (28.6)
Promethazine	2 (10.0)	2 (9.5)
Rabeprazole	1 (5.0)	0
Tramadol	1 (5.0)	1 (4.8)
Tranexamic acid	4 (20.0)	1 (4.8)
Vitamin B complex	0	2 (9.5)

[1] Uppsala Monitoring Centre. *WHODrug Koda API*, March 2024. Uppsala, Sweden: UMC.

https://doi.org/10.1038/s41591-026-04402-w

Extended Data Table 4 | Structural linear mixed effect model for Ct values from *GPC* and *L* genes

LASV Gene	Pharmacodynamic parameter	Estimate	95 % CI
***GPC* gene**	Intercept: Ct_0 [-]		
	Θ_{Ct0}	**34.5**	**33.5; 35.6**
	ω_{IIV} Ct_0	8.4 %CV	5.4; 10.9
	Slope: α [/h]		
	$\Theta_{\alpha,\ ribavirin}$	0.0714	0.0496; 0.1047
	$\Theta_{\alpha,\ favipiravir}$	**0.0467**	**0.0346; 0.0597**
	ω_{IIV} α	35.9 %CV	22.5; 52.7
	Covariance		
	ω_{IIV} Ct_0, α	0.0134 (44 %CV)	-0.0082; 0.0275
	Residual variability		
	$\sigma_{proportional}$	9.0 %CV	7.9; 10.1
***L* gene**	Intercept: Ct_0 [-]		
	Θ_{Ct0}	**35.5**	**34.3; 37.1**
	ω_{IIV} Ct_0	9.7 %CV	6.3; 18.2
	Slope: α [/h]		
	$\Theta_{\alpha,\ ribavirin}$	0.0937	0.0686; 0.1360
	$\Theta_{\alpha,\ favipiravir}$	**0.0606**	**0.0401; 0.0954**
	ω_{IIV} α	34.6 %CV	13.6; 49.9
	Covariance		
	ω_{IIV} Ct_0, α	0.00748 (22 %CV)	-0.02639; 0.02964
	Residual variability		
	$\sigma_{proportional}$	10.6 %CV	8.7; 12.4

Typical pharmacokinetic parameters (Θ), Unexplained Interindividual Variability (ωIIV) of the pharmacodynamic parameters and residual variability of individually predicted vs observed Ct value. ω is calculated from the estimated variance of the normal distribution $\omega = \sqrt{\omega^2}$.

https://doi.org/10.1038/s41591-026-04402-w

Extended Data Table 5 | Simulated dosing regimens

Regimen	Loading dose (day 1)	Maintenance dose (day 2-10)
R0 -study regimen	2400mg - 2400mg - 1200mg	1200mg BID
R1	**2400mg BID**	**1200mg BID**
R2	2400mg BID	1400mg BID
R3*	**2400mg BID**	**1600mg BID**
R4	2400mg BID	1800mg BID
R5	**2400mg BID**	**2000mg BID**
R6	2400mg BID	2400mg BID
R7	**2000mg BID**	**1200mg BID**
R8	2000mg BID	1600mg BID
R9	**2000mg BID**	**1800mg BID**
R10	2000mg BID	2000mg BID

* Regimen proposed for further clinical development. BID, twice daily; R, regimen.

https://doi.org/10.1038/s41591-026-04402-w

Extended Data Table 6 | Percent of time unbound concentrations exceed the IC50, IC90 and IC99 values

Regimen	Day 1 median	Day 1 5th quantile	Day 1 95th quantile	Day 2 to 10 median	Day 2 to 10 -5th quantile	Day2 to 10 -95th quantile	Day 1 to 10 median	Day 1 to 10 -5th quantile	Day 1 to 10 -95th quantile
IC50 value									
R0	98	94	99	100	93	100	100	93	100
R1	98	93	99	100	94	100	100	94	100
R2	98	93	99	100	97	100	100	97	100
R3*	98	93	99	100	99	100	100	99	100
R4	98	93	99	100	100	100	100	99	100
R5	98	93	99	100	100	100	100	99	100
R6	98	93	99	100	100	100	100	99	100
R7	98	91	99	100	94	100	100	94	100
R8	98	91	99	100	99	100	100	98	100
R9	98	91	99	100	100	100	100	99	100
R10	98	91	99	100	100	100	100	99	100
IC90 value									
R0	98	91	99	100	72	100	100	75	100
R1	98	86	99	100	73	100	100	75	100
R2	98	86	99	100	83	100	100	84	100
R3*	98	86	99	100	90	100	100	90	100
R4	98	86	99	100	94	100	100	94	100
R5	98	86	99	100	97	100	100	96	100
R6	98	86	99	100	99	100	100	98	100
R7	97	76	99	100	73	100	100	74	100
R8	97	76	99	100	90	100	100	89	100
R9	97	76	99	100	94	100	100	93	100
R10	97	76	99	100	96	100	100	95	100
IC99 value									
R0	97	66	99	98	33	100	97	39	100
R1	95	50	99	98	35	100	96	39	100
R2	95	50	99	100	47	100	98	49	100
R3*	95	50	99	100	58	100	99	59	100
R4	95	50	99	100	67	100	99	67	100
R5	95	50	99	100	74	100	99	74	100
R6	95	50	99	100	86	100	99	84	100
R7	89	45	99	98	34	100	95	37	100
R8	89	45	99	100	57	100	98	57	100
R9	89	45	99	100	67	100	98	65	100
R10	89	45	99	100	74	100	98	72	100

