U.S. FOOD & DRUG ADMINISTRATION

Antimicrobial Drugs Advisory Committee Meeting

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Tecovirimat for the Treatment of Smallpox

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Framework

- Despite the eradication of naturally acquired smallpox, variola virus remains a possible bioterrorism concern and is categorized by the National Institute of Allergy and Infectious Diseases and the Centers for Disease Control and Prevention as a Category A priority pathogen.
  - Category A pathogens are those that pose the highest risk to national security and public health.
- Though vaccine was available and contributory, no effective drug treatment was identified during smallpox eradication efforts.

Background

- Distinctive features of smallpox that may affect drug development
  - absence of cases for decades; last case in 1978
  - lack of a previously recognized effective drug
  - narrow host range (extremely human-specific pathogen)
  - disease differences between humans and animal models
  - differences among orthopoxviruses (closely related genus members may have very different host specificities and disease manifestations)

2011 Advisory Committee

- Recommendations
  - drug development pathway would be under the Animal Rule – but not rely principally on variola virus models
  - demonstration of reproducible activity in two lethal animal models of non-variola orthopoxvirus infection
    - e.g., NHP/monkeypox and rabbit/rabbitpox models
    - In vitro activity across multiple orthopoxviruses
  - adequate safety data from a human safety trial
  - use of Variola model considered
    - scientific uncertainty about the model related to reproducibility
    - did not mimic human disease
    - feasibility issues related to worldwide restriction of research
    - exploratory studies supportive

Animal Rule
21 CFR part 314, subpart I

- May be used to approve drugs for serious disease caused by toxic substances (including pathogens) when human challenge studies would not be ethical and definitive clinical trials after accidental or hostile exposure not feasible; can only be used if

1) Reasonably well-understood pathophysiological mechanism of both disease and treatment effect
2) Effect is demonstrated in (usually) more than one animal species expected to react with a response predictive for humans
3) Animal study endpoint is related to desired human benefit (usually, survival or prevention of major morbidity)
4) PK/PD (human and animal) allows effective human dose selection

Some Study Design Considerations Based on Animal Rule Guidance

- Number of surviving animals as primary endpoint, with clearly agreed euthanasia criteria (as humane euthanasia largely determines mortality in experimental animal studies)
- Clinically relevant treatment triggers and on-study observations, randomization and blinding of treatment assignment
- Virologic data including strain description, route and quantity of challenge, assessments of viral burden and resistance (resistance pathways will not be discussed by agency or applicant in this meeting for security reasons)
- Animal welfare measures including husbandry, supportive/palliative care, other veterinary interventions

Data to Support Tecovirimat Efficacy for the Treatment of Smallpox

- √ Clearly established, virus-targeted mechanism, with a highly conserved viral target (~98% AA identity across orthopoxviruses)
- √ Broad and consistent antiviral activity against orthopoxviruses, including several independent isolates of variola virus
- √ Efficacy evaluated in two lethal, well-studied animal models of non-variola orthopoxvirus infection (NHP/monkeypox and rabbit/rabbitpox), with disease characteristics relevant to human smallpox
- √ Pharmacokinetic (PK) and pharmacodynamic (PD) data from animal studies to assess potential for an effective human dose

Question for the Committee

Based on the available data, does the risk-benefit profile of tecovirimat support its use for the treatment of human smallpox?

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Tecovirimat for Treatment of Human Smallpox

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Antimicrobial Drugs Advisory Committee Meeting
May 1, 2018

Outline

- Tecovirimat Basics
- Summary of 2011 Antiviral Drugs Advisory Committee (AVDAC) meeting
- Overview of tecovirimat development program for treatment of human smallpox
  - Animal Efficacy
  - Pharmacokinetics and Dose Selection
  - Human Safety
- Adequacy of available data to meet FDA's Animal Rule requirements

Tecovirimat Basics

- Dosage Form: Oral Capsule
- Mechanism of Action: Inhibits viral spread to uninfected cells by targeting an orthopoxvirus protein (P37) involved in the production of extracellular enveloped virus
- Antiviral activity only against orthopoxviruses

