ORIGINAL ARTICLE

Tecovirimat for the Treatment of Mpox

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ABSTRACT

BACKGROUND

Tecovirimat is approved for smallpox treatment under the Food and Drug Administration Animal Rule on the basis of efficacy in nonhuman primate models of mpox (previously known as monkeypox). However, the clinical efficacy of tecovirimat against human clade II mpox is unclear.

METHODS

In a phase 3, international, double-blind, randomized, placebo-controlled trial, we evaluated the efficacy of oral tecovirimat in adults with laboratory-confirmed clade II mpox. Participants were randomly assigned in a 2:1 ratio to receive tecovirimat or placebo for 14 days. The primary outcome was clinical resolution, assessed in a time-to-event analysis in participants with active skin or mucosal lesions. Secondary outcomes included reduction in pain, assessed in all participants with laboratory-confirmed mpox and in those with severe pain at baseline (pain score, 7 to 10; scale, 0 [no pain] to 10 [worst pain imaginable]); complete lesion healing (assessed in a time-to-event analysis); viral DNA clearance; and safety.

RESULTS

Of 412 participants who underwent randomization (275 to tecovirimat and 137 to placebo), 344 had laboratory-confirmed mpox, and 336 had active skin or mucosal lesions and were included in the primary analysis. By day 29, the estimated cumulative incidence of clinical resolution was 83% with tecovirimat and 84% with placebo; the competing-risks hazard ratio for clinical resolution was 0.98 (95% confidence interval [CI], 0.74 to 1.31; P=0.89). No substantial between-group differences were seen in pain reduction among participants with severe pain (difference, 0.1 point; 95% CI, −0.8 to 1.0), in complete lesion healing (competing-risks hazard ratio, 0.97; 95% CI, 0.75 to 1.26), or in viral DNA clearance. The incidence of adverse events of grade 3 or higher was similar in the two groups (4% with tecovirimat and 3% with placebo).

CONCLUSIONS

This trial showed no evidence that tecovirimat therapy shortened the time to clinical resolution, reduced pain, or increased viral clearance among adults with clade II mpox. (Funded by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health; STOMP/A5418 ClinicalTrials.gov number, NCT05534984.)

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Human mpox virus (hMPXV) represents an important public health threat worldwide. Recently, public health emergencies of international concern have been declared for both clade II hMPXV, which has caused more than 100,000 infections and 220 deaths across more than 100 countries where mpox (previously known as monkeypox) has historically not been endemic, and clade Ib hMPXV, which is associated with more severe disease and an increased risk of transmission.[1,2] These trends underscore the pandemic potential of orthopoxviruses.

Although the overall mortality rate of clade II mpox is low, persons with immunosuppression have higher morbidity and case fatality rates of up to 7%.[3] Many of these persons also have severe symptoms and a prolonged time to lesion healing, which can lead to isolation for extended periods. These findings highlight the need for effective therapeutic agents to prevent transmission, alleviate symptoms, reduce the risk of severe disease, and expedite recovery.

Tecovirimat (also called TPOXX), which has been approved by the Food and Drug Administration (FDA) for the treatment of smallpox, emerged as a potential candidate for mpox treatment on the basis of its in vitro and preclinical in vivo activity against hMPXV.[4] Tecovirimat targets the p37 envelope protein, which is conserved across orthopoxviruses and is essential for the formation of extracellular enveloped virus particles. The approval of tecovirimat for the treatment of smallpox is under the FDA Animal Rule and was based on efficacy data from preclinical lethal models of orthopoxvirus infection.[5] However, the efficacy of tecovirimat against mpox in humans remains unclear. We conducted the Advancing Clinical Therapeutics Globally Study of Tecovirimat for Human Mpox Virus (STOMP/A5418) to evaluate the safety and efficacy of tecovirimat treatment in persons with clade II mpox.

Methods

Trial Design

We conducted a phase 3, international, double-blind, randomized, placebo-controlled trial of tecovirimat for the treatment of mpox in adults. The trial was conducted at 49 sites in seven countries (Argentina, Brazil, Japan, Mexico, Peru, Thailand, and the United States). The protocol (available with the full text of this article at NEJM.org) included a separate open-label group that enrolled participants with, or at high risk for, protocol-defined severe mpox, including children, pregnant or lactating persons, and those with high immunosuppression, as well as persons with ocular lesions or high-risk skin lesions.

Participants who underwent randomization and in whom protocol-defined severe mpox developed or who had severe pain (score of 7 to 10 points, assessed on an 11-point numerical pain-rating scale, with 0 indicating no pain and 10 the worst pain imaginable) at day 6 could discontinue blinded tecovirimat or placebo and start a 14-day course of open-label tecovirimat with the initial trial-group assignment remaining blinded. This rescue strategy, which allowed both placebo and tecovirimat recipients to switch to open-label tecovirimat, was necessary to preserve blinding and because tecovirimat was the only widely available therapeutic option at the time that was considered to be safe. Results from participants who had been randomly assigned to receive either tecovirimat or placebo are reported here.



A Quick Take is available at NEJM.org



Trial Oversight

The protocol was approved by an institutional review board or ethics committee at each site; a single institutional review board was used by U.S. sites. All the participants provided written informed consent. An independent data and safety monitoring board that had been appointed by the National Institute of Allergy and Infectious Diseases reviewed the trial at least annually. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Participants

Participants eligible for randomization were adults (≥18 years of age) with presumptive or laboratory-confirmed symptomatic mpox according to an FDA-authorized nucleic acid or antigen test performed on a skin lesion or oropharyngeal or rectal swab obtained within 7 days before trial entry, symptom onset less than 14 days before trial entry, and one or more active (not yet scabbed) skin or mucosal lesions or proctitis with or without skin lesions. Complete eligibility criteria are provided in the protocol.