* Regimen proposed for further clinical development. IC, inhibitory concentration; R, regimen (described in Extended data – Table 5).

https://doi.org/10.1038/s41591-026-04402-w

Extended Data Table 7 | List of protocol deviations occurring during the study conduct

#	Participant ID	Treatment	Topic	Deviation
Irrua Specialist Teaching Hospital				
1	SAFARI-1001	Ribavirin	Study flow	Eligibility criteria were checked in the source document before screening samples were processed
2	SAFARI-1001	Ribavirin	Study flow	Study drug administered before processing the screening samples for eligibility
3	SAFARI-1001	Ribavirin	Drug administration	Study drug not administered as stated in the protocol. All dosage for day 1 was administered at visit D1H0 instead of dividing between D0H0 and D0H8
4	SAFARI-1001	Ribavirin	Laboratory	Creatinine kinase not processed at screening visit
5	SAFARI-1007	Ribavirin	ECG performance	ECG performed after blood collection at D4H0
6	SAFARI-1009	Favipiravir	Blood sampling	Inability to obtain blood samples at D2H0
7	SAFARI-1009	Favipiravir	Vital signs	Vital signs measured after study drug administration at D10H12
8	SAFARI-1018	Ribavirin	Drug administration	Delayed study drug administration (+6 hrs) at D2H0
9	SAFARI-1018	Ribavirin	Drug administration	No venous access to administer ribavirin on time at D3H0, extrapolating the 30 min tolerance of delay
10	SAFARI-1022	Ribavirin	Blood sampling	Blood collection performed after study drug administration at D4H0
Federal Medical Centre Owo				
1	SAFARI-2001	Favipiravir	Drug administration	11 tablets (2200mg) of favipiravir swallowed by participant instead of 12 tablets (2400mg) at D1H0
2	SAFARI-2001	Favipiravir	ECG performance	ECG performed after blood collection and drug administration at D2H0
3	SAFARI-2001	Favipiravir	PK and PCR sample freezing	Delay of more than 2 hours in freezing PK and PCR samples at D2H0
4	SAFARI-2001	Favipiravir	Blood sampling	Blood collection performed after study drug administration at D6H0
5	SAFARI-2037	Ribavirin	Eligibility criteria	Participant included based on a 10-day old positive PCR result. The PCR test from the screening visit resulted negative. By that time participant had already received D1H0, D1H8, D2H0 and D3H0 doses. The participant was withdrawn from the study.

https://doi.org/10.1038/s41591-026-04402-w

Extended Data Table 8 | Schedule of study procedures

STUDY EXAM	Pre-screen	Screening	Before 1st study drug admin	D1 h0	D1 h0.5	D1 h1	D1 h3	D1 h5	D1 h8	D1 h12	D1 h16	D2 h0	D2 h12	D3 h0	D3 h12	D4 h0	D4 h12	D5 h0
Written informed consent		X																
Medical history		X																
Previous medication		X																
Baseline characteristics		X																
Body temperature		X			X							X		X		X		X
Vital signs		X			X							X		X		X		X
Signs and symptoms		X														X		
Physical examination		X														X		
Urine pregnancy test		X																
Urine dipstick		X														X		
ECG		X										X		X*		X		
Blood sample for hematology		X										X				X		
Blood sample for biochemistry		X										X				X		
Blood sample for PK only					X†	X†	X†	X‡	X‡	X‡								
Blood sample for PK and PCR			X									X				X		
PCR result from routine diagnostic	X																	
In/Exclusion criteria		X																
Randomization		X																
Intravenous drug administration – ribavirin #				X[1]					X[1]			X[2]		X[2]		X[2]		X[2]
Oral drug administration – favipiravir #				X[a]					X[a]		X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]
Concomitant medication/ treatment				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

STUDY EXAM		D5 h12	D6 h0	D6 h12	D7 h0	D7 h1	D7 h4	D7 h12	D8 h0	D8 h12	D9 h0	D9 h12	D10 h0	D10 h12	UFV
Written informed consent															
Medical history															
Previous medication															
Baseline characteristics															
Body temperature			X		X				X		X			X	(X)
Vital signs			X		X				X		X			X	(X)
Signs and symptoms														X	(X)
Physical examination														X	(X)
Urine pregnancy test															(X)
Urine dipstick													X		(X)
ECG													X		(X)
Blood sample for hematology			X						X				X		(X)
Blood sample for biochemistry			X						X				X		(X)
Blood sample for PK only					X	X†	X†								
Blood sample for PK and PCR			X						X				X		(X)
In/Exclusion criteria															
Randomization															
Drug administration – ribavirin #			X[2]		X[2]				X[3]		X[3]		X[3]		
Drug administration – favipiravir #		X[b]	X[b]	X[b]	X[b]			X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	
Concomitant medication/ treatment		X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	(X)

as randomized - study drug will be administered after examinations and blood sampling, at the end of the visit; [1]100mg/kg on D1, dose is divided: 2/3 of dose on D1h0, 1/3 of dose at D1h8, max dose on D1 is 7g; [2] 25mg/kg; [3] 12.5mg/kg; [a] loading dose; [b] maintenance dose; † ± 10 min; ‡ ± 15 min; * ECG for the patients treated with favipiravir; UFV unforeseen visit; (X) as medically indicated.