

ORIGINAL ARTICLE

Oral Tecovirimat for the Treatment of Smallpox

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ABSTRACT

BACKGROUND

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Smallpox was declared eradicated in 1980, but variola virus (VARV), which causes smallpox, still exists. There is no known effective treatment for smallpox; therefore, tecovirimat is being developed as an oral smallpox therapy. Because clinical trials in a context of natural disease are not possible, an alternative developmental path to evaluate efficacy and safety was needed.

METHODS

We investigated the efficacy of tecovirimat in nonhuman primate (monkeypox) and rabbit (rabbitpox) models in accordance with the Food and Drug Administration (FDA) Animal Efficacy Rule, which was interpreted for smallpox therapeutics by an expert advisory committee. We also conducted a placebo-controlled pharmacokinetic and safety trial involving 449 adult volunteers.

RESULTS

The minimum dose of tecovirimat required in order to achieve more than 90% survival in the monkeypox model was 10 mg per kilogram of body weight for 14 days, and a dose of 40 mg per kilogram for 14 days was similarly efficacious in the rabbitpox model. Although the effective dose per kilogram was higher in rabbits, exposure was lower, with a mean steady-state maximum, minimum, and average (mean) concentration (C_{\max} , C_{\min} , and C_{avg} , respectively) of 374, 25, and 138 ng per milliliter, respectively, in rabbits and 1444, 169, and 598 ng per milliliter in nonhuman primates, as well as an area under the concentration–time curve over 24 hours ($\text{AUC}_{0-24\text{hr}}$) of 3318 ng×hours per milliliter in rabbits and 14,352 ng×hours per milliliter in nonhuman primates. These findings suggested that the nonhuman primate was the more conservative model for the estimation of the required drug exposure in humans. A dose of 600 mg twice daily for 14 days was selected for testing in humans and provided exposures in excess of those in nonhuman primates (mean steady-state C_{\max} , C_{\min} , and C_{avg} of 2209, 690, and 1270 ng per milliliter and $\text{AUC}_{0-24\text{hr}}$ of 30,632 ng×hours per milliliter). No pattern of troubling adverse events was observed.

CONCLUSIONS

On the basis of its efficacy in two animal models and pharmacokinetic and safety data in humans, tecovirimat is being advanced as a therapy for smallpox in accordance with the FDA Animal Rule. (Funded by the National Institutes of Health and the Biomedical Advanced Research and Development Authority; ClinicalTrials.gov number, NCT02474589.)

SMALLPOX IS CAUSED BY VARIOLA VIRUS (VARV)¹ and is highly infectious by the respiratory route. Susceptible persons have up to a 90% chance of contracting the disease if they are exposed to someone who is infected,² and the overall fatality rate is estimated at 30% among those who have not been vaccinated. Although the naturally occurring disease was declared eradicated in 1980,³ smallpox remains a concern because of the potential for deliberate release of VARV as an act of biowarfare or bioterrorism.⁴ The possible existence of clandestine stores of VARV⁵ and the ability to recreate the virus from published genomic sequences through synthetic biologic methods are also of concern.⁶ A single case of smallpox anywhere in the world would be a global health emergency. The available vaccines are not routinely used because of the risk of adverse events, and they would not be used in the general population unless VARV exposure were known or suspected. An antiviral drug against VARV would be beneficial in scenarios in which the vaccine is not effective, such as postexposure prophylaxis 4 to 5 or more days after exposure, before the onset of clinical signs, but most importantly as postexposure therapy after the development of fever and rash.

Because it is not possible to conduct clinical trials involving patients with naturally occurring smallpox and it would be unethical to expose humans to VARV intentionally, the development of tecovirimat has been conducted in accordance with the Food and Drug Administration (FDA) Animal Efficacy Rule, or Animal Rule. The Animal Rule was enacted⁷ to provide an alternative drug-development pathway for diseases in which natural occurrence is rare or nonexistent and ethical concerns do not allow the conduct of more traditional clinical efficacy trials. The rule gives the FDA authority to approve drugs on the basis of animal efficacy data, provided that all other aspects of drug development are completed satisfactorily.

