HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

The regulatory approval of Tecovirimat for orthopoxviruses in the EU

Éadaoin Griffin and Jeanette McCallion

Non-clinical data for regulatory decision-making on the efficacy of medical countermeasures

24-25 November, EMA

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

What are we going to talk about?

- Brief introduction to Orthopox viruses and Tecovirimat
- Regulatory journey of Tecovirimat
- Data that were used for regulatory approval
- Clinical considerations
- Relevance of clinical efficacy data available post-approval and impact on future use of animal models for CBRN threats

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

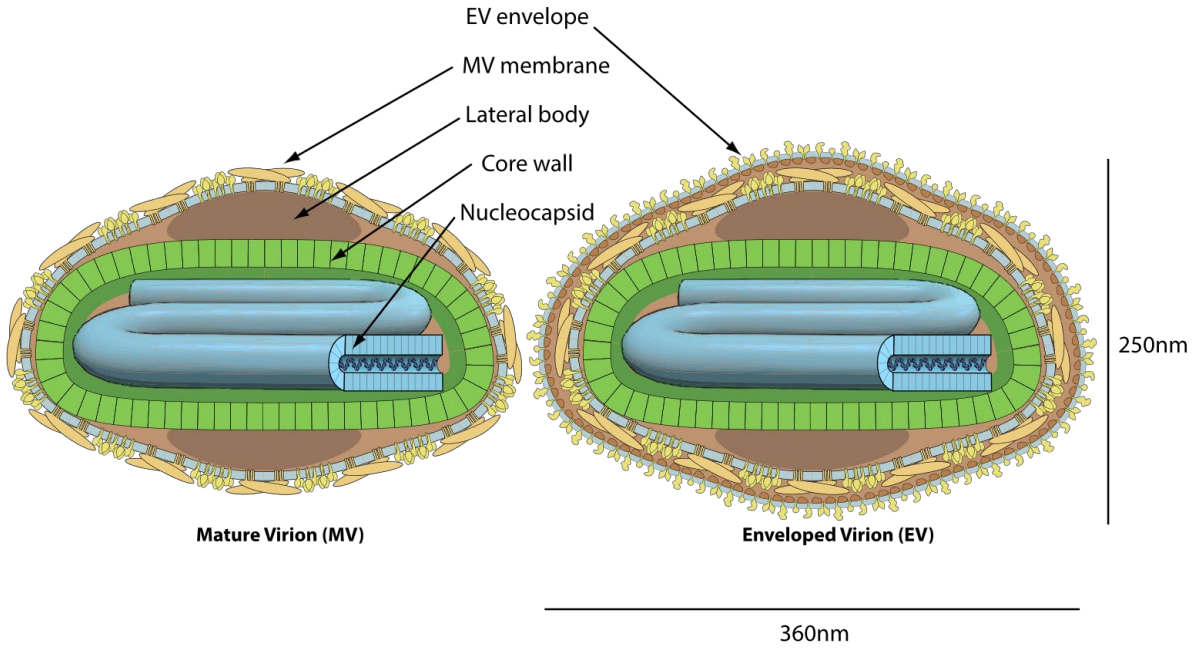
Introduction to Orthopox viruses and Tecovirimat (and its antiviral action)

Orthopoxviruses

- Orthopoxviruses belong to the family Poxviridae and are known for causing diseases in humans and animals. This genus includes several notable viruses, such as:
  - **Variola virus**: The causative agent of smallpox, which has been eradicated since 1980.
  - **Monkeypox virus**: An emerging zoonotic virus that has gained attention due to recent outbreaks.
  - **Cowpox virus**: Historically significant in the development of the smallpox vaccine.
  - **Vaccinia virus**: Used in the smallpox vaccine.

