Smallpox Therapeutics Overview

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Committee on the Current State of Research, Development, and Stockpiling of Smallpox MCMS

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The BARDA Model

BARDA develops and makes available medical countermeasures (MCMs) by forming unique public-private partnerships to drive innovation off the bench to the patient to save lives.

- Flexible, nimble authorities
- Multi-year funding
- Cutting edge expertise
- Facilitate partnerships
- Promote innovation

ASPR's mission:
Assist the country in **preparing for**, **responding to**, and **recovering from** public health emergencies and disasters.

Smallpox Therapeutics Overview

Tecovirimat (TPOXX®; ST-246) (Siga)

- Capsule (7 year expiry) and IV (48+ mo expiry) formulations FDA approved for smallpox; goal of IV with 5 year expiry
- Capsules: store in the original bottle at 20°C to 25°C; excursions permitted 15°C to 30°C
- Injection: store at 2°C to 8°C

TEMBEXA®
brincidofovir
10 mg/mL oral suspension | 100 mg tablets

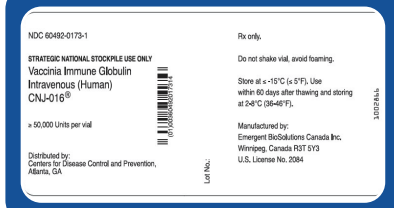
TEMBEXA® (Brincidofovir) (Emergent)

- Tablet (48 mo) and suspension (48 mo) formulations FDA approved for smallpox; goal of extending expiry to 7 years
- Tablet and suspension: Store at 20°C to 25°C; excursions permitted from 15°C to 30°C

Biofactura

BFI-753 (Biofactura)

- IND antibody product
- Anticipate IV administration and indication for treatment of human smallpox disease in adults and pediatric patients