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RANDOMIZATION AND TRIAL PROCEDURES

Eligible participants were randomly assigned in a 2:1 ratio to receive oral tecovirimat or matching placebo for 14 days, with the dose level based on body weight. Randomization was stratified according to the number of days from symptom onset to enrollment (≤5 vs. >5) and the initial presence or absence of severe pain (<7 points vs. 7 to 10 points).[6-8] After the trial was modified to allow remote participation (i.e., without in-person trial visits), stratification according to the initial presence or absence of severe pain was replaced with enrollment type (in-person vs. remote).

In-person participants with presumptive diagnoses had skin, oral, or rectal swabs obtained at screening for hMPXV diagnostic testing at a centralized laboratory. Participants who tested negative for mpox discontinued tecovirimat or placebo and were followed for 7 days for adverse events before being discontinued from the trial. Skin-lesion, oral, and rectal swabs and blood samples were obtained at baseline (trial day 1) and on days 8, 15, 22, 29, and 57. For skin lesions, an index lesion was selected at enrollment and was swabbed at each visit. Remotely enrolled participants did not provide biospecimens but were required to have laboratory-confirmed infection. Intensive pharmacokinetic assessments were performed in a subgroup of participants on day 8 (see the Supplementary Methods section in the Supplementary Appendix, available at NEJM.org).

Participants monitored their lesions daily from enrollment (day 1) through day 29 and had their reports of resolution confirmed during an in-person or remote visit. All the participants also completed the numerical pain-rating scale through day 29 and recorded the blinded administration of the investigational product or placebo in a diary through day 15. Data on adverse events were collected through day 57. Adverse events were graded with the use of the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, corrected version 2.1.[9]

OUTCOMES

The primary outcome was clinical resolution, which was assessed in a time-to-event analysis and was defined as the first day on which all skin lesions were scabbed, desquamated, or healed and all visible mucosal lesions were healed. Secondary outcomes included a reduction in pain intensity from the intensity of pain before the receipt of tecovirimat or placebo, which was assessed on the 11-point pain-rating scale with the use of a time-weighted average of the summed difference in pain intensity[10] over the first 5 days of tecovirimat or placebo use; complete lesion healing, which was assessed in a time-to-event analysis and defined as the first day on which all skin lesions were reepithelialized and all visible mucosal lesions were healed; hMPXV DNA level in skin lesions and in oral, rectal, and blood samples; and adverse events of grade 3 or higher. Exploratory outcomes included the predicted area under the concentration-time curve from administration to 12 hours ($AUC_{0–12h}$) and concentration at 12 hours after the receipt of the dose on day 8 (C_{12h}) for tecovirimat in plasma (see the Supplementary Appendix).

STATISTICAL ANALYSIS

We estimated a sample size of 530 to target 357 events of clinical resolution and calculated that this sample size would provide the trial with 85% power to detect a 40% improvement in the competing-risks hazard ratio for clinical resolution up to 28 days after trial entry in the tecovirimat group with the use of a two-sided alpha level of 0.05. The complete statistical analysis plan is provided with the protocol.

Prespecified interim efficacy analyses were conducted after approximately 33% and 67% of the events of clinical resolution had occurred, with the use of the Lan–DeMets spending-function analogue of the O'Brien–Fleming boundaries to control for the overall type I error. At the request of the data and safety monitoring board, a futility analysis of the primary outcome was conducted at the time of the second planned efficacy review on November 26, 2024. At that time, 267 events (75% of the targeted number) had occurred. The data and safety monitoring board recommended stopping the randomized portion of the trial owing to futility (see the Supplementary Appendix). The data presented here are those reviewed by the data and safety monitoring board, with the exception of the hMPXV DNA data, which were updated with data that were expected but had been unavailable at the time of the data and safety monitoring board review owing to shipping lags.

The time to clinical resolution (primary outcome) and the time to complete lesion healing were evaluated in a modified intention-to-treat analysis, which excluded participants who did not

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have laboratory-confirmed mpox or who had proctitis without active skin or visible mucosal lesions. Fine and Gray subdistribution proportional-hazards models were used to estimate competing-risks hazard ratios with associated confidence intervals. Intercurrent events of death from any cause, the use of other antiviral agents with expected activity against mpox (i.e., that have shown efficacy against orthopoxviruses in in vitro studies and studies in animals), and a treatment change to open-label tecovirimat due to disease progression or severe pain were considered to be competing events (see the Supplementary Appendix). The evaluation for nonproportional hazards was conducted by means of graphical inspection, with no evidence found.

