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Non-clinical models for orthopoxviruses therapeutics (mpox)

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The Case for the Animal Rule for the Development of Medical Countermeasures

Society is facing biological, chemical and nuclear threats that may post catastrophic risks to human health

FDA's Animal Rule is an indispensable regulatory mechanism for enabling development of medical countermeasures where human efficacy trials are unethical or infeasible

EU/EMA does not have Animal Rule but provides regulatory flexibility in some circumstances under exceptional circumstances

Key Nonclinical Model Expectations under Animal Rule/Exceptional Circumstances

- Animal models (one or more) must be well characterized and predictive of the natural history and pathophysiology of human disease
- Efficacy endpoint must correspond with an important clinical patient outcome
- Mechanism of action of drug must support extrapolation of results from animals to humans
- Animal dosing must allow extrapolation to human clinically relevant dose

Irrespective of nonclinical model(s) selection, sponsors must always plan for post-marketing surveillance and additional data collection when available and appropriate

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Development of Tecovirimat Originated as a Smallpox Therapeutic and Is Evolving

Need for MCM Against Deadly Biothreats

2001

- **Smallpox** as grave threat to national security due to high rate of respiratory transmission and **high morbidity and mortality**
- Tecovirimat as a **biodefense MCM** against smallpox threat

Regulatory Pathway for Smallpox

- **Animal Rule** pathway developed in collaboration with FDA, NIAID, CDC, and Dept of Defense
- **Animal model data was triangulated with safety and PK data in humans**

Nonclinical/ Clinical Trial Data

- Efficacy has been demonstrated in **>50 studies** using multiple animal species infected with variola, mpox, cowpox, vaccinia, and ectromelia viruses
- **Safety in 17 *clinical* trials** involving administration in **1,300+** healthy human volunteers

On-Going Development and Post-Marketing Surveillance

2025+

- 2022 mpox outbreak enabled execution of 6 academic-agency sponsored mpox trials to assess safety, efficacy, PK
- MAH sponsored PEP trial ongoing to assess safety and potential impact on vaccine immunogenicity in event of smallpox outbreak

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U.S. FDA Advisory Committee on Animal Models for Smallpox (2013)

Human efficacy trials for smallpox or related orthopoxviruses are not feasible

- Smallpox has been eradicated, making deliberate human infection **unethical** and unjustifiable
- Monkeypox field trials in endemic regions were also deemed **impractical and unreliable** due to the sporadic and unpredictable nature of outbreaks, uncertain exposure timing, and uncontrolled confounding factors (co-infections, variable access to care, delayed diagnosis)

FDA Animal Rule provides the **only scientifically and ethically appropriate pathway** to establish efficacy for smallpox therapeutics

- Three animal models were recognized as predictive of human smallpox disease and sufficient when evaluated collectively:

Ectromelia virus (ECTV) in mice 	Rabbitpox virus (RPXV) in rabbits 	Monkeypox virus (MPXV) in nonhuman primates (NHP) 

- **Survival was endorsed as the primary efficacy endpoint**
- Additional parameters—viremia, lesion counts—were accepted as supportive secondary endpoints.

- **Demonstration of a survival benefit across these complementary models**, combined with **human PK/PD bridging data**, constitutes a **scientifically sufficient basis for regulatory approval under the FDA Animal Rule**

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Comparison of Tecovirimat Nonclinical Models for Smallpox

