TPOXX: An Orthopox Antiviral

Dennis Hruby, Ph.D.
EVP & Chief Scientific Officer
SIGA Technologies, Inc.

SIGA®
Human BioArmor®

Orthopoxvirus infections can cause a spectrum of febrile rash illnesses in humans, from fairly benign, localized skin infections to severe systemic infections.

There are four orthopoxvirus species known to cause human disease:

Vaccinia virus

Vaccinia virus is used as the smallpox vaccine and it causes sporadic disease in vaccinees, contacts of vaccinees, and laboratory workers. Infection can be lethal in immunocompromised individuals.

Cowpox virus

Human cowpox virus infection is classically associated with occupational exposure to cattle; however, other animals, including rats, pet cats, and zoo and circus elephants, have been implicated. Infection can be lethal in immunocompromised individuals.

Mpox virus

Mpox virus causes intermittent human infections, primarily in Central and West Africa, although isolated outbreaks have been identified in the United States and Sudan. Individual cases have been identified in the US, UK, Singapore, and Israel prior to the 2022 outbreak and in 115 regions since the outbreak began. The disease is very similar to smallpox. Case fatality rates range from <1% to >10% depending on virus clade.

Variola virus

Smallpox… a deadly killer

SIGA Human BioArmor®

Medical Countermeasures for Smallpox/mPox

antivirals → | ← *vaccines* →

TPOXX®
Tecovirimat SIGA
(ST-246/tecovirimat)

- **The first FDA-approved antiviral drug with an indication for treatment of smallpox**
- **Targets the VP37 protein of orthopoxviruses and prevents envelopment and release of virions from the cell**
- **Exhibits antiviral activity against all orthopoxviruses tested in vitro (nanomolar concentrations) and in all animal models**
- **Demonstrated to be well-tolerated in human clinical trials**

TPOXX approved by US, Canada, EU, UK.

TEMBEXA®
(CMX001/brincidofovir)

- Recently FDA-approved antiviral drug with an indication for treatment of smallpox
- Targets the E9L DNA polymerase of orthopoxviruses and inhibits DNA synthesis
- Exhibits antiviral activity against orthopoxviruses tested in vitro (nanomolar concentrations) and in two animal models as well as against other DNA viruses
- Black box warning due to increased mortality with prolonged use and various toxicities

TEMBEXA not approved outside U.S.

ACAM2000®
(plus other replicating vaccinia vaccine)

- Live vaccinia virus smallpox vaccine currently licensed in the USA, Australia, and Singapore
- It may cause serious adverse reactions (including death), especially in individuals who are very young or very old, or immunocompromised (e.g., those with eczema or atopic dermatitis)
- 20-25% of the population would be contraindicated to receiving the vaccine
- The vaccine is ineffective if given later than ~4 days post-exposure

ACAM2000 approved by US, Australia, SIngapore.

IMVANEX/IMVAMUNE/ JYNNEOS®
(MVA-BN®)

- Modified vaccinia virus Ankara smallpox vaccine approved in Europe, Canada and US
- Due to its high level of attenuation, it is no longer replication-competent in mammalian cells
- Appears well-tolerated but requires two doses administered 28 days apart for full efficacy