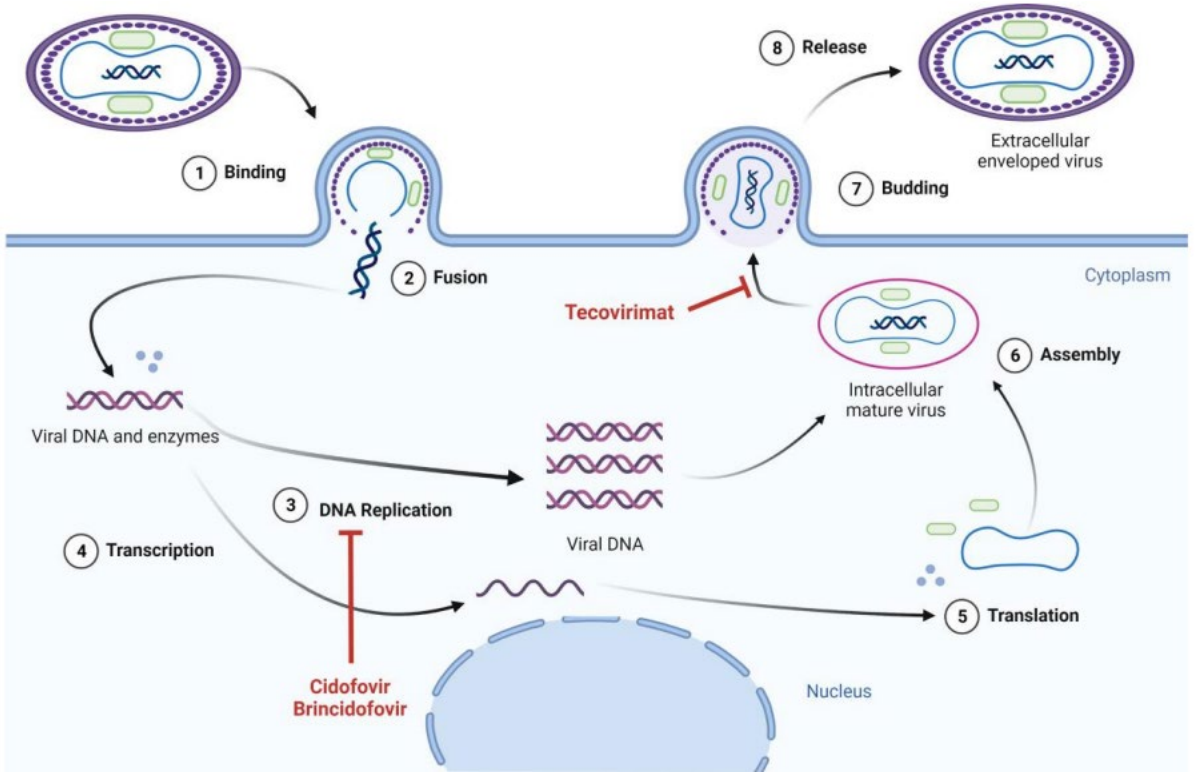


Vaccinia Immune Globulin Intravenous (VIGIV)

- Licensed for treatment of complications from vaccinia vaccination
- CDC has emergency IND protocol for use against other orthopoxviruses
- **Not discussed in this presentation**

Smallpox Antiviral Products and Approach

- **2004:** Smallpox determined to be a material threat to national security; MTD issued by Department of Homeland Security
- **2008:** Requirement to advance two antivirals with **different mechanisms of action**
- TPOXX and TEMBEXA were licensed through **FDA's Animal Rule**
  - Pivotal nonclinical nonhuman primate (mpox), mouse (ectromelia), and/or rabbit (rabbitpox) models provided evidence of efficacy
  - Human safety data informed product approval
  - Requirement for human clinical efficacy study remains
- BARDA continues to consider additional products that may have superior operational use or efficacy compared to the licensed products



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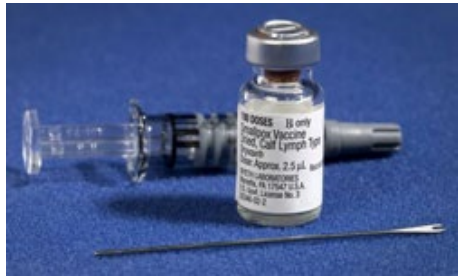
TPOXX

- Small molecule that inhibits viral envelope formation and spread of the virus by targeting VP37



Capsule: FDA approval in 2018

Dosage and Administration

- Supplied in 200 mg capsules
- Should be taken within 30 minutes after a full meal of moderate or high fat
- Adults: 600 mg twice daily for 14 days
- Pediatrics patients dosed based on weight for patients weighing **at least 13 kg**

Intravenous: FDA approval in 2022

Dosage and Administration

- Approved for patients weighing **at least 3 kg,** with dosing based on weight
- Dosing every 12 hours by IV infusion for up to 14 days
- If IV treatment is necessary, **conversion from IV to oral TPOXX is recommended** as soon as oral treatment can be tolerated

- **Pediatric powder for reconstitution** (mix with water) formulation identified, current scale up and CMC activities underway, IND submission expected 2024

TEMBEXA

EMERGENT

Lipid conjugate of cidofovir (CDV), which is a **nucleotide analog**

- Active diphosphate form inhibits viral DNA polymerase-mediated synthesis of viral DNA

Tablet and suspension: FDA approval in 2021

- Approved for the treatment of human smallpox disease in adult and pediatric patients, including neonates

Dosage and Administration:

- Once weekly dosing for two weeks; dose dependent on weight

Label Notes:

- *Testing:* Before initiation and during treatment with TEMBEXA perform hepatic laboratory testing and pregnancy testing
- TEMBEXA label contains warnings about potential carcinogenicity and fertility concerns and a black box label

