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Favipiravir for Lassa fever: an open-label, randomized controlled phase 2 trial

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A list of authors and their affiliations appears at the end of the paper

Lassa fever (LF) is a viral hemorrhagic fever endemic to West Africa, with high case fatality in hospitalized patients and limited treatment options, including ribavirin. Preclinical evidence suggests high-dose favipiravir is a promising antiviral treatment alternative. We conducted a randomized controlled open-label phase 2 clinical trial at two reference hospitals in Nigeria to evaluate favipiravir in the treatment of LF. Primary endpoints were the description of classic pharmacokinetic parameters (maximum plasma concentration, time to reach maximum plasma concentration, area under the curve (AUC), half-life and volume of distribution) as well as the safety and tolerability of favipiravir compared with ribavirin in the treatment of acute LF. Hospitalized adult patients with mild-to-moderate RT-PCR-confirmed LF were eligible to participate. In total, 41 patients were randomized (ribavirin $n = 21$; favipiravir $n = 20$), and 36 completed the 10-day follow-up period. A total of 19 (46.3%) participants were female, and the median age was 37 years. The primary endpoints were met. Pharmacokinetic analysis of favipiravir in a one-compartment model indicated reliable exposure with maximum plasma concentration of 50.9 (IQR 42.1 to 75.1) mg l^{-1} in steady state, half-life of 10.9 (IQR 8.2 to 17.1) h and AUC (0–240 h) of 9,275 (IQR 7,139.4 to 15,794.8) mg l^{-1} h^{-1}. The 30 drug-related treatment-emergent adverse events were evenly distributed between the treatment arms; 16 (53.5%) events occurred in the favipiravir group, and none of these were classified as severe or serious. Anemia was the most frequently observed adverse event in the ribavirin arm and vomiting in the favipiravir arm. All study participants survived and were successfully discharged from the isolation ward. This trial indicates favipiravir's potential as a safe and well-tolerated alternative treatment regimen for LF and pharmacokinetic data suggest an optimized favipiravir regimen for future clinical evaluation. Clinicaltrials.gov: NCT04907682.

Lassa fever (LF) is an acute febrile illness caused by the Lassa virus (LASV). It may progress to severe disease leading to substantial mortality[1]. Although transmission primarily occurs by spill-over events from its main reservoir, the rodent *Mastomys natalensis*, human-to-human transmission occurs most commonly in the healthcare setting[2–4]. Endemic to West Africa, the highest disease burden occurs in Nigeria, with highest annual case numbers in the states Edo and Ondo[5]. In total, 1,309 confirmed cases were reported in Nigeria in 2024, with a case fatality rate of 16.3%[6]. The World Health Organization has initiated a global strategy and a preparedness plan following the West African Ebola disease crisis to ensure that research and development provides appropriate medical technologies for future epidemics[7,8]. This list of priority diseases includes LF. As of now, there are no approved vaccines for LF, although results from a phase I trial assessing a rVSVΔG-LASV-GPC vaccine are promising[9]. In addition, current treatment options for LF are limited. Even though ribavirin is used as the standard treatment in

e-mail: michael.ramharter@ctm.bnitm.de

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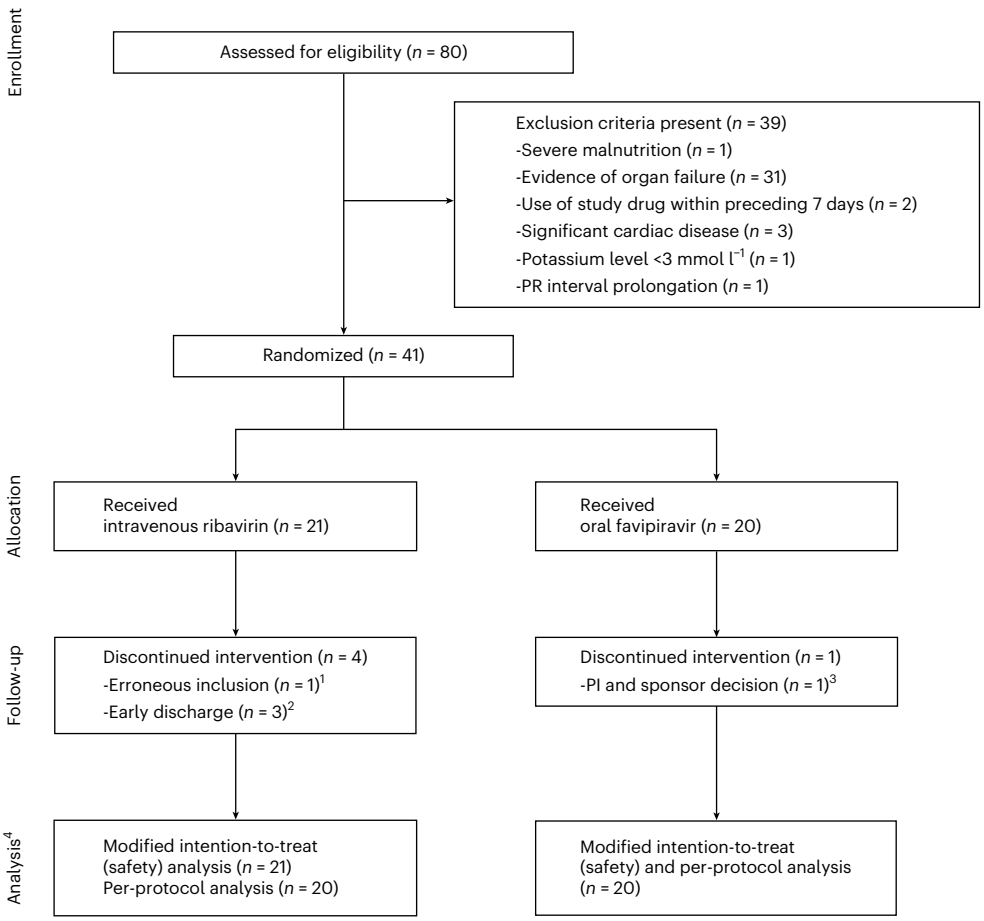

Fig. 1 | Consolidated Standards of Reporting Trails diagram. [1]A patient was included in the study on the basis of a positive RT–PCR test for LASV. It was realized only after recruitment by the investigators that the test result was 10 days old. As the repeat RT–PCR was negative, the participant was removed from the clinical trial. [2]In total, three participants in the ribavirin arm were discharged early (days 5 and 7 after the start of treatment) owing to substantial clinical improvement and negative follow-up PCR results. [3]A participant was withdrawn on the second day of follow-up owing to first-degree atrioventricular block as a precautionary measure by the principal investigator (PI) and sponsor. [4]Safety, a coprimary endpoint, was evaluated in the modified intention-to-treat population. Pharmacokinetics, also a coprimary endpoint, and the secondary endpoints were evaluated in the per-protocol population.

Nigeria, its efficacy, risk–benefit balance and mode of action remain uncertain because of critical risk of bias in the pivotal underlying studies from the 1980s[10–12]. Additional promising therapeutic candidates currently in early clinical development include the small molecules ARN-75039 and LHF-535[13–15]. In preclinical studies, other potential candidates include monoclonal antibodies, stampidine, 4′-fluorouridine and several others[16,17].

Favipiravir is a promising antiviral drug candidate against LASV[18]. Initially developed and registered for the treatment of influenza, this pyrazinecarboxamide derivative inhibits the RNA polymerase of a wide range of negative-strand RNA viruses[19]. Favipiravir is considered safe and well tolerated as evidenced by clinical trials including healthy individuals and patients with influenza, coronavirus disease 2019 (COVID-19) and Ebola virus disease[20–22]. Furthermore, several in vitro studies and preclinical in vivo models including nonhuman primates corroborate its potential in the treatment of LF[23–26]. In addition, favipiravir was used successfully in combination with ribavirin for the treatment of two patients with LF[27]. However, so far, there are no clinical trials systematically assessing its safety and efficacy in human subjects with LF. Data extrapolated from nonhuman primates suggest that a high-dose regimen previously studied for the treatment of Ebola virus disease may conjure substantial antiviral activity against LASV[21,26]. Evidence for favipiravir's pharmacokinetic properties at higher doses is currently under investigation (FAVIDOSE trial, NCT06024421).

Almost 40 years since the last interventional clinical trial in LF has been published[28], the SAFARI clinical phase 2 trial was implemented in a high-transmission region of Nigeria to evaluate the clinical usefulness of favipiravir in the treatment of acute LF. The main objectives of this randomized, controlled phase 2 clinical trial were the evaluation of the pharmacokinetics, safety and tolerability of favipiravir in patients with LF. In addition, virological and clinical efficacy data were analyzed to inform the risk–benefit balance of this drug.