A number of drugs and biologic agents developed under the Animal Rule have been approved by the FDA, although most had previous approvals for related indications.⁸ In December 2012, the FDA approved the monoclonal antibody raxibacumab for treatment of inhalation anthrax as the first new anti-infective drug (biologic) developed solely according to the rule. Since then, the FDA has approved additional biologic agents for prophylaxis or treatment of anthrax (obiltoximab

[Anthim] and anthrax immune globulin [Anthrasil]) and botulism (botulism antitoxin heptavalent [BAT]).⁸ For each of these products, efficacy was shown in more than one animal model that was accepted by the FDA as reasonably predictive of human response. The exposure–response relationship was determined, and critical pharmacokinetic measures and exposure levels that were correlated with efficacy and target exposures in humans were identified. Drug safety was then assessed in humans at a dose and exposure that were equal to or greater than those found to provide a survival benefit in animals. Tecovirimat development has followed a similar path (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

METHODS

STUDY AGENT

Tecovirimat (previously ST-246) was identified through screening of a chemically diverse library of more than 350,000 unique compounds⁹ (Fig. S2 in the Supplementary Appendix). The compound specifically inhibits all orthopoxviruses tested in vitro, including VARV (mean half maximal effective concentration [EC₅₀], 0.010 to 0.068 μmol per liter), with no activity against other viruses.⁹ Tecovirimat inhibits p37, a protein that is present and highly conserved (approximately 98% amino acid identity) in all orthopoxviruses; the inhibition of p37 prevents the formation and egress of enveloped virions, which are essential for virulence.^{10–15} For studies in animals, tecovirimat was formulated in a suspension vehicle consisting of 1% weight per volume hydroxypropyl methylcellulose (HPMC) and 0.5% weight per volume Tween 80 ready to be administered to the animals by oral gavage. For clinical studies, tecovirimat drug product was supplied for oral administration as immediate-release opaque hard gelatin capsules, size “0,” containing 200 mg of tecovirimat plus excipients. All the inactive ingredients are conventional, United States Pharmacopeia–National Formulary grade, and generally accepted as safe. Additional metabolic and toxicologic findings are described in the Supplementary Appendix.

EFFICACY STUDIES IN ANIMALS

In pilot studies, tecovirimat was shown to provide protective efficacy in multiple small-animal and nonhuman primate models of orthopoxvi-



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rus disease.^{9,16-23} Subsequently, the efficacy of tecovirimat has been evaluated in lethal intravenous-injection monkeypox and intradermal-injection rabbitpox models of human smallpox, which have been well characterized for the evaluation of smallpox countermeasures^{24,25} (an overview of the animal models and comparisons with human smallpox is provided in the Supplementary Appendix).

Four pivotal studies in nonhuman primates and two pivotal studies in rabbits were conducted. Investigations included a dose exploration to determine the minimum fully effective dose and an infected-animal pharmacokinetic study in both animal models, as well as studies of treatment delay and treatment duration in nonhuman primates. Animal care and use protocols were approved by the institutional animal care and use committees of the institutions at which the studies were conducted (the Southern Research Institute, the Army Medical Institute of Infectious Diseases, and the Lovelace Respiratory Research Institute).

In all studies in nonhuman primates, crab-eating macaques were infected on day 0 with a lethal dose of monkeypox virus (Zaire 1979 strain) by intravenous inoculation with 5×10^7 plaque-forming units (PFU) per animal. In the studies in rabbits, New Zealand white rabbits were infected on day 0 with a lethal dose of rabbitpox virus Utrecht by intradermal inoculation with 1000 PFU per animal. Additional methodologic details and overviews of the study design for the studies in nonhuman primates and rabbits are provided in the Animal Study Methods section and Tables S1 through S6 in the Supplementary Appendix. In both models, tecovirimat treatment was initiated on or after day 4 after exposure, after the onset of clinical signs (pock lesions in nonhuman primates and fever and viremia in rabbits). In all studies, survival was the primary end point, and lesion formation (nonhuman primates) and viral load (both animal models) were secondary pharmacodynamic end points.

In the first study in nonhuman primates, tecovirimat doses of 0 (placebo), 0.3, 1, 3, and 10 mg per kilogram of body weight were evaluated for efficacy. The second study examined the pharmacokinetics of tecovirimat in infected nonhuman primates to allow the development of a population pharmacokinetic model in addition to

providing a larger sample of animals for survival analysis. The tecovirimat regimen included 14 daily doses of 0 (placebo), 3, 10, and 20 mg per kilogram. Two additional studies were conducted in nonhuman primates to evaluate the effect of a delay in the initiation of treatment and of treatment duration. The results of the study of delays in the initiation of treatment were previously reported by Berhanu et al.²⁶ All studies included a placebo control group.