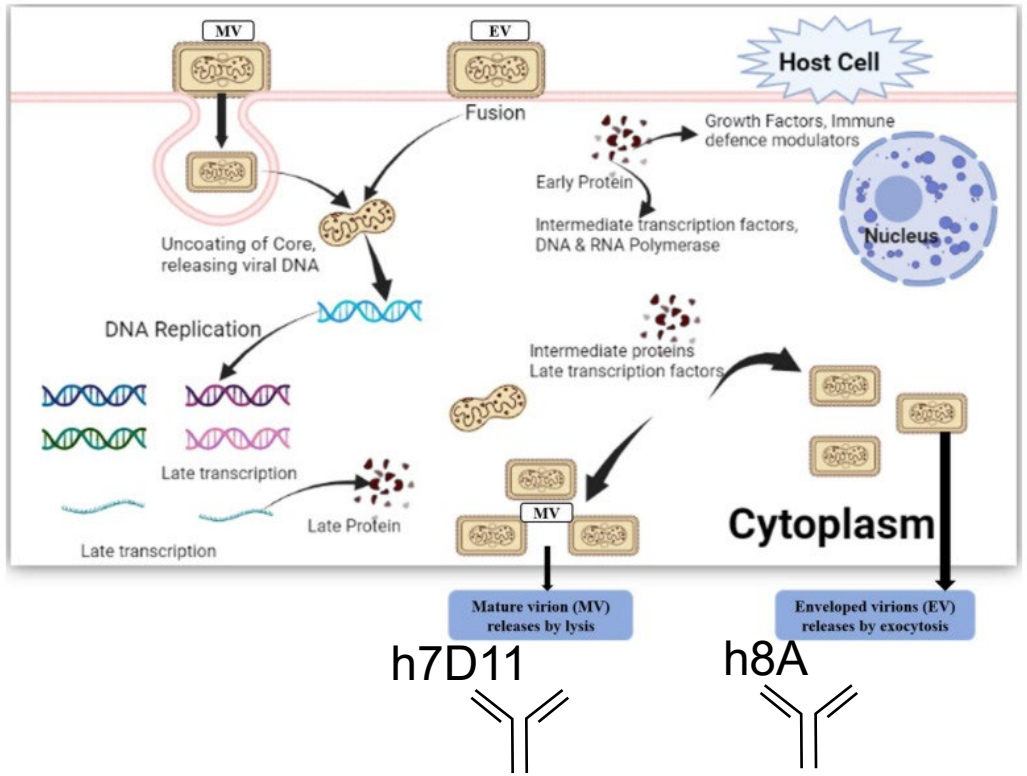
WARNING: INCREASED RISK FOR MORTALITY WHEN USED FOR LONGER DURATION

See full prescribing information for complete boxed warning.

An increased incidence of mortality was seen in TEMBEXA-treated subjects compared to placebo-treated subjects in a 24-week clinical trial when TEMBEXA was evaluated in another disease *[see Warnings and Precautions (5.1)]*.

BFI-753 Antibody cocktail

- **h7D11: anti-L1 subunit protein**
  - Neutralizes **mature virions**
  - Discovered from vaccinated mice, then later humanized
- **h8A: anti-B5 subunit protein**
  - **Neutralizes enveloped virions** in a complement dependent manner
  - Discovered from a phage display library generated from peripheral lymphocytes of a vaccinated chimpanzee, later humanized
- **Current status:** IND anticipated FY25
- **Use case:**
  - High safety profile of mAbs makes this product a strong candidate for special populations, including immunocompromised individuals
    - Risk mitigation against TPOXX resistance
    - Potentially superior safety profile than TEMBEXA
  - Anticipated indication is treatment



Therapeutics Landscape and Considerations

- **The portfolio of the three products and multiple routes of administration provides a comprehensive defense against smallpox events**
- Next steps for FDA approved therapeutics:
  - BARDA holds contracts for both TPOXX (Siga) and TEMBEXA (Emergent)
    - Pediatric formulation for TPOXX
    - Improving operational use (infusion options) for IV TPOXX
    - Scale up manufacture of suspension TEMBEXA
  - DoD is supporting post-exposure prophylaxis studies for TPOXX
- In the pipeline:
  - Biofactura's BFI-753 in development; anticipate IND submission FY25
    - Target: single intravenous dose
  - DoD supporting Just-Evotec effort to develop mAb product targeting orthopoxviruses
  - ST357 – early preclinical small molecule being developed by Siga

medicalcountermeasures.gov
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