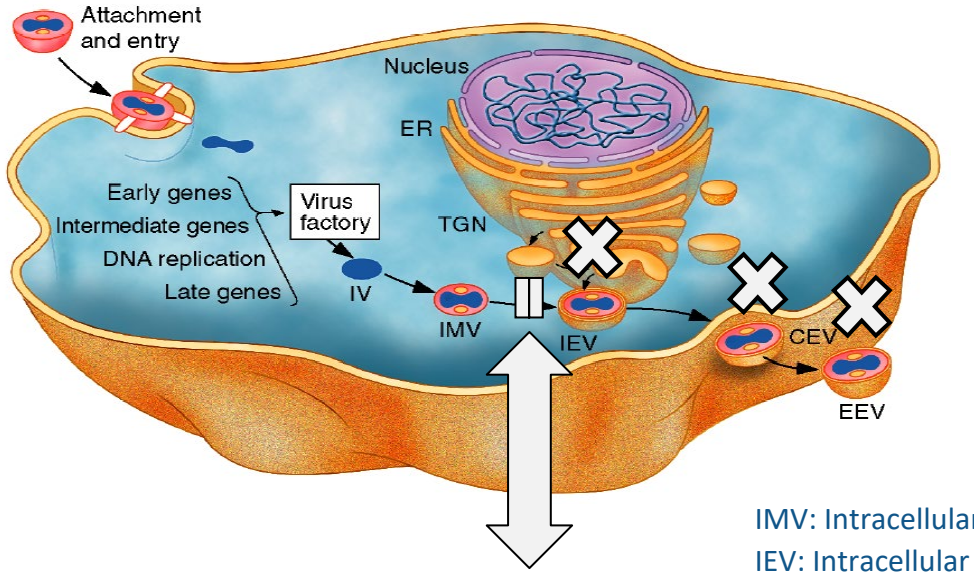
MVA-BN approved by US, Canada, EU

Vaccinia Immune Globulin Intravenous is approved in the US for the treatment of complications resulting from smallpox vaccination, but was used "off-label" (EA-IND) for the treatment of mpox, and may be used similarly for smallpox. MAb's are in development for use in mpox and smallpox infections.

SIGA Human BioArmor®

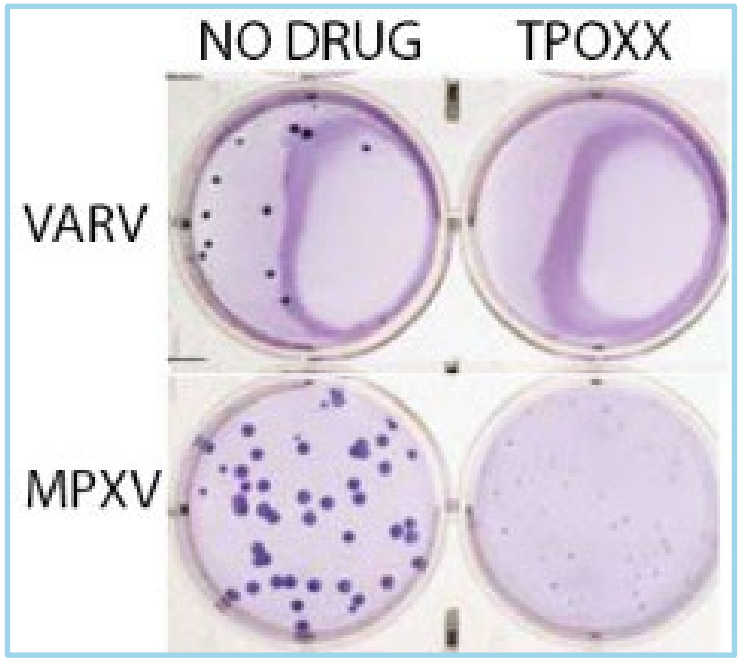
TPOXX Mechanism of Action

- Smallpox dissemination and pathogenicity is dependent on the formation of a secondary envelope surrounding the virus
- This allows the virus to leave the cell, spread cell-to-cell, and enter the bloodstream
- TPOXX's mechanism of action **inhibits maturation, preventing release and spread of viral particles to other cells**



IMV: Intracellular Immature Virus
IEV: Intracellular Enveloped Virus
EEV: Extracellular Enveloped Virus

Inhibits the viral envelope formation and spread of the virus



Low mutation rate: 2 X 10^{-7}

Image adapted from Byrd CM and Hruby DE. Viral proteinases – targets of opportunity. Drug Dev Res. 2006;67:501-510.;