Summary of 2011 AVDAC Meeting on Drug Development for Treatment of Smallpox under FDA's Animal Rule

Animal Rule Requirement #1

(Summary of 2011 AVDAC meeting)

Animal Rule Requirement:

- There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance, and its prevention or substantial reduction by the product

FDA perspective/AVDAC conclusion:

- Because smallpox was eradicated over 3 decades ago, pathophysiology of variola virus infection (smallpox) is not fully understood
- This requirement cannot be wholly met, but uncertainties can be addressed, to the extent feasible, if data from at least two lethal animal models of non-variola orthopoxvirus infection are obtained to evaluate drug efficacy

Animal Rule Requirement #2

(Summary of 2011 AVDAC meeting)

Animal Rule Requirement:

- 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

FDA perspective/AVDAC conclusion:

- Scientific limitations of the available NHP/variola model preclude definitive efficacy assessments
- Uncertainty exists whether an adequate variola model can be developed
- Data from combination of lethal animal models of non-variola orthopoxvirus infection should be obtained to evaluate drug efficacy

Animal Rule Requirement #3

(Summary of 2011 AVDAC meeting)

Animal Rule Requirement:

- The animal study endpoint is clearly related to the desired benefit in humans
  - Generally the enhancement of survival
  - Prevention of major morbidity

FDA perspective/AVDAC conclusion:

- Primary endpoint of survival
- Euthanasia based on prospectively defined criteria
- At the time of the 2011 meeting, Applicant appears to have met this requirement in one lethal animal model of non-variola orthopoxvirus infection (non-human primate/monkeypox virus)

Animal Rule Requirement #4

(Summary of 2011 AVDAC meeting)

Animal Rule Requirement:

- The data or information on the pharmacokinetics (PK) and pharmacodynamics (PD) of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans

FDA perspective/AVDAC conclusion:

Tecovirimat program

- Has collected PK/PD in non-human primate/monkeypox virus
- Needs PK/PD in second animal model

Applicant's plan (post-AC):

- Rabbit/rabbitpox virus as second animal model

Summary of Animal Efficacy

Non-Human Primate (NHP)/Monkeypox Virus (MPXV) Model

- Cynomolgus macaques were challenged intravenously with 5 x 10^7 plaque-forming units (PFU) of MPXV Zaire ’79 strain
- Disease in NHP/MPXV model is rapid, causes systemic viremia and disease signs such as fever, rash and skin lesions that resemble features of human smallpox
- Mortality is nearly universal, with a mean time to death or moribund disease requiring humane euthanasia at approximately 14 days post-challenge
- Appearance of skin lesions, which first occurs 3-4 days post-challenge, was selected as a clinically relevant trigger for initiation of tecovirimat treatment

NHP/MPXV Model: Conclusions

- Applicant completed 4 randomized, placebo-controlled studies (3 of 4 were double-blinded) with tecovirimat started at the time of lesion onset
- Statistically significant treatment benefit over placebo was demonstrated for the primary endpoint of survival when tecovirimat was dosed at 3, 10, and 20 mg/kg/day for 14 days starting at day 4 after virus inoculation
  - Effective dose: 3 mg/kg
  - For the purpose of human dose selection, a NHP dose of 10 mg/kg/day was used to provide exposures that exceed those associated with fully effective dose
- Inspections confirmed study quality and integrity
- Studies in this model appear sufficient to constitute one of the two acceptable models to meet the Animal Rule criteria for approval

Rabbit/Rabbitpox Virus (RPXV) Model

- 16-week-old New Zealand white rabbits were challenged intradermally with 1,000 PFU of the RPXV Utrecht strain
- Disease in rabbit/RPXV model is rapid and universally fatal, and consistent with what is known about variola virus infection of humans, only a very low viral challenge dose is required to cause severe disease
- Disease signs include fever, changes in respiration rate and erythema, edema, scabbing and necrosis at the injection site
- Systemic viremia is observed by Day 3-4 post-challenge and increases to high levels until the time of death (approximately 6-9 days after lethal challenge)
- Fever, which consistently occurs by Day 4 post-challenge, was selected as a clinically relevant trigger for initiation of tecovirimat treatment

