AVI-7288 for Marburg Virus in Nonhuman Primates and Humans


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<tr>
<td>DOI</td>
<td>10.1056/NEJMoa1410345</td>
</tr>
<tr>
<td>Publisher</td>
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</tr>
<tr>
<td>Version</td>
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AVI-7288 for Marburg Virus in Nonhuman Primates and Humans

Alison E. Heald, M.D., Jay S. Charleston, Ph.D., Patrick L. Iversen, Ph.D., Travis K. Warren, Ph.D., Jay B. Saoud, Ph.D., Mohamed Al-Ibrahim, M.B., Ch.B., Jay Wells, B.S., Kelly L. Warfield, Ph.D., Dana L. Swenson, Ph.D., Lisa S. Welch, B.S., Peter Sazani, Ph.D., Michael Wong, M.D., Diane Berry, Ph.D., Edward M. Kaye, M.D., and Sina Bavari, Ph.D.

BACKGROUND
AVI-7288 is a phosphorodiamidate morpholino oligomer with positive charges that targets the viral messenger RNA that encodes Marburg virus (MARV) nucleoprotein. Its safety in humans is undetermined.

METHODS
We assessed the efficacy of AVI-7288 in a series of studies involving a lethal challenge with MARV in nonhuman primates. The safety of AVI-7288 was evaluated in a randomized, multiple-ascending-dose study in which 40 healthy humans (8 humans per dose group) received 14 once-daily infusions of AVI-7288 (1 mg, 4 mg, 8 mg, 12 mg, or 16 mg per kilogram of body weight) or placebo, in a 3:1 ratio. We estimated the protective dose in humans by comparing pharmacokinetic variables in infected nonhuman primates, uninfected nonhuman primates, and uninfected humans.

RESULTS
Survival in infected nonhuman primates was dose-dependent, with survival rates of 0%, 30%, 59%, 87%, and 100% among monkeys treated with 0 mg, 3.75 mg, 7.5 mg, 15 mg, and 30 mg of AVI-7288 per kilogram, respectively (P<0.001 with the use of the log-rank test for the comparison of survival across groups). No safety concern was identified at doses up to 16 mg per kilogram per day in humans. No serious adverse events were reported. Drug exposure (the area under the curve) was dose-dependent in both nonhuman primates and humans; drug clearance was independent of dose but was higher in nonhuman primates than in humans. The protective dose in humans was initially estimated, on the basis of exposure, to be 9.6 mg per kilogram per day (95% confidence interval, 6.6 to 12.5) for 14 days. Monte Carlo simulations supported a dose of 11 mg per kilogram per day to match the geometric mean protective exposure in nonhuman primates.

CONCLUSIONS
This study shows that, on the basis of efficacy in nonhuman primates and pharmacokinetic data in humans, AVI-7288 has potential as postexposure prophylaxis for MARV infection in humans. (Funded by the Department of Defense; ClinicalTrials.gov number, NCT01566877.)
Marburg hemorrhagic fever is a rare human disease that is caused by Marburg virus (MARV), a single-stranded, negative-sense RNA virus. Marburg hemorrhagic fever was first identified during an outbreak in Marburg, Germany, in 1967, when laboratory workers were infected while dissecting African green monkeys from Uganda. Since then, infections in humans have occurred in Africa, as well as sporadically outside Africa in travelers returning home from that continent. The next MARV outbreak is likely to occur without warning, similar to the recent epidemic of the closely related Ebola virus (EBOV).

MARV infects the host when mucosal surfaces or abraded skin are exposed to infected body fluids; infection also occurs through parenteral inoculation. Mortality associated with MARV infection has been reported to be as high as 88%. Marburg has been classified as a potential category A agent of bioterrorism. The need for effective therapy and prophylaxis is evident; other than supportive care, no vaccine or established therapy is available for MARV infection.

AVI-7288, a drug intended for the postexposure prophylaxis of MARV infection, is a 23-mer antisense phosphorodiamidate morpholino oligomer (PMO) with positively charged residues incorporated in its backbone. AVI-7288 specifically targets the messenger RNA (mRNA) sequence of the MARV nucleoprotein, the major nucleoprotein involved in RNA encapsidation, physically blocking its translation (Fig. 1). The positive charges in the molecule are hypothesized to nonspecifically enhance binding to negatively charged viral RNA, possibly subverting the evolution of resistant viral mutants.