Structure and transmission

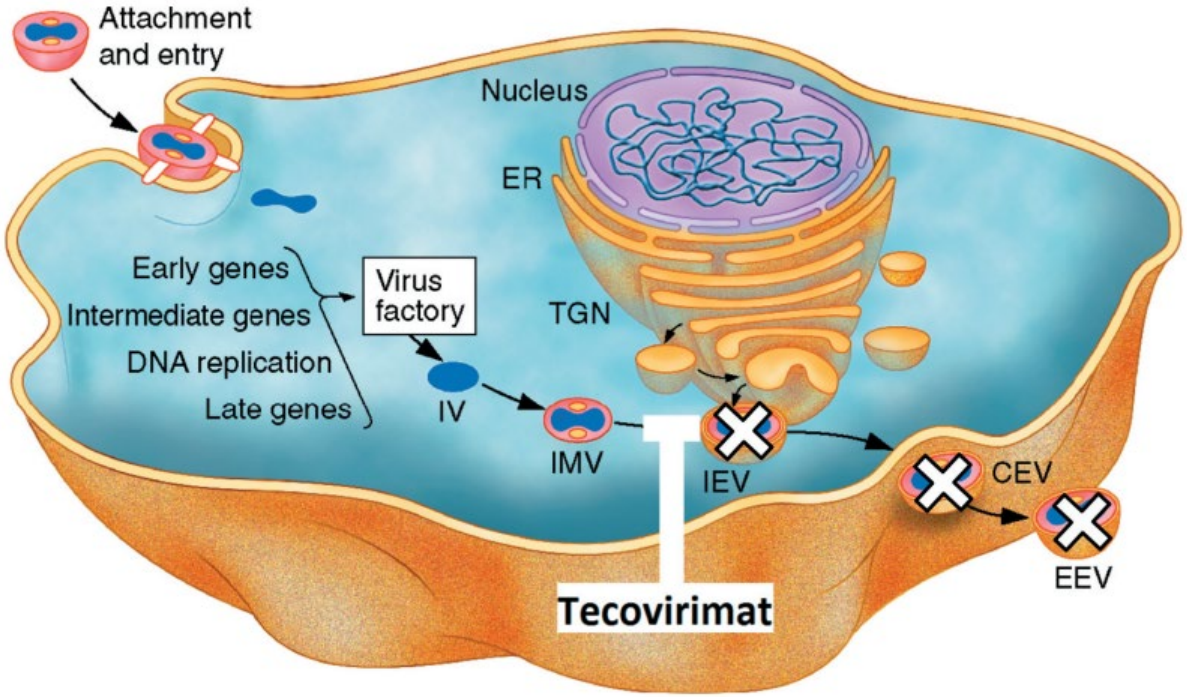
- Orthopoxviruses are large complex DNA viruses with brick shaped virions
- They have a linear double stranded DNA genome that can vary from 170-250 kilo bases
- Spread through direct contact with infected individuals or animals, respiratory droplets and contaminated materials
- Zoonotic (animal to human) transmission is common, especially with cowpox and mpox.

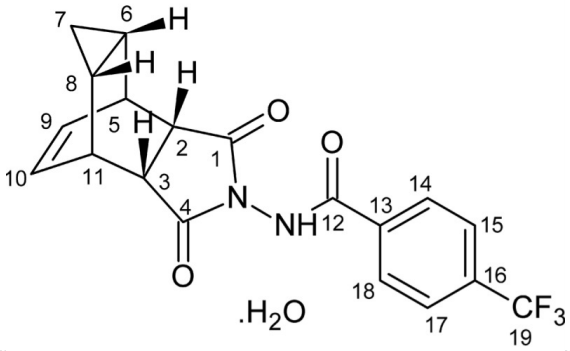


Orthopoxvirus ~ ViralZone

Tecovirimat Mechanism of Action

- Tecovirimat inhibits the orthopoxvirus protein p37, blocking cell-to-cell viral transmission
- p37 is a protein that is present and highly conserved (approximately 98% amino acid identity) in all orthopoxviruses
- The inhibition of p37 prevents the formation and egress of enveloped virions, which are essential for virulence
  - Grosenbach (2018) DOI: 10.1056/NEJMoa1705688
  - Russo (2021) DOI: 10.1080/14787210.2020.1819791





