



# Approaches to Antiviral Drug Development for Treatment of Human Smallpox

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# Advisory Committee Objectives

- Discuss key scientific issues and challenges in the development of antiviral products for the treatment of human smallpox under the Animal Rule
  - 21CFR314.600
- Obtain input on potential paths forward for developing drugs to treat human smallpox in the setting of an outbreak

# Smallpox Drug Development

- Establishing safety and efficacy of an antiviral product for smallpox is not straightforward
- Many knowledge gaps and scientific uncertainties;
- Important differences from vaccines

## **Additional examples of distinctive features of smallpox that may affect drug development approaches**

- Absence of cases for decades
- Narrow host range
- Limited information on pathophysiology of human smallpox
- Disease differences between humans and NHPs
- Differences between variola and other orthopoxviruses – disease characteristics, drug susceptibility, host range
- Lack of a previously recognized effective drug
  - several drugs were studied, but none found to have reproducible and reliable efficacy for treatment; toxicity profiles were limiting

# Scientific Challenges

- Variola virus stocks are limited to two centers
- Restricted laboratories for scientific investigations
  - need for WHO authorization
- No widely accepted animal model using variola
  - Variola models don't fully reproduce human smallpox
- Unethical to conduct human challenge studies with smallpox (variola)
- Questions raised about relevance of animal data to humans using a surrogate virus in a surrogate host
  - using a surrogate endpoint if mortality is not used

## Animal models in drug development programs for treatment of smallpox

- Models using other orthopoxviruses also do not reproduce human smallpox but may add to overall understanding of disease
  - Viral genetic relatedness has not been a good predictor of wide variations in pathogenicity across viral and host species
  - Consider effects of viral inoculum, exposure route, strain
  - Consistent results across multiple models may be helpful, but are they reasonably likely to predict human treatment responses?
  - Under the Animal Rule human studies are still needed for safety, PK (might differ in ill patients), confirmation of benefit when appropriate

# Agenda

- Historical perspective
- Preparedness
- Animal rule
- Orthopoxvirus properties
- Animal models
  - Mousepox, rabbitpox, monkeypox, variola
- Sponsor presentations
- Study design issues

## Questions

- Animal models for extrapolating efficacy of a drug to human smallpox
- Study design issues
  - Route of viral challenge, viral inoculum, etc.
  - Selection of endpoints
  - Clinical manifestations underlying when to treat
- Potential role of human data from related naturally occurring diseases



# Historical perspective on smallpox

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## Focus of historical overview:

### Perspective of product evaluation

- What is typically useful to know about a disease for which antiviral treatment is being studied?
- What is known from past smallpox experience that might assist in assessment of treatments proposed for preparedness in case of future outbreak threats?
  - Information gleaned from published literature, mostly anecdotal, not comprehensive
  - Naturally occurring human disease eradicated more than 30 years ago, hoped never to occur again
  - Eradication depended on surveillance/containment, vaccination, absence of animal reservoir

# Outline of historical overview

- General clinical picture of smallpox
  - Outcomes of interest
- Possible outcome predictors
  - Viral, host, clinical and pathologic factors
- Historical attempts at therapy
- Context of other diseases/interventions

# Clinical picture and classification

- Conventional picture of smallpox (much variability)
  - Human-to-human transmission, asymptomatic (~ 2 wk) incubation, then few days nonspecific symptoms & fever
  - Centrifugal rash (macule-papule-vesicle-pustule 1-2 days each, scabs evolving over several weeks, then scars)
  - Variants: fulminating with purpura, death before characteristic rash; “flat” or “malignant” rash evolution
  - Varying extent of mucosal involvement, bacterial superinfection, organ system involvement
- Different case types within typical outbreak
- Multiple classification systems based on extent and nature of skin and systemic manifestations