Results

Study design

SAFARI was a randomized, controlled, open-label, phase 2 clinical trial that investigated favipiravir in the treatment of LF. As per protocol, the primary endpoints were the description of classical pharmacokinetic parameters of favipiravir (maximum plasma concentration, time to reach maximum plasma concentration, area under the curve (AUC), half-life and volume of distribution) and the proportion of drug-related adverse events and serious adverse events. The secondary endpoints were the mutagenicity of ribavirin and favipiravir; the description of RNA concentrations, infectious titers and serological status during treatment; pharmacokinetic modeling and simulation of different loading regimens to characterize time to target concentration attainment; the assessment of covariates impacting drug exposure; and the relationship between drug exposure and viral elimination dynamics,

length of hospital stay, mortality and blood component therapy use. However, owing to the limitations of the sensitivity of assays described in the Methods, it was technically not possible to assess mutagenicity and infectious titers of LASV. Efficacy was listed as a secondary endpoint in the study protocol as descriptive analysis of mortality in the respective treatment arms. Details about patient selection, trial design and protocol deviations are provided in the Methods.

Study participants

Eligible participants were consenting adults with diagnosis of LF confirmed by reverse-transcription polymerase chain reaction (RT–PCR). Exclusion criteria were the inability to give informed consent, current or planned pregnancy or lactation, severe malnutrition, intolerance to ribavirin or favipiravir, history of hemoglobinopathies and/or hemophilia, inability to take oral drugs, use of ribavirin or favipiravir within the preceding 7 days and evidence of organ failure or severe anemia. Medical history of clinically important cardiac disease, potassium level <3.0 mmol l^{-1} and PR interval ≥200 ms were added as exclusion criteria following a protocol amendment, applicable from the fourth to the last recruited participant.

The first participant was enrolled on 12 August 2021 and the last participant on 31 October 2022. In total, 41 participants were included, 21 randomized in the ribavirin and 20 in the favipiravir treatment arm (Fig. 1). A case of screening failure was incorrectly randomized in the ribavirin arm and was therefore immediately discontinued from the study. The 10-day treatment, which coincided with the follow-up period, was completed for 36 (88%) participants. Three participants in the ribavirin arm were discharged prematurely upon the investigators' discretion (days 5 and 7 after the start of treatment) owing to substantial clinical improvement and complete viral clearance in follow-up RT–PCR results. One participant in the favipiravir arm was withdrawn on day 2 owing to new onset of PR prolongation, as described below. Among the 20 participants who received favipiravir, the median age was 40 years old (range 20–70), and 55% were female and 100% of African descent (Table 1). Data from the 41 participants that received at least one dose of the study treatment were used for the safety analysis, whereas data from the 40 participants correctly randomized were used for pharmacometric analyses and for other secondary endpoints.

Table 1 | Baseline characteristics of participants[a]

Characteristic	Favipiravir (*N*=20 participants)	Ribavirin (*N*=21 participants)
Age in years (IQR)	**40 (25–51)**	**36 (27–46)**
Sex		
Female (*n* (%))	11 (55)	8 (38)
Male (*n* (%))	9 (45)	13 (62)
Black/African	20 (100)	21 (100)
Weight in kg (IQR)	63 (56 to 72)	64 (59 to 69)
Height in m (IQR)	1.67 (1.58 to 1.75)	1.7 (1.65 to 1.75)
Axillary temperature in °C (IQR)	37.4 (36.8 to 37.8)	37.5 (36.8 to 38.0)
Blood pressure, systolic (mmHg) (IQR)	108 (102 to 120)	120 (110 to 130)
Blood pressure, diastolic (mmHg) (IQR)	68 (64 to 80)	70 (61 to 75)
Heart rate (bpm) (IQR)	82 (74 to 97)	80 (67 to 98)
O_2 saturation (%) (IQR)	98 (97 to 99)	97 (96 to 98)

[a]Variables presented as median and IQRs, except for sex, presented as numbers and proportions.

Pharmacokinetics of favipiravir and covariates impacting drug exposure

The pharmacokinetics of favipiravir were best described by a one-compartment model with oral absorption, absorption lag-time and linear elimination. A nonlinear elimination (Michaelis–Menten) was not supported given the available study data (delta Akaike information criterion of +2.0043). Interindividual variability was found on clearance and absorption lag-time and interoccasion variability on absorption rate constant and bioavailability. Body weight was included as covariate on clearance (delta objective function value of −6.290, $P = 0.012$), where increasing body weight was correlated with increasing clearance. The structural pharmacokinetic model of ribavirin was a three-compartment model with first-order disposition and interindividual variability on clearance, distributional clearance (Q2) and central volume of distribution (V1). Sex was found as covariate on clearance (delta objective function value of −8.144, $p = 0.004$), where female participants displayed a 36.6% lower clearance compared with males. The phamacokinetic parameters for favipiravir and ribavirin are summarized in Table 2. The final population pharmacokinetic model for favipiravir and ribavirin are summarized in Extended Data Table 1. The individual profiles indicated good model fit for both ribavirin and favipiravir (Fig. 2).

Safety

A total of 86 treatment-emergent adverse events (TEAEs) were reported during the study, which were overall evenly distributed between treatment arms (Table 3). Among those, 56 (65%) were considered as not related with the study drug. A total of 30 drug-related TEAEs were reported, evenly distributed between treatment arms. Extended Data Table 2 summarizes the characteristics of TEAEs. No drug-related TEAEs were considered certainly associated with the drugs. Anemia was the most common drug-related TEAE described in the ribavirin group ($n = 5$; 36%), whereas it was reported in one participant (6%) in the favipiravir group. Conversely, vomiting was most frequent in the favipiravir group ($n = 6$; 38%) and was reported in two participants (14%) in the ribavirin group. Pyrexia was reported as a TEAE in four instances in participants receiving favipiravir. One episode was considered as possibly related to the study drug in a participant afebrile at baseline presenting a temperature of 39.1 °C 12 h after drug administration on day 1. The remaining episodes of pyrexia reported as TEAE were considered as unlikely associated with the study drug, and two episodes were reported in the same participant on days 0 and 6. Moreover, two participants in this arm presented new onset of pyrexia, defined as body temperature ≥38.0 °C, which were considered as typical manifestation of LF; hence, they were not reported as TEAE. Although pyrexia was not reported as TEAE in participants receiving ribavirin, it was observed in four participants and considered as a typical manifestation of LF.

No deaths occurred in this trial. One life-threatening TEAE, anemia, was observed in a participant in the ribavirin group, also leading to substantial temporary incapacity and reported as serious adverse event. This 62-year-old woman did not report preexisting chronic conditions, but the baseline electrocardiogram (ECG) was indicative for hypertrophic cardiomyopathy. At inclusion, the hemoglobin level was 13.0 g dl^{-1}. On the day of treatment initiation, the participant became restless and hypothermic, with tachypnea and oxygen desaturation. Intranasal oxygen was provided at 4–5 l min^{-1}. The symptoms subsided in a few hours, but she continued receiving oxygen. On day 2, considering the diagnosis of pulmonary thromboembolism, the managing team prescribed dabigatran 150 mg twice daily. On day 4, the hemoglobin level decreased to 10.3 g dl^{-1}, when anemia was reported as an adverse event, and hematinics were prescribed. On day 6, supplemental oxygen was weaned off. On day 8, hemoglobin further decreased to 7.5 g dl^{-1}, associated with dizziness, asthenia and necessitating blood transfusion. At this occasion the event was reported as serious. There were no signs of active bleeding throughout the study period. Ribavirin was discontinued owing to its propensity to induce hemolytic anemia. On

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Table 2 | Pharmacokinetic parameters of ribavirin and favipiravir described as median and IQR

Drug	Parameter	Median	IQR
Favipiravir	AUC_{240h} (mg l^{-1} h^{-1})	9,275.0	7,139.4 to 15,794.8
	AUC_{24h} (mg l^{-1} h^{-1})	1,472.7	1,131.3 to 1,983.6
	C_{max} first 24 h (mg l^{-1})	87.3	69.3 to 110.9
	C_{max} steady state (mg l^{-1})	50.9	42.1 to 75.1
	T_{max} first 24 h (h)	10.5	10.3 to 14.8
	T_{max} steady state (h)	145.3	74.1 to 149.2
	$T_{½}$ (h)	10.9	8.2 to 17.1
	Clearance (l h^{-1})	2.7	1.7 to 3.5
	Volume of distribution (l)	41.5	–
Ribavirin	AUC_{240h} (mg l^{-1} h^{-1})	1,397.4	1,229.3 to 1,593.8
	AUC_{24h} (mg l^{-1} h^{-1})	263.4	241.6 to 307.0
	C_{max} (mg l^{-1})	111.1	103.8 to 130.2
	$T_{½}$ 1-CMT (h)	0.5	0.4 to 0.6
	$T_{½}$ 2-CMT (h)	5.6	5.3 to 6.9
	$T_{½}$ 3-CMT (h)	117.3	99.3 to 147.6
	Clearance (l h^{-1})	10.2	7.6 to 11.3
	Volume of distribution (l)	37.2	32.0 to 40.0
	Vp1 (l)	934.2	–
	Vp2 (l)	97.2	–

CMT, compartment; $T_{½}$, half-life; T_{max}, time to maximum concentration; Vp, peripheral compartment.

day 12, dabigatran was discontinued. On day 14, the participant was discharged with clinical improvement and a stable hemoglobin at 9.8 g dl^{-1}. A total of 7 units of erythrocyte concentrate were administered throughout the admission.

