ORIGINAL ARTICLE

Tecovirimat for Clade I MPXV Infection in the Democratic Republic of Congo

The PALM007 Writing Group

ABSTRACT

BACKGROUND

Tecovirimat is available for the treatment of mpox (formerly known as monkeypox) in Europe and the United States, on the basis of findings from efficacy studies in animals and safety evaluations in healthy humans. Evidence from randomized, controlled trials of safety and efficacy in patients with mpox is lacking.

METHODS

We conducted a double-blind, randomized, placebo-controlled trial of tecovirimat in patients with mpox in the Democratic Republic of Congo (DRC). Patients with at least one mpox skin lesion and positive polymerase-chain-reaction results for clade I MPXV were assigned in a 1:1 ratio to receive tecovirimat or placebo. All patients received supportive care. The primary end point was resolution of mpox lesions, measured in number of days after randomization. Safety was also assessed.

RESULTS

From October 7, 2022, through July 9, 2024, a total of 597 patients underwent randomization — 295 to receive tecovirimat and 302 to receive placebo. The median time from randomization to lesion resolution was 7 days with tecovirimat and 8 days with placebo; the competing-risks hazard ratio for lesion resolution was 1.13 (95% confidence interval [CI], 0.97 to 1.31; P=0.14). Results were similar whether patients began the trial regimen within 7 days after the reported onset of symptoms (competing-risks hazard ratio, 1.16; 95% CI, 0.98 to 1.37) or more than 7 days after onset (competing-risks hazard ratio, 1.00; 95% CI, 0.71 to 1.40). Overall mortality was 1.7%, which was lower than the case fatality rate of 4.6% reported in the DRC in 2023. At 14 days, the percentages of patients who had blood, lesion, and oropharyngeal samples negative for MPXV by PCR were similar in the two groups. Adverse events occurred in 72.9% of the patients in the tecovirimat group and 70.5% of those in the placebo group, and serious adverse events were reported in 5.1% and 5.0%, respectively.

CONCLUSIONS

Tecovirimat did not reduce the number of days to lesion resolution in patients with mpox caused by clade I MPXV. No safety concerns were identified. (Funded by the National Institute of Allergy and Infectious Diseases and others; PALM007 ClinicalTrials.gov number, NCT05559099.)

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Cases of mpox (formerly known as monkeypox) are increasing in sub-Saharan Africa, particularly in the Democratic Republic of Congo (DRC), where the first human infection was identified in 1970. The increasing burden of mpox is due, in part, to a growing population without cross-protective immunity after cessation of smallpox vaccination in the early 1980s.[1,2] Case fatality rates and morbidity associated with clade I MPXV have been high historically.[3] Given the absence of specific therapies, clinical management of mpox has relied on supportive care.

Tecovirimat, originally developed for the treatment of smallpox, is an oral orthopoxvirus-selective antiviral agent with activity against MPXV in nonhuman primate models.[4] Tecovirimat prevents the release of viral particles from infected cells by inhibiting viral envelopment during the final stages of viral maturation.[5] The safety profile of tecovirimat was established in trials involving healthy volunteers.[4,6] In early 2021, a government-to-government partnership between the Institut National de la Recherche Biomédicale (INRB) of the DRC Ministry of Health and the National Institute of Allergy and Infectious Diseases (NIAID) — known as PALM (Pamoja Tulinde Maisha; "Together, Save Lives" in the Kiswahili language) — began planning the PALM007 trial to evaluate the safety and efficacy of tecovirimat for the treatment of adult and pediatric patients with mpox caused by clade I MPXV.

In 2022, a worldwide outbreak of clade IIb MPXV led to more than 90,000 cases of mpox,[7] declaration of a Public Health Emergency of International Concern (PHEIC),[8] and renewed interest in effective therapeutics for mpox. Widespread human-to-human transmission of MPXV and the high morbidity among those infected placed mpox treatments at the forefront of public health and scientific research agendas in many countries. Tecovirimat is being evaluated as a potential therapeutic for mpox from clade IIb in trials such as STOMP (Study of Tecovirimat for Human Mpox Virus; ClinicalTrials.gov number, NCT05534984), UNITY (Assessment of the Efficacy and Safety of Tecovirimat in Patients with Monkeypox Virus Disease; NCT05597735), and EPOXI (European Randomized Clinical Trial on Mpox Infection; NCT06156566).

In the DRC, the incidence of mpox increased from 2.96 cases per 100,000 in 2010 to 11.5 per 100,000 in 2023.[9] Furthermore, cases have been detected in previously unaffected regions of the DRC. Since late 2023, a newly identified clade Ib MPXV variant has been associated with a large outbreak in eastern DRC that is notable for increased human-to-human spread, including sexual transmission,[10] and limited zoonotic spillover. In response to the upsurge in the DRC and cross-border spread to countries where mpox is not endemic, the World Health Organization (WHO) declared a new PHEIC on August 14, 2024,[11] a move that highlighted the need to identify an effective therapeutic.

Although tecovirimat was approved for the treatment of mpox by the European Medicines Agency and made available in the United States under an expanded-access investigational new drug application, the efficacy of tecovirimat in mpox remains unknown. Here, we report results from PALM007, a randomized, placebo-controlled trial of the safety and efficacy of tecovirimat for the treatment of clade I MPXV mpox in Congolese patients in a region with endemic disease.