In the first study in rabbits, different doses of tecovirimat, including 0 (placebo), 20, 40, 80, and 120 mg per kilogram, were evaluated for efficacy. The second study in rabbits was a pharmacokinetic study in infected rabbits, conducted to develop a population pharmacokinetic model and expand the survival analysis population. In this study, tecovirimat dosing was initiated at 4 days after exposure and included doses of 40, 80, and 120 mg per kilogram.

Pharmacokinetic and pharmacodynamic models were developed for both animal models to establish the tecovirimat exposure–survival response relationship. Model-based and noncompartmental approaches were used to contrast the exposures in nonhuman primates and rabbits treated at the maximally effective dose for each model to identify the more conservative animal model (i.e., the model requiring higher tecovirimat exposures for maximal benefit).

EXPANDED SAFETY TRIAL

Pharmacokinetic and safety data from phase 1 and phase 2 dose-escalation and repeat-dose studies^{27,28} were used to model the dosing in humans. The expanded safety trial was a multicenter, randomized, double-blind, safety trial involving healthy volunteers 18 to 79 years of age. The chosen dose targeted an exposure level that was a multiple of that required for maximal efficacy in nonhuman primates but below the highest level that had been established as being associated with no adverse effects in toxicologic studies in animals. The institutional review board of each participating center approved the protocols. All the volunteers provided written informed consent. Full details of the trial design are provided in the protocol, available at NEJM.org.

A lead-in cohort of 40 participants was randomly assigned in a 4:1 ratio, in either a fed or a fasting state, to receive 600 mg of tecovirimat

administered orally twice daily or matching placebo. After a blinded interim analysis of safety and pharmacokinetic data showing that sufficient levels in blood had been achieved, as well as FDA review of the data, the trial was expanded to provide a large enough database for evaluation of product safety by randomly assigning an additional 412 participants at 11 sites to receive tecovirimat or placebo in the fed state only. Participants recorded all adverse events and concomitant medications in a diary and during interviews with clinic staff from the start of the trial period to completion of the trial at the follow-up visit on day 28. Adverse events were also recorded during physical examinations and through laboratory evaluations on scheduled clinic days. A follow-up visit or telephone contact at day 45 for the evaluation of adverse events was conducted only for participants in whom adverse events or serious adverse events were present on the day 28 follow-up visit.

RESULTS

EFFICACY STUDIES IN ANIMALS

In aggregate, 1 of 20 nonhuman primates that received placebo survived infection with monkeypox virus and no rabbits that received placebo survived rabbitpox virus infection (Figs. 1 and 2, and Tables S7 and S8 in the Supplementary Appendix). Additional results for viral load and lesion counts are provided in Figures S4, S5, and S6 in the Supplementary Appendix. On the basis of the results of the first two studies in nonhuman primates, the minimum effective dose was determined to be 3 to 10 mg per kilogram (Fig. S3 in the Supplementary Appendix), which provided nearly full protection from death (i.e., a survival rate of approximately 95%, as compared with 5% in the placebo group) and reduced viral loads and lesion counts. Subsequent studies were conducted with the dose of 10 mg per kilogram, because this dose reduced viral load and lesion counts to a greater extent than the dose of 3 mg per kilogram.

As previously reported by Berhanu et al.,²⁶ in the treatment-delay study, a dose of 10 mg per kilogram initiated at 4 or 5 days after exposure resulted in a survival rate of 83%, whereas treatment initiation 6 days after exposure resulted in a survival rate of 50%. In the treatment-duration

study, 3 daily doses at 10 mg per kilogram initiated 4 days after exposure resulted in a survival rate of 50%, whereas 5 and 7 daily treatments resulted in a survival rate of 100%. Ten daily treatments resulted in 80% survival. The pharmacokinetic study in nonhuman primates showed that after the 14th dose (steady state) of 10 mg per kilogram, the mean values in plasma that were associated with efficacy were a maximum concentration (C_{max}) of 1444 ng per milliliter, a minimum concentration (C_{min}) of 169 ng per milliliter, an average (mean) concentration (C_{avg}) of 598 ng per milliliter, and an area under the concentration–time curve over 24 hours (AUC_{0-24hr}) of 14,352 ng×hours per milliliter (Table 1).