# Outcomes of principal concern and potential predictors in historical smallpox

- Principal outcome of concern was death
  - Less common variants (“fulminating”; “hemorrhagic”; “flat”) had higher case-fatality but accounted for fewer total deaths than more common clinical types of disease
  - Pain, discomfort, isolation, complications increased morbidity
  - Sequelae in survivors included scarring (common but variable) and blindness (incidence uncertain, maybe decreasing?)
- Limited data on outcome correlates and/or predictors
  - Baseline characteristics
  - Characteristics that might be modifiable after diagnosis
  - Was there any (lab or clinical) disease measurement that might have been a surrogate for clinical outcome?
  - Next slides address several possible influences or predictors

# Viral factors: Strain, Route & Size of Inoculum Exposure

- Viral strain
  - Variola major: mortality ~5% to >40% in different outbreaks; strain relationships hypothesized but not well documented
  - Variola minor <2% mortality, different strains and epidemiology from major -- not clinically distinct at individual case level
- Route (most thought upper respiratory droplet>airborne)
  - Percutaneous exposure (deliberate variolation or accidental) associated with usually less severe rash and systemic illness
- Size of viral inoculum
  - Infectious dose hypothesized very small in humans (based mostly on occasional remote transmission reports)
  - Intensive exposure increased likelihood of infection (less clear effect on disease severity)

# Viral factors:

## Measurements of Viral Burden

- Replication location/extent during incubation not known
  - Hypothesized very active period based on data from other hosts/viruses: (Fenner 1948, mousepox) suggest first replication at entry site/local nodes, primary viremia seeding spleen/liver/marrow macrophages, secondary viremia seeding skin, all during incubation; symptom onset near peak replication; early antibody possibly important, complex patterns
- Throat cultures often positive at time of early rash
  - And in some contacts who did not develop disease
- Virus sometimes detected in blood very early in disease
  - Typically not detectable at time of characteristic rash; more detection, higher levels reported in more severe disease forms
  - In cases that did have virus detected at presentation, very limited data suggested decrease over time, even in very ill patients
- Persistent in scabs: no correlation disease stage/severity<sub>7</sub>

## Host factors: Patient demographics, and type of source case causing exposure

- Patient characteristics affecting outcome
  - More severe disease/mortality in pregnancy, maybe in immune suppression (not many reports)
  - Extremes of age (interaction with vaccine status)
  - Possibly early antibody response (few, complex data)
- Effect of vaccination status (if disease occurred)
  - Smallpox case series typically assessed vaccine status from scars (might not know timing and quality of vaccination)
  - Could see range of illness but average severity less than unvaccinated (proportionally fewer severe cases)
- Effect of source case type on contact (secondary) cases
  - Could affect likelihood of transmission (hypothesized relationships to amount of viral shedding, closeness of contact)
  - Did not determine nature of contact case (severe index case could lead to mild disease in contact and vice versa)

## Clinical factors: Pre-eruptive symptoms and timing of lesion appearance

- Initial fever pattern, severity and duration of pre-eruptive symptoms not reliably related to outcome
- “Fulminating”, “purpuric” or “early hemorrhagic” smallpox could be fatal before pock lesions clinically recognized
- Initial lesions could be few or nonspecific, delaying diagnosis and making time of onset difficult to pinpoint
- Lesion appearance could be synchronous or near-synchronous (e.g. most lesions starting in 24h period)
  - Successive “crops” of lesions (like chickenpox) occasionally reported in less severe cases, with individual lesions progressing more rapidly but delay in time to full complement of lesions
  - Delayed or “poor” rash development in severe disease also reported

## Clinical factors: Number of skin lesions and severity of their sequelae

- Lesion counts were convenient classifiers – but did not necessarily determine (or fully predict) outcome
  - Lesion morphology/evolution, and toxic status, often considered more important than lesion number (“flat semiconfluent” or “flat discrete” reported more fatal than “ordinary confluent”; “malignant semiconfluent” than “benign confluent”)
  - Variola minor could have as many lesions as major, less severe illness, much lower mortality
  - Vaccinated patients could have (though not as often) as many lesions as unvaccinated, less severe illness, lower mortality
- Determinants of scarring could be multifactorial
  - Survivors of most severe disease could have superficial scars
  - Pitting scars could appear late (months after acute illness), attributed to sebaceous gland collapse; role of bacterial superinfection debated