A Quick Take is available at NEJM.org

METHODS

TRIAL DESIGN

We conducted this double-blind, randomized, controlled trial to compare tecovirimat, administered orally over 14 days, with placebo in patients with mpox. Patients with at least one mpox skin lesion who tested positive for MPXV by a polymerase-chain-reaction (PCR) assay of a blood, oropharyngeal, or skin-lesion sample were eligible for the trial, regardless of age or pregnancy status. Patients were excluded if they weighed less than 3 kg, had severe anemia (specified as a hemoglobin level of <7 g per deciliter), or were currently using (or were planning to use) meglitinide or midazolam. All patients or their legal guardians provided written informed consent. In addition, written assent was obtained from children 12 to 17 years of age, as required in the DRC.

Enrolled patients were randomly assigned in a 1:1 ratio to receive tecovirimat or placebo and were stratified according to the number of days since the onset of symptoms (≤7 days versus >7 days)

and the trial site. Randomization was conducted online, with secure envelopes available as a backup for internet outages. Pharmacists performed randomization with knowledge of patients' weights for the purpose of determining doses and prepared medications in a restricted-access pharmacy but had no contact with patients.

The resolution of mpox lesions, measured as the number of days from randomization to the first day on which all skin lesions were scabbed or desquamated, was the primary end point, chosen on the basis of analyses of data from Pittman et al.[12] as a marker of the end of clinical disease. Mucosal lesions were not included in the primary end point. All patients were hospitalized for the 14-day dosing period and then discharged when lesions resolved and two consecutive blood samples were negative for MPXV by PCR. Patients attended a follow-up visit 28 days after randomization, with an optional visit at 58 days. Full details of the trial design are provided in the protocol, available with the full text of this article at NEJM.org.

TRIAL OVERSIGHT AND CONDUCT

The trial was approved by the ethics committee of the School of Public Health, University of Kinshasa, and authorized by the Congolese Pharmaceutical Regulatory Authority (ACOREP). An independent data and safety monitoring board oversaw the trial. The protocol was carried out in compliance with the International Council for Harmonisation E6 guidelines for Good Clinical Practice. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

The trial was conducted at Tunda and Kole general reference hospitals in Maniema and Sankuru provinces, respectively, by trained local staff, with oversight provided by the INRB. Kinshasa-based staff rotated between sites regularly, with 2-month site rotations and interim rest periods, to ensure across-site standardization.

PROCEDURES

Patients were evaluated by site clinicians daily throughout hospitalization for mpox-related signs and symptoms, complications, and abnormalities in laboratory test results. Malnutrition status (severe acute, moderate acute, or none) was assessed at baseline and managed daily throughout hospitalization (Table S2 in the Supplementary Appendix, available at NEJM.org) by site clinicians and nutritionists.

All patients received supportive care, including symptom relief, nutritional support, skin care, and oropharyngeal care. When indicated, intravenous fluid, correction of hypoglycemia and electrolyte abnormalities, blood transfusion, antimalarial agents, broad-spectrum antibiotics, and antifungal treatment were provided. All participants who did not require treatment with broader-spectrum antibiotics received prophylactic treatment with cloxacillin.

The tecovirimat dose was based on body weight according to specifications listed in the protocol (section 6.2). Patients who weighed less than 13 kg were given fractional capsule doses not covered by approved labeling. Patients received three meals per day and were evaluated daily by trial nutritionists to ensure intake of at least 600 kcal of high-fat food before the trial product was administered.

Psychological support was provided to all participants throughout the trial. A social mobilization and communication team engaged local communities to raise awareness about mpox and clinical research and to address rumors.

END POINTS AND ASSESSMENTS

To measure the primary end point (lesion resolution), a dermatologist or trained clinician assessed lesions daily until resolution occurred. Whole-body counts of unresolved lesions were performed at baseline, and illness severity was classified according to modified WHO criteria based on the number of lesions (Table S1).[13]

During the trial, new lesions developed in some patients after initial lesion resolution. An optional visit was added to identify recrudescent disease, with confirmed recrudescence specified as the presence of new skin lesions consistent with mpox and an MPXV-positive result from a PCR assay of a skin swab specimen or blood sample. Cases without confirmatory PCR results available for skin or blood samples were deemed probable recrudescent cases. A primary-end-point adjudication committee whose members were unaware of trial-group assignments reviewed all potential cases and identified cases of confirmed and probable recrudescence.

Real-time PCR testing for MPXV in blood and oropharyngeal samples occurred every other day until two consecutive negative results were

obtained or until discharge from the hospital. PCR testing of lesion specimens was performed every other day until lesion resolution. At each site, MPXV nucleic acid was detected with the use of the RADI platform (KH Medical) mpox detection kit with specific fluorescence channels for clade I MPXV, clade II MPXV, and generic orthopoxvirus. Real-time PCR cycle-threshold values less than 40 were considered to indicate positive results, according to manufacturer guidelines. Samples were stored for MPXV sequencing.

Details about point-of-care clinical laboratory testing and pharmacokinetic processing are provided in the Supplementary Appendix. Rapid diagnostic testing for malaria was conducted at baseline and during treatment, if indicated. Pregnancy status was determined in all female patients of childbearing age. Serologic testing for human immunodeficiency virus type 1 (HIV-1) was performed retrospectively.

Before patients received their scheduled dose of tecovirimat or placebo on day 7, pharmacokinetic analyses were performed to determine the steady-state concentration of tecovirimat with the use of a validated high-performance liquid chromatography–tandem mass spectrometry method.[14] The targeted concentration of at least 169 ng per milliliter was based on findings from a study involving nonhuman primates.[4]

SAFETY ASSESSMENTS

Adverse events were assessed daily from trial enrollment through hospital discharge and at follow-up visits. Grading criteria are provided in the protocol. All pregnancy outcomes were documented.