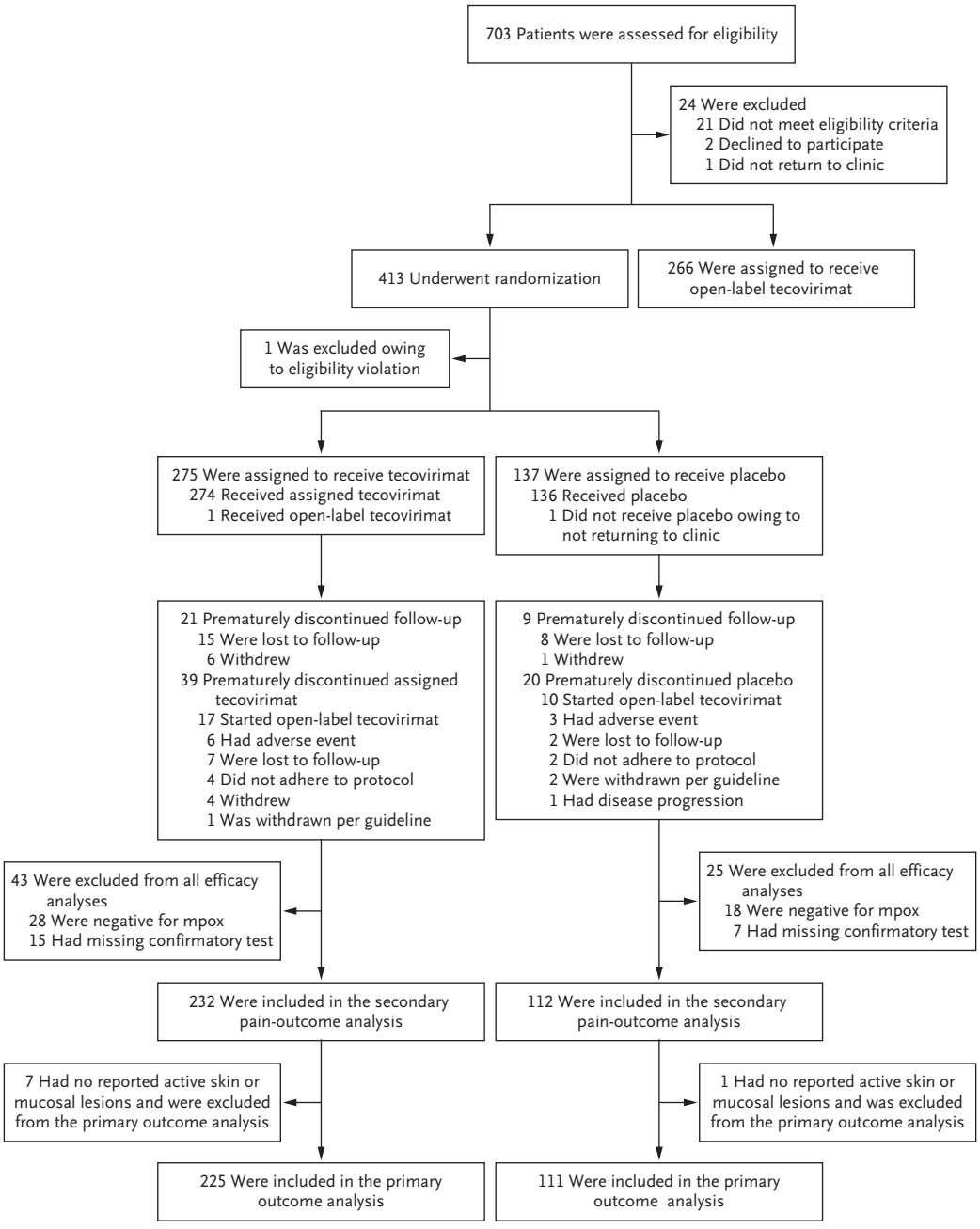


Figure 1. Randomization and Follow-up of the Participants.

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Treatment effects for the primary outcome were evaluated in prespecified subgroups defined according to age (<40 or ≥40 years), sex, race (White or non-White), ethnic group (Hispanic or non-Hispanic), enrollment type (in-person or remote), symptom duration (≤5 or >5 days), pain level (<7 or 7 to 10 points), previous receipt of at least one dose of a smallpox or mpox vaccine (yes or no), presence or absence of proctitis, and human immunodeficiency virus (HIV) status (i.e., living with HIV or not living with HIV) and in post hoc subgroups defined according to shorter symptom duration (≤3 or >3 days), lesion count (<10 or ≥10), and hMPXV DNA in the index lesion (detected or not detected) (see the Supplementary Appendix). Reduction in pain intensity was evaluated in all participants with laboratory-confirmed mpox and in those who reported severe pain (score, 7 to 10) at baseline. A hierarchical testing approach was used to control the familywise error rate across the primary outcome and the secondary pain outcomes (see the

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Tecovirimat (N=232)	Placebo (N=112)	Total (N=344)
Median age (IQR) — yr	34 (27–40)	34 (28–41)	34 (28–40)
Male sex — no. (%)	228 (98)	111 (99)	339 (99)
Gender — no. (%)			
Cisgender	226 (97)	107 (96)	333 (97)
Transgender spectrum	6 (3)	5 (4)	11 (3)
Race or ethnic group — no. (%)†			
White	121 (52)	61 (54)	182 (53)
Black	29 (12)	11 (10)	40 (12)
Asian	14 (6)	13 (12)	27 (8)
Native Hawaiian or other Pacific Islander	2 (1)	0	2 (1)
American Indian or Alaska Native	1 (<1)	0	1 (<1)
Other	24 (10)	7 (6)	31 (9)
Multiple	5 (2)	3 (3)	8 (2)
Unknown	36 (16)	17 (15)	53 (15)
Hispanic or Latino ethnic group — no. (%)†			
Yes	107 (46)	44 (39)	151 (44)
No	122 (53)	64 (57)	186 (54)
Unknown	3 (1)	4 (4)	7 (2)
Enrollment type — no. (%)			
In-person	179 (77)	84 (75)	263 (76)
Remote	53 (23)	28 (25)	81 (24)
Symptom duration			
Median (IQR) — days	8 (6–10)	8 (6–10)	8 (6–10)
≤5 days — no. (%)	57 (25)	28 (25)	85 (25)
Median pain score (IQR)‡	5 (2–7)	5 (3–7)	5 (2–7)
Median no. of lesions (IQR)	9 (5–18)	8 (3–17)	9 (4–18)
Proctitis — no. (%)	85 (37)	37 (33)	122 (35)
Receipt of ≥1 dose of smallpox or mpox vaccine — no. (%)	54 (23)	24 (21)	78 (23)
Living with HIV — no./total no. (%)	86/228 (38)	31/109 (28)	117/337 (35)

* Percentages may not total 100 because of rounding. HIV denotes human immunodeficiency virus, and IQR interquartile range.
† Race and ethnic group were reported by the participant.
‡ The pain score was assessed on a scale from 0 (no pain) to 10 (worst pain imaginable).