	Variola Virus (VARV) Challenge Model– Nonhuman Primates	New Zealand White rabbit / RPXV model	Cynomolgus macaque/ MPXV model
Challenge strain	*Variola virus* (VARV) **Harper strain**, originally isolated from a human case	*Rabbitpox virus (RPXV) Utrecht strain*	*Monkeypox virus (MPXV) Zaire strain (Clade I)*
Species	Cynomolgus macaque	New Zealand White rabbit	Cynomolgus macaque
Dose / Route	10^8 plaque-forming units intravenous (IV)	10^3 PFU intradermal (ID) or aerosol exposure	5×10^7 PFU intravenous (IV) inoculation
Disease Course	• ~3–4 days incubation before onset of fever and lymphadenopathy • Rash appears ~Day 4–5, progressing to generalized pustular eruption • Viremia peaks ~Day 5–7, followed by rapid clinical deterioration	• ~2–3 days incubation before fever and viremia onset • Generalized rash and secondary lesions *may* appear by Day 4–5 • Viremia peaks and severe systemic illness occur by Day 6–8	• ~3–4 days incubation before fever, lymphadenopathy, and viremia onset. Lesions appear on Day 4. • Disseminated rash and lesion count increases, resembling human smallpox progression • Peak viremia Days 7 - 12 with high viral loads in blood and tissues
Outcome (untreated)	***Irreproducible lethality***, with mean time-to-death of ~8–9 days post-challenge	**Uniformly lethal**; mean time-to-death 7.6 days post-challenge	Typically, **≥90% mortality**; mean time-to-death **~9–12 days post-challenge**
Relevance	• Replicates the disseminated phase of smallpox • Serves as a stringent test of antiviral efficacy due to rapid progression and high viral burden.	• Closely mimics disseminated smallpox, including rash, viremia, and mortality kinetics • Highly reproducible, GLP-qualified, and responsive to antiviral therapy. Typically, ≥90% mortality; mean time-to-death 6-10 days post-challenge	• **Best physiological analog of human smallpox** • Replicates natural disease course, tissue tropism, and pathology • Serves as a **pivotal model** for bridging animal efficacy to expected human benefit

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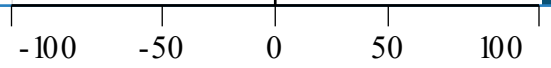
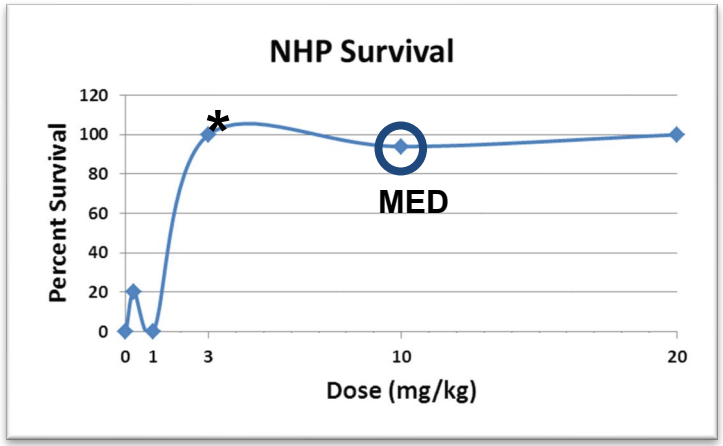
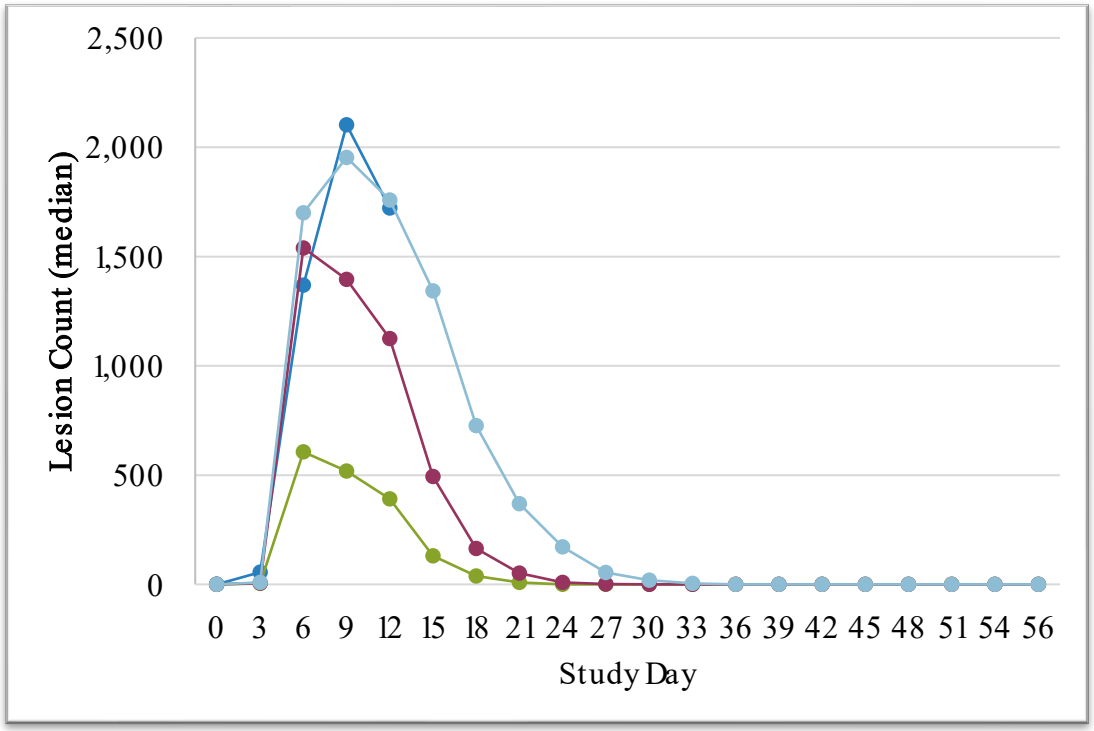
Tecovirimat Effect on Survival in Pivotal Animal Models – Dose and Timing Matter