Initially, AVI-7288 was developed to be part of a two-drug combination (in a 1:1 ratio) with AVI-7287 (a positively charged PMO that targets MARV viral protein 24). This drug combination, termed AVI-6003 (Fig. 1), was shown to be the best candidate for postexposure prophylaxis in early studies involving challenges with MARV that was adapted to be lethal in mice and guinea pigs. However, subsequent studies involving a lethal challenge with MARV in the cynomolgus macaque showed that AVI-7288 was the active component in AVI-6003. A lethal challenge with MARV in nonhuman primates is likely to more accurately represent the human disease condition than is a challenge with lethally adapted MARV in mice and guinea pigs; therefore, recent clinical development has featured AVI-7288 administered as a single component.

Because definitive efficacy studies that involve exposing healthy human volunteers to MARV are unethical and field trials after accidental or intentional human exposure are not feasible, regulatory approval in the United States for AVI-7288 is being sought under the Food and Drug Administration (FDA) Animal Rule (Code of Federal Regulations, 21 CFR 314.600). Postinfection efficacy studies, including delays in treatment initiation of up to 96 hours after viral challenge, were conducted by means of a lethal challenge involving nonhuman primates. A multiple-ascending-dose study was conducted to assess the safety in humans. The pharmacokinetics of AVI-7288 were
assessed in uninfected monkeys, MARV-infected monkeys, and uninfected humans to estimate a protective dose in humans.

**METHODS**

**EFFICACY IN NONHUMAN PRIMATES**

We conducted a series of studies that involved a lethal challenge in nonhuman primates to determine the efficacious dose of AVI-7288 (Table 1, and Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). In the lethal challenge, cynomolgus macaques (1 to 10 monkeys per group) were injected subcutaneously with a target dose of 1000 plaque-forming units of MARV (Musoke variant) and then treated with the combination product (AVI-6003), one component of the combination product (either AVI-7287 or AVI-7288), a combination-product control with activity against EBOV instead of MARV (AVI-6002; Fig. 1), or a saline control. The primary end point of each study was survival after a challenge with MARV.

**PHARMACOKINETICS AND PHARMACODYNAMICS IN NONHUMAN PRIMATES**

We performed dedicated studies of pharmacokinetics (Table 1, and Table S1 in the Supplementary Appendix) to determine the relationship between pharmacokinetics and pharmacodynamics in infected and uninfected monkeys. AVI-7288 at a dose of 3.75 mg, 7.5 mg, or 15 mg per kilogram of body weight was administered intravenously over a period of 2 to 3 minutes once daily for 14 days to infected and uninfected nonhuman primates (six primates per group). Intensive plasma sampling was performed on 4 dosing days. Plasma levels of AVI-7288 were determined with the use of a hybridized fluorescent oligonucleotide probe that was subjected to analysis by capillary gel electrophoresis (Helix Diagnostics). The timing of plasma sampling and details of the bioanalytic assay are provided in the Supplementary Appendix.

**SAFETY AND PHARMACOKINETICS IN HUMANS**

We conducted a randomized, placebo-controlled, multiple-ascending-dose study to determine the safety, adverse-event profile, and pharmacokinetic data associated with multiple intravenous infusions of AVI-7288 in healthy volunteers. After they provided written, informed consent, 40 volunteers were enrolled in five sequential cohorts of 8 persons each and received 14 once-daily, 30-minute intravenous infusions of AVI-7288 at one of five dose levels (1 mg, 4 mg, 8 mg, 12 mg, or 16 mg per kilogram) or placebo, in a 3:1 ratio. Study participants were men and women between 18 and 50 years of age who were in good general health and had a glomerular filtration rate of at least 90 ml per minute per 1.73 m² of body-surface area and a ratio of urinary albumin to creatinine of 30 mg per gram or lower. The study design included prespecified individual and cohort stopping rules. Safety was monitored through reporting of adverse events and serial blood testing, urine testing, and electrocardiography. Intensive plasma sampling to determine AVI-7288 levels was completed on 2 dosing days. Plasma levels of AVI-7288 were determined with the use of a hybridized fluorescent oligonucleotide probe that was subjected to analysis by capillary gel electrophoresis, as described in the Supplementary Appendix. Study details are included in the research protocol, which is available at NEJM.org.