First-degree atrioventricular block, defined as PR interval >200 ms on ECG, was reported as drug-related TEAE on the second day of follow-up for two participants. One episode occurred in a participant receiving ribavirin. The PR interval was 192 ms, increased to 206 ms on day 2 and normalized thereafter. The other event was observed in a 24-year-old participant without relevant medical history in the favipiravir group. The PR interval was 196 ms at inclusion and increased to 320 ms (ΔPR 124 ms) on day 2. Although not associated with any clinical sign or symptom, the unexpectedness of this finding and the need for further evaluation by the data safety monitoring board (DSMB) led to the withdrawal of the participant from the clinical trial on the basis of the decision of the investigator. The PR interval normalized thereafter, and the participant was successfully discharged after completion of the standard treatment with ribavirin.

Table 4 summarizes the results of laboratory parameters at inclusion and the further evolution during the study period. Hemoglobin decreased during the follow-up period (−1.0 (−1.6 to −0.5) g dl^{-1}; ribavirin), whereas the median uric acid levels increased over time, more evidently in participants treated with favipiravir, (2.35 (1.75 to 3.55) mg dl^{-1}), compared with participants treated with ribavirin (1.9 (1.2 to 2.9) mg dl^{-1} median increase). Some degree of hyperuricemia was observed in 12 (60.0%) and 6 (28.6%) participants in the favipiravir and ribavirin arms, respectively. All cases were asymptomatic and not considered clinically relevant, and no additional intervention was required. Those cases have not been reported as TEAEs. In both treatment arms, median baseline aspartate aminotransferase (AST) and creatinine phosphokinase (CPK) were above the upper limit of normality and similarly decreased by the end of the study. The list of concomitant medications is presented in Extended Data Table 3.

Description of viremia

In univariate analysis, median baseline glycoprotein complex (*GPC*) gene RT–PCR cycle threshold (Ct) values were similar in both treatment arms (34.4, ribavirin, and 34.9, favipiravir). Median increase in the Ct values during the study period was comparable (9.4, ribavirin, and 8.9, favipiravir). The same held true for the *L* gene RT–PCR Ct values (35.4, ribavirin, and 36, favipiravir) and the median increase during the study period (9.6, ribavirin, and 8.4, favipiravir). These findings are summarized in Table 4.

Drug exposure and viral elimination dynamics

On the basis of the study data, a pharmacokinetic–pharmacodynamic model was established for further exploratory analysis. The model parameters for the final exploratory model describing the time course of the Ct values as an indirect surrogate marker of viral kinetics of the *GPC* and *L* genes can be found in Extended Data Table 4. The predicted Ct values from *GPC* and *L* genes versus time are depicted in Extended Data Fig. 1. No significant differences in Ct_0 values were found regarding sex, drug and study site. The covariate analyses on α indicated a slower increase of Ct values in the favipiravir compared with ribavirin group on the basis of the indirect surrogate marker of Ct values (delta objective function value of −5.046, $P = 0.025$). For favipiravir, a significant correlation of Ct_0 and α was observed. A higher viral load at hospitalization was therefore statistically correlated with a lower increase of Ct values for favipiravir. For ribavirin, no significant correlation was found. No other significant covariates were identified.

Pharmacokinetic modeling and simulation of optimized favipiravir loading regimens

To improve the empiric high-dose favipiravir regimen with a substantial loading dose used in this trial, alternative dosing regimens were modeled on the basis of the study data to reduce peak plasma concentrations potentially associated with adverse drug reactions and, at the same time, maximizing overall drug exposure during the treatment period to optimize antiviral efficacy. The final population pharmacokinetic model was used for dosing simulations considering the unbound fraction of favipiravir. The loading dose of the study regimen led to 98% (94–99%, 5th–95th percentile) time above half-maximal inhibitory concentration (IC_{50}) within the first day. The percentage of time above the 90% inhibitory concentration (IC_{90}) and 99% inhibitory concentration (IC_{99}) was 98% (91–99%, 5th–95th percentile) and 97.5 (66–99%, 5th–95th percentile), respectively. For the maintenance dose, the median percentage of time above IC_{50} and IC_{90} was 100% with the lower fifth percentile ranging from 93% or 72% for the time above IC_{50} and IC_{90}, respectively. The alternative dosing simulations are provided in Extended Data Tables 5 and 6. The simulation with regimen 3 (2,400 mg twice daily on day 1 followed by 1,600 mg twice daily from day 2 to 10) resulted in an optimal balance between the pharmacokinetic profile and a potentially safe and tolerable dosage. Its individually predicted (unbound) concentrations versus time and the percentage of time above IC_{50}, IC_{90} or IC_{99} within 24 h per day is depicted in Extended Data Fig. 2.

Drug exposure and other secondary endpoints

Blood component therapy was used in one single participant treated with ribavirin, a 62-year-old female with baseline creatinine of 2.6 mg dl^{-1}. This case of anemia was also the only SAE reported in the study. In this participant, the AUC of ribavirin in 240 h was 3840 mg l^{-1} h^{-1}, and the clearance was 3.5 l h^{-1}. Those values deviated from the median values of the remaining participants receiving the drug, namely, $AUC_{(0–240\ h)}$ 1,384 mg l^{-1} h^{-1} (interquartile range (IQR) 1,129 to 1,581) and clearance 10.6 l h^{-1} (IQR 7.8 to 11.9). The median length of hospital stay was 10 days in both the ribavirin (range 5–23) and favipiravir (range 2–10) arms. The participant with the longest

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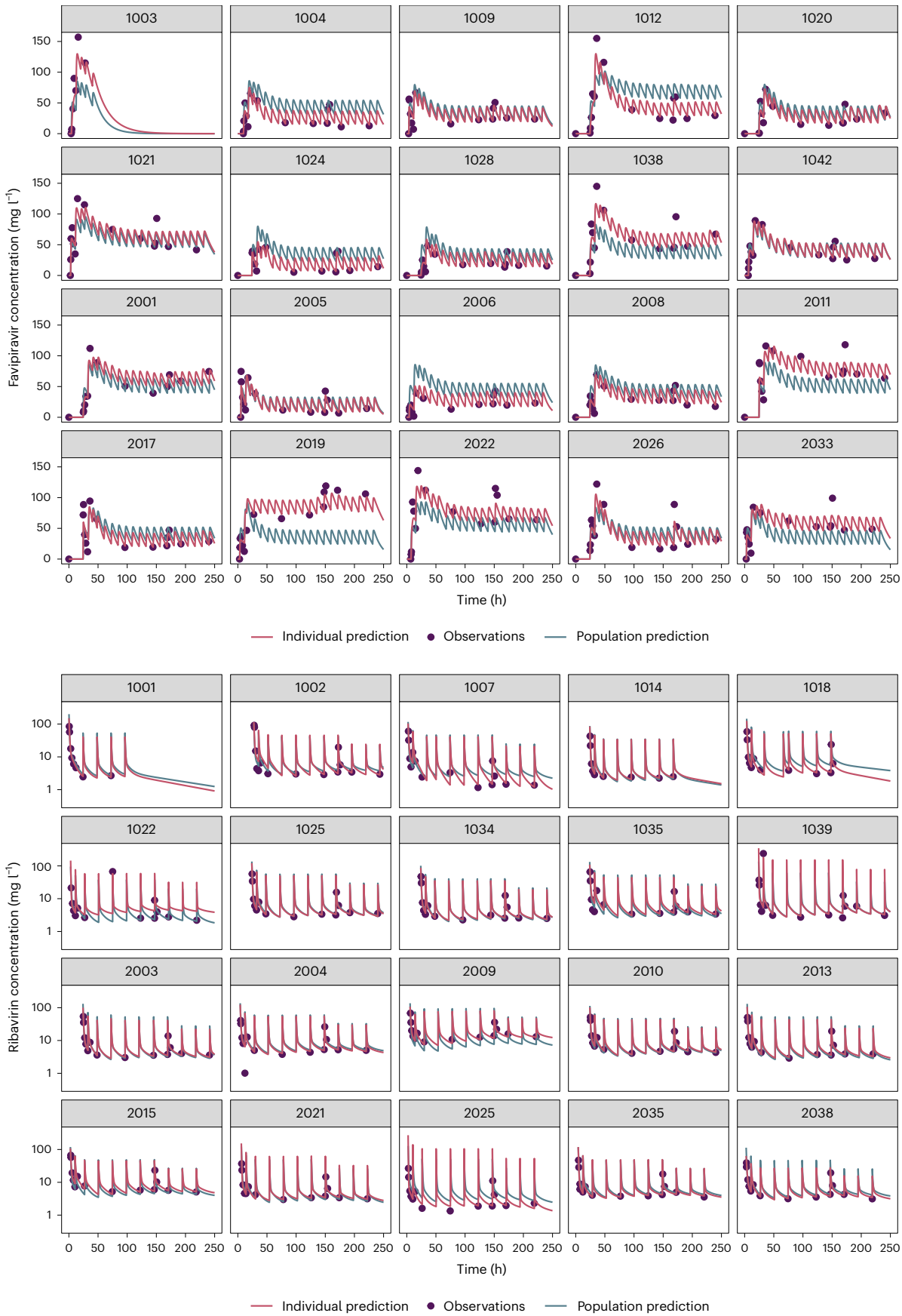