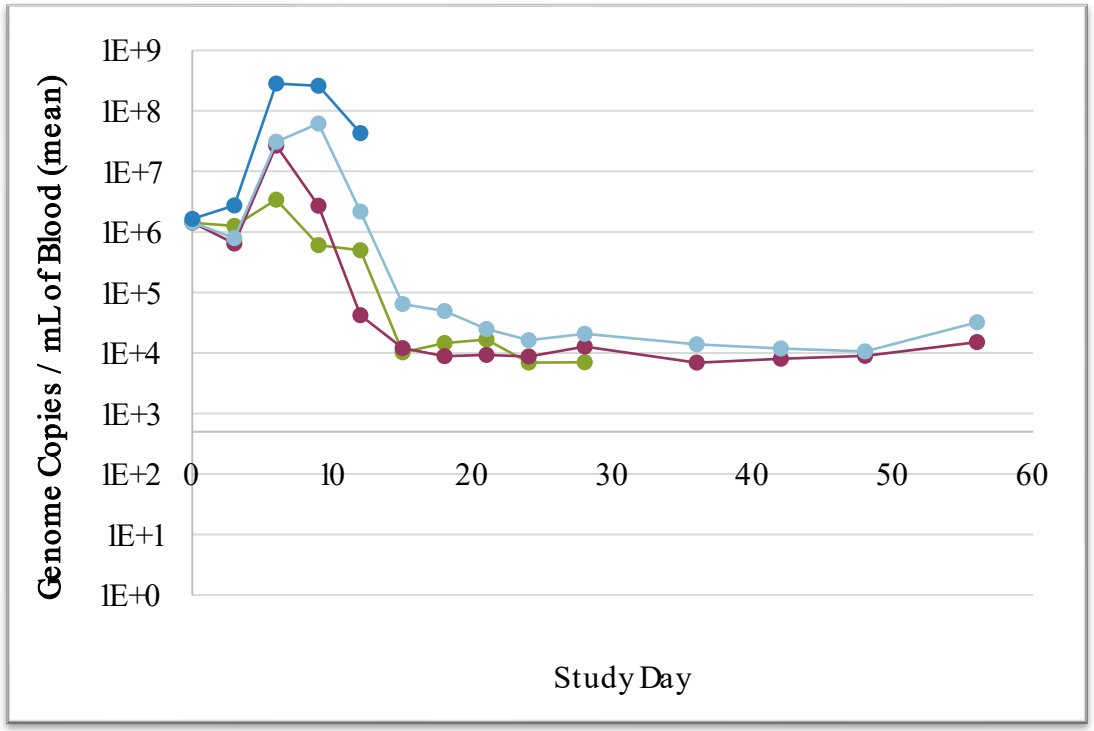
Comparison		Difference and 95% CI	Conclusions
		Favors Placebo | Favors Active	
NHP	3 mg/kg (days 4–17) vs Placebo (days 4–17)		All doses >3mg/kg effective in NHPs
	10 mg/kg (days 4–17) vs Placebo (days 4–17)		
	20 mg/kg (days 4–17) vs Placebo (days 4–17)		
NHP	0.3 mg/kg (days 4–17) vs Placebo (days 4–17)		Doses <3mg/kg not effective
	1 mg/kg (days 4–17) vs Placebo (days 4–17)		
	3 mg/kg (days 4–17) vs Placebo (days 4–17)		
	10 mg/kg (days 4–17) vs Placebo (days 4–17)		
NHP	10 mg/kg (days 4–17) vs Placebo (days 4–19)		Treatment initiation Days 4 and 5 effective; Day 6 loses efficacy
	10 mg/kg (days 5–18) vs Placebo (days 4–19)		
	10 mg/kg (days 6–19) vs Placebo (days 4–19)		
NHP	10 mg/kg (days 4–6) vs Placebo (days 4–13)		Treatment must last at least 5 days
	10 mg/kg (days 4–8) vs Placebo (days 4–13)		
	10 mg/kg (days 4–10) vs Placebo (days 4–13)		
	10 mg/kg (days 4–13) vs Placebo (days 4–13)		