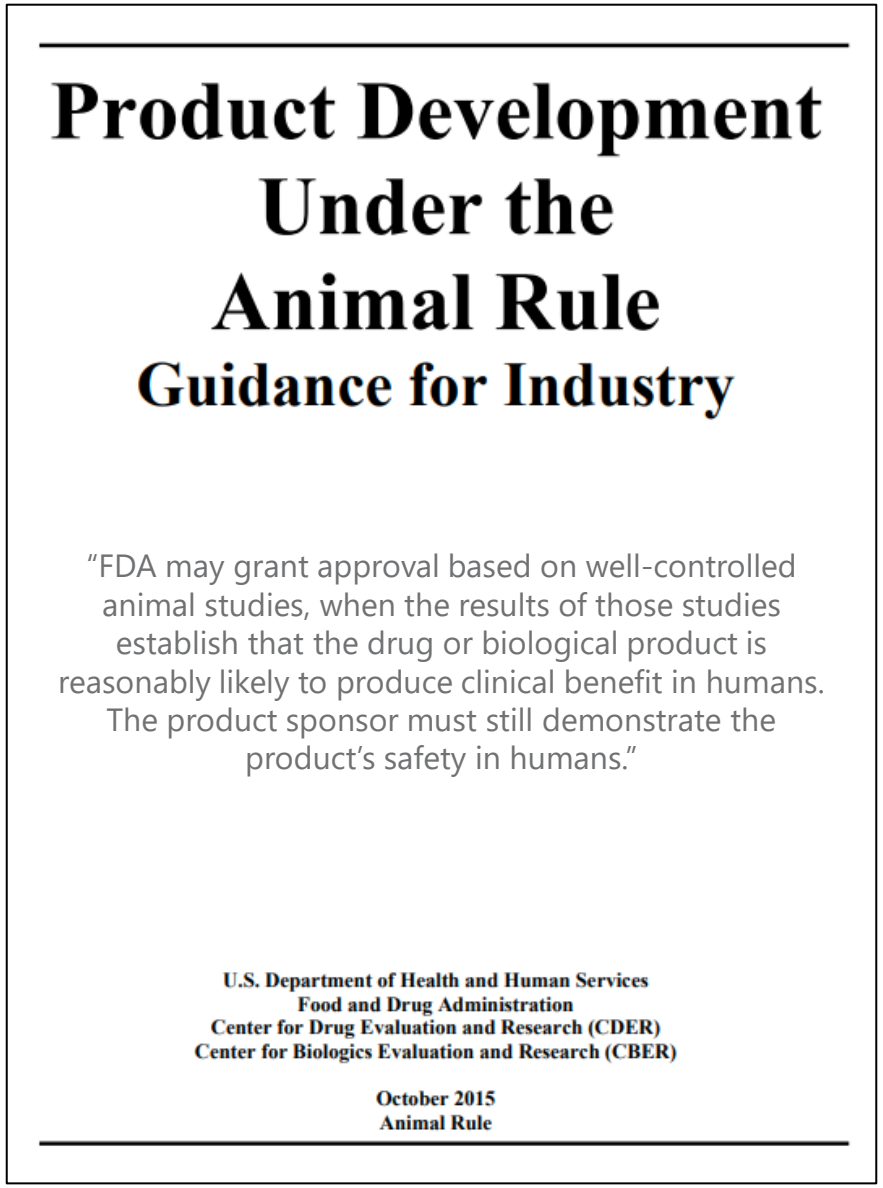
HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Regulatory journey of tecovirimat and the basis for its approval

Tecovirimat - USA

- Approved by the FDA in July 2018
- Tecovirimat was originally developed under the "Animal Rule" developed by the U.S. FDA. and intended for the treatment of patients with smallpox, providing a necessary medical countermeasure in the event of an intentional or accidental outbreak
- Approved Indication;

TPOXX® is indicated for the treatment of human smallpox disease caused by variola virus in adults and pediatric patients weighing at least 3 kg.



Product Development Under the Animal Rule

Guidance for Industry

"FDA may grant approval based on well-controlled animal studies, when the results of those studies establish that the drug or biological product is reasonably likely to produce clinical benefit in humans. The product sponsor must still demonstrate the product's safety in humans."

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2015
Animal Rule

https://www.fda.gov/emergency-preparedness-and-response/preparedness-research/animal-rule-information
https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214518s000lbl.pdf

Tecovirimat – EU

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

- Approval in EU under ***exceptional circumstances***, 6th January 2022

"the applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because the condition to be treated is rare or because collection of full information is not possible or is unethical."

- <u>The approved indications for tecovirimat are:</u>

'the treatment of the following viral infections in adults and children with body weight at least 13 kg:

- **Smallpox**
- **Mpox**
- **Cowpox**

Tecovirimat SIGA is also indicated to treat complications due to replication of vaccinia virus following vaccination against smallpox in adults and children with body weight at least 13 kg.'

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 November 2021
EMA/703119/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tecovirimat SIGA

International non-proprietary name: tecovirimat

Procedure No. EMEA/H/C/005248/0000

Approval basis- Overview

- ✓ The benefits of tecovirimat in humans were predicted from studies in animal models of orthopoxvirus disease.
- ➢ **No clinical studies in patients were possible due to the nature of the viruses to be treated and their lack of or rare circulation in humans, at that time**
- ✓ Human pharmacokinetic (PK) and PK-pharmacodynamic (PD) studies supported the clinical posology for adults and children from 13kg
- ✓ The mechanism of action (MOA) of tecovirimat combined with in vitro pharmacology evaluations, along with the highly conserved drug target, provided the basis for including in the indication smallpox, mpox, cow pox vaccina virus.
- ✓ Safety data was available from HV studies
- ✓ The approval was on an ***exceptional basis*** and subject to annual review. The authorisation is subject to two ***Specific Obligations***