In rabbits, the minimum effective dose was determined to be 20 to 40 mg per kilogram, which provided protection from death and illness equivalent to that of the higher doses we evaluated (80 and 120 mg per kilogram) (Figs. 1 and 2, and Fig. S3 in the Supplementary Appendix). The dose of 40 mg per kilogram was selected as the standard for fully effective dosing. A population pharmacokinetic model was developed on the basis of plasma exposures after days 1, 7, and 14 of treatment. The mean values in plasma at steady state that were associated with efficacy after treatment with the dose of 40 mg per kilogram were a C_{max} of 374 ng per milliliter, a C_{min} of 25 ng per milliliter, a C_{avg} of 138 ng per milliliter, and an AUC_{0-24hr} of 3318 ng×hours per milliliter (Table 1).

Although the efficacious exposure values in nonhuman primates treated with 10 mg per kilogram and in rabbits treated with 40 mg per kilogram were similar after the first dose (ratios of exposure in nonhuman primates as compared with that in rabbits ranged from 1.1 to 1.4), the exposure values in nonhuman primates were higher at steady state, with ratios (nonhuman primates:rabbits) of 3.9 for C_{max} , 6.9 for C_{min} , 4.3 for C_{avg} , and 4.3 for AUC_{0-24hr} (Table 1). These data suggest that the nonhuman primate is the more conservative animal model, since it requires higher exposure for maximum efficacy and would result in a higher predicted dose in humans for achieving efficacy against smallpox.

TECOVIRIMAT CLINICAL TRIAL

In the expanded safety trial, 851 volunteers were screened, of whom 452 underwent randomiza-

