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MEDICINES  
AGENCY

## Overview of available therapeutics, those in the pipeline, and approaches to evaluate their efficacy

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WHO Monkeypox research, 3 June 2022

Dr. Marco Cavaleri, EMA

An agency of the European Union



# Tecovirimat

## ❑ Regulatory status:

- Authorized in EU for the treatment of orthopoxvirus associated infections (smallpox, monkeypox, cowpox, vaccinia virus) since January 2022 under exceptional circumstances
- Authorized in US for the treatment of smallpox disease under FDA's Animal Rule since July 2018. Approved in Canada.
- The evidence for the anticipated antiviral effect in humans comes from the in-vitro and in-vivo nonclinical studies. PK-PD analyses to support the clinical dose regimen and safety data derive from clinical studies in healthy individuals.

## ❑ MoA:

- Tecovirimat targets the membrane protein VP37 of vaccinia virus required for the production of extracellular forms of viruses. EC50 is similar for all orthopoxviruses tested in vitro.
- It is proposed that this blocking of viral spread allows for development of an adaptive immune response to clear the virus. Potentially important implications for immunocompromised persons who may not develop an adequate cell mediated response.

## ❑ Posology:

- Oral capsules, 200 mg. Dose varies by body weight: 200-600 mg BID for 14 days. US FDA recently approved IV formulation

## ❑ Non-clinical efficacy:

- Pivotal studies in cynomolgus macaques infected with monkeypox virus and rabbits infected with rabbitpox virus.
- Early treatment (<6 days post challenge) with tecovirimat for 14 days resulted in statistically significant improvement in survival.

## ❑ Safety profile:

- Most common AE: headache, nausea, abdominal pain. DDI: repaglinide, midazolam. No data in pregnancy.

## ❑ Low resistance barrier:

- Amino acid substitutions in the VP37 protein can confer reductions in antiviral activity. No cross resistance with Brincidofovir and no antagonistic effect: suitability for combination therapy.

# Brincidofovir

## ❑ **Regulatory status:**

- Approved by FDA in June 2021 under the agency's Animal Rule treatment of human smallpox disease caused by variola virus in adult and pediatric patients, including neonates.
- Not approved in EU.
- Efficacy findings derives from animal studies. Safety findings comes from clinical trials for non-smallpox indications (CMV infection in patients who received hematopoietic stem cell transplants).

## ❑ **MoA:**

- Brincidofovir (lipid conjugate of cidofovir) is an orthopoxvirus nucleotide analog DNA polymerase inhibitor.

## ❑ **Posology (adults):**

- Oral tablets, 100 mg (suspension available). 200 mg once weekly for 2 doses (on Days 1 and 8).

## ❑ **Non-clinical efficacy:**

- Efficacy studies were conducted in the rabbitpox model and the mousepox model.
- Early treatment (<6 days post challenge) with brincidofovir resulted in significant improvement in survival relative to placebo.

## ❑ **Safety profile:**

- Most common AEs are diarrhea, nausea, vomiting. Elevation in hepatic transaminases. Increased risk for mortality when used for longer duration (24 weeks). May cause embryo-fetal toxicity.

## Cidofovir

- Authorised at EU level and US for the treatment of CMV retinitis in patients with AIDS and normal renal function.
- Proven activity against poxviruses in in vitro and animal studies.
- Important nephrotoxicity which limit its use as a first line therapeutic option.

## Vaccinia Immunoglobulin

- No data on the effectiveness of vaccinia Immunoglobulin in treatment of monkeypox complications.
- The use can be considered for the treatment of monkeypox complications or for post-exposure prophylaxis in person with T-cell function impairment (severe immunodeficiency).