Tecovirimat Significantly Improves Lesion and Viral Load–Especially with Early Administration in Lethal NHP Clade I Animal Models





Placebo (Start Day 4) — 10 mg/kg (Start Day 4) — 10 mg/kg (Start Day 5) — 10 mg/kg (Start Day 6)

- Tecovirimat demonstrated efficacy in secondary endpoints such as lesion count and viral load
- Benefits of tecovirimat seen when administered before peak viremia (Day 6)

All NHP arms treated for 14 days
Ref: Study 37F, 38F

Orthopoxviruses Range in Disease Severity

Orthopoxviruses have a common biology but they differ in the course of disease, severity and clinical outcome. While the goal of treatment for both is to improve patient outcomes, for smallpox, the objective is to save lives.

SMALLPOX
Variola Virus

MPOX
Monkeypox Virus

More Severe		**Less Severe**
Protect **National Security**	Unmet Need	Improve **Patient Outcomes**
Reduce / prevent Mortality	Clinical Outcomes	**Reduce Lesions**
Respiratory (saliva droplets)	Transmission	Direct **Physical Contact**
>30%	Case Fatality Rate	**~5%** Clade I, **~0.5%** Clade II
Over **300 million deaths** in 20th century	Global Impact	Less than **1,000 deaths** since 2022

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Learnings from Recent Mpox Clinical Data

Topline results across studies did not demonstrate a benefit in lesion resolution when tecovirimat was administered on average ~6-8 days post symptom onset

Academic/agency sponsored studies included a broad range of mpox patients identified at the time of lesion presentation