**STUDY OVERSIGHT**

The experiments involving nonhuman primates were performed at biosafety level 4 containment facilities at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) at Fort Detrick, Frederick, Maryland. USAMRIID designed the studies in collaboration with Sarepta and collected and analyzed the data. Research was conducted according to a protocol approved by the Institutional Animal Care and Use Committee and in compliance with the Animal Welfare Act, Public Health Service Policy, and other federal statutes and regulations relating to animals and experiments involving animals.

The clinical study was approved by the institutional review board before enrollment. The study was overseen by an independent data and safety monitoring board, which reviewed available data after each cohort had completed its assigned regimen of the study drug, before enrollment of the subsequent cohort. Sarepta designed and conducted the study; Sarepta collected the data, monitored study conduct, and performed the statistical analysis.

The Department of Defense contracted with Sarepta for the manufacture of the drugs for both the nonclinical and the clinical studies. All
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<th>Study</th>
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<th>Equivalent Dose of AVI-7288</th>
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<td>96-hr delay in time to treatment with AVI-7288</td>
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<td>AVI-7288 pharmacokinetics in uninfected macaques</td>
<td>Intravenous</td>
<td>3 M, 3 F</td>
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</table>

* Except as noted in the AVI-7288 delayed-time-to-treatment studies, the drugs were administered 1 hour after exposure (time of administration of the drug was not applicable for the AVI-7288 pharmacokinetics study involving uninfected macaques).
the authors vouch for the completeness and accuracy of the data and the analyses presented, and three employees of Sarepta and the principal investigator (the sixth author) attest that the clinical study was conducted in accordance with the protocol. The first author wrote the first and subsequent drafts of the manuscript. The investigators, participating institutions, and Sarepta agreed to maintain the confidentiality of the data before publication.

STATISTICAL ANALYSIS

Survival data from all the nonhuman primate efficacy studies were combined, and the Kaplan–Meier method was used to generate survival curves according to the equivalent dose of AVI-7288 administered to each animal. Dose was treated as a categorical variable, and a log-rank test with five degrees of freedom was used to compare the survival curves using GraphPad Prism, version 6.0.

The pharmacokinetics of AVI-7288 were determined from blood samples, with the use of a model-independent (noncompartmental) approach appropriate for a bolus injection in nonhuman primates and a constant rate infusion in humans.21 The pharmacokinetic variables of AVI-7288 that were assessed included its maximum plasma concentration (Cmax), its plasma half-life, the time at which Cmax occurred, the area under the plasma concentration–time curve from time 0 to 24 hours after the start of infusion of the study drug (AUC0-24), the volume of distribution under steady-state conditions, and the plasma clearance. Pharmacokinetic analyses were performed with the use of WinNonlin, version 5.2 (Pharsight). Results were reported and graphed as means and standard errors, unless otherwise noted.

We estimated the protective human dose of AVI-7288 by comparing key pharmacokinetic variables (AUC0-24 and plasma clearance) in infected monkeys with those in uninfected monkeys to see whether viral infection affected the pharmacokinetics of AVI-7288; we then calculated the human dose that corresponded to the protective dose in nonhuman primates. AUC0-24 and plasma clearance were plotted against dose with the use of GraphPad Prism software, version 6.0, and linear regression was used to determine whether the slope of each line was different from 0 and to calculate the slope and associated standard error. The resulting equation for AUC0-24 was solved to determine the protective dose in humans on the basis of the protective dose in nonhuman primates. The associated errors were propagated through the calculations to determine the 95% confidence intervals in association with the estimated protective dose.

To further evaluate the estimated protective human dose, Monte Carlo simulations were performed. R software, version 3.0.2 (R Project for Statistical Computing), was used to generate 10,000 estimates of plasma clearance in nonhuman primates (with the use of the mean and standard deviation values of clearance in nonhuman primates), and 10,000 estimates of plasma clearance in humans (with the use of the mean and standard deviation values of clearance in humans). From those values, exposure estimates (AUC from time 0 to infinity [AUC0-∞]) were generated with the use of the following relationship: \( \text{AUC}_{0-\infty} = \text{dose} ÷ \text{plasma clearance} \). A dose of 15 mg per kilogram was used for nonhuman primates, and doses of 9.6 mg, 10 mg, 11 mg, and 15 mg per kilogram were used for humans.