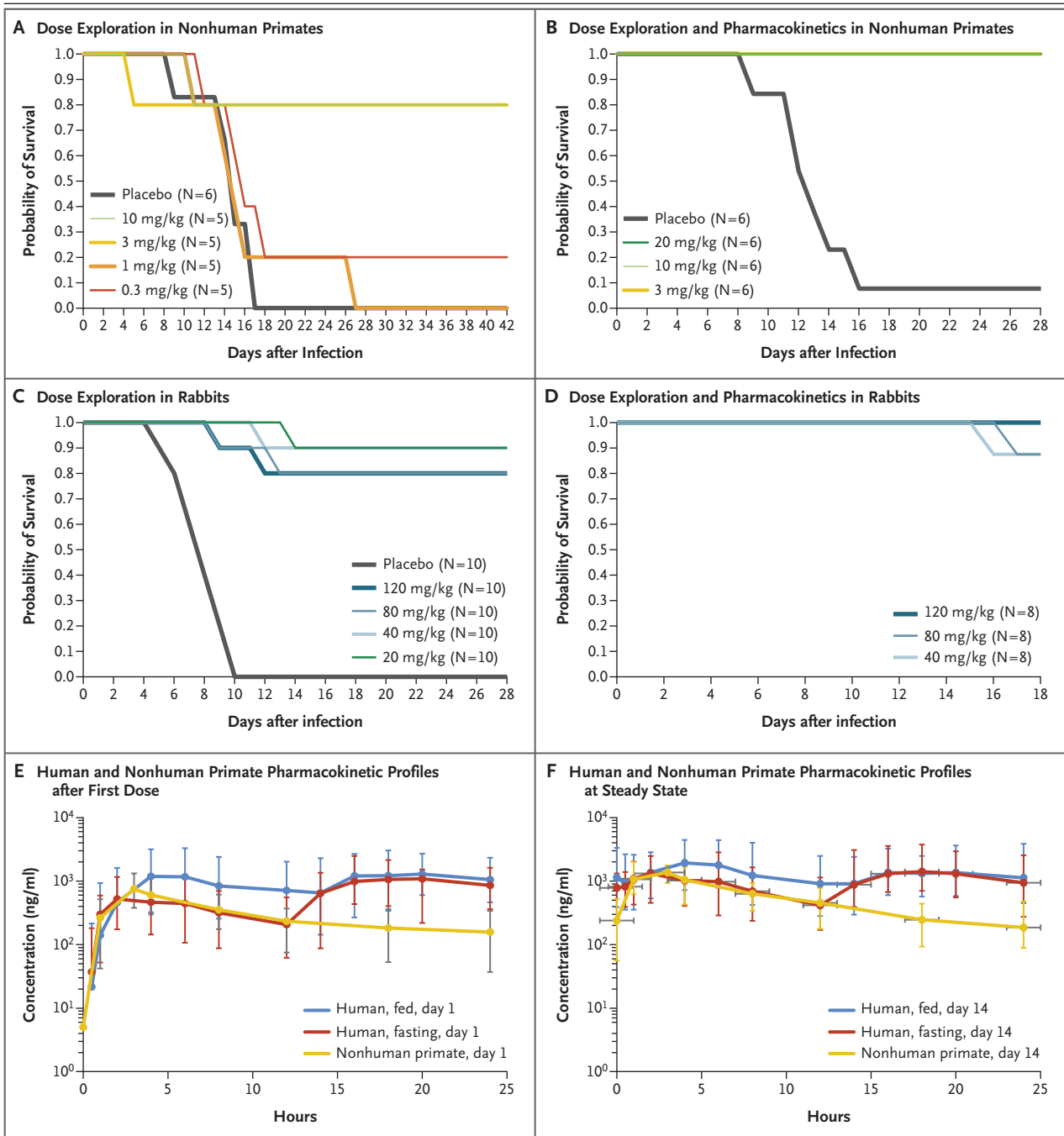


Figure 1. Efficacy and Pharmacokinetic Profiles of Tecovirimat in Animal Models.

On day 0, nonhuman primates (Panels A and B) and rabbits (Panels C and D) were infected with a lethal dose of monkeypox virus or rabbitpox virus, respectively. Survival was monitored for 18 to 42 days after infection, indicated on the horizontal axis labels. Tecovirimat was administered by oral gavage at doses ranging from 0.3 to 20 mg per kilogram of body weight in nonhuman primates and from 20 to 120 mg per kilogram in rabbits. Tecovirimat was administered for 14 consecutive daily doses starting on day 4 after infection, after the onset of clinical signs (pock lesions in nonhuman primates and fever and viremia in rabbits) in each study. Comparison of the exposures required for efficacy in rabbits and nonhuman primates showed that the nonhuman primate was the more conservative model, with higher exposures required for full effectiveness. Therefore, the exposure profiles of tecovirimat in plasma in nonhuman primates and humans were compared after the first dose (Panel E) and after the last dose at steady state (Panel F) to evaluate whether exposures in humans exceeded those in nonhuman primates, providing a reasonable expectation of efficacy in humans.