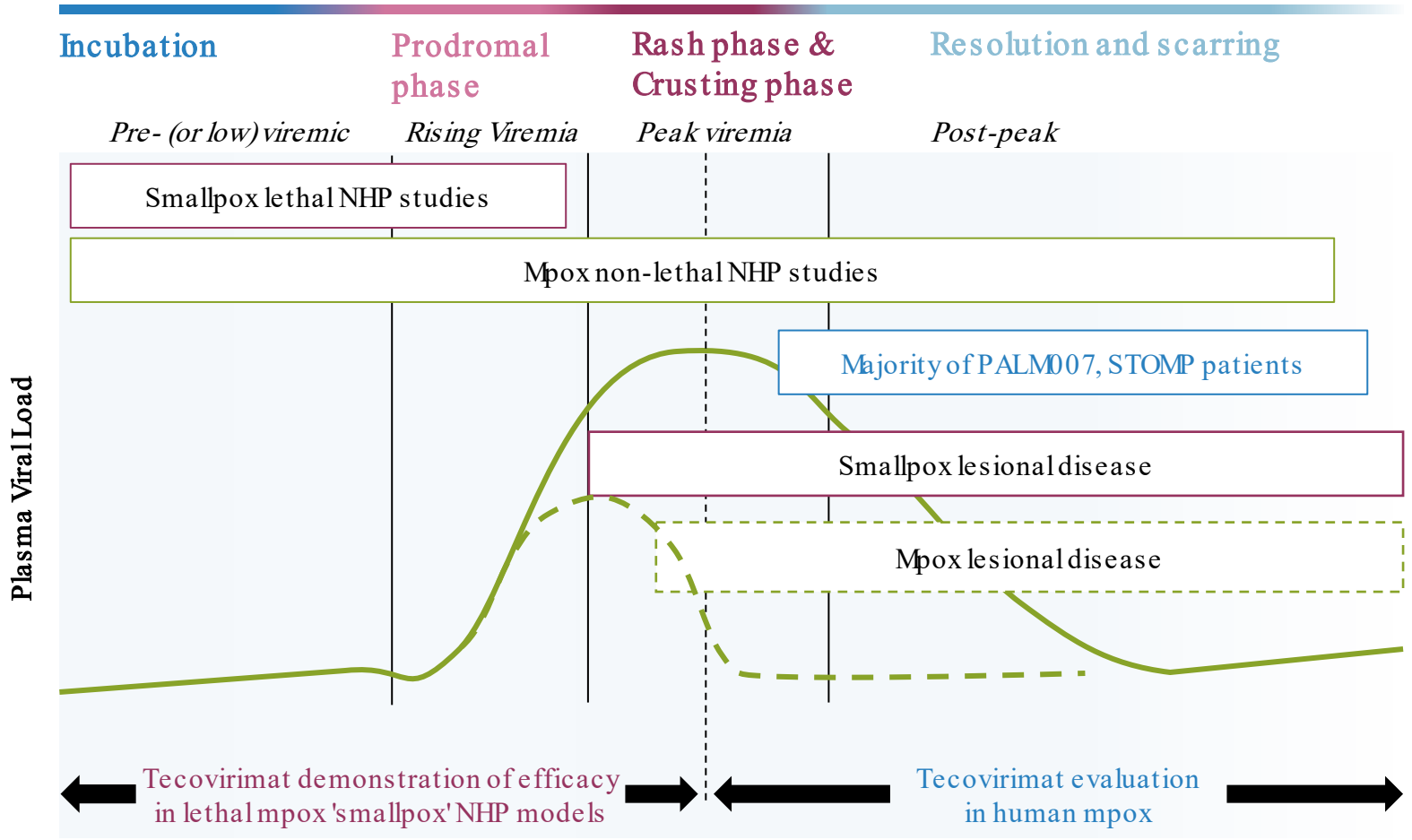
By inclusion criteria, patients in all trials had active lesions suggesting peak-viral load had passed. Tecovirimat was administered on average ~6-8 days after reported symptom onset and the endpoint was to assess time to lesion resolution.

While secondary endpoints vary, mortality was measured but was not informative (<1% regardless of treatment arm in PALM007, none in STOMP)

Post hoc clinical analysis show potential drug activity benefits in reduction in viral load and improvement in symptoms for grave/severe patients

Timing of administration matters!

Understanding Disease Phases and Correlation with Nonclinical and Clinical Data Critical



Tecovirimat developed to reduce mortality from smallpox leveraging lethal animal models

Significant clinical data has been collected on mpox (STOMP, PALM007 etc.), were patients predominantly in the post-peak viral load phase