SIGA Human BioArmor®

Smallpox/Orthopoxvirus Antiviral

Oral TPOXX®/Tecovirimat SIGA (Tecovirimat/ST-246)

- US FDA approval (July 2018), indicated for the treatment of human smallpox disease in adults and pediatric patients weighing at least 13 kg
- Health Canada approval (November 2021), indicated for the treatment of human smallpox disease in adults and pediatric patients weighing at least 13 kg
- EMA approval (January 2022) and MHRA approval (June 2022), indicated for the treatment of smallpox, monkeypox (mpox), cowpox, and vaccinia vaccine complications in adults and pediatric patients ≥13 kg
- Exhibits antiviral activity against all orthopoxviruses tested *in vitro* (nanomolar concentrations) and in animal models
- No drug-related SAEs in clinical trials
- The most frequently reported adverse reactions were headache and nausea
- 84-months stability
- Inventory maintained in the SNS

Full US TPOXX prescribing information is available at:
https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=fce826ab-4d6a-4139-a2ee-a304a913a253

Full Canada TPOXX prescribing information is available at:
https://pdf.hres.ca/dpd_pm/00063782.PDF

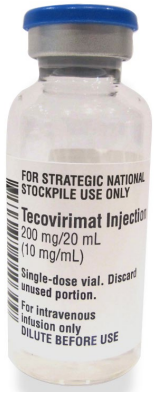
Full EU Tecovirimat SIGA prescribing information is available at:
https://www.ema.europa.eu/en/medicines/human/EPAR/tecovirimat-siga

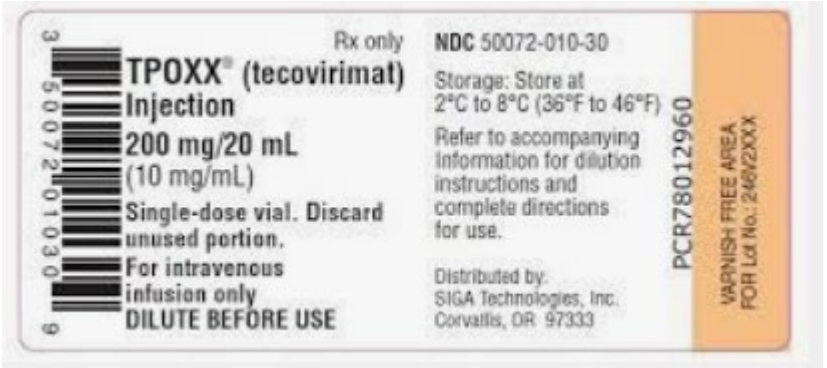
SIGA®
Human BioArmor®

Smallpox/Orthopoxvirus Antiviral

Intravenous (IV) TPOXX® (Tecovirimat/ST-246)

- US FDA-approved (May 2022)
- For patients that are too sick or unable to take oral TPOXX capsules
- Anticipate transitioning from IV to oral TPOXX as symptoms improve
- No drug-related SAEs in clinical trials
- The most frequently reported adverse reactions were infusion site pain & swelling
- 42-months stability
- Inventory maintained in the SNS





Full US TPOXX prescribing information is available at:
https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=fce826ab-4d6a-4139-a2ee-a304a913a253

SIGA
Human BioArmor®

TPOXX Oral Dosage for Adults and Pediatric Patients Weighing at Least 13 kg

Weight (kg)	Dosage (No. of Capsules)	Drug Food Preparation Instructions for Patients Who Cannot Swallow Capsules
13 – <25kg	200 mg (1 capsule) every 12 hours	Carefully open the required number of capsules and mix contents of capsule(s) of TPOXX with 30 mL of liquid (e.g., milk, chocolate milk) or soft food (e.g., apple sauce, yogurt). The entire mixture should be administered within 30 minutes of its preparation.
25 – <40kg	400 mg (2 capsules) every 12 hours	
40 – <120 kg	600 mg (3 capsules) every 12 hours	
≥120kg	600 mg (3 capsules) every 8 hours	