Specific Obligations

Description	Due date
SOB 1: In order to further characterise the efficacy and safety of tecovirimat in the treatment of smallpox, the MAH should submit the results of the following open-label controlled phase 4 trial, upon the occurrence of a smallpox outbreak (as per protocol): A Multicenter, Open-Label, Randomized, Controlled Phase 4 Trial to Evaluate the Efficacy and Safety of Brincidofovir, Tecovirimat, and Brincidofovir Plus Tecovirimat for the treatment of Smallpox in Adult and Paediatric Participants.	Annually (with annual re-assessment) and no later than 12 months after the last administration of tecovirimat for the treatment of smallpox
SOB 2: In order to ensure adequate monitoring of safety and efficacy of Tecovirimat in the treatment of the Smallpox, Mpox, Cowpox viral infections and complications due to replication of vaccinia virus following vaccination against smallpox in adults and children with body weight at least 13 kg, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of Tecovirimat.	Annually (with annual reassessment)

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Data that were used for regulatory approval- *the basis for approval*

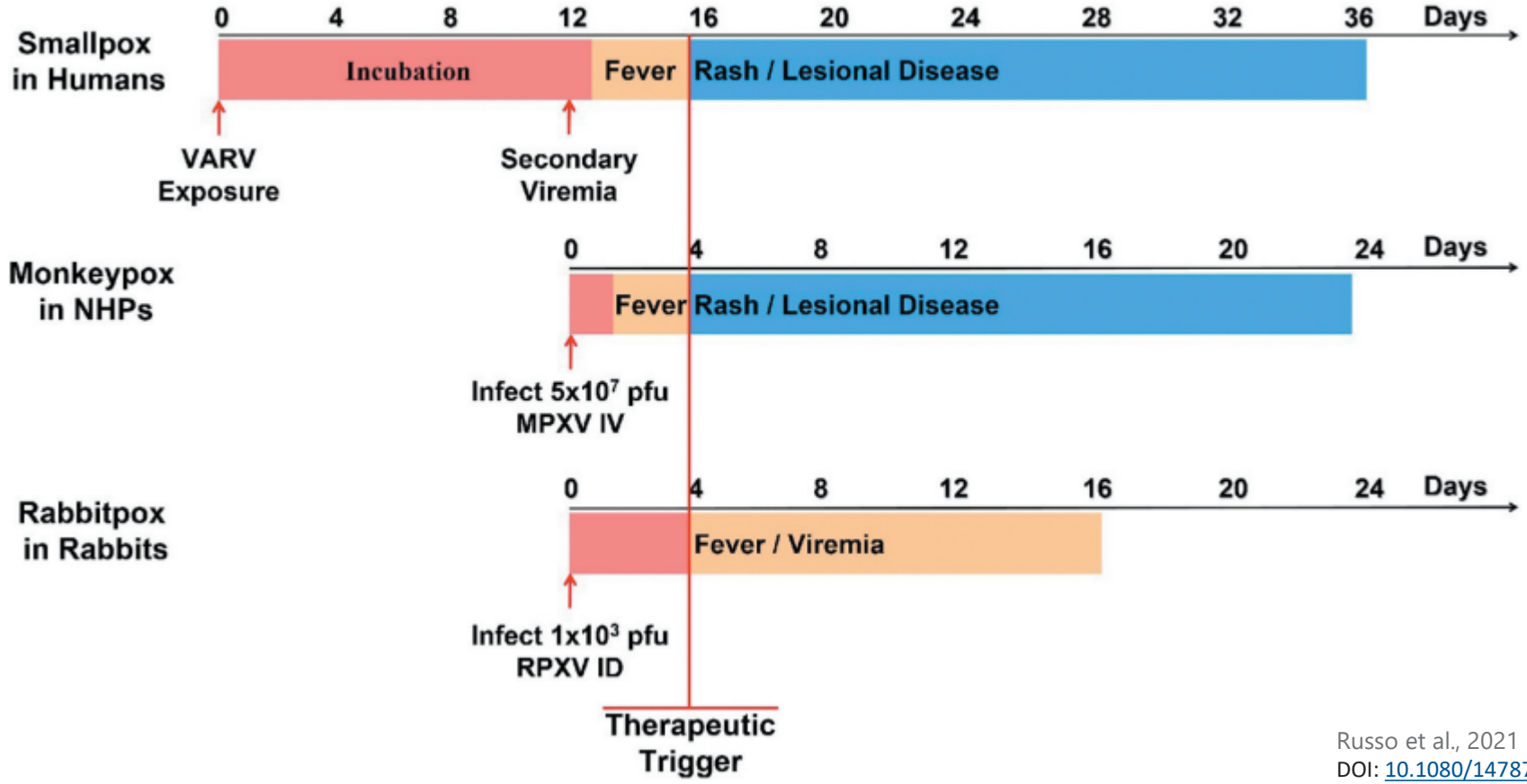
In vitro pharmacology data

- *In vitro* efficacy studies have demonstrated that tecovirimat shows antiviral specificity against multiple members of the orthopoxvirus genus (EC50 in the ~10 to 70 nM range), including variola, mpox, cowpox, vaccina, rabbitpox and camelpox.
- *In vitro* studies demonstrated the ability of tecovirimat to inhibit virus replication (as demonstrated by the inhibition of plaque formation) as well as extracellular virus formation, indicating that tecovirimat can prevent cell-to-cell spread and long-range dissemination of orthopoxviruses.
- *In vitro* studies have demonstrated the ability of tecovirimat to inhibit its molecular target, the VP37 protein, from interacting with intracellular transport components, thus preventing the production of enveloped egress-competent virus.

In vivo pharmacology

- No single animal model recapitulates all known aspects of human orthopoxvirus (Chapman et al., 2010).
  - https://doi.org/10.1177/0300985810378649
- The Applicant therefore chose a range of animal models infected with orthopoxvirus
  - NHP, rabbit, mouse, prairie dog and golden ground squirrel
- Monkeys and rabbits are considered to be the primary models for clinical effects, mimicking certain aspects of human smallpox, following orthopoxvirus infection.

Comparison of the course of smallpox in humans with monkeypox in NHPs and rabbitpox in rabbits



Russo et al., 2021
DOI: 10.1080/14787210.2020.1819791

Pivotal nonclinical animal efficacy studies