Rabbit/RPXV Model: Conclusions

- Applicant completed 2 randomized, double-blinded studies (1 of 2 was placebo-controlled) with tecovirimat started at the time of fever onset
- Statistically significant treatment benefit over placebo was demonstrated for the primary endpoint of survival when tecovirimat was dosed at 20, 40, 80 and 120 mg/kg/day for 14 days starting at day 4 after virus inoculation
  - Effective dose: 20 mg/kg
  - For the purpose of human dose selection, a rabbit dose of 40 mg/kg/day was used to provide exposures that exceed those associated with fully effective dose
- Inspections confirmed study quality and integrity
- Studies in this model appear sufficient to constitute one of the two acceptable models to meet the Animal Rule criteria for approval

Pharmacokinetics and Dose selection

Selection of an Effective Dose in Humans Under the Animal Rule: Information that is Needed

- √ ADME (absorption, distribution, metabolism, and excretion) and PK profile of an investigational drug in animals and humans
- √ The drug exposures associated with efficacy in the adequate and well-controlled animal efficacy studies
- √ Effects of the challenge agent-induced disease or condition on the PK of the investigational drug in animals
- √ The relationships between exposure parameters (e.g., AUC, Cmax, Cmin) and the primary endpoint (survival) of at least three doses and the shape of the exposure-response (E/R) curves established in dose range-finding studies

Selection of an Effective Dose in Humans under the Animal Rule: Tecovirimat Human Dose Selection

Assuming a similar exposure-response relationship between animal models and humans and *use of a conservative approach to human dose selection*

Select the fully effective dose in animal models → *"Doses should be selected for humans that provide exposures that exceed those associated with the fully effective dose in animals, ideally by several-fold, if the drug's safety profile allows such dosing"*

Tecovirimat Dose-Response Relationship for Survival

Combined efficacy – MPXV/NHPs

Dose (X 14 days)	Survival
Placebo	0 % (0/13)
0.3 mg/kg/day	20% (1/5)
1.0 mg/kg/day	0% (0/5)
3 mg/kg/day	**91% (10/11)**
10 mg/kg/day	**88% (15/17)**
20 mg/kg/day	100% (6/6)

- Combined efficacy results from AP-09-026G, SR-10-037F, and FY10-087; Tecovirimat was administered upon the onset of lesion in NPXV/NHPs