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Supplementary Appendix). Since the primary outcome did not differ between the two trial groups, no formal statistical testing of the pain outcomes between groups was conducted.

Virologic analyses were restricted to participants with laboratory-confirmed mpox who had been enrolled in-person and provided biospecimens. Post hoc analyses of undetectable hMPXV DNA were done within subgroups on the basis of symptom duration (≤3 vs. >3 days, and ≤5 vs. >5 days), HIV status, and vaccination status. Safety analyses included participants who received at least one dose of tecovirimat or placebo and were based on the actual intervention received.

The competing-risks hazard ratio for clinical resolution (the primary outcome) is presented with a 95% confidence interval that was adjusted for interim monitoring. For all other analyses, results are reported as point estimates with two-sided 95% confidence intervals without adjustment for multiplicity. Statistical analyses were conducted with the use of SAS software, version 9.4 for Linux (SAS Institute).

RESULTS

PARTICIPANT ENROLLMENT, BASELINE CHARACTERISTICS, AND FOLLOW-UP

From September 8, 2022, to October 21, 2024, a total of 412 eligible participants were randomly assigned to receive tecovirimat (275) or placebo (137) across all the trial sites (Table S1 in the Supplementary Appendix). In total, 344 participants tested positive for hMPXV, among whom 336 had at least one active skin or visible mucosal lesion and were included in the primary analysis population (Fig. 1). Treatment discontinuation occurred in 36 of 232 participants (16%) in the tecovirimat group and in 18 of 112 (16%) in the placebo group.

The characteristics at baseline among the 344 participants with laboratory-confirmed mpox were similar in the two trial groups (Table 1 and Table S2). The median age of the participants was 34 years (interquartile range, 28 to 40). A total of 99% of the participants were men, and 44% were Hispanic or Latino. The median number of days from symptom onset to trial entry was 8 (interquartile range, 6 to 10), the median number of lesions at enrollment was 9 (interquartile range, 4 to 18), 122 participants (35%) reported proctitis, and 116 (34%) reported severe pain. Of 337 participants with known HIV status,