STATISTICAL ANALYSIS

The primary analysis was performed in the intention-to-treat population; we evaluated differences between groups in the number of days to lesion resolution using Gray's test of the competing-risks hazard ratio (also known as the subdistribution hazard ratio)[15] to account for death as a competing event, with the patients stratified according to the onset of symptoms (≤7 days vs. >7 days before randomization). Given the low mortality, results from the Fine–Gray and Cox proportional-hazards models (with deaths censored at 28 days) are similar.[16] Results from Cox models and Kaplan–Meier estimates are reported in addition to Fine–Gray results for the primary analysis (and are the only values reported for other analyses). When applicable, censoring was applied on the day of confirmed recrudescence. Longitudinal analyses of virologic results included the last observation carried forward and imputation of PCR values for skin-lesion specimens as negative for MPXV after lesion resolution, when PCR testing stopped.

We calculated that 318 resolution events would provide the trial with 85% power to detect a 40% reduction in the time to lesion resolution, with a two-sided type I error rate of 5%. As a result of the unexpectedly high influx of patients, the target was increased to 550 resolution events, without knowledge of interim data. The full statistical analysis plan, which includes prespecified secondary and subgroup analyses and interim monitoring procedures, is available in the Supplementary Appendix. A post hoc analysis adjusted for site-specific imbalances in disease severity and trial-group assignment, as described in the Supplementary Appendix.

RESULTS

PATIENTS

From October 7, 2022, through July 9, 2024, we screened 793 patients; 616 tested positive for clade I MPXV, and 597 underwent randomization — 295 to receive tecovirimat and 302 to receive placebo (Table 1 and Fig. S1).

At baseline, the majority of patients (64.3%) were less than 18 years of age; 48.9% were female. Most (79.2%) underwent randomization within 7 days after the reported onset of symptoms; 65.0% presented with disease categorized as severe or grave (i.e., >100 lesions) according to WHO criteria. The mean (±SD) lesion count was 487±994 (median, 185; range, 1 to 10,264). The baseline PCR result was positive for MPXV in 96.5% of lesion specimens, 87.2% of oropharyngeal swab specimens, and 54.0% of blood samples. Malaria was diagnosed and treated in 19.6% of patients at baseline. Moderate or severe malnutrition was recorded in 18.6% of cases. Four patients (0.7%) were seropositive for HIV-1 infection and were referred for care. Pregnancy was observed in 16 patients. Baseline characteristics were similar in the two groups, although the tecovirimat group included a slightly higher percentage of patients with severe or grave illness than the placebo group (67.5% vs. 62.6%) (Table 1).

Table 1. Baseline Demographic and Clinical Characteristics in the Intention-to-Treat Population.*

Characteristic	Overall		Onset ≤7 Days before Randomization		Onset >7 Days before Randomization	
	Tecovirimat (N=295)	Placebo (N=302)	Tecovirimat (N=234)	Placebo (N=239)	Tecovirimat (N=61)	Placebo (N=63)
Trial site — no. (%)						
Tunda	155 (52.5)	158 (52.3)	120 (51.3)	122 (51.0)	35 (57)	36 (57)
Kole	140 (47.5)	144 (47.7)	114 (48.7)	117 (49.0)	26 (43)	27 (43)
Age†						
Median (IQR) — yr	13.0 (5.0–24.0)	10.0 (5.0–23.0)	13.0 (4.0–23.0)	11.0 (5.0–24.0)	13.0 (7.0–25.0)	10.0 (4.5–20.5)
Mean — yr	16.4±13.9	15.3±13.9	16.2±14.1	15.4±13.7	16.9±13.1	15.1±15.0
Range — yr	0–71	0–65	0–71	0–65	0–43	1–59
Category — no. (%)						
<2 yr	29 (9.8)	37 (12.3)	23 (9.8)	30 (12.6)	6 (10)	7 (11)
2 to <5 yr	44 (14.9)	37 (12.3)	38 (16.2)	28 (11.7)	6 (10)	9 (14)
5 to <13 yr	70 (23.7)	96 (31.8)	53 (22.6)	75 (31.4)	17 (28)	21 (33)
13 to <18 yr	41 (13.9)	30 (9.9)	32 (13.7)	23 (9.6)	9 (15)	7 (11)
≥18 yr	111 (37.6)	102 (33.8)	88 (37.6)	83 (34.7)	23 (38)	19 (30)
Female sex — no. (%)	141 (47.8)	151 (50.0)	107 (45.7)	124 (51.9)	34 (56)	27 (43)
Days since onset of symptoms						
Mean	5.9±2.5	5.9±2.8	5.0±1.4	4.9±1.5	9.6±2.1	10.1±2.7
Range	2–16	2–21	2–7	2–7	8–16	8–21
Lesion count						
Median (IQR)	208 (68–440)	178 (62–517)	194 (71–404)	160 (66–500)	226 (57–496)	227 (52–564)
Mean	492±1081	482±902	464±1103	475±897	600±993	511±929
Range	5–10,264	1–8528	5–10,264	1–8528	6–4730	1–5896
Illness severity — no. (%)‡						
Mild	33 (11.2)	42 (13.9)	25 (10.7)	32 (13.4)	8 (13)	10 (16)
Moderate	63 (21.4)	71 (23.5)	50 (21.4)	58 (24.3)	13 (21)	13 (21)
Severe	78 (26.4)	69 (22.8)	64 (27.4)	59 (24.7)	14 (23)	10 (16)
Grave	121 (41.0)	120 (39.7)	95 (40.6)	90 (37.7)	26 (43)	30 (48)