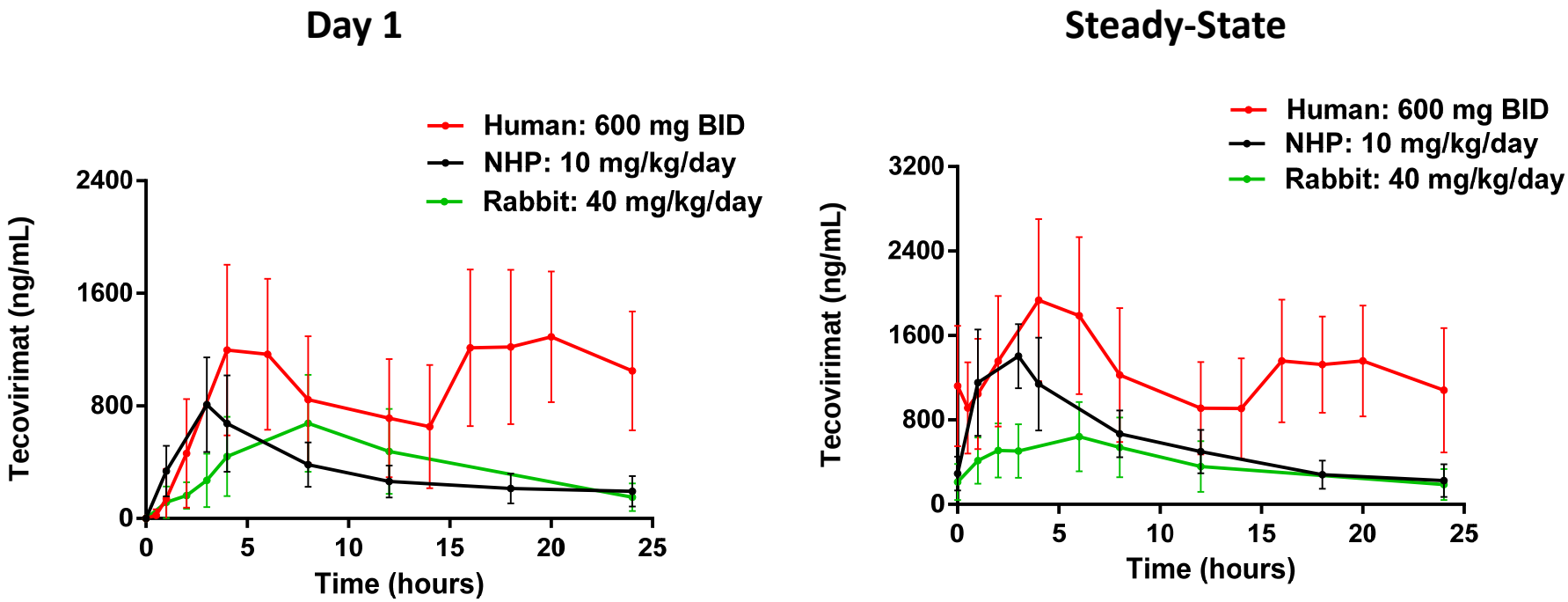
Combined efficacy – RPXV/rabbits

Dose (X 14 days)	Survival
Placebo	0% (0/10)
20 mg/kg/day	**90% (9/10)**
40 mg/kg/day	**88% (16/18)**
80 mg/kg/day	83% (15#/18)
120 mg/kg/day	89% (16#/18)

- Combined efficacy results from SR13-025F and SR14-008F; Tecovirimat was administered upon the onset of fever in RPXV/rabbits
- # One animal in this group died likely due to gavage procedure, not from rabbitpox virus infection

- In both animal models, tecovirimat demonstrated survival benefit over placebo
  - Fully effective dose: 10 mg/kg/day in NHPs, 40 mg/kg/day in rabbits
- **600 mg twice daily (BID) for 14 days was selected as an effective dosing regimen in humans** based on available information

Comparison of Tecovirimat Plasma Concentrations in NHPs, Rabbits, and Humans



Tecovirimat plasma concentrations:

600 mg BID in humans > 10 mg/kg/day in NHPs > 40 mg/kg/day in rabbits

Tecovirimat PK parameters in NHPs and Humans

		C_{max} (ng/mL)	AUC_{24hr} (ng·hr/mL)	C_{min} (ng/mL)
Day 1	Human (n=48)	1516 (761-3290, 32%)	20879 (10627-45733, 35%)	477 (143-2020, 65%)
	NHP (n=6)	749 (378-1320, 42%)	7629 (4577-13294, 39%)	134 (37.3-339, 56%)
	Human/NHP	2.0	2.7	3.6
Day 14	Human (n=48)	2106 (1120-4460, 33%)	28791 (15504-73569, 35%)	689 (2.5-1360, 38%)
	NHP (n=6)	1403 (936-2010, 27%)	13650 (6975-18615, 31%)	156 (88.7-344, 56%)
	Human/NHP	1.5	2.1	4.4

NHP - 10 mg/kg once daily for 14 days (FY-10-087); Human- 600 mg twice daily under fed conditions (Study 008)
C_{min} is defined as the lowest concentration after the first C_{max}.
Data are expressed as geometric mean (min-max, %CV).