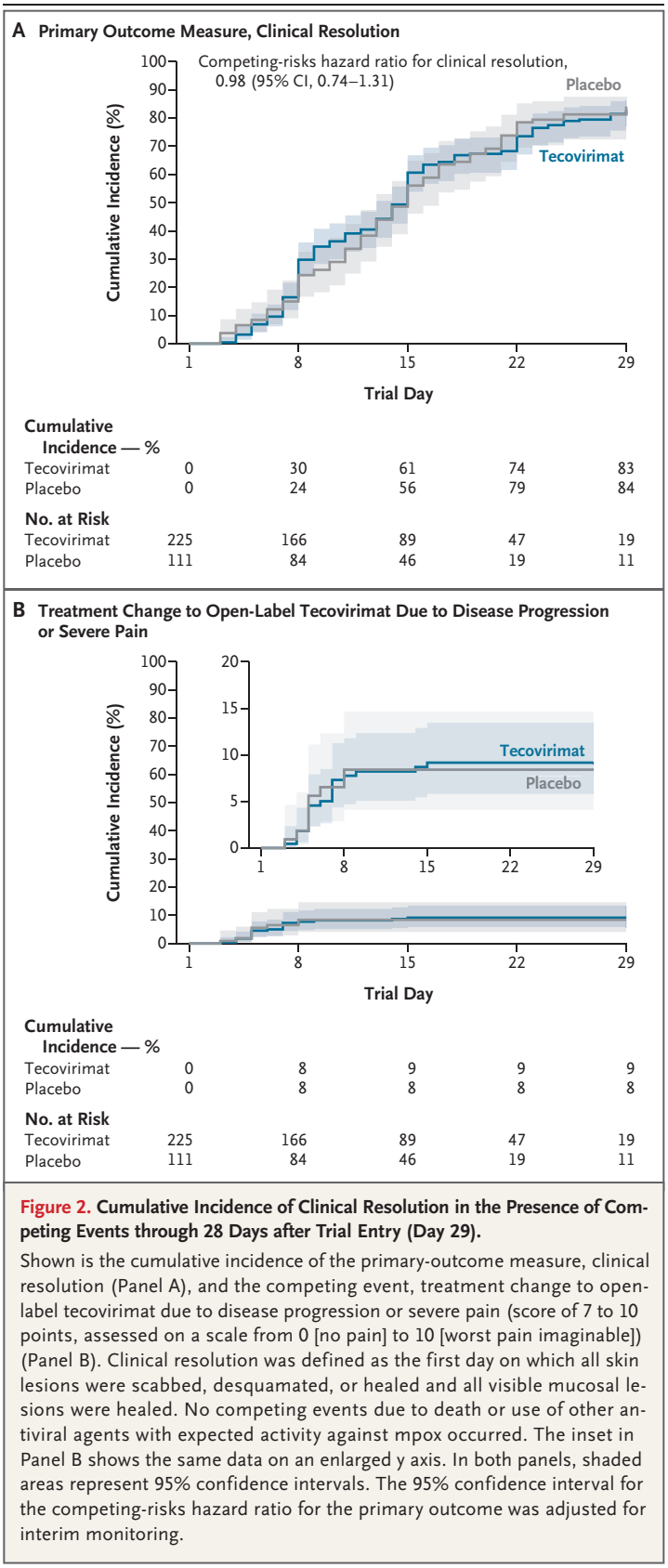


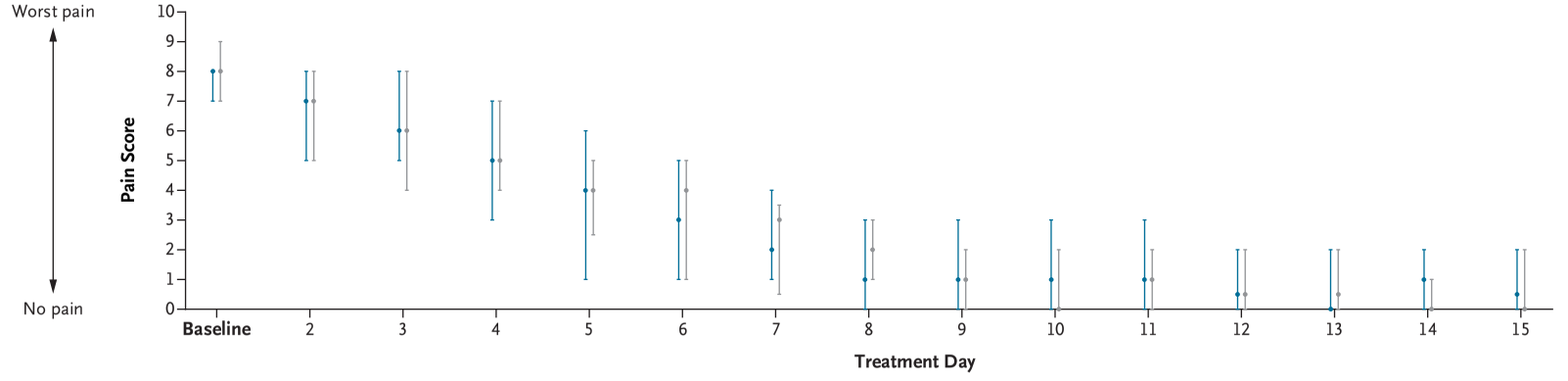
Figure 2. Cumulative Incidence of Clinical Resolution in the Presence of Competing Events through 28 Days after Trial Entry (Day 29).

Shown is the cumulative incidence of the primary-outcome measure, clinical resolution (Panel A), and the competing event, treatment change to open-label tecovirimat due to disease progression or severe pain (score of 7 to 10 points, assessed on a scale from 0 [no pain] to 10 [worst pain imaginable]) (Panel B). Clinical resolution was defined as the first day on which all skin lesions were scabbed, desquamated, or healed and all visible mucosal lesions were healed. No competing events due to death or use of other antiviral agents with expected activity against mpox occurred. The inset in Panel B shows the same data on an enlarged y axis. In both panels, shaded areas represent 95% confidence intervals. The 95% confidence interval for the competing-risks hazard ratio for the primary outcome was adjusted for interim monitoring.

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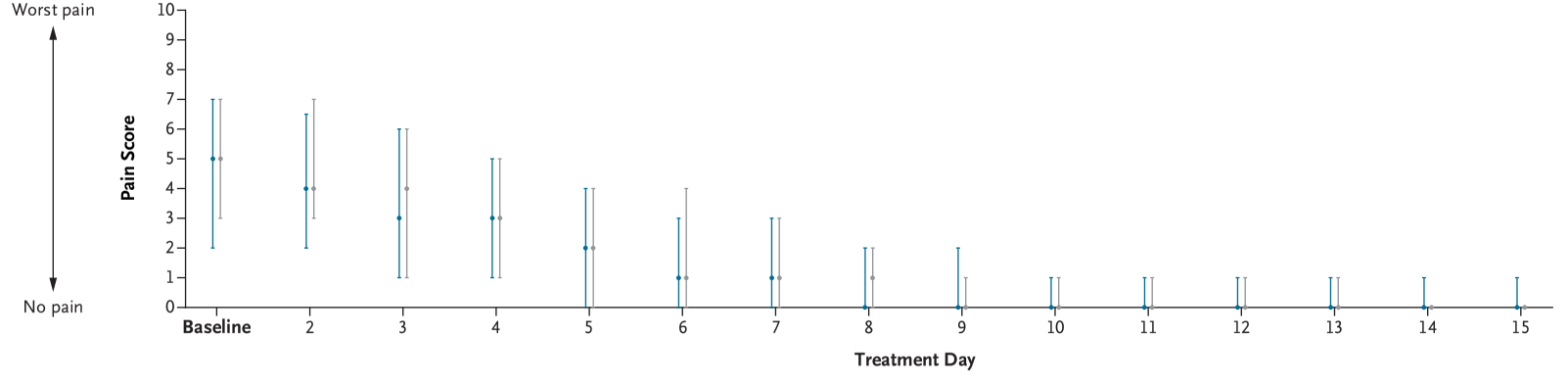
● Tecovirimat ● Placebo

A Pain Score among Participants with Laboratory-Confirmed Mpox Who Reported Severe Pain at Baseline