Fig. 2 | Individual plots of favipiravir and ribavirin concentrations versus time. A description of observed favipiravir and ribavirin concentrations, individual predictions (considering dosing scheme, covariate effects and drug measurements) and population predictions (considering dosing scheme and covariate effects but no drug measurements) versus time. In the case of participants 1002, 1014, 1025, 1034, 1035, 1039, 2003 and 2010, although it appears that the dosing started at 24 h, in fact, it was still day one. This discrepancy is due to the baseline covariate measurements included in the modeling being performed on the day before the treatment initiation.

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Table 3 | List and characteristics of TEAEs presented by participants treated with ribavirin and favipiravir according to relatedness with the study drugs

Reported adverse event in MedDRA terms	Favipiravir (*N*=20 participants)—*n* (%)		Ribavirin (*N*=21 participants)—*n* (%)	
	Any grade	Maximum grade 3/4 or serious	Any grade	Maximum grade 3/4 or serious
At least possibly related with study drug[a]				
Clinical				
Blood pressure increased	0	0	1 (4.7)	0
Cellulitis	1 (5.0)	0	0	0
Dizziness	0	0	1 (4.7)	0
Pyrexia	1 (5.0)	0	0	0
Rash	1 (5.0)	0	0	0
Tachycardia	1 (5.0)	0	0	0
Visual impairment	1 (5.0)	0	0	0
Vomiting	6 (30.0)	0	2 (9.5)	0
Electrocardiographic				
ECG PR prolongation	1 (5.0)[b]	0	1 (4.7)	0
Laboratory				
Amylase increased	0	0	1 (4.7)	0
Anemia	1 (5.0)	0	5 (23.8)	1 (4.7)[c]
Hepatic enzyme increased	2 (10.0)	0	2 (9.5)	0
Hypokalemia	1 (5.0)	0	0	0
Monocytosis	0	0	1 (4.7)	0
Unlikely related with study drug				
Clinical				
Abdominal pain upper	0	0	1 (4.7)	0
Blood pressure increased	1 (5.0)	0	2 (9.5)	0
Constipation	1 (5.0)	0	0	0
Dyspepsia	2 (10.0)	0	1 (4.7)	0
Flank pain	1 (5.0)	0	1 (4.7)	0
Hematuria	1 (5.0)	0	0	0
Hypothermia	0	0	1 (4.7)	0
Hypoxia	0	0	1 (4.7)	0
Insomnia	0	0	1 (4.7)	0
Malaria	0	0	1 (4.7)	0
Melaena	1 (5.0)	0	0	0
Meningism	0	0	1 (4.7)	0
Musculoskeletal stiffness	1 (5.0)	0	0	0
Edema peripheral	1 (5.0)	0	0	0
Pain[d]	1 (5.0)	0	0	0
Pyelonephritis	0	0	1 (4.7)	0
Pyrexia	3 (15.0)	0	0	0
Thrombophlebitis	1 (5.0)	0	1 (4.7)	0
Visual impairment	0	0	1 (4.7)	0
Vomiting	1 (5.0)	0	3 (14.3)	0
Electrocardiographic				
ECG PR prolongation	1 (5.0)	0	0	0
ECG QT prolonged	1 (5.0)	0	0	0
Laboratory				
Amylase increased	0	0	1 (4.7)	0
Anemia	1 (5.0)	0	0	0

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Table 3 (continued) | List and characteristics of TEAEs presented by participants treated with ribavirin and favipiravir according to relatedness with the study drugs

Reported adverse event in MedDRA terms	Favipiravir (*N*=20 participants)—*n* (%)		Ribavirin (*N*=21 participants)—*n* (%)	
	Any grade	Maximum grade 3/4 or serious	Any grade	Maximum grade 3/4 or serious
Blood CPK increased	0	0	1 (4.7)	0
Blood uric acid increased	0	0	1 (4.7)	0
Hypoalbuminemia	5 (25.0)	0	1 (4.7)	0
Hypokalaemia	4 (20.0)	0	4 (19.0)	0
Monocytosis	1 (5.0)	0	0	0
Protein urine	0	0	1 (4.7)	0
Thrombocytopenia	1 (5.0)	0	1 (4.7)	0
White blood cell count decreased	0	0	1 (4.7)	0

[a]TEAEs whose association with the study drug was certain, probable/likely or possible. No TEAE as certainly associated. One TEAE (cellulitis) was reported as probably/likely related with favipiravir, and two TEAEs (anemia) were reported as probably/likely related with ribavirin. The remaining TEAEs were reported as possibly related with the study drugs. [b]Graded as moderate (grade 2). Led to study withdrawal owing to its unexpectedness and for evaluation by the DSMB. [c]Graded as life-threatening (grade 4), also reported as a serious adverse event. Blood transfusion required. [d]Waist pain. Term not defined in MeDRA.

hospital stay, 23 days treated with ribavirin, was the same participant who developed life-threatening anemia with the need of blood component therapy. In the favipiravir arm, no participant had a hospital stay longer than 10 days.

Efficacy

Efficacy was included as a secondary endpoint in the study protocol as descriptive analysis of the predefined secondary outcome mortality in the respective treatment groups. Owing to the small sample size in phase 2, only preliminary observations can be made. All participants of this study survived and were successfully discharged by the end of the treatment period. Among participants in the favipiravir arm, 11 (55%) presented a negative LASV RT–PCR result by the end of the follow-up period, whereas in the ribavirin arm, this occurred in 15 individuals (75%). Median changes in the RT–PCR Ct value were similar in both treatment arms. In the last study visit, LF symptoms were absent in 16 (76%) of participants receiving ribavirin and in 18 (90%) of participants receiving favipiravir. Fever clearance was observed in 20 (100%) and 19 (95%) participants receiving favipiravir and ribavirin, respectively. The only participant without clearance presented fever continuously from screening to the end of the study, attributed to LF.

Discussion

This phase 2 clinical trial constitutes an interventional clinical trial evaluating the use of favipiravir compared with standard ribavirin therapy in the treatment of LF. To mitigate potential risks, a cautious approach has been used by including patients with mild-to-moderate disease, known to have lower risk for organ failure and death than patients with severe LF. The study set out to investigate the pharmacokinetics, safety and tolerability of favipiravir in the treatment of LF. Data were further explored by pharmacokinetic–pharmacodynamic modeling and optimized dosing regimens for further clinical evaluation of favipiravir against viral hemorrhagic fevers.

A linear, one-compartment model was the model that best fit the data for favipiravir with body weight as a significant covariate on favipiravir clearance, indicating that higher weight is associated with higher clearance. The determined model structure and pharmacokinetic parameters were in a similar range as previously described in other indications, supporting the external validity of our findings[29]. For example, the volume of distribution found in this study was 41.5 l whereas it was 41.6 l in the study by Irie et al.[29]. Similarly, clearance for a typical individual weighing 62.5 kg was 2.42 l h^{-1} in this study, whereas it was 3.34 l h^{-1} in the study by Irie et al. Higher exposure was observed on day 1 as compared with steady state, indicating the rapid attainment of therapeutic concentrations due to the high-dose loading regimen used. Importantly, drug exposure remained consistently above the estimated effective concentration throughout treatment, supporting the adequacy of the investigated dosing regimen. Although the data were best described by a linear model, nonlinearity cannot be excluded on the basis of the sample size of this trial[30]. Ribavirin pharmacokinetics were linear and best described by a three-compartment model. Sex was identified as a covariate on clearance. Overall, pharmacokinetic parameters were very similar compared with the results from the PAIRR study, in which we characterized ribavirin pharmacokinetic in patients with LF[11].