- Four pivotal studies in non-human primates and two pivotal studies in rabbits were conducted. NHPs were infected with a lethal dose of Clade I Monkeypox virus (MPXV) and rabbits infected with a lethal dose of rabbitpox virus (RPXV).
- Studies included dose exploration to determine the minimum fully effective dose and infected-animal pharmacokinetic (PK) studies in both animal models, as well as studies of treatment delay and treatment duration in non-human primates (NHPs).
- Oral (gavage) administration of tecovirimat resulted in a reduction in the primary and secondary outcomes of orthopoxvirus infection in both NHPs and rabbits.

NHPs

- Cynomolgus macaques were infected on Day 0 with a lethal dose of monkeypox virus Zaire '79 strain by IV inoculation with $5x10^7$ plaque-forming units (pfu) per animal.
- Tecovirimat at dose levels of ≥ 3 mg/kg/day for 14 days (initiated **no later than post-infection Day 4**) resulted in decreases in the incidences of mortality (> 95% survival compared to < 5% survival in monkeys treated with tecovirimat at dose levels of ≥ 3 mg/kg/day and ≤ 3 mg/kg/day, respectively).
- Tecovirimat at dose levels of ≥ 10 mg/kg/day for 14 days (initiated no later than post-infection Day 4) did not result in further increases in survival but did result in lower circulating MPXV DNA levels, fewer pock lesions (verifying the findings of the in vitro studies that tecovirimat reduces viral dissemination), and fewer clinical signs of infection (unresponsiveness, dyspnoea and fever, and lymphadenopathy).
- All untreated NHPs died.

Rabbits

- New Zealand White rabbits were infected on Day 0 with a lethal dose of rabbitpox virus strain Utrecht by ID inoculation with 1,000 pfu per animal.
- Studies in rabbits demonstrated that oral (gavage) administration of tecovirimat at dose levels of ≥ 20 mg/kg/day for 14 days (administered no later than post-infection Day 4) resulted in decreases in the incidences of mortality, blood RPXV levels, and clinical signs of infection (including dyspnoea, fever, and respiratory distress).
- All untreated rabbits succumbed to disease.

Table 5: Survival Rates in Tecovirimat Treatment Studies in Cynomolgus Macaques and NZW Rabbits Exhibiting Clinical Signs of Orthopoxvirus Disease

	Treatment Initiation[a]	Survival Percentage (No. survived/n)		p-value[b]	Survival Rate Difference[c] (95% CI)[d]
		Placebo	Tecovirimat		
Cynomolgus Macaques					
Study 1	Day 4	0% (0/7)	80% (4/5)	0.0038	80% (20.8%, 99.5%)
Study 2	Day 4	0% (0/6)	100% (6/6)	0.0002	100% (47.1%, 100%)
Study 3	Day 4	0% (0/3)	83% (5/6)	0.0151	83% (7.5%, 99.6%)
	Day 5		83% (5/6)	0.0151	83% (7.5%, 99.6%)
	Day 6		50% (3/6)	0.1231	50% (-28.3%, 90.2%)
NZW Rabbits					
Study 4	Day 4	0% (0/10)	90% (9/10)	< 0.0001	90% (50.3%, 99.8%)
Study 5	Day 4	NA[e]	88% (7/8)	NA	NA

[a]Day post-challenge tecovirimat treatment was initiated.