## **Clinical-pathologic factors: Terminal events – what was the proximate determinant of outcome?**

- Mode of death not well understood, may have been multifactorial and varied among patients
- Skin findings were most prominent but often not considered to be adequate explanation of death
- Hypotheses for mode of death included
  - Toxemia, exhaustion, heart failure, pulmonary edema
  - Circulating immune complexes, DIC-like or burn-like effects
  - Respiratory obstruction, fluid/electrolyte disturbance, hemorrhage, encephalitis, liver/kidney effects
  - Bacterial superinfection (skin, lung, blood)
  - Recent perspectives include discussion of potential roles of multi-organ cytopathic effects and/or cytokine storm

## **Clinical-pathologic factors: Organ system involvement – examples from autopsy series**

- Councilman et al. 1904 (54 autopsies, author summary):
  - “Lesions...due to...parasite peculiar to the disease” skin and mucous membranes
  - “Associated lesions of indeterminate specificity” (“due to the action of toxins”) hematopoietic, kidney, liver, adrenal
  - “Associated lesions, bacterial in origin” above sites plus bronchopulmonary
- Bras 1952 (177 autopsies, author summary):
  - “true variola lesion” skin, mucous membranes
  - “bronchopneumonia in minor degree” (sometimes aspiration)
  - Spleen, marrow, liver RES cells hyperplasia/necrosis
  - Renal hemorrhage/nephritis/nephrosis various case types/stages
- Spatial/temporal/mechanistic relation between virus and various organ system findings??

## Attempts at pharmaceutical interventions in the pre-eradication era

- Vaccine as cornerstone of pharmaceutical prevention
  - Used pre-exposure and sometimes in first few days post-exposure
- Unmet need for treatment of established illness
  - Multiple attempts, mostly anecdotal information
  - Supportive care, antibacterial agents, convalescent serum
- Early antivirals
  - Several entered clinical trials based on in vitro and animal data (e.g. thiosemicarbazones, arabinosides)
  - Some with suggestion of benefit from prophylactic or anecdotal treatment use
  - None confirmed as useful for treatment of established illness

## **Context of other diseases and interventions**

- How does understanding of smallpox and potential therapies (past or future) compare to examples of other, more familiar (though also highly challenging), diseases and/or established interventions?
- How might these comparisons affect approaches to drug development?

## Diseases that could be confused with smallpox

- Pre-eruptive: any “influenza-like illness,” many other conditions (even mistaken for surgical acute abdomen)
- Early rashes: measles, scarlet fever, drug rash, etc.
- Purpuric: sepsis, leukemia, etc.
- Vesiculopustular: chickenpox, vaccination, etc.
- Confusion and delay in diagnosis could occur even in outbreak setting with experienced clinicians
- Possible implications:
  - Many things could “look like” smallpox in some circumstances
  - If there were an outbreak, clinical uncertainty could cause delay in diagnosis/treatment (even if diagnostic technology is better)

## Diseases related to smallpox (species in orthopoxvirus genus)

- Broad cross-immunogenicity but variable host specificity
- Highly host-specific: smallpox, camelpox, mousepox
  - Variola (smallpox): natural host humans, occasional infections in monkeys but no natural nonhuman transmission/reservoir
  - Camelpox: reported closest relative but human disease rare (few case reports of local skin lesions) vs severe camel disease
  - Ectromelia (mousepox): specific to mice (strain variability)
- Broad host range: cowpox, monkeypox, vaccinia
  - Cowpox: sporadic human disease (mostly local lesions, can be necrotic); cow, cat, or rodent contact; presumed first vaccine
  - Vaccinia: several strains used in vaccine campaigns; source unknown (might have come from horsepox?); occasional recent transmission in nature (cattle, buffalo, and human contacts of either animal or human cases); mostly local lesions
- Varied immunomodulatory/immunomimicry products