## Preemptive Tecovirimat Use in an Active Duty Service Member Who Presented With Acute Myeloid Leukemia After Smallpox Vaccination

David A. Lindholm,<sup>1,2</sup> Raymond D. Fisher,<sup>2</sup> Jay R. Montgomery,<sup>3</sup> Whitney Davidson,<sup>4</sup> Patricia A. Yu,<sup>5</sup> Yon C. Yu,<sup>5</sup> Jillybeth Burgado,<sup>4</sup> Kimberly Wilkins,<sup>4</sup> Brett W. Petersen,<sup>4</sup> and Jason F. Okulicz<sup>1,2</sup>

<sup>1</sup>Infectious Disease Service, and <sup>2</sup>Department of Medicine, San Antonio Military Medical Center, Joint Base San Antonio–Fort Sam Houston, Texas; <sup>3</sup>Immunization Healthcare Branch, Defense Health Agency, Falls Church, Virginia; and <sup>4</sup>Division of High-Consequence Pathogens and Pathology (Poxvirus and Rabies Branch) and <sup>5</sup>Division of Preparedness and Emerging Infections (Regulatory Affairs), National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Smallpox vaccine is contraindicated in immunosuppression due to increased risk for adverse reactions (eg, progressive vaccinia). We describe the first-ever use of tecovirimat as a preemptive vaccinia virus treatment strategy during induction chemotherapy in an active duty service member who presented with acute leukemia and inadvertent autoinoculation after smallpox vaccination.

**Keywords.** vaccinia; tecovirimat; ST-246; smallpox vaccine; leukemia.

## MAJOR ARTICLE

## Progressive Vaccinia: Case Description and Laboratory-Guided Therapy With Vaccinia Immune Globulin, ST-246, and CMX001

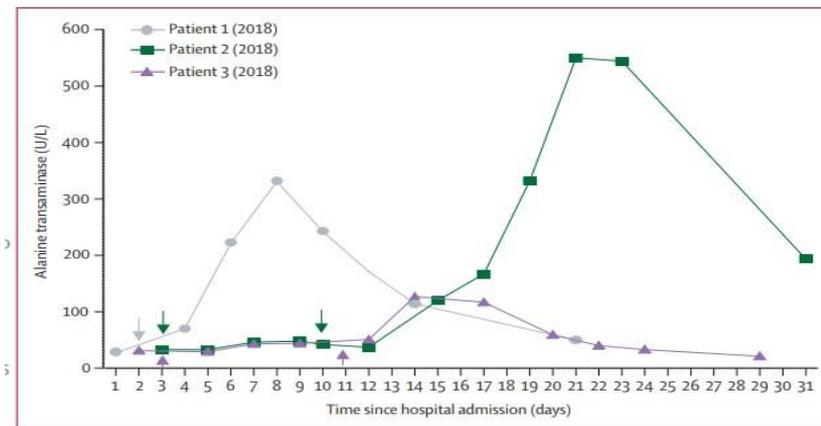
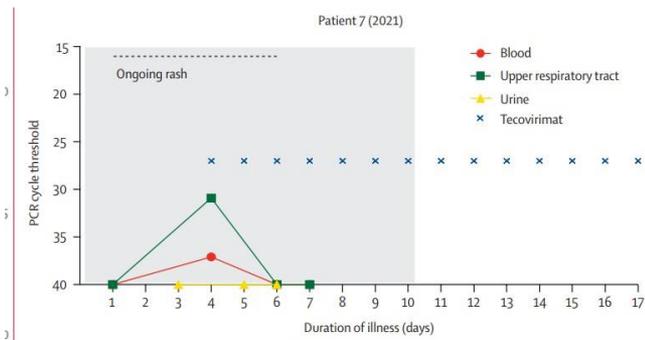
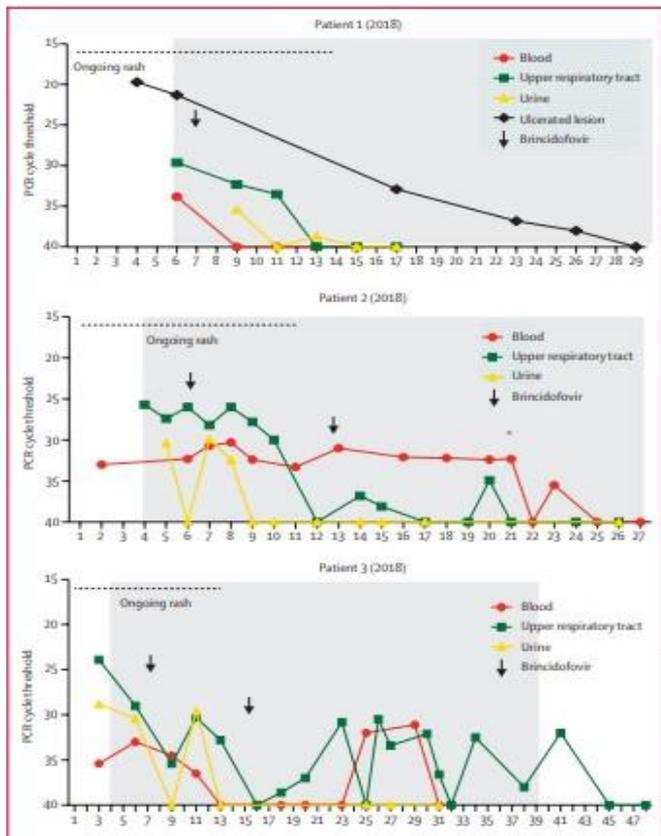
Edith R. Lederman,<sup>1,3a</sup> Whitney Davidson,<sup>1</sup> Harold L. Groff,<sup>2</sup> Scott K. Smith,<sup>1</sup> Tyler Warkentien,<sup>2</sup> Yu Li,<sup>1</sup> Kimberly A. Wilkins,<sup>1</sup> Kevin L. Karem,<sup>1</sup> Rama S. Akondy,<sup>2</sup> Rafi Ahmed,<sup>2</sup> Michael Frace,<sup>1</sup> Wun-Ju Shieh,<sup>1</sup> Sherif Zaki,<sup>1</sup> Dennis E. Hruby,<sup>4</sup> Wendy P. Painter,<sup>2</sup> Kimberly L. Bergman,<sup>6</sup> Jeffrey I. Cohen,<sup>7</sup> and Inger K. Damon<sup>1</sup>