[b]p-value is from 1-sided Boschloo Test (with Berger-Boos modification of gamma = 0.000001) compared to placebo.

[c]Survival percentage in tecovirimat treated animals minus survival percentage in placebo treated animals.

[d]Exact 95% confidence interval based on the score statistic of difference in survival rates.

[e]A placebo control group was not included in this study.

KEY: NA = Not Applicable

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Clinical considerations

Relying on animal studies as a predictor of human efficacy- some considerations

- **No single animal model is likely to be fully predictive of human disease outcome**, but the use of multiple animal models using host adapted viruses or viruses that cause smallpox-like disease in a surrogate host are informative in assessing antiviral activity and predicting efficacy in humans.
- Tecovirimat inhibits the orthopoxvirus protein p37, and p37 is highly conserved (approximately 98% amino acid identity) in all orthopoxviruses
- Clinical course of human smallpox infection resembles that of rabbitpox (RPXV) infection of rabbits, where acute systemic infection results from inoculation with a small amount of virus at the periphery.
- Intravenous MPXV(Clade I) infection of non-human primates closely mimics human smallpox from the point of the eruptive phase of disease, including fever and viraemia and the development of dermal lesions that progress in a manner identical to human smallpox.

- **6 pivotal animal studies, using these 2 animal models, demonstrated strong antiviral efficacy of tecovirimat .**
- **These animal studies were therefore considered to be predictive of human efficacy in smallpox, mpox, cowpox, and vaccina virus, in the context of an impossibility at the time of attaining human efficacy data**

Additionally:

- The duration of treatment in nonclinical studies was the same as was proposed for humans(14 days). This was based on expectation of inhibition of systemic virus dissemination by tecovirimat until development of sufficient neutralizing antibody to clear the virus. NHPs and rabbits were shown to mount such an immune response within this timeframe.
- The timing of starting tecovirimat dosing in the animal studies was after animals had developed clinical signs of disease, specifically lesions in cynomolgus macaques and fever in rabbits.

Establishing a human dose

- Human dosing and target exposures were based on PK-PD analyses of NHP studies
- PK/PD modelling established a protective plasma concentration threshold (Cmin 169 ng/mL)
- The final recommended 600 mg BID dose taken in the fed state gives human exposures that substantially *exceed* efficacious exposures in NHPs dosed at 10mg/kg(confirmed in a Pivotal human PK study)