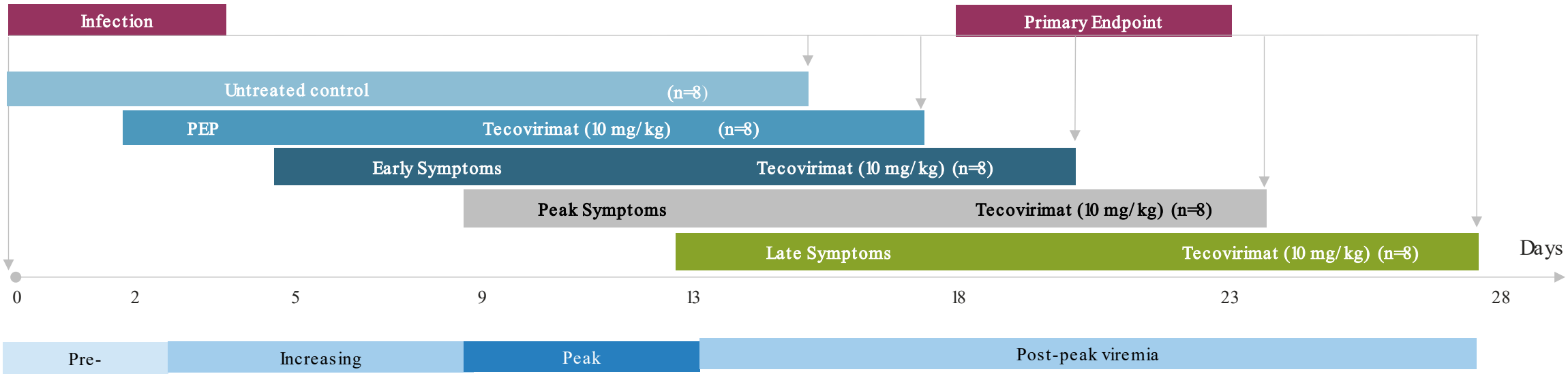
Potential tecovirimat benefit in mpox patients; new nonclinical mpox study designed to help optimize clinical treatment paradigm in mpox patients

Need for a Clinically Relevant Mpox Model to Assess Treatment Optimization

Ideal non-lethal mpox model requires animals to have milder infection, comparable human viral load peak, and **timing of disease progression and resolution is similar to human mpox** as seen in current clinical presentation

	Smallpox Model	Mpox Model
Description	• ***Lethal*** infection of NHPs with Clade I MPXV • Compressed incubation and prodrome but ***similar to human smallpox*** post-lesion onset • High peak viremia ~10^8 pfu/ml of blood • Whole body lesion counts, ~500 – 2000 • ***~100% mortality*** without treatment (rare survivors)	• ***Non-lethal*** infection of NHPs with Clade II MPXV • Compressed incubation and prodrome, but ***similar to human mpox*** throughout the course of disease • Low peak viremia ~10^4 pfu/ml of blood • Whole body lesion counts, ~100 • ***~100% survival*** without treatment (rare deaths)
Study Objectives	• ***Powered for mortality endpoint*** to demonstrate death prevention • Develop PK/PD models to define the exposure-response relationship establishing the human dosing regimen	• ***Powered for virological endpoints*** to demonstrate that burden of disease (lesions and viral load) reduction and potentially speed recovery • ***Identify the optimal timing of tecovirimat treatment*** to modify disease outcome and reduce clinical symptoms of mpox.

Non-lethal Clade II Mpox Infection of NHPs



Assumptions	Key Data Collection	Primary Objective	Primary endpoint	Key Secondary endpoints
• BSL3 Facility • Pilot studies to understand dose, route, and incubation period ongoing now to be completed prior to 5-arm study • Availability of Clade II stock and NHPs • All animals become infected • Model is not lethal, animals develop 100s of lesions, viral load in 5 to 6 log range at peak, timing of disease progression and resolution to adequately model human disease	• Frequent virology (blood, OP, saliva) • Lesion counts • Clinical signs • PK at key timepoints • Humoral immune responses	• To evaluate the efficacy of tecovirimat compared to untreated animals in preventing development of mpox infection after MPXV infection	• Incidence of symptomatic mpox disease within 14 days of first treatment	• Viral load (from infection to 14 days post-treatment) • Number of skin lesions (from presentation to 14 days post-treatment for any animal who develops lesions) • Severity of mpox symptoms (from presentation to 14 days post-treatment for any animal who develops symptoms)