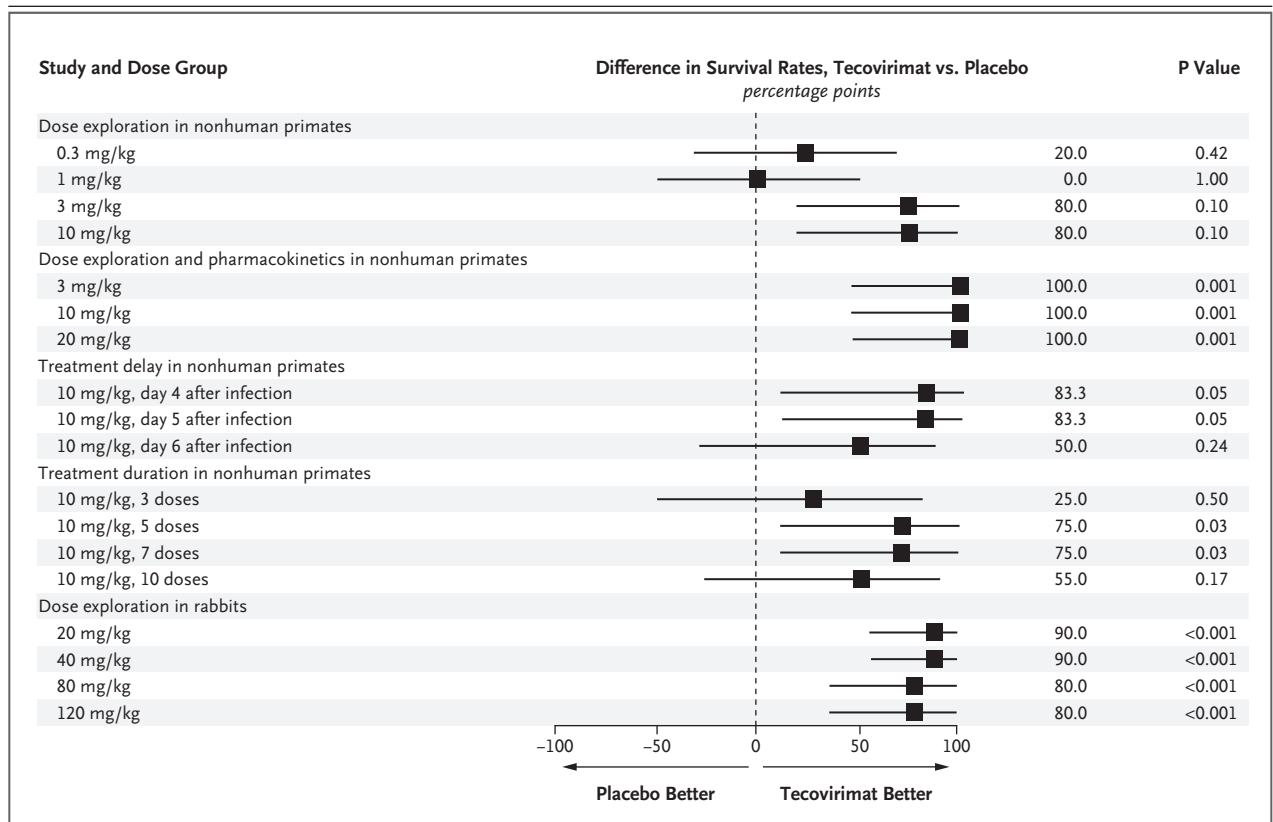


Figure 2. Differences in Survival Rates with Tecovirimat as Compared with Placebo.

Shown is a forest-plot summary comparing differences in survival rates between tecovirimat and placebo in each study. The exact 95% confidence intervals (horizontal bars in the forest plot) are based on the score statistic of the difference in survival rates. The P value is from a one-sided Fisher’s exact test for the comparison of tecovirimat with placebo. Data from the study of dose exploration and pharmacokinetics in rabbits are not shown on the forest plot, since the study did not include a placebo control.

tion and were assigned to receive tecovirimat at a dose of 600 mg twice daily (361 participants) or matching placebo (91 participants) for 14 consecutive days (Fig. S7 in the Supplementary Appendix). On the basis of the exposure–response relationship in animal models and previous clinical pharmacokinetic data over a range of doses,^{27,28} modeling and simulation studies²⁹ predicted that a dose of 600 mg twice daily would provide exposure in excess of that provided by the efficacious doses in animals. Although studies in animals have shown that five daily doses is the minimum number that is sufficient to provide a survival advantage similar to that associated with longer dosing durations, the 14-day regimen was selected on the basis of the kinetics of the humoral immune response in smallpox,³ which is necessary to clear the virus and prevent

recrudescence of disease. The demographic and baseline characteristics of the trial participants were well balanced in the trial groups (Table 2). A total of 431 participants completed the trial. The overall rate of adherence was 94.4% in the placebo group and 93.6% in the tecovirimat group; the corresponding rates among participants in the pharmacokinetic portion of the trial were 100% and 96.9%.

The pharmacokinetic profiles and exposures of approximately 48 participants in a fed state are presented to compare with those in the nonhuman primate model (Fig. 1E and 1F and Table 1, and Table S9 and Fig. S8 in the Supplementary Appendix). There were 386 nonserious adverse events reported throughout the trial by 164 participants; 208 of these events were thought to be related to tecovirimat or placebo (Table 3,

Table 1. Geometric Mean of Noncompartmental Exposures in Nonhuman Primates, Rabbits, and Humans — Identification of the Most Conservative Animal Model and Comparison with Human Exposures.*