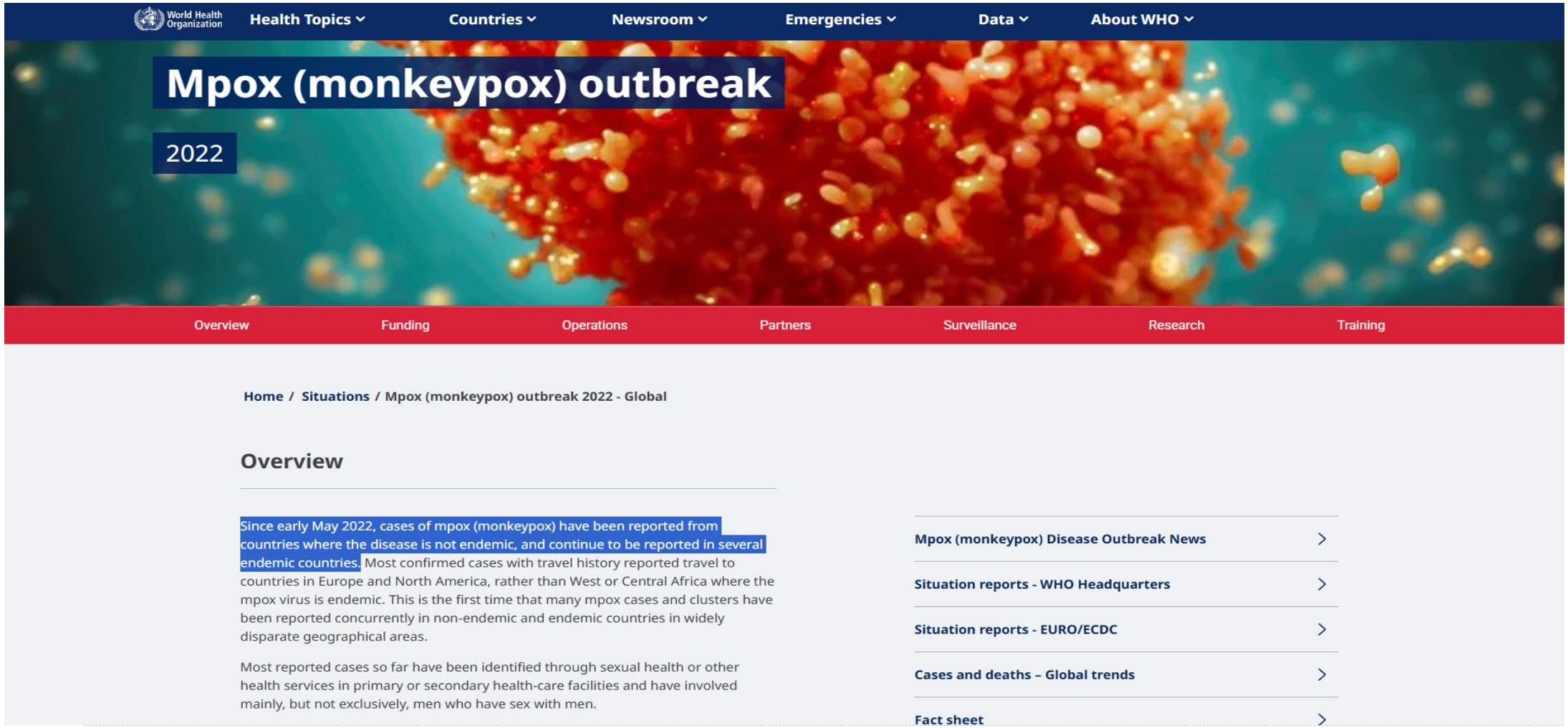
Clinical safety- at time of MAA

- 788 HV adults exposed to tecovirimat , overall, across 11 Phase I studies.
- In SIGA-246-008(PK pivotal study): 359 subjects took at least one dose of tecovirimat of which 95% took drug for at least one week. The median duration of treatment was 14 days.
- In SIGA-246-015(DDI study): 78 subjects received 600 mg BID on Days 8-22.
- Overall, the safety profile of 600 mg BID taken with food in uninfected subjects was considered acceptable.

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Post approval

Mpox outbreak 2022



Globally several mpox tecovirimat RCTs (not sponsored by the MAH) began recruiting…. 3 key RCTs being

	Location, Clade	Final numbers recruited
PALM007	Clade I DRC	n=597
STOMP	Clade II Argentina, Brazil, Japan, Mexico, Peru, Thailand and the United States	n=412
UNITY	Clade II Brazil, Argentina, Switzerland	n=480

	Primary results- as available publicly
PALM007 https://www.nejm.org/doi/full/10.1056/NEJMoa2412439	'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).'
STOMP https://www.niaid.nih.gov/news-events/nih-study-finds-tecovirimat-was-safe-did-not-improve-mpox-resolution-or-pain ACTG Presents Data from Mpox Study STOMP at CROI	'A planned interim analysis at 75% of the study's target enrollment showed there was no difference in the time to lesion resolution between participants treated with tecovirimat compared with those who received a placebo.'
UNITY Large international trial UNITY reports no clinical benefit from tecovirimat for mpox resolution - ANRS	'The primary outcome —time to full lesion resolution— showed no significant difference between the two arms. The estimated time ratio was 1.02 (p=0.73), indicating no meaningful clinical benefit for tecovirimat compared to placebo. '

Article 20 Referral – July 2025

EMA starts review of Tecovirimat SIGA

Review follows concerns over effectiveness in treatment of mpox

EMA has started a review of Tecovirimat SIGA (tecovirimat) following emerging data from recent clinical trials suggesting a lack of effectiveness in the treatment of mpox (a disease caused by the monkeypox virus).

Preliminary results from two completed studies, PALM007 and STOMP, both sponsored by the United States' National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, suggested that patients with mpox who received Tecovirimat SIGA did not recover from skin lesions faster than those who received placebo (a dummy treatment). Preliminary results recently published from a third study, UNITY, also do not indicate faster skin lesions resolution compared to placebo in patients treated with tecovirimat.

Additional results and analyses from ongoing studies or recently completed ones[1,2,3] are still awaited and will also inform EMA's assessment.

Based on the information available so far, there are no new safety concerns precluding the use of the medicine. The most common side effects with Tecovirimat SIGA are headache (which may affect more than 1 in 10 people) and nausea (feeling sick) (which may affect up to 1 in 10 people).