<sup>1</sup>National Center for Zoonotic Vector Borne and Enteric Disease, Centers for Disease Control and Prevention; and <sup>2</sup>Vaccine Center, Emory University School of Medicine, Atlanta, Georgia; <sup>3</sup>Division of Infectious Diseases, Naval Medical Center San Diego, California; <sup>4</sup>Siga Technologies, Corvallis, Oregon; <sup>5</sup>Chimerix, Durham, North Carolina; <sup>6</sup>Office of Clinical Pharmacology, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring; and <sup>7</sup>Medical Virology, National Institute of Allergy and Immunology, National Institutes of Health, Bethesda, Maryland

**Progressive vaccinia (PV) is a rare but potentially lethal complication that develops in smallpox vaccine recipients with severely impaired cellular immunity. We describe a patient with PV who required treatment with vaccinia immune globulin and who received 2 investigational agents, ST-246 and CMX001. We describe the various molecular, pharmacokinetic, and immunologic studies that provided guidance to escalate and then successfully discontinue therapy. Despite development of resistance to ST-246 during treatment, the patient had resolution of PV. This case demonstrates the need for continued development of novel anti-orthopoxvirus pharmaceuticals and the importance of both intensive and timely clinical and laboratory support in management of PV.**

- Anecdotal experience in immunosuppressed individuals with (or risk of) progressive vaccinia
- Emergence of resistance and role of combination therapy