Conclusion: At the proposed dosing regimen, C_{max}, AUC, and C_{min} are approximately 2-fold, 2-fold, and 4-fold higher, respectively, in humans as compared to those in NHPs at 10 mg/kg/day

Translation to the Effective Human Dose of Tecovirimat

- **Effects of infection on tecovirimat PK**
  - No significant PK differences between uninfected and infected NHPs
- **No need to adjust doses based on differences in protein binding**
  - Tecovirimat *in vitro* plasma protein binding: 88% in NHPs, 80% in humans
- **Doses higher than 600 mg twice daily were not pursued**
  - 600 mg three times daily: some subjects may reach Cmax concentrations associated with an adverse event (seizure) in dogs
  - Doses above 600 mg: exposures increase less than dose proportionally

Tecovirimat Dose Selection – Food Effects, Intrinsic/Extrinsic Factors

- **Effects of food**
  - Higher absorption under fed conditions as compared to fasted conditions
  - Recommendation: take tecovirimat under fed conditions
  - Under fasted conditions, tecovirimat exposures are still comparable to those associated with the fully effective dose in NHPs
- **Specific populations**
  - Based on available data, no dose adjustment is necessary; renal or hepatic impairment, sex, age, weight, race
- **The potential for drug interactions**
  - Effects of tecovirimat on other drugs: a weak inducer of CYP3A, weak inhibitor of CYP2C8 and CYP2C19
  - Effects of other drugs on tecovirimat: potentially UGT1A inhibitor/inducer

Dosing Regimens for Pediatric Patients

Pediatric dosing regimens that are predicted to produce comparable tecovirimat exposures to adults have been determined by modeling and simulation.

FDA recommended pediatric dosing regimen

Weight	Dose
40 kg and above	**600 mg BID (Adult dose)**
25 kg to < 40 kg	**400 mg BID**
13 kg to < 25 kg	**200 mg BID**
6 kg to < 13 kg	*Doses lower than 200 mg will not be included in labeling until successful completion and review of a human factor study*
Less than 6 kg	

Summary of Human Safety

Human Safety Database

- As part of drug development under Animal Rule, an adequate human safety database is required
- Size and composition of human safety database necessary to support drug approval depend on the proposed indication, the toxicity profile, and/or extent of the Agency's experience with a particular drug class
- For a drug intended for treatment of life-threatening disease or condition, greater known risks or greater uncertainty about undefined risks may be acceptable when the drug offers a clear benefit for those patients
- For tecovirimat, a minimum database of 300 individuals at the intended treatment dose and duration was recommended

Study 008

- Phase 3, double-blind, randomized, placebo-controlled, multi-center
  - Healthy adults randomized 4:1 to receive tecovirimat (600 mg BID x 14 days) or placebo
- Initial PK (i.e. lead-in) cohort: n=40 (20 fed, 20 fasted)
  - Tecovirimat (n=32) vs. Placebo (n=8)
- Expanded cohort in fed subjects: n=382
  - Tecovirimat (n=306) vs. Placebo (n=76)
- Overall target: Tecovirimat (n=338) vs. Placebo (n=84)

Demographics

Demographic Parameters	Tecovirimat (N=359) n (%)	Placebo (N=90) n (%)	Total (N=449) n (%)
Sex			
Male	148 (41%)	36 (40%)	184 (41%)
Female	211 (59%)	54 (60%)	265 (59%)
Age			
Mean years (SD)	40 (15.7)	42 (15.9)	41 (15.7)
Median (years)	38	41	39
Min, max (years)	18, 79	18, 80	18, 80
Age Group			
< 65 years	323 (90%)	79 (88%)	402 (90%)
≥ 65 years	36 (10%)	11 (12%)	47 (10%)
Race			
White	249 (69%)	62 (69%)	311 (69%)
Black	101 (28%)	26 (29%)	127 (28%)
Asian	3 (1%)	1 (1%)	4 (1%)
Other[1]	6 (2%)	1 (1%)	7 (2%)
Ethnicity: Hispanic/Latino			
Yes	43 (12%)	5 (6%)	48 (11%)
No	315 (88%)	85 (94%)	400 (89%)
Not disclosed	1 (<1%)	0	1 (<1%)