Comparison	C_{max}	C_{min}	C_{avg}	AUC_{0-24hr}
Efficacious exposure in animal models				
Day 1 (first dose)				
Nonhuman primate, 10 mg/kg daily	749	158	318	7,629
Rabbit, 40 mg/kg daily	518	144	292	7,004
Nonhuman primate:rabbit ratio	1.4	1.1	1.1	1.1
Day 14 (steady state)				
Nonhuman primate, 10 mg/kg daily	1444	169	598	14,352
Rabbit, 40 mg/kg daily	374	25	138	3,318
Nonhuman primate:rabbit ratio	3.9	6.8	4.3	4.3
Nonhuman primate and human exposure†				
Day 1 (first dose)				
Human, 600 mg twice a day	1591	560	924	25,876
Nonhuman primate, 10 mg/kg daily	749	158	318	7,629
Human:nonhuman primate ratio	2.1	3.5	2.9	3.4
Day 14 (steady state)				
Human, 600 mg twice a day	2209	690	1270	30,632
Nonhuman primate, 10 mg/kg daily	1444	169	598	14,352
Human:nonhuman primate ratio	1.5	4.1	2.1	2.1

* AUC_{0-24hr} denotes area under the concentration–time curve over 24 hours, C_{avg} the average (mean) concentration, C_{max} the maximum concentration, and C_{min} the minimum concentration.

† The values for human exposure are the arithmetic means from the expanded safety trial.

and Table S10 in the Supplementary Appendix). The adverse events related to the trial regimen that occurred or worsened during the trial period were similar in the two groups (Table S11 in the Supplementary Appendix). Adverse events of grade 3 or higher occurred or worsened during treatment at a frequency of 1.1% in both the tecovirimat group and the placebo group (Table S12 in the Supplementary Appendix) and included headache, osteoarthritis, and hidradenitis. One fatal adverse event was found to be related to a pulmonary embolism that occurred in a participant 1 week after completion of tecovirimat treatment. The participant had a history of recent recurrent deep-vein thromboses but was not being treated with anticoagulant agents. Toxicologic testing revealed no ethanol or drugs of abuse, and the death was judged by the investigators to be unrelated to tecovirimat. Eight participants (2 in the placebo group and 6 in the tecovirimat group) discontinued the trial regi-

men because of adverse events (Table S13 in the Supplementary Appendix).

Pharmacokinetic analysis revealed that the C_{max} and AUC_{0-24hr} of tecovirimat under fed conditions were up to 50% and 45% greater on day 1 and day 14, respectively, than they were under fasting conditions (Fig. 1E and 1F). Multiple-day dosing in humans resulted in drug accumulation, with steady-state drug exposures that were approximately 50% (AUC_{0-24hr}) and 40% (C_{max}) higher than those after the first dose. Steady-state levels of tecovirimat were achieved by day 6, and elimination half-life values were similar (approximately 23 hours) in the fasting and fed groups (Table S9 in the Supplementary Appendix). However, clearance was 55.3 and 39.2 liters per hour in fasting and fed participants, respectively, findings consistent with the previous observation that food altered the presystemic bioavailability of tecovirimat but not the systemic elimination of the drug.³⁰

Table 2. Demographic and Clinical Characteristics of the Participants at Baseline (Safety Population).*

Population and Characteristic	Placebo (N=90)	Tecovirimat (N=359)	Total (N=449)
Sex — no. (%)			
Male	36 (40)	148 (41)	184 (41)
Female	54 (60)	211 (59)	265 (59)
Race — no. (%)†			
White	62 (69)	249 (69)	311 (69)
Black	26 (29)	101 (28)	127 (28)
Asian	1 (1)	3 (1)	4 (1)
American Indian or Alaska Native	0	3 (1)	3 (1)
Native Hawaiian or other Pacific Islander	1 (1)	1 (<1)	2 (<1)
Other	0	2 (1)	2 (<1)
Ethnic group — no. (%)†			
Hispanic or Latino	5 (6)	43 (12)	48 (11)
Not Hispanic or Latino	85 (94)	315 (88)	400 (89)
Other	0	1 (<1)	1 (<1)
Age — yr‡			
Mean	41.9±15.8	40.4±15.7	40.7±15.7
Median	40.5	38.0	39.0
Range	18–80	18–79	18–80
Weight — kg§			
Mean	89.7±29.2	88.6±22.8	88.8±24.2
Median	84.0	85.4	85.1
Range	51.4–240.6	49.1–188.0	49.1–240.6
Height — cm¶			
Mean	168.7±9.0	169.3±9.4	169.2±9.3
Median	168.2	168.7	168.7
Range	152.4–190.5	144.7–194.3	144.7–194.3
Body-mass index			
Mean	31.5±9.7	30.9±7.6	31.0±8.1
Median	29.0	29.4	29.3
Range	19.5–78.1	17.4–61.1	17.4–78.1

* Plus–minus values are means ±SD.