- Palatability/taste masking study conducted in healthy volunteers
  - Foods tested were expected to be commonly found in households (e.g. yogurt, applesauce, baby food, milk)
  - All food mixtures were well tolerated by subjects
- Pharmacokinetic (PK) study conducted in healthy volunteers
  - Foods tested: applesauce & milk
  - No clinically significant difference when compared to oral capsule

SIGA Human BioArmor®

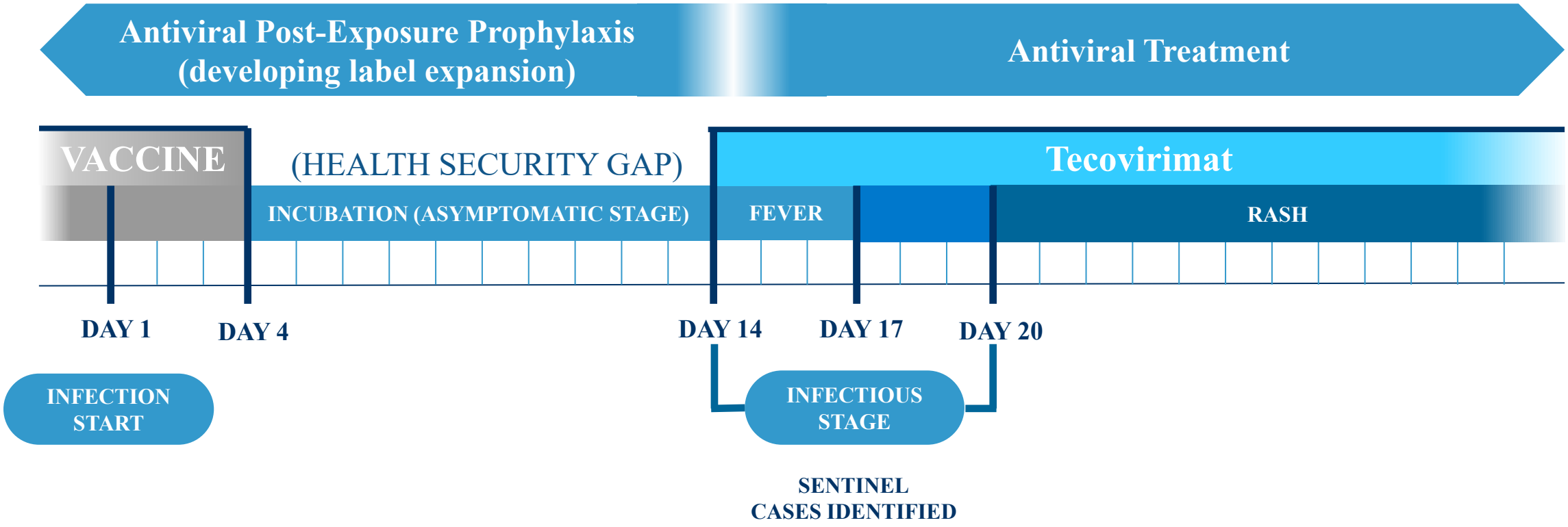
TPOXX – Powder for Reconstitution (PfR) Formulation

- TPOXX Powder for Reconstitution (PfR) formulation currently under development for infants <13 Kg

- Potential Advantages:
  - No need to mix with foodstuff (water only)
  - Straightforward instructions
  - Accurate dosing

- PfR formulation optimization & scale-up activities are underway

Health Security Gap



Post-Exposure Prophylaxis (PEP)

- Currently approved smallpox countermeasures (ACAM2000, Imvamune/JYNNEOS vaccines and Tecovirimat/Tembexa therapies) leave a significant health security gap between the time of exposure and the onset of clinical signs (~2 weeks)
- Expanding the current tecovirimat indication to include PEP would address this vulnerability
- Tecovirimat could be used as a standalone prophylactic or in combination with vaccination to ensure immediate *and* lasting protection from smallpox
- Availability of tecovirimat for first responders (healthcare workers, emergency services personnel, etc.), who are greatest risk of exposure to smallpox, would provide confidence that they will remain protected in the event of an emergency and ensure that critical services continue to be provided