# Monkeypox in humans

- Monkeypox principal reservoir may be rodents
  - Also infects monkeys in endemic areas
- Most human cases reportedly zoonotic
  - Similar skin lesions, typically lower mortality/transmission and more striking lymphadenopathy than variola major; immunomodulatory gene differences
  - Limited clinical and pathologic information
  - Incidence uncertain but may be increasing
  - Most cases occur in areas with poor healthcare access; single US outbreak (2003, prairie dogs and humans) reportedly less virulent clade than strains circulating in Democratic Republic of Congo

## Comparison to evidence base for other types of development decisions

- What do other types of development programs have that smallpox drug development lacks? A few examples:
  - Smallpox vaccines have history of closely related accepted product (vaccinia strains used as vaccines), relevant biomarkers of effect (skin “take”, antibody response: see 2011 workshop)
  - Anthrax PEP quinolones have extensive human safety/efficacy information in related diseases, animal model with same pathogen and similar disease, extensive studies of toxin roles
  - Chemical protectants typically have defined molecular mechanism of toxic substance, animal models using same toxic substance, varying amounts of human data
  - Antivirals for chronic HIV or HCV have clinical trial data with biomarker roles and time course well documented in absence of therapy, response to therapy, and relation to clinical outcomes
  - Differences could affect Animal Rule discussions, endpoint selection, level of uncertainty regarding potential product benefit

## Summary considerations for further discussion

- Understanding of events during human smallpox is limited (and we hope for no more cases ever)
- The limited available information suggests
  - profound variability in host susceptibility (determinants not well delineated)
  - complex (not well defined) relationships between putative prognostic factors and outcome
  - difficult to define any clearcut surrogates for outcome
- Historical records and their limitations underscore the challenges of defining pathways for development of new antivirals for smallpox



# The Animal Rule

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# Presentation Objectives

- **Animal Rule – What is it?**
- **Animal Rule Requirements**
- **Animal Models – Essential Elements to Address Efficacy under the Animal Rule**
- **Safety Information**

# The Animal Rule

- **What it is**
  - **The Animal Rule provides a regulatory mechanism to approve drugs and license biologics when human studies are not ethical or feasible**
- **What it is not**
  - **The Animal Rule is not a simplified or expedited route to develop drugs/biologics compared to traditional product development**

# The Animal Rule - Requirements

- There is a reasonably well-understood **pathophysiological mechanism of the toxicity** of the substance, and its prevention or substantial reduction by the product.
- The **effect is demonstrated in more than one animal species** expected to react with a response predictive for humans.
  - Unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans.

# The Animal Rule - Requirements

- The animal **study endpoint** is clearly related to the desired benefit in humans
  - Generally the enhancement of survival
  - Prevention of major morbidity
  
- The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows **selection of an effective dose in humans.**

# Characteristics of the Threat Agent that Influence the Disease or Condition

- **The challenge agent**
- **Pathogenic determinants**
- **Route of exposure**
- **Quantification of exposure**

# Host Susceptibility and Response to Etiologic Agent

- **The animal species should be susceptible to the threat agent**
- **The response to the etiologic agent (illness or injury) in the animal model should be similar to the response seen in humans**

# Natural History of Disease: Pathophysiologic Comparability

- **Time to onset of disease/condition**
- **Time course of progression of disease/condition**
- **Manifestations (signs and symptoms)**
- **Fidelity of the animal model to the human disease/condition**
- **Lack of relevant human data**

# Characterization of Medical Intervention

- **Product class**
- **Mechanism of action**
- **In vitro activity**
- **Activity in disease/condition of similar pathophysiology**
- **PK in unaffected animals/humans**
- **PK/PD in affected animals/humans**
- **PK interactions with medical products likely to be used concomitantly**
- **Synergy or antagonism of medical products likely to be used in combination**