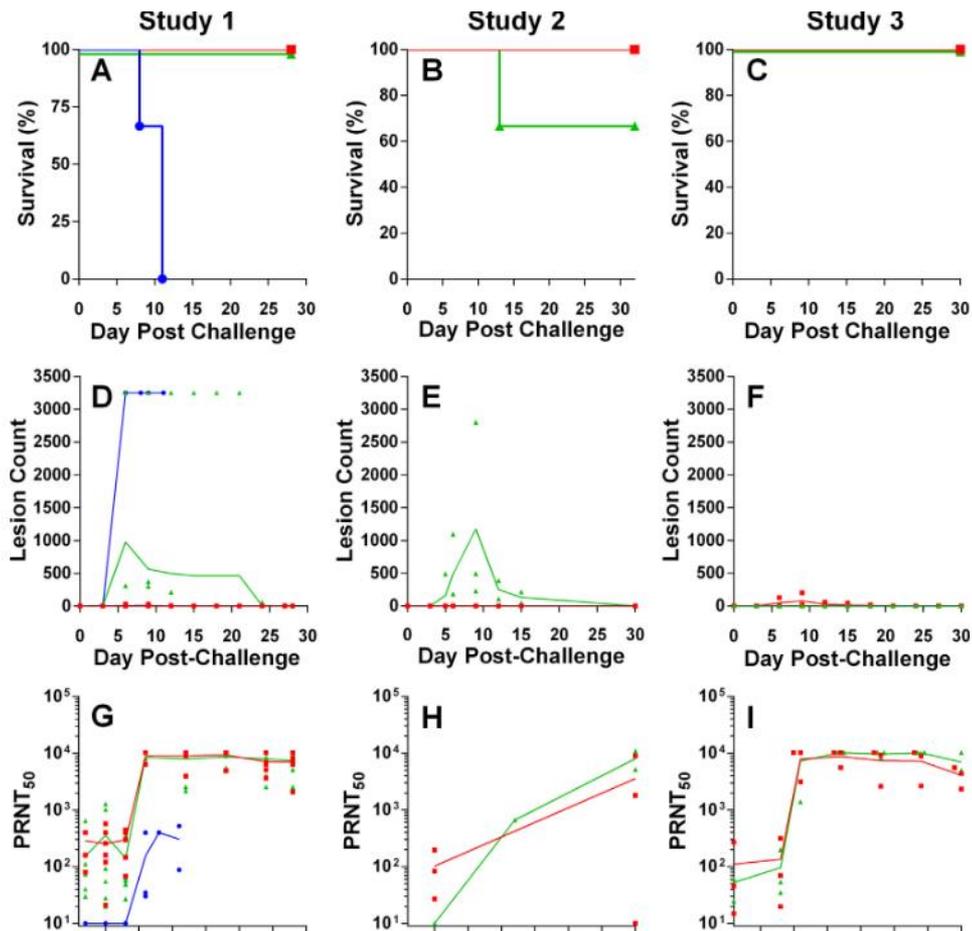
# Clinical features and management of human monkeypox: a retrospective observational study in the UK (thelancet.com)



**Figure 3: Alanine transaminase values of the three patients who received therapy with brincidofovir**  
 Doses of brincidofovir are denoted by arrows, with the colour of the arrow corresponding with the colour of the relevant patient's alanine transaminase graph. Normal range of alanine transaminase is less than 30 U/L.

[Co-administration of tecovirimat and ACAM2000 in non-human primates: Effect of tecovirimat treatment on ACAM2000 immunogenicity and efficacy versus lethal monkeypox virus challenge | Elsevier Enhanced Reader](#)

Possible interference on immune response to the vaccine



## EVALUATION OF EFFICACY

- Regulatory approval for antivirals for treatment of orthopoxviruses is achievable based on use of animal models of infection and safety/PK/PD data in humans
- However, since no clinical efficacy data were part of the approvals, it is demanded that in the context of outbreaks efforts for collecting clinical efficacy and safety data are in place
- This outbreak represent a case for which further clinical evidence should be collected
- Harmonised data collection for safety and clinical outcome would represent a desirable starting point in the context of an outbreak such as current one
- Chances for randomised controlled studies should be considered as well
- Especially in low-risk individuals with mild-moderate disease the feasibility of conducting placebo-controlled studies to determine time to clinical recovery (lesions healing – resolution of signs and symptoms) and viral clearance should be explored

## EVALUATION OF EFFICACY

- For high-risk patients, such as immunocompromised patients, the role of combination therapy could be investigated for example according to a factorial study design
- Studies aimed at identifying the role of antivirals in the context of post exposure prophylaxis (e.g. in addition or as an alternative to vaccination) could also be considered
- Studies to determine the impact of antivirals on vaccines immune response would be also of relevance in the context of PEP use
- Other vulnerable groups such as pregnant women and young children should be included as much as possible into clinical studies - separate cohorts looking primarily at PK and safety could be an alternative option

# Any questions?

## Further information

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**Official address** Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

**Telephone** +31 (0)88 781 6000

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