Ongoing Clinical Trials to Support the PEP Indication

- **Tecovirimat 28-day safety study (completed)**
  - Considering that the asymptomatic phase of smallpox may be up to 17 days post-exposure and that induction of protective immunity occurs within 10 days of the onset of symptoms, up to 28 days of Tecovirimat PEP dosing may be necessary
  - The 28 day safety study is designed to demonstrate the safety of Tecovirimat as PEP

- **Tecovirimat + JYNNEOS immunogenicity study (completed)**
  - Once Tecovirimat is approved as PEP, there is a possibility that the indications for Tecovirimat and the smallpox vaccine (ACAM2000 or JYNNEOS) will overlap.
  - This study is designed to evaluate any impact of Tecovirimat on JYNNEOS immunogenicity
  - Tecovirimat and JYNNEOS were co-administered on day 1 and Tecovirimat dosing continued for 28 days.
  - A JYNNEOS boost was administered after 28 days.
  - Immune responses to JYNNEOS are being evaluated after the prime and boost vaccinations.

Global Mpox Outbreak 2022

- As of 27 September 2023, the current global mpox outbreak includes **92,048 "reported" cases**
- Mpox symptoms are reportedly **extremely painful**, and full recovery takes weeks to a month or more
- A **number of deaths (167)** have been reported, although this clade of mpox is not typically fatal
- **Vaccine has been deployed (MVA-BN)**, potentially helping to slow the spread.
- In the U.S**., the CDC distributed > 80,000 bottles of oral TPOXX and > 13,000 vials of IV TPOXX**
- TPOXX supplied to 27 Countries around the world during the ongoing mpox outbreak