The emergence of drug-related TEAEs was similar in both treatment arms, and neither severe nor serious adverse events were observed in the favipiravir group. Furthermore, there were no TEAEs certainly associated with the study drugs. The adverse events observed may reflect to a large extent the many signs and symptoms of LF. It is inherently difficult to disentangle the causality of adverse events in such clinical trials, as well as to define the level of relatedness between an adverse event and the study drug, considering that this assessment is to some extent subjective. However, the observation of largely similar proportions of treatment-related adverse events between the control (n = 16) and intervention (n = 14) arms, as well as the total number of adverse events (41 versus 45, respectively), hint toward the understanding that there were no major differences in tolerability and safety of the antiviral drugs. Anemia was most frequently associated with ribavirin and vomiting with favipiravir, in accordance with findings from other studies[31,32]. Administration of blood transfusion was required for one participant treated with ribavirin. This drug is known to be associated with the occurrence of hemolytic anemia, which is particularly problematic in patients suffering from viral hemorrhagic fevers. The lower propensity of favipiravir to induce anemia reinforces its relevance as a more tolerable treatment option, constituting a clinically relevant advantage in the treatment of patients with LF as they have already a substantial risk for chronic or acute bleeding. Vomiting as an adverse event associated with favipiravir may have been caused by the oral drug formulation necessitating the repeated intake of a considerable number of tablets. It is worth noting that vomiting is also a symptom of LF, which makes its definition as adverse event as well as the determination of its relatedness with the study drug challenging. The recent development of a parenteral drug formulation may overcome this tolerability problem in the future[33]. Although pyrexia was reported as TEAE only in the favipiravir group, increased body temperature was equally observed in participants receiving

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Table 4 | Baseline laboratory parameters and changes at the end of the study follow-up period

Parameter	Favipiravir (*N*=20 participants)		Ribavirin (*N*=21 participants)	
	Baseline on day 0; median (IQR)	Change at the end of follow-up[a]; median (IQR)	Baseline on day 0; median (IQR)	Change at the end of follow-up[a]; median (IQR)
Virology				
GPC gene RT–PCR (Ct)[b]	34.9 (33.1 to 37.1)	8.9 (4.6 to 10.8)	34.4 (33.1 to 38.7)	9.4 (6.2 to 12.1)
L gene RT–PCR (Ct)[b]	36.0 (32.5 to 37.3)	8.4 (6.2 to 10.1)	35.4 (33.8 to 37.8)	9.6 (7.5 to 11.4)
Biochemistry				
Albumin ($g\,dl^{-1}$)	3.6 (3.05 to 3.7)	0 (−0.25 to 0.2)	3.5 (3.0 to 4.0)	0.1 (−0.2 to 0.3)
ALT ($U\,l^{-1}$)	45 (23.5 to 98)	−3 (−27 to 15.5)	39 (29 to 57)	-4 (−19 to 2)
AST ($U\,l^{-1}$)	58.5 (34 to 102)	−14 (−40 to 4.5)	47 (30 to 63)	−16 (−31 to 0)
Amylase ($U\,l^{-1}$)	93 (67 to 117)	8 (−2 to 30.5)	81 (50 to 96)	27 (2 to 65)
Bilirubin ($mg\,dl^{-1}$)	0.55 (0.45 to 0.8)	−0.05 (−0.1 to 0)	0.5 (0.4 to 0.8)	0.1 (0 to 0.3)
BUN ($mg\,dl^{-1}$)	9 (6 to 11.5)	−1 (−2 to 0)	7 (6 to 11)	0 (−3 to 1)
Creatinine ($mg\,dl^{-1}$)	0.6 (0.5 to 0.75)	−0.1 (−0.1 to 0)	0.6 (0.6 to 0.8)	0 (−0.1 to 0)
CPK ($U\,l^{-1}$)	373 (133 to 579)	−158 (−366.5 to −30)	373 (167 to 595)	−169 (−340 to 37)
GGT ($U\,l^{-1}$)	70 (38.5 to 110.5)	−0.5 (−14 to 11.5)	54 (33 to 118)	3 (−8 to 11)
Potassium ($mmol\,l^{-1}$)	3.5 (3.25 to 3.85)	0 (−0.5 ;0.5)	3.5 (3.2 to 3.7)	0.1 (−0.3 to 0.4)
Sodium ($mmol\,l^{-1}$)	137.5 (135 to 138.5)	1 (−1 to 3.5)	138 (136 to 139)	2 (1 to 4)
Uric acid ($mg\,dl^{-1}$)	3.05 (2.2 to 4.25)	2.35 (1.75 to 3.55)	3.2 (2.5 to 3.9)	1.9 (1.2 to 2.9)
Hematology				
Granulocytes (%)	56.35 (52 to 63.8)	−5.4 (−9.35 to 1.6)	63 (54.1 to 64.5)	3.8 (−9.4 to 10)
Hematocrit (%)	35.55 (32.05 to 39.95)	−1.6 (−2.55 to −1.1)	37.6 (31.9 to 39.5)	−3.2 (−5.8 to −0.8)
Hemoglobin ($g\,dl^{-1}$)	11.85 (10.45 to 12.9)	−0.45 (−0.9 to 0.8)	12.3 (11 to 13)	−1 (−1.6 to −0.5)
Lymphocytes (%)	35.05 (28.9 to 38)	5.35 (− 2.05 to 9.15)	30.6 (26 to 37.3)	−3 (−9.6 to 5.9)
Monocytes (%)	7.95 (5.75 to 9.4)	0.85 (−3.25 to 1.85)	8 (6 to 8.6)	−0.4 (−2.1 to 0.7)
Platelets ($10^3 mm^{-3}$)	244 (166.5 to 292)	26.5 (−14.5 to 155.5)	270 (213 to 326)	24 (−13 to 79)
Red blood cells ($10^6 mm^{-3}$)	4.25 (3.93 to 4.99)	−0.19 (−0.39 to 0.06)	4.44 (3.83 to 4.78)	−0.37 (−0.68 to −0.12)
White blood cells ($10^3 mm^{-3}$)	5.3 (3.8 to 6.4)	0.75 (−1 to 2.65)	6.1 (5.1 to 6.9)	−0.1 (−1.2 to 0.8)

ALT, alanine aminotransferase; BUN, blood urea nitrogen; GGT, gamma-glutamyl transferase. [a]The change during study follow-up period was calculated considering the difference between the value of the last sample and the value at baseline of each of the 41 participants. A positive and negative difference indicates increase and decrease, respectively, of the values during the study period. [b]As the Ct value for a negative RT–PCR result is not defined, it was set as Ct >45, and the minimum change for the lower boundary (Ct of 46) was calculated.

ribavirin. Considering that pyrexia is also a typical clinical sign of LF, its definition as adverse event as well as the determination of its relatedness relies on the subjective interpretation of the investigator considering its temporal relationship with drug administration and its clinical importance.

A case of first-degree atrioventricular block, defined as a prolonged PR interval, was the cause of discontinuation of favipiravir after 2 days of treatment in the setting of mild hypokalemia (3.2 mmol l^{-1}). The event was asymptomatic and did not require additional medical intervention, but the treatment was interrupted as a precautionary measure to enable a detailed review by the DSMB and an external cardiologist. This and other electrocardiographic alterations observed in this study have been discussed by Erameh et al.[34]. PR prolongation is frequently observed in clinical practice and is mostly considered benign, not requiring any specific intervention in asymptomatic individuals. The etiology of new-onset PR prolongation may include electrolyte imbalances, certain medications and infections resulting in myocarditis[35]. It has also been described before in a patient treated for COVID-19 with favipiravir in a single study[36]. At this stage, on the basis of the evidence that favipiravir can cause oxidative stress and genotoxocity in cardiac cells[37], and a previous report on atrial fibrillation during favipiravir therapy[27], a causal relationship between PR prolongation and the use of favipiravir cannot be completely ruled out. However, in our study, factors such as hypokalemia and LASV-induced myocarditis need to be considered. Further evaluation of this potential adverse drug reaction is, however, warranted in future clinical trials.

An increased risk of hyperuricemia is a known side-effect of favipiravir therapy[38]. A minor increase in the median uric acid levels, without further clinical relevance and being more prominent in the favipiravir arm, was observed in our study. Similarly, increased AST levels which decreased subsequently during the study period were documented in both treatment arms. Hepatitis is a known complication of LF, and AST >150 IU l^{-1} at baseline is a known risk factor for increased mortality[1,39,40]. Although previous data from a meta-analysis suggest that favipiravir may be associated with increased liver enzymes, this was not observed in our study[38].

Viral clearance was comparable between the treatment groups in univariate analysis of Ct values over the study period. In an exploratory analysis of viral kinetics by a linear mixed-effects model, participants treated with ribavirin exhibited a more rapid increase of Ct values compared with favipiravir (0.071 versus 0.047 /h, $P = 0.025$). No other covariate effects on viral load kinetics were identified in this exploratory model. This unexpected finding requires a cautious interpretation. The high baseline Ct values associated with mild LF and the lack of detail about the onset of symptoms before study inclusion introduce substantial bias. In addition, although the baseline Ct value is a relevant prognostic factor[41], the importance of viral kinetics throughout the

course of the disease is uncertain. Therefore, drawing conclusions from these results is challenging.