† The categories for race and ethnic group were the standard categories used by INC Research (now Syneos Health), the company that conducted the clinical trial. Participants chose their answers from a drop-down menu; if the category “Other” was chosen, the participant was asked to specify the answer.

‡ Age was calculated as the date of the day 1 visit minus the date of birth, divided by 365.25.

§ Measurement was performed at screening.

¶ Data were missing for one participant in the tecovirimat group.

|| Body-mass index is the weight in kilograms divided by the square of the height in meters.

DISCUSSION

Because the risk of VARV infection persists, developing antiviral therapy to treat it is important. Because the smallpox vaccine is no longer used

in the general population, herd immunity is minimal, and the vaccine is largely ineffective after the onset of clinical illness. These gaps could be mitigated by an effective smallpox antiviral drug to treat people who have clinically

Table 3. Adverse Events That Occurred or Worsened during Receipt of Tecovirimat or Placebo in the Overall Summary Safety Population.

Type of Event*	Placebo (N=90)		Tecovirimat (N=359)		Total (N=449)	
	No. of Participants (%)	No. of Events	No. of Participants (%)	No. of Events	No. of Participants (%)	No. of Events
Any event	30 (33.3)	68	134 (37.3)	318	164 (36.5)	386
Event related to the trial agent	15 (16.7)	32	71 (19.8)	176	86 (19.2)	208
Event leading to discontinuation of trial agent	2 (2.2)	3	6 (1.7)	16	8 (1.8)	19
Serious events and events leading to death	0	0	1 (0.3)†	1	1 (0.2)	1

* The adverse events considered here included any newly occurring event or previous condition that increased in severity or frequency since administration of the first dose of tecovirimat or placebo.

† The death was due to a pulmonary embolus that was judged by the investigators not to be related to tecovirimat.

evident disease as well as those who have been exposed or potentially exposed to smallpox. A smallpox antiviral drug could be an important stopgap measure until the standard vaccine can be effectively deployed, while complementing the protective efficacy of the vaccine once it has been deployed.

The eradication of smallpox and the limited usefulness and availability of animal models of VARV infection pose unique challenges in the development and validation of potential smallpox antiviral drugs. In contrast to other Animal Rule investigational scenarios, smallpox antiviral exploration requires the use of surrogate pathogens and hosts for human smallpox. Because of this unique complexity, the FDA convened an advisory panel on the subject of smallpox antiviral-drug development in December 2011. The panel concluded that lethal monkeypox virus infection in nonhuman primates and rabbitpox virus infection in rabbits allowed meaningful evaluation of potential smallpox antiviral drugs, although studies in human volunteers would be necessary to confirm that the doses in humans can safely provide similar exposure to that required for efficacy in animals. The FDA subsequently stipulated that human exposure achieved with drug candidates evaluated under the Animal Rule should provide a multiple of the effective exposure in animals³¹ as an additional threshold to increase the likelihood of efficacy on the basis of animal models.

This report represents the triangulation of safety, pharmacokinetic, and efficacy data from two animal models and noninfected human volunteers (Fig. S1 in the Supplementary Appendix). The efficacy findings in our studies in rabbits

confirmed the earlier observations from studies in nonhuman primates that efficacious drug exposures in the nonhuman primate model were higher than required in the rabbit model. Dosing in humans was, therefore, targeted to achieve a multiple of the efficacious exposure in the nonhuman primate model. The exposures achieved with a dose of 600 mg twice daily exceeded the efficacious exposures in nonhuman primates. For C_{\min} in humans, which has been established as a key pharmacokinetic measure most closely correlated with efficacy in animals,²⁹ the exposure was 4 times as high as the maximally efficacious exposure in nonhuman primates. No safety concerns were identified in association with tecovirimat use in human volunteers without smallpox who were receiving a 14-day course. Most reported adverse events were mild, and all events, with the exception of the death, resolved without sequelae. Discontinuation of the trial was rare among the participants. The aggregation of the results from these multiple studies involving animals and humans supports tecovirimat as a potential smallpox antiviral drug.

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