Preliminary Non-Lethal NHP Clade II Animal Findings

Key Observations

Infected NHP controls showed the expected pathogenesis following non-lethal Clade II mpox challenge;

- Viral load peaks at Day 9 whereas lesions peak on Day 13

Timing of tecovirimat treatment critical where lesion count (AUC) and viral load reduction benefit maximized when administered early

- Minimal symptom reduction benefit post viremia peak

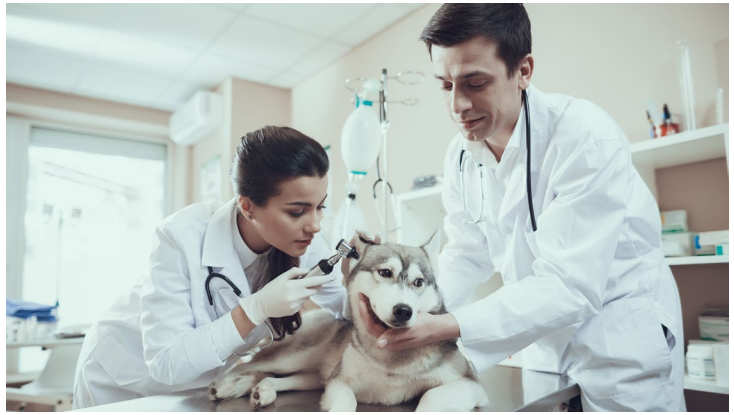
Tecovirimat showed benefit in symptom reduction throughout disease progression in infected animals

Pivotal Studies: 4 NHP, 2 rabbit (approved Animal Rule models of smallpox)

Key Take-Aways

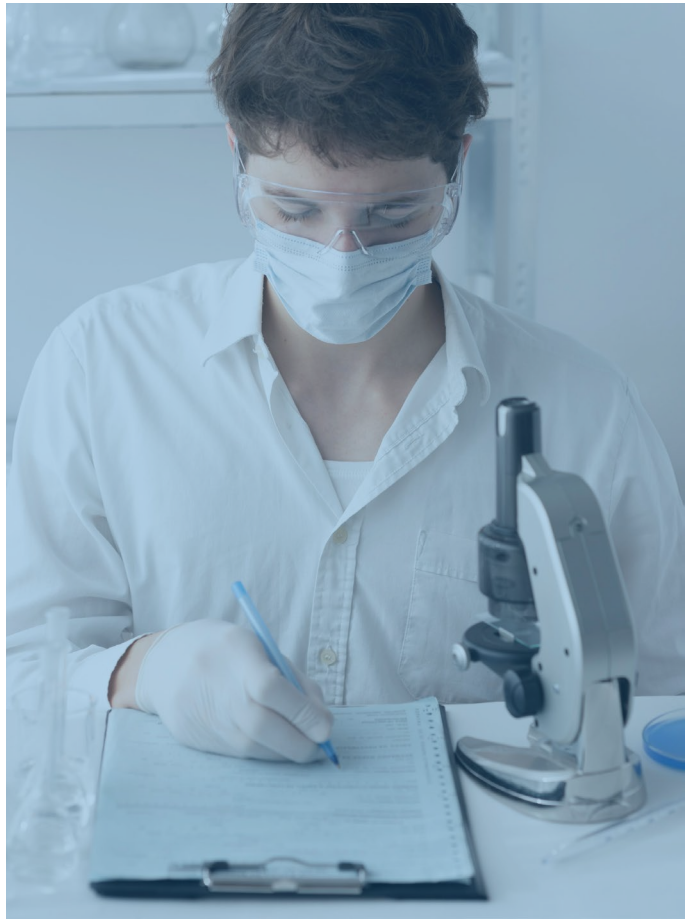
Animal models necessary and essential component in development of MCMs where clinical trials are unethical or not feasible

Data to satisfy regulatory requirements should be case specific, reflect the nature of the disease and the circumstances surrounding data collection, and be adaptive to incorporate new findings



Post-approval learnings drive continuous improvement in the development of clinically relevant animal models for life threatening diseases

Forward Looking Statements



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