# Design Considerations for Efficacy Studies

- **Study design issues**
  - **Indication dependent/clinical scenario**
    - **Timing of and triggers for intervention**
  - **Adequate and well-controlled**
    - **Randomization/blinding/statistics**
  - **Route of administration**
  - **Dosing regimen**
  - **Endpoints**
  - **GLP**
  - **Supportive care**

# Safety Information

- **Human safety database**
  - **Considerations:**
    - **Can be performed in healthy volunteers or other appropriate populations**
    - **Size of human safety database**
      - **New biologic/drug vs. approved product**
      - **Indication sought**
    - **Dose/duration**

# Summary

- **Animal rule can be used in the setting of smallpox for therapeutic products**
- **Recognizing the unique circumstances for smallpox, CDER prepared to be flexible**

# Additional Information

- **Website for the draft guidance**
  - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078923.pdf>
- **Contact Rosemary Roberts, M.D.**
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# Challenges and Issues in Drug Development for Treatment of Smallpox

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## Examples of Desirable Study Design Elements

- Primary endpoint of mortality
- Euthanasia based solely on clinical criteria
- Ability to produce clinical manifestations of disease with consistent mortality after low viral inoculum; and exploration of higher inocula, if needed, to confirm treatment effect
- Route of inoculation similar to that for human smallpox
- Adequate dose exploration
- Timing of treatment initiation relative to clinical manifestations of disease
- Evaluation of optimal duration of treatment
- Evaluation of viral resistance
- Pharmacokinetic (PK) and pharmacodynamic (PD) information from animals and PK information from humans sufficient to establish effective dose

# Drugs Currently in Active Development for Treatment of Human Smallpox

- CMX001 (Chimerix)
- ST-246 (SIGA)

# CMX001

- Lipid pro-drug; cidofovir derivative
- Tablet, solution (oral)
- Mechanism of action: targets viral DNA polymerase and prevents genome replication
- Antiviral activity against orthopoxviruses and other double-stranded DNA viruses, such as herpesviruses, adenoviruses

## Current Status:

### Available Animal Data for CMX001

Animal Models/orthopoxviruses evaluated:

- **Mouse (ectromelia, vaccinia, cowpox)**
- Dormice (monkeypox)
- **Rabbit (rabbitpox)**
- Non-Human Primates (NHPs), i.e.  
cynomolgus macaques (monkeypox)

No animal efficacy studies performed or currently planned with variola virus.

# Animal Studies with CMX001: Issues

- Adequate CMX001 plasma exposure was not achieved in NHPs (cynomolgus macaques) with oral dosing of CMX001; this complicates efforts to develop a macaque model for oral CMX001. Administration of CMX001 by intramuscular injection, which achieves higher plasma CMX001 exposure, was explored in one monkeypox virus study in macaques.
- Sponsor proposes to use the mouse-ectromelia virus model and the rabbit-rabbitpoxvirus model for pivotal efficacy studies to fulfill Animal Rule criteria for treatment of human smallpox.

# Mouse-ectromelia studies with CMX001

- Preliminary study reports under review
- Low inoculum size
- Respiratory (intranasal) route of inoculation
- Dose ranging and treatment duration
- Studies were non-Good Laboratory Practices (GLP)-compliant, non-blinded; randomization not clearly defined.
- Which clinical manifestations in the mouse are most appropriate for treatment initiation needs further discussion.

# Summary of Recent Rabbit-Rabbitpox

## Studies with CMX001

- Studies UF-010, UF-011, UF-012: randomized, blinded, placebo-controlled studies
- Route of inoculation: intradermal challenge
- Relatively low inoculum size (100 pfu)
- Treatment initiation at time of skin lesion onset
- Mortality based on clinical criteria for euthanasia:
  - Scheduled euthanasia of surviving animals occurred at the end-of-study, i.e. Day 14 post-inoculation (PI).
  - Unscheduled euthanasia of moribund animals occurred at earlier study time-points prior to the end-of-study.
- CMX001 dose: 20 mg/kg (oral)