Disposition

	Study 008	
	Tecovirimat (600 mg BID) 14 Days	**Placebo (BID) 14 Days**
Randomized	361	91
Treated	359 (100%)	90 (100%)
Completed treatment	334 (93%)	85 (94%)
Discontinued treatment		
Adverse Event (AE)	6 (2%)	2 (2%)
Subject request	4 (1%)	0
Lost to follow-up	6 (2%)	0
Protocol violation	4 (1%)	0
Inability to complete study procedures	1 (<1%)	1 (1%)
Other*	4 (1%)	1 (1%)

***Includes positive drug test at screening, non-compliance with study drug, sponsor request to withdraw subject**

Summary of Safety Events

Subjects Experiencing Event n (%)	Tecovirimat (600 mg BID) 14 Days N=359	Placebo BID 14 Days N=90
Any AE	134 (37%)	30 (33%)
Grade 2, 3, or 4	30 (8%)	8 (9%)
Grade 3 or 4	4 (1%)	1 (1%)
Related AE	71 (20%)	15 (17%)
Related Grade 3 or 4	1 (<1%)	0
Serious Adverse Event (SAE)*	1 (<1%)	0
Related SAE	0	0
Discontinuation of study drug due to AE	6 (2%)	2 (2%)
Death*	1 (<1%)	0

*Not related to study drug

AEs (all Grade) Related to Tecovirimat that occurred with ≥ 2% Frequency and at Higher Rates in Tecovirimat than Placebo

Dictionary Derived Term	Study 008	
	Tecovirimat 14 Days N=359	Placebo 14 Days N=90
Headache	44 (12%)	7 (8%)
Nausea	16 (5%)	4 (4%)
Abdominal pain*	7 (2%)	1 (1%)
Vomiting	7 (2%)	0 (0%)

*Includes abdominal pain, abdominal pain upper, abdominal distension, abdominal discomfort, abdominal pain lower, epigastric pain

Death/SAE

- Total of 1 death, in subject receiving tecovirimat
- 46 y/o female with h/o irregular menstruation, h/o deep venous thrombosis (4 yrs prior to study); Con meds - Depo-Provera Q3 months
  - Completed 14 days of tecovirimat
  - No AE prior to event
  - Grade 1 glucose elevation at Day 15
  - 7 days post-completion of dosing developed acute shortness of breath and chest pain at home; subject was talkative when EMS arrived; pulseless electrical activity developed en route to hospital and subject died
  - Autopsy: extensive pulmonary embolism, no other significant findings
  - Toxicology report negative
  - Cause of death: pulmonary embolism

Discontinuations due to AEs Considered Related to Tecovirimat

- Discontinuations due to AEs were infrequent across groups
  - 6 subjects in tecovirimat group (2%)
    - Grade 1 abnormal EEG on treatment day 5; remained clinically asymptomatic
    - Grade 1 abdominal discomfort, dry mouth, dysphoria, disturbance in attention on treatment day 3
    - Grade 3 headache, Grade 1 fever, Grade 2 diarrhea, Grade 1 nausea on treatment day 3
    - Grade 1 nausea on treatment day 8
    - *Grade 1 palpable purpura on treatment day 2
    - *Grade 1 erythema, pruritus, facial swelling on treatment day 2

Discontinuations due to AEs (select events)

- Palpable purpura:
  - 58 y/o Caucasian female with h/o depression and hyperthyroidism
  - Con meds: levothyroxine 50 µg QD, sertraline hydrochloride 50 mg QD.
  - Grade 1 palpable purpura on treatment day 2
  - Drug discontinued on treatment day 2 (received a total of 4 doses)
  - No other interventions
  - On Day 15, investigator noted fading rash/palpable purpura
  - Event resolved on Day 16
- Facial erythema, pruritus, facial swelling:
  - 37 y/o Caucasian female with h/o ulcerative colitis; no con meds
  - Grade 1 facial erythema, pruritus, facial swelling on AM of treatment day 2
  - Drug discontinued on Day 2 (received a total of 2 doses)
  - No other interventions
  - Events resolved on Day 5

