# Tecovirimat in clade I mpox: why PALM007 did not show benefit

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> Mpox, caused by the mpox virus, presents a significant public health challenge, particularly with the more severe clade I infections. While supportive care remains the cornerstone of management, specific antiviral therapies have been explored to mitigate disease severity and accelerate recovery. The search for effective treatments continues to be a priority for clinicians managing these patients.

**KEY TAKEAWAYS**

- The Pivot: Tecovirimat, an antiviral with activity against orthopoxviruses, did not show a clinical benefit in patients with clade I mpox.
- The Data: The trial did not meet its primary endpoint of reduced time to lesion healing.
- The Action: Clinicians should continue to rely on established supportive care measures for mpox, as specific antiviral benefit for clade I has not been demonstrated.

Mpox, previously known as monkeypox, is a zoonotic disease caused by the mpox virus, a member of the Orthopoxvirus genus. The disease typically presents with a characteristic rash, fever, headache, muscle aches, and lymphadenopathy. While most cases are self-limiting, severe disease, particularly with clade I infections, can lead to complications such as secondary bacterial infections, pneumonia, encephalitis, and vision loss, necessitating hospitalisation and intensive supportive care. The global health community has sought specific antiviral interventions to improve outcomes, especially in vulnerable populations.

Tecovirimat is an antiviral agent approved for the treatment of orthopoxvirus infections, including mpox, smallpox, and vaccinia. Its mechanism of action involves inhibiting the viral envelope protein VP37, which is essential for the formation of mature virions. This inhibition prevents the virus from exiting infected cells and spreading to new ones. Despite its established antiviral activity in vitro and in animal models, the clinical efficacy of tecovirimat in human mpox infections, particularly severe forms, has been a subject of ongoing investigation.

## Understanding the PALM007 Trial Design

The PALM007 trial aimed to evaluate the clinical efficacy of tecovirimat in patients with clade I mpox. This was a randomised, placebo-controlled clinical trial, designed to provide robust evidence on the drug's impact on disease progression. Patients enrolled in the study presented with confirmed clade I mpox infection, encompassing a spectrum of disease severity, though specific inclusion criteria focused on those requiring hospitalisation or at high risk of severe outcomes.

The primary endpoint of the trial was the time to resolution of skin lesions, a clinically relevant measure reflecting

disease activity and patient recovery. Secondary endpoints included overall survival, duration of hospitalisation, and the incidence of mpox-related complications. Investigators also monitored viral load kinetics and safety profiles. The trial's design sought to address the urgent need for evidence-based treatments for this severe form of mpox, particularly given the limited therapeutic options available.

## The Outcomes: No Benefit Observed

Tecovirimat did not demonstrate a significant clinical benefit in patients with clade I mpox in the PALM007 trial. The primary endpoint, time to lesion healing, showed no statistically meaningful difference between the tecovirimat arm and the placebo arm. This outcome was consistent across various subgroups analysed, including those with more severe disease presentations or specific comorbidities. The lack of efficacy on this key measure raises questions about the drug's utility in this specific clinical context.

Secondary endpoints also failed to show a discernible advantage for tecovirimat. There was no reduction in overall mortality, duration of hospitalisation, or the frequency of mpox-related complications. Viral load measurements, while showing some trends, did not translate into improved clinical outcomes. The safety profile of tecovirimat was generally consistent with previous reports, with no new or unexpected adverse events identified. This indicates that while the drug is well-tolerated, its clinical impact on clade I mpox appears limited.

## Why the Drug Did Not Work

The lack of observed benefit for tecovirimat in clade I mpox, despite its in vitro activity, points to several potential factors. One consideration is the timing of intervention. Mpox, like many viral infections, often has a critical window for antiviral efficacy. If treatment is initiated too late in the disease course, after significant viral replication and immune activation have already occurred, antivirals may have diminished impact. The trial may have enrolled patients beyond this optimal therapeutic window, particularly those with more advanced lesions.

Another factor could be the specific characteristics of clade I mpox itself. Clade I is known to be more virulent than clade II, potentially leading to a more aggressive disease progression that is less amenable to a single antiviral agent. The viral kinetics or host immune response in clade I infections might differ in ways that reduce tecovirimat's effectiveness in a clinical setting. It is also possible that the dose or duration of tecovirimat administered in the trial was not optimal for achieving a therapeutic effect against clade I mpox, although the regimen was based on prior pharmacokinetic and pharmacodynamic data.

The trial's patient population might also play a role. While the study included patients with varying disease severities, the overall clinical picture of those enrolled may have been too advanced for tecovirimat to significantly alter the disease trajectory. The pathophysiology of severe viral infections often involves complex host-pathogen interactions that extend beyond direct viral replication, making it challenging for antivirals alone to reverse established pathology. Clinicians often find that a comprehensive approach, including robust supportive care, remains paramount.

Still, the findings do not negate the potential role of tecovirimat in other orthopoxvirus infections or in different clinical scenarios for mpox. For instance, its efficacy might be more pronounced in early-stage disease, in immunocompromised individuals, or in specific prophylactic settings. The PALM007 trial focused specifically on established clade I infections, and its results should be interpreted within that context. The challenges of developing effective antivirals for emerging pathogens are well-documented, and this outcome underscores the complexity involved.

## Implications for Clinical Practice

The PALM007 trial's results reinforce the current reliance on supportive care for patients with clade I mpox. This includes meticulous wound care, pain management, fluid and electrolyte balance, and aggressive treatment of secondary bacterial infections. For clinicians, the Oxford Handbook of Infectious Diseases and Microbiology remains a valuable resource for managing complex viral infections and their complications. The absence of a clear benefit from tecovirimat means that its use in this specific population should be re-evaluated, moving away from routine administration.

The findings also highlight the need for continued research into alternative therapeutic strategies for severe mpox. This could involve exploring novel antiviral compounds, combination therapies, or immunomodulatory agents that target the host response. Understanding the precise mechanisms of clade I virulence and identifying biomarkers that predict treatment response will be essential for guiding future drug development efforts. The broader fight against emerging infectious diseases requires a multi-pronged approach, and this trial provides critical data for refining that strategy.

The trial was not powered to detect differences in very rare outcomes or in highly specific, small subgroups. That gap matters for understanding the full spectrum of tecovirimat's potential utility. Whether benefits extend to other orthopoxvirus infections or to very early-stage mpox remains unclear from this particular study. The data simply did not support a broad clinical benefit in the population studied.

### CLINICAL IMPLICATIONS

The PALM007 trial delivers a clear message: tecovirimat did not work for clade I mpox in the studied population. Clinicians should not expect to see a significant impact on lesion healing or overall clinical course from this drug in patients presenting with established clade I disease. This means the focus must remain squarely on robust supportive care, which has always been the bedrock of managing severe mpox.

For patients, this outcome is a disappointment, as it leaves a significant unmet need for specific antiviral treatments for severe mpox. The expectation that an approved orthopoxvirus antiviral would translate directly to clinical benefit in a severe human infection was not met. This underscores the complexity of viral diseases and the limitations of extrapolating in vitro data to real-world patient outcomes.

The pharmaceutical industry must now re-evaluate its approach to mpox therapeutics. This trial provides valuable, albeit negative, data that should inform future research and development. Investing in novel compounds or exploring combination strategies that address the unique challenges of clade I mpox, perhaps targeting different stages of the viral life cycle or host response, will be essential. The next trial needs to show a clear, measurable clinical benefit to justify any widespread adoption.



### REFERENCES

1. 1. Zargar AA. Mpox and the one health approach. Dialogues Health. 2026;8:100293. doi:10.1016/j.dialog.2026.100293

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