On the basis of the mode of action of favipiravir as an inhibitor of the RNA-dependent RNA polymerase causing termination of viral replication and induction of missense mutations, it may be speculated that favipiravir exposure leads to multiple circulating RNA fragments with inactive missense mutations that may still be amplified in RT–PCR. This finding may lead to results being interpreted as viral load measurement, whereas, in reality, RT–PCR detection may indicate nonreplicating and biologically inactive remnants. Moreover, ribavirin is thought to exhibit a substantial stabilizing effect on cells through immunomodulatory mechanisms, which may lead to a reduction in shedding of RNA from the intracellular replication process. Thus, Ct values following treatment with favipiravir or ribavirin may not constitute a biologically informative endpoint for the pharmacodynamics of these antiviral drugs. A more refined molecular analysis of the rate of missense mutations will be necessary for a better understanding of this finding. However, these analyses are currently beyond the technical capacities for this biosafety level 4 pathogen.

Pharmacokinetic data from this trial demonstrate consistent, adequate drug exposure over the study period. Modeling indicated that an improved regimen with lower loading dose of favipiravir may similarly lead to sufficient drug exposure while mitigating the risk for adverse drug reactions associated with high peak plasma concentrations. At the same time, a higher maintenance dose could be considered in future studies to further enhance time above IC_{99} under steady-state conditions and thus leading to sustained antiviral activity during treatment. On the basis of this analysis, the following favipiravir regimen is proposed for further clinical development: 2,400 mg twice daily on day 1 followed by 1,600 mg twice daily from day 2 to 10.

The survival and successful discharge of all study participants with full recovery is highly encouraging. Concordantly, at the last study visit, LF symptoms were absent in 16 (76%) of participants receiving ribavirin and in 18 (90%) of participants receiving favipiravir. Fever clearance was observed in 100% and 95% of participants receiving favipiravir and ribavirin, respectively. One participant treated with ribavirin was hospitalized for a duration beyond the study period owing to anemia requiring blood transfusion. This participant also presented drug exposure well above the median levels of the other participants. These factors may be due to advanced age and impaired renal function, but it highlights the importance of the current search for alternative treatment regimens to ribavirin as the current standard of care. Importantly, this study provides evidence that favipiravir may constitute a safe and well-tolerated treatment option for LF, associated with a lesser incidence of anemia, one of the main complications of ribavirin therapy.

This study constitutes a regulatory-compliant, randomized controlled clinical trial evaluating a new treatment for LF, which has not been done for the past four decades. The conduct of this study evaluating a new treatment candidate for LASV in the highest-transmission region of West Africa is a landmark achievement and became only possible on the basis of a highly successful North–South collaboration of the partner institutions over the past two decades. This facilitated continued investment in the establishment of diagnostic, therapeutic and clinical research infrastructures and human resource capacity building and biosafety measures necessary for the successful conduct of a clinical trial involving a high-consequence pathogen. The limitations of this study include the restriction of participants to only mild-to-moderate LF owing to ethical reasons, reducing its direct generalizability to patients with more severe disease. Furthermore, the small sample size limited the study power to detect statistically significant differences between the study arms.

Our results provide important evidence for the pharmacokinetics of favipiravir in the treatment of LF, its safety and efficacy, providing data that support the further clinical evaluation of favipiravir alone or in combination regimens for the treatment of severe LF in later clinical stage trials. In addition, our findings suggest avenues for optimized oral favipiravir dosing regimens for future clinical trials. The further clinical development of favipiravir is currently underway in a large platform trial that aims to identify the next generation of direct antiviral and adjunct treatments for LF (INTEGRATE trial, NCT 06212336 PACTR 202312770983740). This large clinical trial program will allow the evaluation of treatments for LF in regions where the different clinically important LASV lineages circulate. This will potentially pave the way for changes in treatment guidelines by providing evidence-based treatment options for patients with LF.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, Supplementary Information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-026-04402-w.

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Cyril Erameh[1,2,13], Kevin Okwaraeke[3,4,13], Christine Kleist[5], Osahogie Edeawe[1,6], Nelson Adedosu[3], Enomen Ekata[1], Chukwuyem Abejegah[3], Sampson Owhin[3], Femi Babatunde[1], Till Omansen[2], Augusto Meneguim[2], Alexandre Duvignaud[7,8], Johannes Mischlinger[2], Ndapewa Ithete[9], Lisa Oestereich[9,10], Julia Hinzmann[9,10], Liasu Ahmed[3], Sophie Duraffour[9,10], Reuben Eifedyi[1], Sylvanus Okogbenin[1], Peter Akhideno[1], Oladele Oluwafemi Ayodeji[3], Stephan Günther[9,10], Sebastian G. Wicha[5,14], Marie Jaspard[4,11,14], Meike Pahlmann[9,10,14], Michael Ramharter[2,10,12,14] ✉ & Mirjam Groger[2,10,14]

[1]Irrua Specialist Teaching Hospital, Irrua, Nigeria. [2]Center for Tropical Medicine, Bernhard Nocht Institute for Tropical Medicine and Department of Medicine University Medical Center Hamburg-Eppendorf, Hamburg, Germany. [3]Federal Medical Centre, Owo, Nigeria. [4]The Alliance for International Medical Action, Paris, France. [5]Department of Clinical Pharmacy, Institute of Pharmacy, University of Hamburg, Hamburg, Germany. [6]Department of

Pharmacology and Therapeutics, College of Medicine, Ambrose Alli University, Ekpoma, Nigeria. [7]University of Bordeaux, National Institute for Health and Medical Research UMR 1219, Research Institute for Sustainable Development EMR 271, Bordeaux Population Health Research Centre, Bordeaux, France. [8]Department of Infectious Diseases and Tropical Medicine, Groupe Hospitalier Pellegrin, CHU Bordeaux, Bordeaux, France. [9]Department of Virology, Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany. [10]German Center for Infection Research, Partner Site Hamburg–Lübeck–Borstel–Riems, Hamburg, Germany. [11]Sorbonne Université, INSERM, Institut Pierre Louis d'Epidemiologie et de Santé Publique, APHP, Hopital Saint-Antoine, Infectious and Tropical diseases, Paris, France. [12]Centre de Recherches Médicale de Lambaréné, Lambaréné, Gabon. [13]These authors contributed equally: Cyril Erameh, Kevin Okwaraeke. [14]These authors jointly supervised this work: Sebastian G. Wicha, Marie Jaspard, Meike Pahlmann, Michael Ramharter, Mirjam Groger. ✉e-mail: michael.ramharter@ctm.bnitm.de

Methods

Study design

This randomized, controlled, open-label, phase 2 clinical trial 'Pharmacokinetics, Tolerability and Safety of Favipiravir and Ribavirin for the Treatment of Lassa Fever (SAFARI)' was conducted to assess favipiravir for the treatment of LF[42]. Favipiravir was evaluated as investigational drug, and ribavirin was used in the control arm as standard of care. Ribavirin treatment followed the so-called Irrua regimen. The Irrua ribavirin regimen (details provided below) was originally conceived at the Irrua Specialist Teaching Hospital (ISTH) and has since become the current standard of care in Nigeria and other endemic countries[43]. It differs from the original so-called McCormick regimen by using a higher loading dose and subsequent lower total daily dose. Ribavirin is administered once daily in the Irrua regimen to reduce the biohazards for the healthcare personnel while providing constant drug exposure[44].

As per protocol, the primary endpoints were the description of classical pharmacokinetic parameters of favipiravir (for example, maximum plasma concentration, time to reach maximum plasma concentration, AUC, half-life, volume of distribution and so on) in patients with PCR confirmed LF and the proportion of drug-related adverse events and serious adverse events. The secondary endpoints were the mutagenicity of ribavirin and favipiravir measured via nucleotide exchange rate in individual virus genomes (deep sequencing of minor and major variants); the description of RNA concentrations, infectious titers and serological status during treatment; pharmacokinetic modeling and simulation of different loading regimens to characterize time to target concentration attainment; the assessment of covariates impacting drug exposure; and the relationship between drug exposure and viral elimination dynamics, length of hospital stay, mortality and blood component therapy use. Efficacy was included as a secondary endpoint in the study protocol as descriptive analysis of mortality in the respective treatment groups. Owing to the small sample size in phase 2, only preliminary observations can be made on the basis of the available data.