	Baseline	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Median Score (IQR)															
Tecovirimat	8 (7–8)	7 (5–8)	6 (5–8)	5 (3–7)	4 (1–6)	3 (1–5)	2 (1–4)	1 (0–3)	1 (0–3)	1 (0–3)	1 (0–3)	0.5 (0–2)	0.0 (0–2)	1 (0–2)	0.5 (0–2)
Placebo	8 (7–9)	7 (5–8)	6 (4–8)	5 (4–7)	4 (2.5–5)	4 (1–5)	3 (0.5–3)	2 (1–3)	1 (0–2)	0 (0–2)	1 (0–2)	0.5 (0–2)	0.5 (0–2)	0 (0–1)	0.0 (0–2)
No. with Data															
Tecovirimat	81	63	66	66	61	58	58	53	54	45	49	46	47	48	48
Placebo	35	29	28	28	28	27	24	23	21	21	20	22	22	21	19

B Pain Score among Participants with Laboratory-Confirmed Mpox



	Baseline	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Median Score (IQR)															
Tecovirimat	5 (2–7)	4 (2–6.5)	3 (1–6)	3 (1–5)	2 (0–4)	1 (0–3)	1 (0–3)	0 (0–2)	0 (0–2)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)
Placebo	5 (3–7)	4 (3–7)	4 (1–6)	3 (1–5)	2 (0–4)	1 (0–4)	1 (0–3)	1 (0–2)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–0)	0 (0–0)
No. with Data															
Tecovirimat	232	188	187	185	184	172	172	163	161	152	150	156	152	149	151
Placebo	111	95	92	92	85	84	79	82	76	65	73	71	69	69	64

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117 (35%) were living with HIV. A total of 78 participants (23%) had received at least one lifetime dose of a smallpox or mpox vaccine. This trial enrolled a population that was broadly representative of persons most affected by mpox during the 2022–2023 outbreak (Table S3).

PRIMARY OUTCOME: CLINICAL RESOLUTION

By day 29, a total of 177 of 225 participants (79%) in the tecovirimat group and 90 of 111 (81%) in the placebo group had clinical resolution of skin lesions. A total of 20 participants in the tecovirimat group and 9 in the placebo group started receiving open-label tecovirimat owing to disease progression or severe pain (Table S4). The estimated cumulative incidence of clinical resolution was 83% (95% confidence interval [CI], 77 to 87) in the tecovirimat group and 84% (95% CI, 76 to 90) in the placebo group, and the competing-risks hazard ratio for clinical resolution was 0.98 (95% CI, 0.74 to 1.31; P=0.89) (Fig. 2A). No between-group difference was seen in treatment change due to disease progression or severe pain (Fig. 2B). No competing events due to death or the use of other antiviral agents with expected activity against mpox occurred. Treatment effects did not differ between the trial groups in any of the subgroups examined (Fig. S1).

SECONDARY OUTCOMES

Pain Reduction

The median pain score at baseline was 5 points in both the tecovirimat group (interquartile range, 2 to 7) and the placebo group (interquartile range, 3 to 7) (Table 1). Pain decreased similarly in both groups (Fig. 3). Among participants with severe pain (score, 7 to 10 points) at baseline, the mean (±SD) time-weighted average reduction from baseline in pain intensity over a 5-day treatment period was 3.2±2.1 points in the tecovirimat group and 3.1±2.0 points in the placebo group (difference in means, 0.1 point; 95% CI, −0.8 to 1.0) (Table S5). Among all the participants with laboratory-confirmed mpox, the mean time-weighted average reduction from baseline over a 5-day treatment period was 1.6±2.2 points in the tecovirimat group and 1.7±2.3 points in the placebo group (difference in means, −0.1; 95% CI, −0.6 to 0.5).

Figure 3 (facing page). Participant-Reported Pain Scores According to Treatment Day.

Shown are the median pain scores (dots) among participants with laboratory-confirmed mpox who reported severe pain at baseline (Panel A) and among all participants with laboratory-confirmed mpox (Panel B). The baseline score was determined by taking the last available score on or before the day that the participant started receiving tecovirimat or placebo. Scores were assessed on a scale from 0 (no pain) to 10 (worst pain imaginable). I bars represent interquartile ranges (IQRs). In each panel, data are shown slightly offset at each time point for better visibility.

Complete Lesion Healing

By day 29, complete lesion healing occurred in 155 participants (69%) in the tecovirimat group and in 78 participants (70%) in the placebo group. The estimated cumulative incidence of complete lesion healing was 75% in each group, and the competing-risks hazard ratio for complete lesion healing was 0.97 (95% CI, 0.75 to 1.26) (Fig. S2).

Virologic Results

The percentage of participants who supplied lesion swabs that did not have hMPXV DNA detected at baseline was similar in the two groups (13% in the tecovirimat group and 17% in the placebo group) (Fig. 4A). By day 8, clearance of hMPXV DNA was observed in 48% of the participants in the tecovirimat group and in 37% of those in the placebo group (difference [based on unrounded data], 12 percentage points; 95% CI, −2 to 26). By day 15, hMPXV DNA was undetectable in 82% of the participants in the tecovirimat group and in 80% of those in the placebo group (difference [based on unrounded data], 1 percentage point; 95% CI, −10 to 13). No between-group differences were observed in the proportion of oral, rectal, or blood samples in which hMPXV DNA was undetectable at baseline, day 8, or day 15 (Fig. 4B, 4C, and 4D). Post hoc subgroup analysis according to HIV status and mpox vaccination showed no differences in treatment effect (Tables S7 and S8, respectively).