RESULTS

EFFICACY IN NONHUMAN PRIMATES

Survival in infected nonhuman primates was dose-dependent (Fig. 2), with survival rates of 0%, 30%, 59%, 87%, 100%, and 100% among monkeys treated with AVI-7287 at a dose of 0 mg, 3.75 mg, 7.5 mg, 15 mg, 20 mg, and 30 mg per kilogram, respectively (P<0.001 with the use of the log-rank test for the comparison of survival across groups). In contrast, none of the monkeys that were treated with AVI-7287 alone, the combination-product control (AVI-6002), or the saline control survived. In an efficacy study involving nonhuman primates that was specifically designed to evaluate the efficacy of AVI-7288 after delayed treatment, treatment with 15 mg per kilogram per day for 14 days starting at 24, 48, and 96 hours after viral challenge provided 83%, 100%, and 83% protection, respectively (Table S1 in Supplementary Appendix). Because the dose of 15 mg of AVI-7288 per kilogram has provided reasonable protection, it is currently considered the target effective dose in nonhuman primates that are undergoing lethal challenge with MARV.

SAFETY IN HUMANS

Twenty men and 20 women participated in the study during the period from April 2013 through
The Kaplan–Meier method was used to generate curves for overall survival rates among nonhuman primates that were treated with various doses of AVI-7288, either alone or in combination with AVI-7287 (i.e., as AVI-6003). The curves are shown according to the equivalent dose of AVI-7288 administered to each animal in a series of studies that involved lethal challenge with MARV. Results of the individual studies were combined. The equivalent doses of AVI-7288 were 30 mg per kilogram (6 monkeys), 20 mg per kilogram (10 monkeys), 15 mg per kilogram (69 monkeys), 7.5 mg per kilogram (22 monkeys), 3.75 mg per kilogram (11 monkeys), and 0 mg per kilogram (36 monkeys). The group that received 0 mg of AVI-7288 per kilogram was composed of nonhuman primates that were treated with AVI-7287 alone (the inactive ingredient of AVI-6003), the combination-product control (AVI-6002), or saline control. The tick marks on the curves indicate when survival data were censored.

Figure 2. AVI-7288 and Effect on Overall Survival in Nonhuman Primates Infected with MARV.

The curves are shown according to the equivalent dose of AVI-7288 administered to each animal in a series of studies that involved lethal challenge with MARV. Results of the individual studies were combined. The equivalent doses of AVI-7288 were 30 mg per kilogram (6 monkeys), 20 mg per kilogram (10 monkeys), 15 mg per kilogram (69 monkeys), 7.5 mg per kilogram (22 monkeys), 3.75 mg per kilogram (11 monkeys), and 0 mg per kilogram (36 monkeys). The group that received 0 mg of AVI-7288 per kilogram was composed of nonhuman primates that were treated with AVI-7287 alone (the inactive ingredient of AVI-6003), the combination-product control (AVI-6002), or saline control. The tick marks on the curves indicate when survival data were censored.

January 2014. The participants’ characteristics are described in Table S2 in the Supplementary Appendix.

All the participants completed follow-up in the 42-day study. One participant in the cohort receiving 12 mg of AVI-7288 per kilogram discontinued treatment on day 6 because the ratio of urinary albumin to creatinine was confirmed to have more than tripled from the predose ratio on day 1, to an absolute value greater than 30 mg per gram, which was an adverse event that met an individual stopping criterion. The ratio returned to the baseline level by day 7.

No safety concern was identified in association with intravenous infusions of AVI-7288 at any of the doses studied (Table 2). Adverse events that occurred during the treatment period were reported by 15 of the 30 participants who received AVI-7288 (50%) and 8 of the 10 participants who received placebo (80%). No serious adverse events were reported; headache was the most common adverse event, reported by 8 of the participants who were treated with AVI-7288 (27%) and 2 of the participants who received placebo (20%). All adverse events that occurred during the treatment period were mild in severity, except for two moderate headaches and one moderate episode each of abdominal pain, diarrhea, pain in the extremities, and nasopharyngitis among participants who received AVI-7288 and one episode of moderate contact dermatitis in a participant who received placebo (Table S3 in the Supplementary Appendix). Adverse events that occurred during the treatment period and were deemed by the principal investigator to be treatment-related were reported by 10 of the 30 participants who received AVI-7288 (33%) and 3 of the 10 participants who received placebo (30%). Headache was the most common treatment-related adverse event that occurred during the treatment period and was reported by 4 of the participants who received AVI-7288 (13%) and 2 of the participants who received placebo (20%) (Table S4 in the Supplementary Appendix).