However, owing to limitations in the sensitivity of currently available protocols, no investigations of infectious titers, serological status during treatment or mutagenicity were performed. As neither ribavirin nor favipiravir are expected to induce dominant mutations but rather lead to an increase in the overall mutation rate, minor variant analysis is required. On the basis of the currently established sequencing protocols for LASV with the aim of analyzing the mutation rate, the current cut-off Ct value for the inclusion in the sequencing pipeline is the Ct value of 30. Samples with a lower RNA concentration are, at this stage, not analyzable for full genomes and will have insufficient sequencing depth to draw any meaningful conclusions about mutations occurring due to treatment. As the Ct values in the participant samples from this study were above the required threshold, the analysis of the drug-induced mutations has not been performed.

The two participating study centers ISTH, Edo, and Federal Medical Center of Owo (FMCO), Ondo, are located in the highest-transmission regions of Nigeria and serve as major national LF case management centers equipped with dedicated isolation wards for high-consequence pathogens. The study protocol was registered before study initiation (Clinicaltrials.gov NCT04907682 and PACTR 202010817169062) and has been included in the Supplementary Information. A DSMB composed of independent experts was involved in the oversight of this trial and advised for the safe conduct of the clinical trial. The study was conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines and the Nigerian National Code for Health Research Ethics. Ethical and other applicable regulatory approvals were obtained before the start of the study from the National Health Research Ethics Committee, ISTH Health Research Ethics Committee, FMCO Health Research Ethics Committee, National Agency for Food and Drug Administration and Control and Ethik-Kommission der Ärztekammer Hamburg, Germany.

An amendment of the study protocol was submitted to and approved by the responsible ethics committees and regulatory bodies resulting from the DSMB's recommendations following an unexpected case of PR prolongation in a participant treated with favipiravir. The amended version of the protocol was applicable from the fourth to the last participant. In this amended protocol, additional exclusion criteria were introduced, namely, medical history of clinically relevant cardiac disease, potassium level at screening <3 mmol l^{-1} and PR interval ≥200 ms. Moreover, an ECG reading on day 3 for participants treated with favipiravir was added. As a precautionary measure, the administration of favipiravir had to be discussed with the medical monitor in case of PR interval measurements between 200 and 240 ms, and the drug had to be stopped if the PR interval was ≥240 ms. The amendment also included a reassessment of the risk profile of the high dose of favipiravir by the sponsor and the DSMB after ten treated participants or in the case of occurrence of an important AE. Finally, additional training on study-specific ECG readings, adequate potassium substitution in case of hypokalemia and management of potential cardiac conduction disorders were conducted. During the clinical trial, protocol deviations were identified and documented, and appropriate corrective actions were undertaken. These included the foremost inappropriate timing of procedures in individual participants, as described in Extended Data Table 7.

Eligibility criteria

After providing written informed consent, participants were screened for eligibility.

Inclusion criteria were as follows.

- Age ≥18 years
- LF confirmed by RT–PCR
- Written informed consent

Exclusion criteria were as follows.

- Inability to give consent (for example unconscious patients or cognitively impaired patients)
- Pregnancy/lactation (evidenced by negative urine pregnancy test in women of child-bearing potential)
- Women who plan to become pregnant within the upcoming 6 months
- Severe malnutrition (body mass index <16)
- Known intolerance to ribavirin or favipiravir
- History of hemoglobinopathies (that is, sickle-cell anemia or thalassemia major) and/or hemophilia
- Organ failure as indicated by:
  - Creatinine ≥3× upper limit of normal
  - AST (GOT) >150 IU/l
  - ACVPU scale score of V, P or U
  - Severe central nervous system features (for example, seizures, restlessness, confusion and coma)
  - O_2 saturation <90%
  - Hematocrit <30%
  - Severe anemia requiring blood transfusion
- Inability to take oral drug (for example, encephalopathy and severe vomiting)
- Patients who received ribavirin or favipiravir within the preceding 7 days
- A medical history of clinically relevant cardiac disease, potassium level <3.0 mmol l^{-1} and PR interval ≥200 ms were added as exclusion criteria following a protocol amendment during the conduct of the clinical trial as described above

Study procedures

After confirming the eligibility to the study, participants were randomized to either the Irrua ribavirin regimen or oral favipiravir in a

1:1 ratio. The computer-generated randomization list was previously prepared by the sponsor with stratification per site, without restriction or blocking. Sealed opaque envelopes were prepared holding the treatment allocation. The envelopes were opened in ascending order upon confirmation of study eligibility and after recruitment into the clinical trial. No blinding of therapeutic regimens was performed after treatment allocation considering that study drugs presented distinct administration formulations.

Study participants were hospitalized in the isolation ward following RT–PCR diagnosis of LF until the 10-day treatment was completed. In the control group, participants received intravenous ribavirin (RIBAVIRIN, Jiangsu Ruinian Qianjin Pharmaceutical). The dosing schedule was 100 mg kg^{-1} on day 1 (divided in two thirds initially and one third 8 h later, maximum 7 g day^{-1}), followed by 25 mg kg^{-1} single dose on days 2–7 and 12.5 mg kg^{-1} single dose on days 8–10. In the intervention group, participants received oral favipiravir formulated as 200-mg tablets (AVIGAN, Toyama Pharmaceuticals), in accordance with a previously reported regimen used for Ebola virus disease[21]. The dosing schedule was 6,000 mg on day 1 (divided in 3 doses, 2,400 mg, 2,400 mg and 1,200 mg), followed by 1,200 mg twice daily on days 2–10. Baseline data included demographic information, medical history, physical examination and signs and symptoms of LF. Sex was assigned following an external examination of body characteristics and self-report. Moreover, ECG was performed and repeated on days 0, 2, 4 and 10 and on day 3 for participants receiving favipiravir. Blood sampling for hematology, biochemistry, electrolytes and LASV RT–PCR with quantification of the Ct values were performed before treatment initiation and repeated every other day. ECGs were interpreted by the study physicians and reviewed by a cardiologist appointed by the trial sponsor. Ribavirin and favipiravir plasma concentrations were assessed by blood sampling before drug administration and on days 1, 2, 4, 6, 7, 8 and 10. Furthermore, plasma was collected after drug administration on day 1 (serial samples after 0.5, 1, 3, 5, 8 and 12 h) and on day 7 (serial samples after 1 and 4 h). Blood samples for phamacokinetic analysis were centrifuged, and plasma was stored at −80 °C within 2 h. Aliquots were shipped to Hamburg, Germany, according to UN2814 regulations, and specimens were inactivated in its biosafety level 4 laboratory for further pharmacokinetic analysis at the Department of Clinical Pharmacology at the Institute of Pharmacy, University of Hamburg. The schedule of study procedures is summarized in Extended Data Table 8.

The appearance of TEAEs, occurring after the first dose of the study drug, was systematically monitored and documented by the investigators during the study period. TEAE were assessed in terms of severity, seriousness, expectedness and association with the study drug. They were coded according to the Medical Dictionary for Regulatory Activities (MedDRA version 28.1) The assessment of association of event or laboratory test abnormalities was performed using the following criteria.

- Certain: plausible time relationship to drug intake; not explained by disease or other drugs; response to withdrawal plausible (pharmacologically and pathologically); event definitive pharmacologically or phenomenologically (that is medical disorder or recognized pharmacological phenomenon); rechallenge satisfactory, if necessary
- Probable/likely: reasonable time relationship to drug intake; unlikely to be attributed to disease or other drugs; response to withdrawal clinically reasonable; rechallenge not required
- Possible: reasonable time relationship to drug intake; could also be explained by disease or other drugs; information on drug withdrawal may be lacking or unclear
- Unlikely: time to drug intake that makes relationship improbable (but not impossible); disease or other drugs provide plausible explanations

Withdrawal from the clinical trial was done in case of withdrawal of consent or in case of important worsening of the health condition of the participant according to the judgment of the treating physician or in case of development of severe LF defined by the national guidelines. In this case, treatment was continued according to the standard of care with ribavirin. If a participant was still RT–PCR-positive at the end of the 10-day study follow-up period, treatment could be extended with ribavirin as recommended by the national guidelines[43].