Pharmacokinetics

Among 14 participants with data from intensive pharmacokinetic assessments, the mean predicted AUC_{0-12h} for tecovirimat in plasma was 14,013 ng·hr per milliliter (95% CI, 10,414 to 17,611) and the mean predicted C_{12h} was 480 ng per milliliter (95% CI, 346 to 615) (Table S9). The mean C_{12h} was approximately 2.8 times as high as the target threshold of 169 ng per milliliter, with 2 participants (14%) having re-

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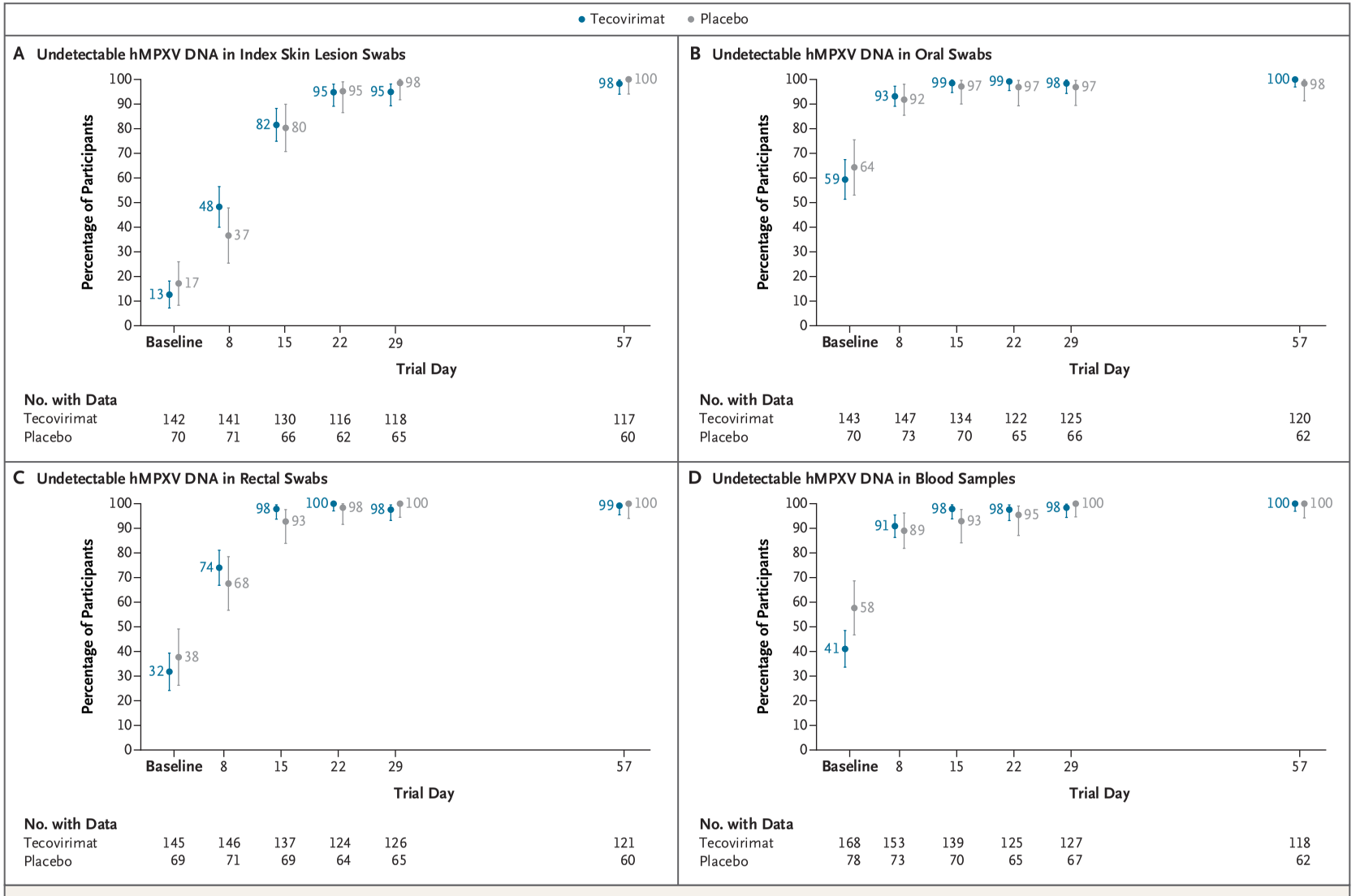


Figure 4. Participants with Undetectable Human Mpox Virus DNA.

Shown are the percentages of participants with undetectable human mpox virus (hMPXV) DNA in index skin-lesion swabs (Panel A), oral swabs (Panel B), rectal swabs (Panel C), and blood samples (Panel D). I bars represent 95% confidence intervals; values for the 95% confidence intervals are provided in Table S6. In each panel, data are shown slightly offset at each time point for better visibility.

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sults that were predicted to fall just below this threshold.

SAFETY

Adverse events of grade 3 or higher occurred in 12 of 275 participants (4%) who received tecovirimat and in 4 of 136 (3%) who received placebo (Table S10). No substantial between-group difference was observed in the incidence of adverse events of grade 3 or higher (difference, 1 percentage point; 95% CI, −5 to 5). Serious adverse events occurred in 6 participants (2%) who received tecovirimat and in 2 (1%) who received placebo. No deaths were reported.