Positivity for clade I MPXV — no./no. tested (%)§						
Blood samples	160/294 (54.4)	162/302 (53.6)	125/233 (53.6)	127/239 (53.1)	35/61 (57)	35/63 (56)
Lesion specimens	280/294 (95.2)	291/298 (97.7)	223/234 (95.3)	232/237 (97.9)	57/60 (95)	59/61 (97)
Oropharyngeal swab specimens	260/294 (88.4)	259/301 (86.0)	204/233 (87.6)	205/239 (85.8)	56/61 (92)	54/62 (87)
Coexisting conditions						
Malaria — no./no. tested (%)¶	54/283 (19.1)	58/287 (20.2)	47/225 (20.9)	40/227 (17.6)	7/58 (12)	18/60 (30)
HIV infection — no./no. tested (%)	3/295 (1.0)	1/302 (0.3)	1/234 (0.4)	1/239 (0.4)	2/61 (3)	0/63 (0)
Other infection — no. (%)‖	17 (5.8)	18 (6.0)	14 (6.0)	15 (6.3)	3 (5)	3 (5)
Lymphadenopathy — no. (%)	270 (91.5)	267 (88.4)	214 (91.5)	211 (88.3)	56 (92)	56 (89)
Nutritional status — no. (%)						
Good nutritional status	242 (82.0)	244 (80.8)	193 (82.5)	191 (79.9)	49 (80)	53 (84)
Moderate acute malnutrition	37 (12.5)	38 (12.6)	27 (11.5)	32 (13.4)	10 (16)	6 (10)
Severe acute malnutrition	16 (5.4)	20 (6.6)	14 (6.0)	16 (6.7)	2 (3)	4 (6)
Previous smallpox vaccination — no. (%)	12 (4.1)	13 (4.3)	12 (5.1)	10 (4.2)	0 (0)	3 (5)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. HIV denotes human immunodeficiency virus, IQR interquartile range, and MPXV the virus that causes mpox.
† Patients less than 1 year of age were represented as having an age of 0 years.
‡ World Health Organization (WHO) criteria were used to assess the severity of disease as mild (1 to 25 lesions), moderate (26 to 100 lesions), severe (101 to 250 lesions), or grave (>250 lesions).
§ Samples were tested with a polymerase-chain-reaction (PCR) assay.
¶ Results from malaria rapid tests at baseline are presented. Patients taking antimalarial medications may test negative.
‖ Other infection includes all other infections reported by patients at baseline: tuberculosis; skin infections; urinary tract infections; ear, nose, and throat infections; pulmonary infections; gastrointestinal infections; genitourinary infections; dental caries; conjunctivitis; meningitis; and mycosis.

Table 2. Efficacy and Safety End Points Overall and According to Symptom Onset in the Intention-to-Treat Population.

End Point	Overall			Onset ≤7 Days before Randomization			Onset >7 Days before Randomization		
	Tecovirimat (N=295)	Placebo (N=302)	Hazard Ratio (95% CI)*	Tecovirimat (N=234)	Placebo (N=239)	Hazard Ratio (95% CI)*	Tecovirimat (N=61)	Placebo (N=63)	Hazard Ratio (95% CI)*
Lesion resolution									
Resolution at 28 days — no. (%)	288 (97.6)	295 (97.7)		230 (98.3)	234 (97.9)		58 (95)	61 (97)	
Median days to resolution (95% CI)†	7 (7–8)	8 (7–9)	1.13 (0.97–1.31)‡	7 (7–8)	8 (7–8)	1.16 (0.98–1.37)	8 (7–10)	8 (7–11)	1.00 (0.71–1.40)
Death§¶									
Within 28 days									
No. of patients	3	4		2	2		1	2	
Percent (95% CI)	1.0 (0.3–2.9)	1.3 (0.5–3.4)		0.9 (0.2–3.1)	0.8 (0.2–3.0)		2 (0–9)	3 (1–11)	
Within 58 days									
No. of patients	5	5		3	3		2	2	
Percent (95% CI)	1.7 (0.7–3.9)	1.7 (0.7–3.8)		1.3 (0.4–3.7)	1.3 (0.4–3.6)		3 (1–11)	3 (1–11)	
Negativity for MPXV at 14 days§									
Blood samples									
No./no. positive at baseline	140/160	141/162		111/125	113/127		29/35	28/35	
Percent (95% CI)	87.5 (81.5–91.8)	87.0 (81.0–91.4)		88.8 (82.1–93.2)	89.0 (82.3–93.3)		83 (67–92)	80 (64–90)	
Oropharyngeal swab specimens									
No./no. positive at baseline	144/260	136/259		110/204	108/205		34/56	28/54	
Percent (95% CI)	55.4 (49.3–61.3)	52.5 (46.4–58.5)		53.9 (47.1–60.6)	52.7 (45.9–59.4)		61 (48–72)	52 (39–65)	
Lesion specimens									
No. of patients with lesion resolution or negative result/no. positive at baseline‖	256/280	259/291		208/223	209/232		48/57	50/59	
Percent (95% CI)	91.4 (87.6–94.2)	89.0 (84.9–92.1)		93.3 (89.2–95.9)	90.1 (85.6–93.3)		84 (73–91)	85 (73–92)	
Pregnancy status or result									
Pregnancy at baseline — no.	8	8		6	7		2	1	
Live birth — no. (%)	4 (50)	4 (50)		3 (50)	4 (57)		1 (50)	0 (0)	
Death of fetus — no. (%)	4 (50)	3 (38)		3 (50)	2 (29)		1 (50)	1 (100)	
Pregnancy ongoing — no. (%)	0	1 (12)		0	1 (14)		0	0	