Nonclinical Adverse Event of Interest: Seizures

- Maximum tolerated dose study in dogs: single oral administration resulted in seizures and death at 300 mg/kg (n=1); findings at 100 mg/kg consisted of tremors, face-twitching, vocalization, licking and excessive salivation
  - Based on these nonclinical data, Applicant selected Cmax 5,575 ng/mL as maximum allowable exposure level for humans
- Human PK (600 mg BID, Study 008): geometric mean value for Cmax = 2106 ng/mL
- Study 008: EEGs assessed at various time-points for lead-in cohort and PK subset of the expanded study (65 in tecovirimat group vs. 16 in placebo)
  - No seizure events; 1 discontinuation due to abnormal EEG

Summary of Human Safety

- Successful completion of Study 008 yielded a safety database for tecovirimat of approximately 300 subjects for the proposed treatment regimen, consistent with FDA's Animal Rule guidance
- Tecovirimat (600 mg BID for 14 days) was generally safe and well tolerated when administered to healthy adult subjects

Have Animal Rule Requirements been Successfully Met for Tecovirimat?

Animal Rule Requirement #1

Animal Rule Requirement:

- There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance, and its prevention or substantial reduction by the product

FDA perspective:

- Because smallpox was eradicated nearly 4 decades ago, pathophysiology of variola virus infection (smallpox) is not fully understood
- This requirement will not be wholly met, but uncertainties have been addressed to the extent feasible via studies demonstrating (1) broad antiviral activity and similar potency of tecovirimat against orthopoxviruses, including variola virus, and (2) clear survival benefit in two well-studied, lethal non-variola orthopoxvirus animal models

Animal Rule Requirement #2

Animal Rule Requirement:

- 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

FDA perspective:

- Scientific limitations of the available NHP/variola model preclude definitive efficacy assessments, and uncertainty exists whether an adequate variola model can be developed
- The Applicant has successfully demonstrated the efficacy of tecovirimat in two well-studied, lethal, non-variola, orthopoxvirus animal models: NHP/MPXV and rabbit/RPXV

Animal Rule Requirement #3

Animal Rule Requirement:

- The animal study endpoint is clearly related to the desired benefit in humans
  - Generally the enhancement of survival
  - Prevention of major morbidity

FDA perspective:

- Primary endpoint of survival
- Euthanasia based on prospectively defined criteria
- The Applicant's NHP/MPXV and rabbit/RPXV studies confirmed treatment benefit using a primary efficacy endpoint that is clearly related to the desired benefit in humans

Animal Rule Requirement #4

Animal Rule Requirement:

- The data or information on the pharmacokinetics (PK) and pharmacodynamics (PD) of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans

FDA perspective:

- Applicant collected PK/PD in NHP/MPXV model and rabbit/RPXV model that enabled selection of an effective dose in humans
- Exposures in healthy humans are significantly higher than those associated with the fully effective doses in either NHPs or rabbits
- FDA agrees with the proposed human dosing regimen of 600 mg BID in adults

Question for the Committee

Based on the available data, does the risk-benefit profile of tecovirimat support its use for the treatment of human smallpox?

Back up Slide Shown

Collective Evidence of Tecovirimat Efficacy for the Treatment of Smallpox

- √ Clearly established, virus-targeted mechanism, with a highly conserved viral target (~98% AA identity across orthopoxviruses)
- √ Broad and consistent antiviral activity against orthopoxviruses, including several independent isolates of variola virus
- √ Efficacy demonstrated in two lethal, well-studied animal models of non-variola orthopoxvirus infection (NHP/monkeypox and rabbit/rabbitpox), with disease characteristics relevant to human smallpox
- √ Pharmacokinetic (PK) and pharmacodynamic (PD) data from animal studies enabled selection of an effective human dose