Sample size determination

The sample size of 20 evaluable participants per arm as defined by the sponsor and the sampling schedule provided sufficient data points for the primary endpoint of characterization of the pharmacokinetics of investigated drugs. Sample size and sampling schedule calculations were performed using clinical trial simulations in NONMEM (v. 7.4, ICON Development Solutions). For pharmacokinetics, assuming prior information on ribavirin pharmacokinetics[45], the proposed sampling design allowed us to determine the structural pharmacokinetic parameters with low absolute relative bias (<2.7%) and low imprecision (<18%). The design also supported the adequate estimation of the pharmacokinetic variability components (interindividual variability: absolute relative bias <3.4%, imprecision <62.0%; intraindividual variability: absolute relative bias <−0.6%, imprecision 4.4%). For favipiravir, an a priori calculation of the optimal sampling time points was not possible owing to the lack of robust prior knowledge on the pharmacokinetics at the time of the conception of the clinical trial protocol, although this has been established posteriorly[29,46,47]. To evaluate the potential link between pharmacokinetics and pharmacodynamics (viral kinetics) in an exploratory analysis, the here-applied sampling schedule of viral load allowed to detect even weak exposure response relations (ribavirin-induced decline in viral load with a viral elimination half-life of 480 h compared with no effect assuming high interpatient variability in pharmacodynamic response of 70% and pharmacodynamic measurement error of 30%) at a statistical power of 99% with adequate accuracy (absolute relative bias <17.3%) and imprecision (<33.2%). Moreover, using the viral kinetic data, differences of 25% in the viral elimination kinetics were detectable between the trial arms with high power (94.4%) and adequate precision (absolute relative bias 1.4%, imprecision 23.5%). We considered this to be appropriate for a phase 2 study, and the sampling schedule was designed to be intensive but pragmatic and achievable for the field conditions.

Statistical analysis

The statistical analysis was defined in a statistical analysis plan. Two study populations were defined. The per-protocol population included all participants randomized and followed-up according to the study protocol. This population was used for efficacy and pharmacometrics analysis. The modified intention-to-treat population included all participants that received at least one dose of the study drugs and was used for the analysis of safety and tolerability. Study data were aggregated for descriptive analysis according to the treatment arm. Quantitative data were described in medians and IQRs and categorical data as numbers and proportions. TEAEs whose association with the study drug was considered certain, probable/likely or possible were classified as drug-related TEAEs.

The objectives of the analyses on the population pharmacokinetics of ribavirin and favipiravir was predefined in the clinical trial protocol and statistical analysis plan following standard pharmacokinetic analysis processes, which were facilitated using NONMEM (Version 7.5, ICON) using first-order conditional estimation with interaction. For favipiravir, one- and two-compartment models with oral absorption and first-order or Michaelis–Menten elimination were tested as structural models. For ribavirin, one-, two- and three-compartment models were assessed as structural model. Interindividual variability and interoccasion variability was evaluated on the structural phamacokinetic parameters assuming a log-normal distribution. Body weight (including allometric scaling), body mass index, ideal body weight

(equations of McCarron and Devine)[48], serum creatinine, bilirubin, uric acid and sex were evaluated as potential covariates on the phamacokinetic parameters. The pharmacodynamics of the study drugs on the LASV were described by a linear mixed-effects model. The increase of the Ct values of the *GPC* gene was modeled with an approach similar to Thielebein et al.[49]. The parameter Ct_0 describes the baseline value at the time of the study inclusion, and α describes the increase of the Ct value per hour ($Ct = CT_0 + \alpha \times t$). Interindividual variation was evaluated on both model parameters (that is, Ct_0 and α) assuming a normal distribution. The M3 method[50,51] was used to handle Ct values above the upper limit of quantification. The potential influence of the categorical covariates sex, study drug (favipiravir or ribavirin) and study site on Ct_0 and α were tested, as prespecified in the statistical analysis plan. Further AUC, maximum serum concentration (C_{max}) and apparent clearance (CL/*F*) were tested on slope, using the pharmacokinetics of the drugs as continuous covariates. The same approach was used to model the Ct values of the *L* gene.

The (prediction-corrected) visual predictive checks, goodness-of-fit plots and the difference in the objective function value were used to guide the model selection. The likelihood ratio test (delta objective function value of −3.84, df of 1, $\alpha = 0.05$) was used to compare nested models. For the comparison of non-nested models, the model selection was guided by the Akaike information criterion. For covariate testing on phamacokinetics and pharmacodynamics, the stepwise covariate modeling procedure was used using the likelihood ratio test ($\alpha = 0.05$ during forward selection and $\alpha = 0.01$ during backward elimination). Parameter uncertainty was quantified by a nonparametric bootstrap ($n = 1{,}500$ samples). The final favipiravir population pharmacokinetic model was used for Monte Carlo simulations assessing the time favipiravir exceeds the IC_{50} (29.3 µM, equal to 4.60 mg l^{-1}), IC_{90} (43.2 µM, equal to 6.79 mg l^{-1}) or IC_{99} (69.6 µM, equal to 10.93 mg l^{-1})[24]. The study dosing regimen was simulated as well as different dosing regimen with loading doses ranging from 2,000 mg twice daily to 2,400 mg twice daily and maintenance doses ranging from 1,200 mg twice daily to 2,400 mg twice daily (Extended Data Table 5). The time above IC_{50}, IC_{90} or IC_{99} of unbound concentrations for each dosing regimen was calculated. Body weight was sampled from the mean and variance of the study population assuming a log-normal distribution. The fraction unbound was set to 0.456 (ref. 52).

Missing data was treated as such in the safety analysis. However, in case of laboratory test results reporting measurements levels below the limit of detection, the imputation of half of the lower limit of detection was applied. In the case of results above the limit of detection, the imputation of upper limit of detection plus one was applied. In the case of missing values of the plasma concentration of the drugs, all nonmissing observations in the series were used. In the case that measured drug concentrations fell below the quantification limit of the bioanalytical methods, appropriate techniques, for example, the so-called M3 method, was used to handle these data points[50]. In case of missing covariates, the population mean of this covariate was imputed for the analysis. Data collected from source documentation were recorded in REDCap (version 10.0.25). Data analysis was performed using STATA (version 17; StataCorp) and NONMEM (Version 7.5, ICON).

Ethics and inclusion statement

This study was conducted within the framework of a long-term partnership of the German and French institutions with the ISTH and the Federal Medical Centre Owo, Nigeria. These institutional collaborations have been established for more than 15 years and are based on an equitable partnership and clear capacity building plan. This equitable partnership forms the basis for the successful conduct of this first interventional clinical trial for next generation LF drugs since four decades. The governance of the clinical trial was shared between the Northern and Southern partners, with principal investigators and lead investigators represented by the Nigerian institutions. Both reference treatment centers are located in the hyperendemic LF regions of Nigeria; hence, they are the primary beneficiaries of the findings of this study, along with the population served by them. The study was conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines and the Nigerian National Code for Health Research Ethics. Ethical and other applicable regulatory approvals were obtained from all study sites before the start of the study from the National Health Research Ethics Committee (NHREC/01/01/2007-14/09/2020), ISTH Health Research Ethics Committee (ISTH/HREC/20201711/128), FMCO Health Research Ethics Committee (FMC/OW/380/VOL.CX/131), National Agency for Food and Drug Administration and Control (NAF/DER/LAG/V&CT/RIBAVIRIN/2021/1) and Ethik-Kommission der Ärztekammer Hamburg, Germany (2020-10299-BO-ff).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The primary data that support the findings of this study are not publicly available owing to legal restrictions on patient privacy, but a deidentified individual-level dataset will be available upon publication of this Article for 25 years upon request to the corresponding author (michael.ramharter@ctm.bnitm.de). The sponsor and the trial steering committee are committed to open data policies and encourage and support the reuse of the data from this clinical trial. Requests for reuse of data should be submitted along with a justification for the research questions, the responsible institutions and individuals and the academic or commercial purposes of the analysis of the data. Each request will be reviewed by the trial steering committee and sponsor of the clinical trial considering the scientific validity of the proposed project, compliance with ethical and legal standards and the protection of participant confidentiality. A decision will be shared within 1 month. If agreed, a signed agreement with the sponsor, a data sharing agreement and request for approval by the responsible ethics committee are required before the data can be accessed.

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Author contributions

M.R., S.G., S.G.W., M.G., S.D., S. Okogbenin, C.E. and M.J. conceptualized the study. M.R., M.G., C.K., L.O., S.D., R.E. and A.D. established the methodology. M.P., T.O., A.M., J.M., N.I. and L.O. handled validation. J.M., A.M. and C.K. performed the formal analysis. C.E., K.O., O.E., E.E., N.A., C.A., S. Okogbenin, S.D., F.B., R.E., J.H., P.A. and O.O.A. carried out the investigation. M.P., N.I., L.O., J.H. and M.G. provided resources. M.P., N.I., J.H. and C.K. curated the data. A.M. and M.R. drafted the manuscript. M.G., C.E., S.G.W., M.J., S.G., C.E., K.O., C.K., M.P., O.E., L.O., S.D., F.B., J.H., N.A., E.E., C.A., R.E., S. Owhin, W.O., A.M., A.D., J.M., N.I., L.A., S. Okogbenin, P.A. and O.O.A. reviewed and edited the manuscript. C.K., A.M. and J.M. created the visualizations. M.R., S.G., S.G.W., S. Okogbenin and L.A. supervised the study. M.G., M.P., P.A., C.E., O.O.A., S. Okogbenin and K.O. managed project administration. S.G., M.G., M.P., S.D., M.R. and L.O. acquired funding.

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to Michael Ramharter.

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