* The Fine–Gray competing-risks hazard ratio is shown. Competing-risks hazard ratios were estimated with the use of a Fine–Gray subdistribution hazard model in which death was treated as a competing event with respect to the event of interest, lesion resolution. The primary analysis was based on a test for the statistical significance of the competing-risks hazard ratio (Gray's test) with stratification according to the timing of symptom onset (≤7 days vs. >7 days before randomization). Cox hazard ratios were 1.15 (95% confidence interval [CI], 0.98 to 1.36) for patients overall, 1.20 (95% CI, 1.00 to 1.44) for those with symptom onset within 7 days before randomization, and 1.00 (95% CI, 0.70 to 1.43) for those with symptom onset more than 7 days before randomization.
† The median days to lesion resolution was estimated by the Kaplan–Meier method, with data from patients who died within 28 days after randomization censored at 28 days.
‡ P=0.14.
§ Confidence intervals for percentages were calculated by Wilson's method.
¶ Causes of death among patients receiving tecovirimat were septic shock (2 patients), mixed shock (1 patient), hepatic failure (1 patient), and complicated malaria (1 patient); causes of death among patients receiving placebo were septic shock (3 patients), hypovolemic shock (1 patient), and peritonitis (1 patient).
‖ Patients who had lesion resolution on or before day 14 after randomization were considered to be negative for MPXV if no valid PCR data were available.

PRIMARY ANALYSIS (INTENTION-TO-TREAT POPULATION)

The stratified competing-risks hazard ratio for days to lesion resolution was 1.13 (95% confidence interval [CI], 0.97 to 1.31; P=0.14), with an estimated one-day improvement in the median days to resolution with tecovirimat as compared with placebo (7 days vs. 8 days). Results were similar when patients were stratified according to the timing of symptom onset; the competing-risks hazard ratio was 1.16 (95% CI, 0.98 to 1.37) for patients with symptom onset within 7 days before randomization and 1.00 (95% CI, 0.71 to 1.40) for patients with onset more than 7 days before randomization (Table 2 and Fig. 1).

SECONDARY ANALYSES

A total of 10 patients (1.7%) died, 5 in each trial group, within 58 days after randomization. Of 16 pregnancies, 7 (44%) ended in intrauterine fetal demise, with no differences between trial groups (Table 2).

At 14 days after randomization, 281 of 322 blood samples (87.3%) tested negative for MPXV by PCR, and 515 of 571 patients (90.2%) either had lesion resolution or had lesion specimens test negative for MPXV by PCR. Only 280 of 519 oropharyngeal samples (53.9%) had a negative PCR result by day 14. There was no difference between the trial groups in the results according to sample type (blood, lesion, or oropharyngeal samples) (Table 2 and Fig. 2).

Prespecified subgroup analyses suggested a treatment-by-site interaction (hazard ratio, 1.59; 95% CI, 1.15 to 2.21), with a treatment effect in Kole but not in Tunda. In Kole, the median time to resolution was 7 days (95% CI, 7 to 8 days) with tecovirimat and 9 days (95% CI, 8 to 10 days) with placebo (Figs. 3 and S3 and Tables S13 and S14). Overall, illness severity based on the percentage of patients with disease rated as severe or grave was greater in Kole than in Tunda (73.2% vs. 57.5%) (Table S3). However, at baseline, more patients assigned to receive tecovirimat in Kole had less severe disease than those assigned to receive placebo, whereas in Tunda the opposite asymmetry was noted (Fig. S18). Models that adjusted for baseline imbalances in lesion counts and PCR cycle-threshold values for blood, oropharyngeal, and skin-lesion samples were explored. With these adjustments, no interaction of treatment effect with site was