No clinically significant or dose-dependent effects of AVI-7288 were reported with respect to any safety end point evaluated, nor were any gross abnormalities in renal function or biomarkers of renal dysfunction observed. The maximum dose of AVI-7288 that could be administered without raising a safety concern was not reached. The protocol was not amended to allow exploration of higher doses of AVI-7288, since funding for the study was limited.

**PHARMACOKINETICS IN NONHUMAN PRIMATES AND HUMANS**

The pharmacokinetics of AVI-7288 were similar in infected nonhuman primates, uninfected nonhuman primates, and uninfected humans (Tables S5, S6, and S7, respectively, in the Supplementary Appendix). The AUCO–24 and Cmax were generally dose-proportional across the range of doses that were tested in nonhuman primates (Fig. S1 in the Supplementary Appendix) and in humans (Fig. 3A, and Fig. S2 in the Supplementary Appendix). Plasma clearance was independent of dose in nonhuman primates and humans (Fig. S3 and S4 in the Supplementary Appendix) but was higher in infected nonhuman primates (198±17 ml per kilogram per hour) and uninfected nonhuman primates (217±20 ml per kilogram per hour) than in uninfected humans (146±6 ml per kilogram per hour), as measured on day 1. The plasma half-life of AVI-7288 was similar in infected nonhuman primates...
Estimation of Protective Human Dose

The AUC₀⁻²⁴ and plasma clearance of AVI-7288 at a dose of 15 mg per kilogram were similar in infected and uninfected monkeys on day 1, day 5, day 10, and day 15 (Fig. S5 in the Supplementary Appendix), which suggests that viral infection did not affect the pharmacokinetics of AVI-7288 in nonhuman primates. The protective human dose that was estimated on the basis of exposure (AUC₀⁻²⁴) is illustrated in Figure 3A. The slope of the line showing the relationship between the AUC₀⁻²⁴ and dose in humans on the last day of dosing was 798±341.6 hr·ng per milliliter per milligram per kilogram. The efficacious exposure (AUC₀⁻²⁴) in infected monkeys that received 15 mg of AVI-7288 per kilogram was 76,395±11,570 hr·ng per milliliter. The human dose corresponding to this exposure was 9.6 mg per kilogram (95% confidence interval [CI], 6.6 to 12.5).

Histograms summarizing the simulated Monte Carlo estimates of AUC₀⁻∞ values for nonhuman primates that received the study drug at a dose of 15 mg per kilogram and for humans who received the drug at one of several doses are shown in Figure 3B. The AUC had log-normal distributions in humans. The AUC values were more variable in nonhuman primates, with a skewed distribution for large exposures. Therefore, median and geometric mean were used to match exposure in nonhuman primates to exposure in humans; this approach indicated that a dose of either 10 mg per kilogram (median) or 11 mg per kilogram (geometric mean) would be appropriate in humans (Table S8 in the Supplementary Appendix).

The protective human dose was not estimated with the use of Cmax for two reasons. First, the efficacy of AVI-7288 does not appear to depend on its Cmax, since the efficacy of AVI-7288 after intramuscular administration in the intramuscular feasibility study was similar to the efficacy after intravenous administration in the other studies involving nonhuman primates (Table S1 in Supplementary Appendix), and as expected, Cmax after intramuscular administration in the intramuscular feasibility study was lower than Cmax after intravenous administration in the pharmacokinetics and pharmacodynamics study.

### Table 2. Adverse Events, According to Dose Group, in the Multiple-Ascending-Dose Clinical Study.*

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<tr>
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<tr>
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<td>1.3 (1.2–1.5)</td>
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<td>Cumulative AVI-7288 exposure for g</td>
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<tr>
<td>Mean</td>
<td>0.9 (0.7–1.1)</td>
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<td>Range</td>
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<tr>
<td>Adverse event occurring during study period — no. of participants (%)</td>
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<td></td>
</tr>
<tr>
<td>Treatment-related adverse event occurring during study period — no. of participants (%)</td>
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<tr>
<td>Adverse event occurring during study period — no. of participants (%)</td>
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* No serious adverse events were reported.
Figure 3. Estimation of the Protective Dose of AVI-7288 in Humans.