DISCUSSION

In this double-blind, randomized, placebo-controlled trial, we found no evidence that tecovirimat therapy shortened the time to resolution of skin lesions, increased hMPXV DNA clearance at any site, or reduced pain in participants with clade II mpox. Results from subgroup analyses showed no evidence of differences among the subgroups in the time to the resolution of skin lesions in subgroups defined according to early enrollment (≤5 or ≤3 days after symptom onset), previous vaccination against orthopoxvirus, age, or HIV status. These results are consistent with findings from the PALM007 trial in clade I mpox, which showed no effect of tecovirimat on the time to clinical resolution.[11] Together, these findings suggest that tecovirimat lacks clinical efficacy against clade I and clade II mpox, a situation that underscores the need for randomized, controlled trials to evaluate investigational therapeutic agents to treat mpox.

Antiviral agents are generally more effective when given early in the disease course.[12,13] The delay in clinical presentation in this trial represents a limitation, with 75% of the participants enrolling more than 5 days after reported symptom onset, despite efforts to expedite enrollment through virtual enrollment and presumptive diagnoses. The observed delay was probably more reflective of overall challenges to mpox diagnosis and treatment, such as early recognition of mpox symptoms and signs by patients and clinicians, limited diagnostic strategies, and access to care in affected populations. Despite this delay, the percentage of participants with clinical resolution through 28 days did not differ between the tecovirimat group and the placebo group, regardless of whether treatment began before or after 3 or 5 days from symptom onset. On the basis of these results, timing does not appear to be the reason for the lack of efficacy of tecovirimat. The lack of efficacy among participants who received treatment earlier is consistent with the results of the PALM007 trial, which showed that tecovirimat did not reduce the number of days to lesion resolution when treatment was started within 4 days after symptom onset.[11]

Although the percentage of participants with undetectable hMPXV DNA in index lesions at day 8 was 12 percentage points higher in the tecovirimat group (48%) than in the placebo group (37%), the 95% confidence interval of −2 to 26 percentage points indicates a wide range of possible treatment effects, including no effect, and no meaningful between-group difference was observed at 15 days (difference, 1 percentage point; 95% CI, −10 to 13). No evidence of a difference in DNA clearance was observed in subgroups defined according to previous receipt of a smallpox or mpox vaccine or according to HIV status. However, samples were obtained at baseline and day 8, which may limit the understanding of the effects of tecovirimat on early viral kinetics. Although no significant differences were observed in the time to the resolution of skin lesions, pain reduction, or viral DNA clearance, our findings were limited to adults who were immunocompetent. Participants with severe immunosuppression (e.g., HIV with CD4 <200 cells per cubic millimeter, HIV type 1 RNA >1000 copies per milliliter, or cancer) or skin conditions that increase the potential for severe mpox, as well as children and pregnant or lactating persons, were assigned to receive open-label tecovirimat, which prevents comparison with placebo. Observational studies suggest that persons with immunocompromise have prolonged illness and poor outcomes despite tecovirimat therapy.[3,14] Consequently, current guidelines from the Centers for Disease Control and Prevention (CDC) recommend the consideration of combination therapy, particularly in patients with immunocompromise, to enhance treatment efficacy and reduce the risk of antiviral resistance.[15] This approach is supported by a study in animals indicating that combining antiviral agents may offer synergistic benefits.[16] Evaluating the efficacy of investigational interventions

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in persons with immunocompromise, who face substantial risks of complications and death, remains an important research priority.

Whether suboptimal exposure to tecovirimat may have also contributed to a lack of clinical efficacy is currently unknown.[17,18] The initial dose-level strategy in humans was selected to achieve concentrations of tecovirimat in plasma that were several times as high as the target concentration of 169 ng per milliliter, which had been associated with improved survival, virologic response, and reductions in lesion counts in nonhuman primates. The predicted C_{12h} in the randomized trial groups was similar to results in the open-label group of the STOMP/A5418 trial,[19] to results in adults in the PALM007 trial,[11] and to results of a separate observational study.[20] The mean predicted C_{12h} exceeded the threshold of 169 ng per milliliters by approximately 2.8 times.[21]

However, the $AUC_{0–12h}$ and C_{12h} values were both lower than those in simulated exposures in healthy volunteers.[15] Analyses of factors affecting the pharmacokinetics of tecovirimat across the randomized and open-label groups, of relationships with clinical and virologic outcomes, and of whether alternative dose levels would help improve therapeutic responses are under way.

The strengths of this trial include the randomized, double-blind design; the enrollment of participants across 49 sites in seven countries; early treatment of participants before confirmed mpox diagnosis; and remote enrollment to reduce treatment delays. The assessment of pain intensity and the obtaining of biospecimens for in-person participants allowed the evaluation of the effects of tecovirimat on both participant-reported outcomes and viral kinetics.

Conducting a randomized, placebo-controlled trial was challenging when the investigational drug is widely available through expanded-access programs. During the 2022 mpox epidemic, more than 7100 persons in the United States received tecovirimat under the Expanded Access Investigational New Drug program of the CDC. Close coordination between the STOMP/A5418 trial team and the CDC facilitated trial enrollment. Although expanded-access and compassionate-use programs are essential for the distribution of promising therapeutic agents, design strategies to balance access with rigorous evaluation of safety and efficacy during emerging infections are important.[22]

The STOMP/A5418 trial showed no evidence that tecovirimat treatment shortened the time to clinical resolution of skin lesions, reduced pain, or accelerated the clearance of hMPXV DNA as compared with placebo. In light of the continued spread of hMPXV across the globe, these findings highlight the need to identify safe and effective therapeutics for mpox and other orthopoxviruses.

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