Tecovirimat SIGA was authorised in January 2022 to treat mpox, smallpox and cowpox in adults and children weighing at least 13 kg. Because mpox, smallpox and cowpox are either eradicated (smallpox) or occur sporadically in the EU, studies to assess whether Tecovirimat SIGA worked in infected people could not be carried out at the time of the initial authorisation. The medicine has therefore been authorised under 'exceptional circumstances' based on animal studies and studies on the medicine's effects in the human body and on the way the medicine is absorbed, modified and removed from the body in humans and animals (pharmacodynamics and pharmacokinetics studies). As a condition of the marketing authorisation, the company marketing Tecovirimat SIGA is required to provide an update annually on the medicine's benefits and risks.

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Relevance of clinical efficacy data available post-approval and impact on future use of animal models for CBRN threats

Relevance of mpox/tecovirimat RCT results

- This is the first available human efficacy data for tecovirimat, for any of the approved indications
- The trials are large RCTs and cover both Clade I and II and different geographical locations
- Multi country or multi site trials
- Subjects were dosed as per authorised indication and posology
- None of the RCT with results available demonstrated a reduction in time to lesion resolution in tecovirimat arms (primary endpoint) or in key secondary endpoints.
- Ongoing referral procedure looking at these data in detail, and any impact on the current indications.

Summary and impact on future use of animal models for CBRN threats

- Tecovirimat Article 20 referral still ongoing
- Tecovirimat provides a valuable opportunity to evaluate the use of nonclinical data for regulatory decision making and to explore any lessons learned in the context of post-authorisation availability of human efficacy data.

- Thank you!
- Any questions?

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Back up

Clinical Studies at time of application

- **Tabular overview of clinical studies**

Study No.	Type of Study	N[a]	Objective(s)
SIGA-246-008	Pivotal Phase 3, proposed clinical dose of oral tecovirimat 600 mg or placebo twice daily for 14 days	419	Safety, tolerability, and PK in fed and fasted healthy subjects
SIGA-246-015	Phase 1 multiple-dose (600 mg tecovirimat twice daily for 15 days); DDI study	77	Safety, tolerability, and effect of repeated doses of tecovirimat on single-dose PK of probe substrates flurbiprofen, omeprazole, midazolam, repaglinide, and bupropion
SIGA-246-002	Phase 1 multiple-dose (250, 400, or 800 mg tecovirimat or placebo once daily for 21 days)	19	Safety, tolerability, and PK in fed state
SIGA-246-004	Phase 2 multiple-dose (400 mg or 600 mg tecovirimat or placebo once daily for 14 days)	101	Safety, tolerability, and PK in fed state
SIGA-246-001	Phase 1 single-dose (500, 1000, or 2000 mg tecovirimat or placebo)	37	Safety, tolerability, and PK in fed and fasted state
SIGA-246-PO-005	Phase 1 single-dose, bioavailability of 2 forms (I and V) of tecovirimat (400 mg)	11	Safety, tolerability, and PK of 2 forms (I and V) of tecovirimat in fed state
SIGA-246-009	Phase 1 single-dose (600 mg tecovirimat and 100 µCi of [^{14}C]-tecovirimat), mass balance	6	Safety, tolerability, mass balance, and routes of elimination of [^{14}C]
SIGA-246-010	Phase 1 single supratherapeutic dose (1000 mg tecovirimat), effects of tecovirimat; thorough ECG study	48	ECG, safety, tolerability, and PK of single doses of tecovirimat 1000 mg, moxifloxacin 400 mg, and placebo in the fed state
SIGA-246-012	Phase 1 single-dose (600 mg tecovirimat), effect of renal impairment	37	PK, safety, and tolerability in subjects with varying degrees of renal impairment including end-stage renal disease requiring HD; effect of HD on the removal of tecovirimat from the bloodstream
SIGA-246-013	Phase 1 single-dose (600 mg tecovirimat), effect of hepatic impairment	32	PK, safety, and tolerability in subjects with varying degrees of hepatic impairment
SIGA-246-018	Phase 1 single-dose (100, 200, or 600 mg tecovirimat), effect of mixing capsule contents with food or liquid	47	PK, safety, and tolerability after administration of a single dose as capsule contents mixed with a food or liquid compared to a single dose as intact capsules
SIGA-246-006	Phase 1 single-dose (600 mg tecovirimat), palatability and drug-masking	21	Palatability/taste assessment in foods; drug was not ingested

[a]N is the number of subjects completing the study.
KEY: DDI = drug-drug interaction; ECG = electrocardiogram; HD = hemodialysis; N = sample size; PK = pharmacokinetics