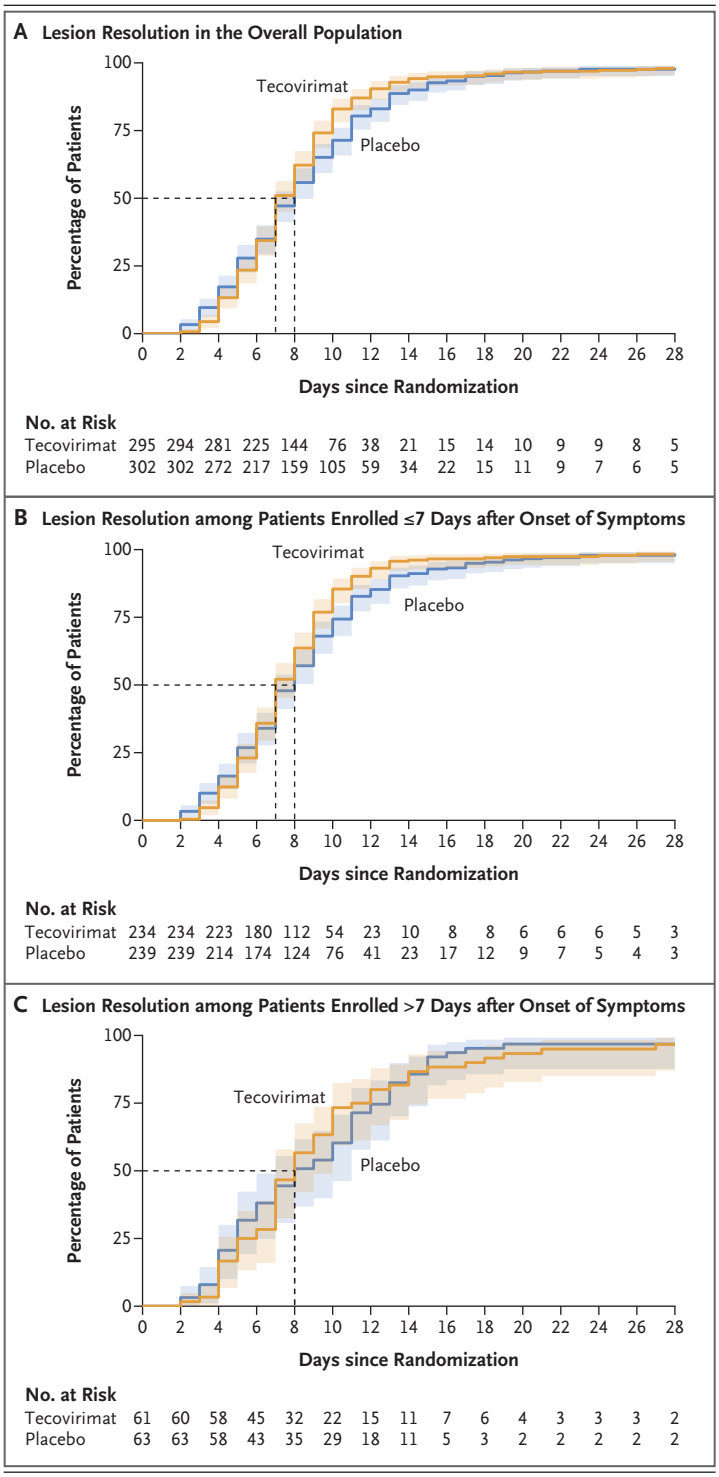

Figure 1. Cumulative Incidence of Lesion Resolution in the Intention-to-Treat Population.

Shown are Kaplan–Meier estimates of the cumulative incidence of lesion resolution in the overall population (Panel A), among those enrolled within 7 days after symptom onset (Panel B), and among those enrolled more than 7 days after symptom onset (Panel C). Dashed lines indicate the day on which 50% of patients had lesion resolution.

observed (Table S21). Site-based analyses of virologic end points over time did not show an independent enhanced rate of negative PCR results (across all sample types) with tecovirimat as compared with placebo (Fig. S6).

The adjudication committee identified a total of 20 cases of recrudescence that were either confirmed (12 cases) or probable (8 cases) among 27 evaluated; 55% of patients with recrudescence (11 of 20) had received tecovirimat, and 45% (9 of 20) had received placebo. Nineteen of the 20 cases (95%) occurred in Tunda, and 7 cases (35%), all of which were confirmed, occurred within 28 days after randomization.

Several baseline characteristics were associated with slower lesion resolution, including higher lesion count; positive PCR results for oropharyngeal or skin-lesion samples; lower PCR cycle-threshold values for blood, oropharyngeal, and skin-lesion samples; the presence of fever or mouth sores; and abnormally high aspartate aminotransferase levels and white-cell counts (Supplementary Appendix). Age, sex, days since symptom onset, malnutrition status, and positivity for malaria at baseline were not associated with slower resolution. Adjustments for each characteristic did not alter conclusions about treatment efficacy (Table S25).

SAFETY

A total of 17 serious adverse events occurred among 15 patients (5.1%) in the tecovirimat group, and 15 serious adverse events occurred among 15 patients (5.0%) in the placebo group (Tables S6 and S7); 72.9% of patients in the tecovirimat group had an adverse event, as compared with 70.5% of patients in the placebo group (Table S8). During the trial, malaria was diagnosed in a higher percentage of patients in the placebo group than in the tecovirimat group (18.2% vs. 12.2%). Gastrointestinal adverse events occurred in 26.4% of patients in the tecovirimat group and 23.8% of those in the placebo group;

abdominal pain was the most frequently reported symptom in both groups.

PHARMACOKINETICS

Among 60 blood samples tested for pharmacokinetic values, 65% had drug concentrations of at least 169 ng per milliliter (Table S9). Drug concentrations tended to be higher (by 214 ng per milliliter) in patients who were at least 19 years of age than in those 6 to 18 years of age and higher (by 236 ng per milliliter) in patients from Tunda than in those from Kole (Table S10 and Fig. S11). Higher drug concentrations were not associated with faster lesion resolution or with negative PCR results at 7 and 14 days (Tables S11 and S12 and Fig. S12).

DISCUSSION

The current trial, conducted in the setting of endemic mpox caused by clade I MPXV, did not show any significant differences between placebo and tecovirimat with regard to the time to lesion resolution or declines in the proportion of positive PCR results. No safety concerns were observed with tecovirimat use.

A prespecified subgroup analysis showed evidence of faster lesion resolution among Kole patients receiving tecovirimat than among those receiving placebo. Exploratory analyses revealed site-level asymmetries in baseline severity between trial groups that may have exaggerated the estimate of tecovirimat efficacy in Kole patients but simultaneously underestimated it in Tunda patients. Models that adjusted for these imbalances reduced site-level differences in treatment effect and provided statistical evidence that was consistent with no effect. Virologic outcomes did not support the site-by-treatment interaction. Other analyses (e.g., those involving alternative clinical end points, longitudinal changes in quantitative PCR results, and viral sequencing) may further elucidate observed site differences and may point to a hypothesis for further testing.