1 Aug 2022 New York Times

How Monkeypox Went from Containment to Crisis

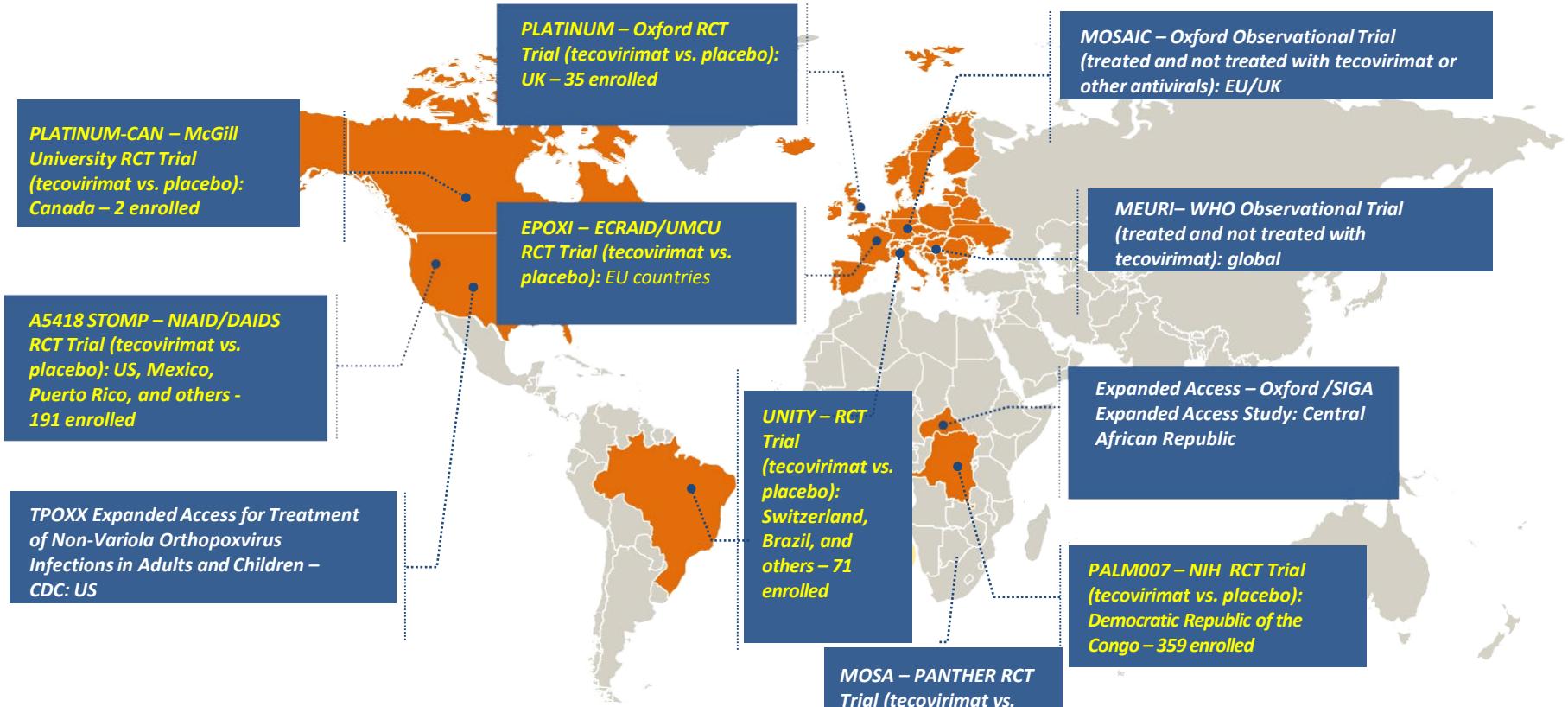
In mid-June, cases of monkeypox were in the double digits in the United States. There were drug treatments and vaccines against it. There didn't seem to be any reason for alarm.
But in the weeks since, the virus has spread rapidly across the country, with some local and state officials declaring public health emergencies.

Tecovirimat SIGA is approved for mpox in Europe and the UK in addition to smallpox, cowpox and vaccinia. In the US, no treatment for monkeypox is FDA-approved, but FDA and CDC have expanded access use of TPOXX, which appears to enhance positive clinical outcomes in these cases – separate from ongoing clinical trials.

SIGA Human BioArmor®

Current and Planned Mpox Clinical Trials for Oral TPOXX/Tecovirimat SIGA

There is global interest in using TPOXX/Tecovirimat SIGA for clinical trials for mpox patients



SIGA
Human BioArmor®

Conclusions

- TPOXX® oral capsules are an approved safe and effective antiviral to treat orthopoxvirus infections to prevent morbidity and mortality for patients greater than 13 kg in weight.
- TPOXX® is also available in an approved IV formulation for individuals with advanced disease or who are unable to take oral medication
- A TPOXX PfR formulation is in advanced development for individuals < 13kg
- Studies to support the regulatory approval of a post-exposure prophylaxis indication for oral TPOXX are nearing completion
- Multiple RCT to determine the safety and efficacy of TPOXX in mpox patients are underway which will hopefully support regulatory approval of TPOXX to treat mpox in the USA
- The mpox response demonstrated the need to maintain an adequate stockpile and a robust manufacturing capacity.
- There are no “perfect” smallpox/mpox countermeasures. Continued development of additional countermeasures is needed to prevent morbidity and mortality in vulnerable populations (e.g. immunocompromised patients)
  - SIGA is developing ST- 357, a smallpox antiviral with a MOA distinct from TPOXX and Tembexa

SIGA Human BioArmor®

SIGA has worked closely with the U.S. Government and continues to cultivate relationships with key health security constituencies

Health Canada

Public Health Agency of Canada

EUROPEAN MEDICINES AGENCY

SIGA

Human BioArmor®