## Summary of Recent Rabbit-Rabbitpox Virus Studies UF-010, UF-011, and UF-012 with CMX001

Study	CMX001 dose	Timing of CMX001 post-inoculation (PI) with rabbitpox virus (at time of skin lesion onset)	Mortality [Day 14 PI] n/N (%) {95% CI for difference from placebo}
UF-010 (Non-GLP)	20 mg/kg x 3 doses	D3, 4 or 5 post-inoculation (PI)	1/12 (8) {-95%, -35%}
	<b>Placebo</b>	<b>Not applicable (N/A)</b>	<b>10/12 (83)</b>
UF-011 (Non-GLP)	20 mg/kg x 1 dose	D3 or 4 PI	5/12 (42) {-80%, -7%}
	<b>Placebo</b>	<b>N/A</b>	<b>11/12 (92)</b>
UF-012 (Non-GLP)	20 mg/kg x 2 doses	D3, 4 or 5 PI	4/12 (33) {-86%, -16%}
	<b>Placebo</b>	<b>N/A</b>	<b>11/12 (92)</b>

# ST-246

- Capsule (oral)
- Mechanism of action: inhibits replication of orthopoxvirus extracellular enveloped virus (EEV) but not intracellular mature virus (IMV)
- Antiviral activity only against orthopoxviruses

## Current Status: Available Animal Data for ST-246

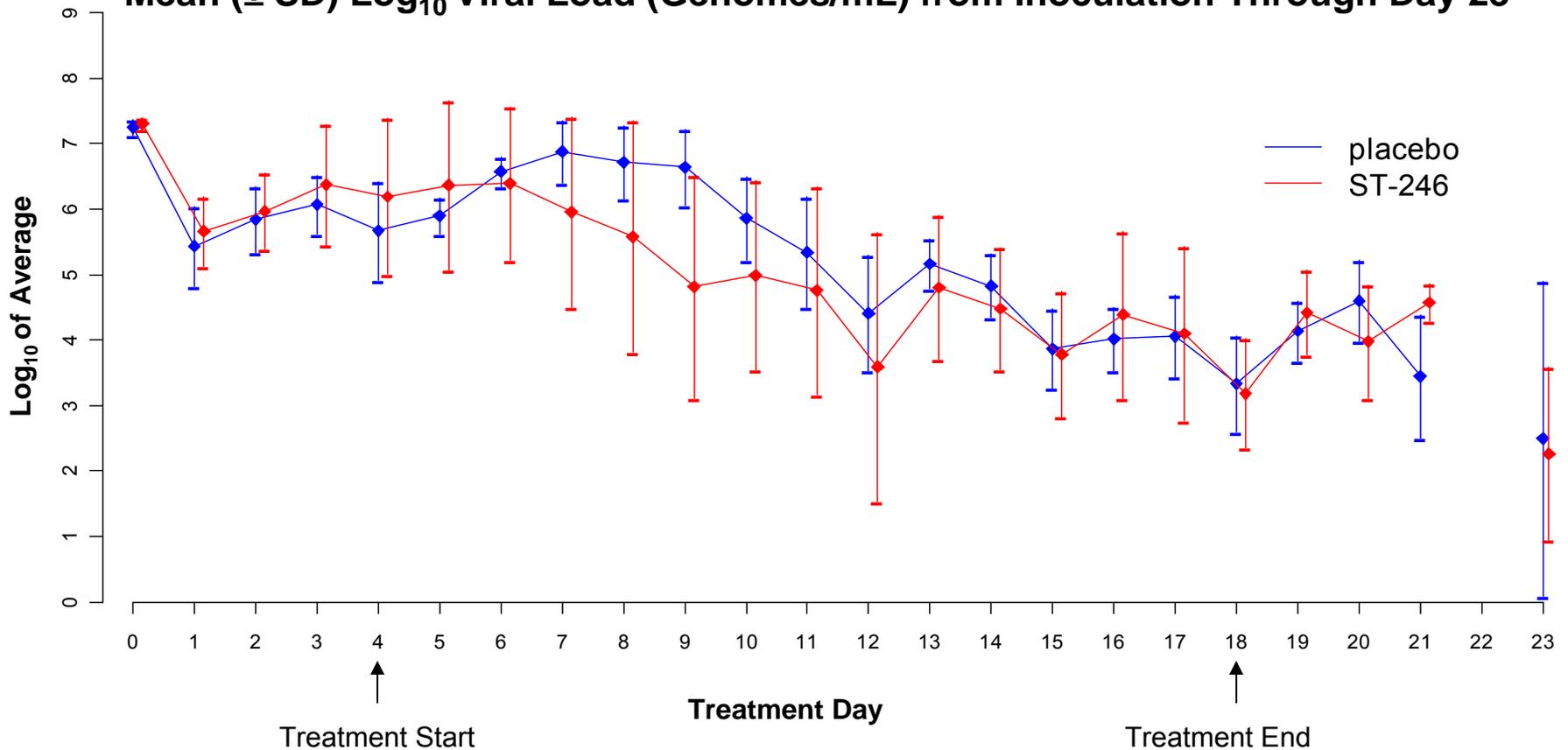
- Animal Models/orthopoxviruses evaluated:
  - Mouse (ectromelia, vaccinia, cowpox), immunodeficient mice (vaccinia)
  - Ground squirrel (monkeypox)
  - Rabbit (rabbitpox)
  - Prairie dog (monkeypox)
  - **Non-human primate (NHP) [cynomolgus macaques] (monkeypox, variola)**
- Sponsor proposes to use the NHP-monkeypox model for pivotal efficacy studies to fulfill Animal Rule criteria for treatment of human smallpox.