All-cause mortality at 58 days (1.7%) was lower than the 4.6% case fatality rate reported from recent DRC surveillance data[9] and may highlight the importance of standardized, aggressive supportive care. Although the level of care provided in the PALM007 trial is likely to have improved patient outcomes, such care may not be easily provided in resource-limited and outpatient settings.

Approximately 50% of oropharyngeal samples remained positive for MPXV by PCR at 14 days, a finding that raises questions about the transmissibility of MPXV after lesion resolution. Viral culture of these positive samples is planned to guide infection control and prevention guidelines.

Current tecovirimat dose recommendations were established on the basis of data from animal models and drug concentrations in healthy human volunteers. Limited data from humans in a clinical setting are available to guide tecovirimat dosing.[6] In a small subgroup of patients with clade IIb mpox in the STOMP trial, tecovirimat levels on day 8 of treatment were lower than those previously reported in healthy volunteers, although all patients had drug levels that exceeded the targeted effective threshold of 169 ng per milliliter.[17] In our trial, 35% of tested samples had drug concentrations below the minimum effective concentration, despite systematic efforts to ensure adequate caloric intake; 59 of 60 samples had concentrations above the level that suppressed viral replication in vitro. Drug concentrations on day 7 did not correlate with faster lesion resolution or with PCR negativity. The reasons for the observed differences in drug concentration by site and age are unclear but may include potential differences in coexisting conditions that affect drug absorption, unknown drug–drug interactions, difficulties achieving adequate food intake, and genetic differences among the population.

The PALM007 trial has many strengths. Patients were eligible for the trial regardless of age and pregnancy status. Hospitalization throughout treatment and strong social mobilization and psychosocial efforts led to low rates of missing data and loss to follow-up. Hospitalization allowed for nutritional support to maximize drug absorption and facilitated monitoring of adverse events and serious adverse events. Staff rotation between sites occurred regularly to standardize practices and procedures across sites.

Among the limitations of the trial is the subjectivity of the primary end point. Although train-

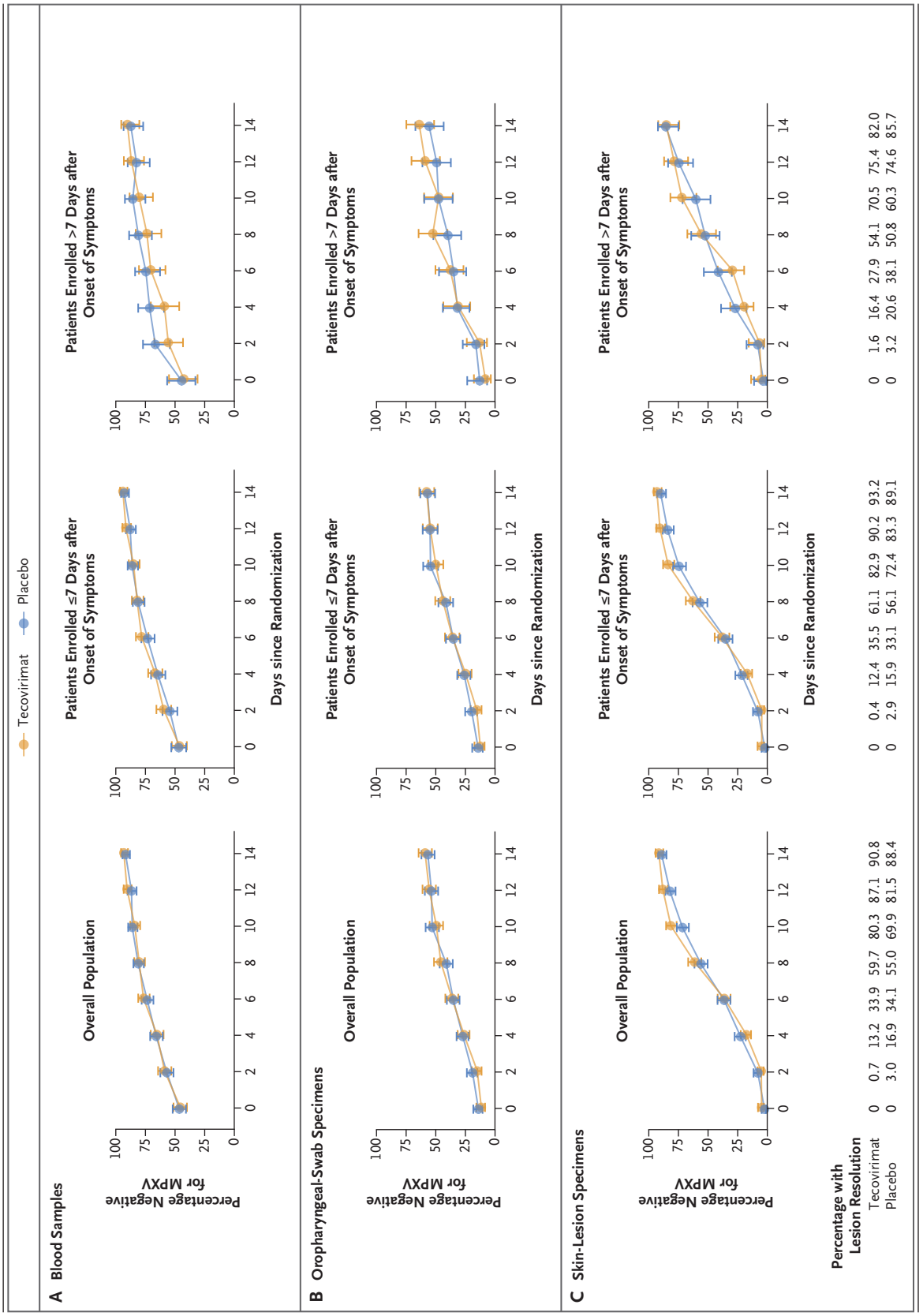

Figure 2 (facing page). Longitudinal PCR Results According to Trial Group and Symptom Onset in the Intention-to-Treat Population.