## Summary of NHP-VARV studies in NHPs with ST-246

Study	Description of variola virus (VARV) study	ST-246 dose and duration	Timing of ST-246 dosing post-inoculation (PI) with VARV	Mortality [Days PI]
1470 (Non-GLP)	Harper strain VARV (1 x 10 <sup>8</sup> pfu, IV inoculum) Randomized, Not blinded	300 mg/kg/day x 14 days	D0 or 1 post-inoculation (PI) (prior to skin lesion onset)	0/6 [D22 PI]
		<b>Placebo</b>	<b>N/A</b>	<b>2/2 [D22 PI]</b>
1745 (Non-GLP)	Harper strain VARV (1 x 10 <sup>8</sup> pfu, IV inoculum) Randomized, double-blinded	10 mg/kg/day x 14 days	D3 or 4 PI (approximate time of skin lesion onset)	1/7 [D23 PI]
		<b>Placebo</b>	<b>N/A</b>	<b>0/7 [D23 PI]</b>

# NHP-VARV and ST-246 (Study 1745):

Mean ( $\pm$  SD)  $\text{Log}_{10}$  Viral Load (Genomes/mL) from Inoculation Through Day 23



# NHP-VARV Model: Issues/Challenges

- Variola virus infection in cynomolgus macaques resembles human smallpox with respect to mild rash illness.
- **Inconsistent (placebo) mortality results using current NHP-variola virus model**
- Clinical and statistical significance of the temporary differences observed in mean virologic response is unclear.
- Potential for further exploration and refinement of model
- CDC is only study site in US
- Potential for destruction of all variola virus stocks in future

## Summary of Recent NHP-Monkeypox Virus Studies with ST-246

- Studies AP-09-026G, SR10-037F, SR10-038F, FY10-087: randomized, blinded, placebo-controlled studies
- Route of inoculation: intravenous challenge
- High virus inoculum ( $5 \times 10^7$  pfu)
- Treatment initiation time: 4 days post-inoculation (in most studies);  $\approx$  time of lesion onset
- Mortality based on clinical criteria for euthanasia:
  - Scheduled euthanasia of surviving animals occurred at the end-of-study, i.e. Day 28, 42 or 56 post-inoculation (PI).
  - Unscheduled euthanasia of moribund animals occurred at earlier study time-points prior to the end-of-study.
- ST-246 doses: 0.3, 1, 3, 10, 20 mg/kg/day