The percentage of patients testing negative for the virus that causes mpox (MPXV) by polymerase-chain-reaction (PCR) assays of blood samples (Panel A), oropharyngeal swab specimens (Panel B), and skin-lesion specimens (Panel C) is shown according to trial group and the timing of symptom onset (≤7 days vs. >7 days before randomization). Patients with a baseline positive or negative PCR result are included. The last-observation-carried-forward method was applied to valid PCR results from baseline to 14 days after randomization. Patients who have lesion resolution are not expected to have further positive PCR results for skin-lesion specimens, so patients who had lesion resolution on or before a given time point were assumed to be negative for MPXV if no valid PCR data were available. I bars indicate 95% confidence intervals.

ing was provided for standardized lesion assessments, interobserver variability in determining the day of lesion resolution may have attenuated effect estimates. Analysis of a subtrial evaluating interobserver variability in the field is under way. Lesion stage (e.g., papule, vesicle, pustule, or scab) was not evaluated owing to the increased burden such assessment would have entailed but may be an important marker of disease stage. Finally, it is important to emphasize that epidemiologic and clinical differences in populations affected by MPXV may limit the generalization of our results to other populations affected by clade Ia, as well as those affected by other MPXV clades.

Our findings highlight the importance of conducting clinical trials of investigational treatments during outbreaks, including trials of products that may have been licensed in the absence of such research. Ongoing randomized, controlled trials of tecovirimat for mpox caused by clade IIb MPXV, including the STOMP and UNITY trials and EPOXI, will provide needed evidence about the efficacy of tecovirimat in other populations. Research identifying and evaluating additional treatments for clade I mpox disease is needed.

Subgroup	No. of Patients		Median Day of Resolution (95% CI)		Cox Hazard Ratio (95% CI)
	Placebo	Tecovirimat	Placebo	Tecovirimat	
Overall (stratified)	302	295	8 (7–9)	7 (7–8)	1.15 (0.98–1.36)
Trial site					
Kole	144	140	9 (8–10)	7 (7–8)	1.46 (1.15–1.85)
Tunda	158	155	7 (6–8)	7 (7–8)	0.92 (0.73–1.15)
Duration of symptoms					
≤7 days	239	234	8 (7–8)	7 (7–8)	1.19 (0.99–1.43)
>7 days	63	61	8 (7–11)	8 (7–10)	1.03 (0.72–1.48)
Duration of symptoms (sensitivity analysis)					
≤4 days	102	89	8 (7–9)	8 (7–8)	1.30 (0.97–1.73)
5–7 days	137	145	8 (7–9)	7 (7–8)	1.12 (0.89–1.42)
>7 days	63	61	8 (7–11)	8 (7–10)	1.03 (0.72–1.48)
Age group					
<5 yr	74	73	8 (6–9)	7 (7–8)	1.25 (0.90–1.74)
5–17 yr	126	111	7 (7–9)	7 (7–8)	1.12 (0.86–1.45)
≥18 yr	102	111	9 (7–10)	8 (7–9)	1.15 (0.87–1.50)
Lesion count at baseline					
1–100 (mild or moderate)	113	96	5 (5–6)	6 (6–7)	1.12 (0.85–1.48)
>100 (severe or grave)	189	199	9 (8–10)	8 (8–9)	1.20 (0.98–1.48)

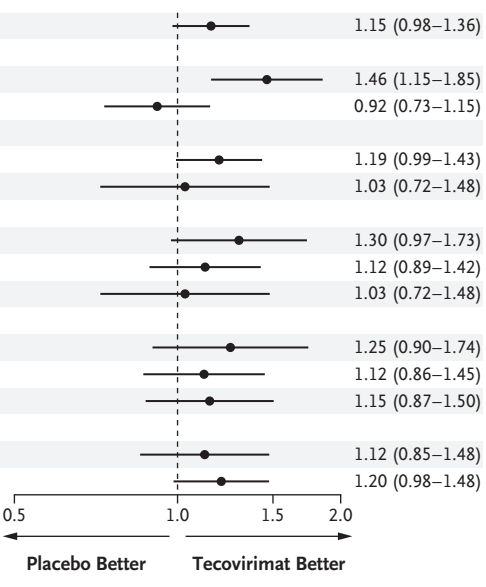

Figure 3. Days to Lesion Resolution According to Subgroup in the Intention-to-Treat Population.

A sensitivity analysis with the timing of symptom onset stratified into three categories (≤4 days, 5 to 7 days, and >7 days before randomization) was post hoc. The overall hazard ratio was estimated with the use of a Cox proportional-hazards model with stratification according to the timing of symptom onset before randomization (≤7 days and >7 days). Other estimates of hazard ratios were derived from Cox models with treatment-by-covariate interaction terms. Median days to resolution was estimated with the Kaplan–Meier procedure. CI denotes confidence interval.

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