## Summary of Recent NHP-Monkeypox Virus Studies AP-09-26G and SR10-037F with ST-246

Study	ST-246 dose and duration	Timing of ST-246 post-inoculation (PI) with monkeypox virus	Mortality n/N (%) [Days PI] {95% CI for difference from placebo}
AP-09-26G (GLP)	0.3 mg/kg/day x 14 days	D4 post-inoculation (PI); (≈ lesion onset)	4/5 (80) [D42] {-72, 36}
	1 mg/kg/day x 14 days		5/5 (100) [D42] {-41, 52}
	3 mg/kg/day x 14 days		1/5 (20) [D42] {-99, -21}
	10 mg/kg/day x 14 days		1/5 (20) [D42] {-99, -21}
	<b>Placebo</b>	<b>N/A</b>	<b>7/7 (100) [D42]</b>
SR10-037F (Non-GLP)	10 mg/kg/day x 14 days	D4 PI (≈ lesion onset)	1/6 (17) [D56] {-100, -7}
	10 mg/kg/day x 14 days	D5 PI (after lesion onset)	1/6 (17) [D56] {-100, -7}
	10 mg/kg/day x 14 days	D6 PI (after lesion onset)	3/6 (50) [D56] {-93, 27}
	<b>Placebo</b>	<b>N/A</b>	<b>3/3 (100) [D56]</b>

Reference: Sponsor study reports

### Summary of Recent NHP-Monkeypox Virus Studies SR10-038F and FY10-087 with ST-246

Study	ST-246 dose and duration	Timing of ST-246 post-inoculation (PI) with monkeypox virus	Mortality n/N (%) [Days PI] {95% CI for difference from placebo}
SR10-038F (Non-GLP)	10 mg/kg/day x 3 days	D4 PI (≈ lesion onset)	2/4 (50) [D28] {-83, 51}
	10 mg/kg/day x 5 days		0/6 (0) [D28] {-99, -8}
	10 mg/kg/day x 7 days		0/6 (0) [D28] {-99, -8}
	10 mg/kg/day x 10 days		1/5 (20) [D28] {-94, 18}
	<b>Placebo</b>		<b>N/A</b>
FY10-087F (GLP)	3 mg/kg/day x 14 days	D4 PI (≈ lesion onset)	0/6 (0) [D28] {-100, -47}
	10 mg/kg/day x 14 days		0/6 (0) [D28] {-100, -47}
	20 mg/kg/day x 14 days		0/6 (0) [D28] {-100, -47}
	<b>Placebo</b>		<b>N/A</b>

Reference: Sponsor study reports

## Examples of potential distinctions between historical human smallpox and various animal models

- Route of viral exposure varies between models; often not similar to human respiratory route.
- Host susceptibility varies (need for high viral inoculum in many models; and differences seen in viral pathogenicity in different orthopoxvirus-host combinations).
- Most models do not have incubation period comparable to historical human descriptions of smallpox.
- Relationship between time course of viremia and clinical manifestations may vary.
- Many unknowns regarding immunomodulatory properties of different viral species; and immune response to different orthopoxviruses in different animal hosts

## Examples of Issues for Additional Discussion

- Standardization and/or consensus on clinical criteria used to determine euthanasia criteria in a given animal model
- How similar should route of inoculation be to that for human smallpox?
- Timing of treatment initiation relative to clinical manifestations of disease
- Which clinical manifestation(s) of disease should be used as the trigger for treatment initiation?
- Adequate exploration of dose and treatment duration
- Evaluation of drug resistance
- How much PK and PD information from animals and PK information from humans is sufficient to establish effective dose?

## Summary: Animal Models for Treatment of Smallpox

- Both investigational drugs show activity in animal models in which they were studied.
- Challenges and issues with all of the orthopoxvirus animal models