Panel A shows the method used for the estimation of the protective dose of AVI-7288 in humans. The dose (in milligrams per kilogram of body weight) was estimated on the basis of the area under the plasma concentration–time curve (AUC) from 0 to 24 hours after the start of infusion of the study drug (AUC_{0-24}) in humans in the multiple-ascending-dose study and after the last dose of AVI-7288 in infected nonhuman primates (NHPs) in the pharmacokinetics and pharmacodynamics study. I bars denote the standard error. Panel B shows histograms summarizing Monte Carlo estimates of AUC values from time 0 to infinity (AUC_{0-\infty}) for nonhuman primates at a dose level of 15 mg of AVI-7288 per kilogram and humans at one of several dose levels (9.6 mg, 10 mg, 11 mg, or 15 mg per kilogram).

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(Fig. S6 in Supplementary Appendix). Second, AVI-7288 was administered through slow intravenous push over a period of 3 minutes in the studies involving nonhuman primates and as an intravenous infusion over a period of 30 minutes in the multiple-ascending-dose study involving humans; this difference precluded a comparison of $C_{\text{max}}$ values.

### Discussion

Sometimes definitive human efficacy studies of a drug are unethical, and sometimes field trials to study effectiveness after accidental or intentional human exposure to a pathogen are not feasible. In such cases, it is necessary to examine efficacy data in animal species and safety data in humans to determine an estimate of the protective human dose of a drug and to establish that the drug is reasonably likely to produce clinical benefit in humans.

The results of a series of studies involving nonhuman primates showed that a lethal challenge with MARV represented a well-characterized model of the human disease condition and was well-suited for assessing the potential clinical benefit in humans under the FDA Animal Rule. The challenge agent, MARV, is the same as the agent that causes disease in humans. Subcutaneous inoculation of nonhuman primates with MARV mimicked human exposure of mucosal surfaces or abraded skin to infected body fluids or human parenteral exposure. The inoculum size of 1000 plaque-forming units, targeted in studies involving nonhuman primates, was similar to the exposure anticipated after accidental needlestick injury, and may be representative of a realistic case scenario after mucosal exposure. The disease course after a lethal challenge with MARV in nonhuman primates was remarkably similar to the disease course in humans, with similar time from exposure to onset of disease, time course, and disease manifestations. The lethal challenge with MARV in nonhuman primates had a higher case-fatality ratio than that in humans, with 100% of monkeys dying 9 to 13 days after viral inoculation. Nevertheless, AVI-7288 showed significant efficacy in the nonhuman primates that were subjected to a challenge with MARV, which suggests that AVI-7288 is likely to ameliorate a less severe challenge with the virus in humans.

Monkeys treated with AVI-7288, either alone or together with AVI-7287 (i.e., as AVI-6003), survived in a dose-dependent manner. AVI-7288 at a dose of 15 mg per kilogram per day for 14 days resulted in a survival rate of 83 to 100% when administered up to 4 days after infection with MARV, as compared with a survival rate of 0% among control monkeys. On the basis of a comparison of exposure among infected nonhuman primates, uninfected nonhuman primates, and uninfected humans, the initial estimate of the protective dose in humans was 9.6 mg per kilogram per day (95% CI, 6.6 to 12.5) for 14 days. Monte Carlo simulations supported a dose of 11 mg per kilogram per day to match the geometric mean protective exposure in nonhuman primates. We expect that this dose will be refined as additional studies in nonhuman primates are conducted to evaluate the efficacy of AVI-7288 after inoculation with other variants of MARV and after exposure to MARV through other means of transmission, such as aerosols.

In the multiple-ascending-dose study reported here, no safety concern associated with AVI-7288 use was identified at doses up to 16 mg per kilogram per day for 14 days. No clinically significant toxic effects were observed at doses exceeding the estimated protective human dose, and the maximum dose that could be administered without raising a safety concern was not reached. In summary, on the basis of an evaluation of the efficacy in nonhuman primates and the preliminary safety and pharmacokinetics data in humans, AVI-7288 shows potential as prophylaxis after documented or suspected exposure to MARV.

The views expressed here are those of the authors and do not necessarily represent the views or official position of the Department of Defense (DOD), the Medical Countermeasure Systems Joint Project Management Office (JPM-MCS), or BioDefense Therapeutics (BD-Tx). The opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the U.S. Army.

This work was conducted under contract with the Joint Project Management Office of BD-Tx. BD-Tx is a component of the JPM-MCS within the DOD Joint Program Executive Office for Chemical and Biological Defense. Dr. Bavari was also supported by the Joint Science and Technology Office of the Defense Threat Reduction Agency.
Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

We thank the following people at the U.S. Army Medical Research Institute of Infectious Diseases: Nicole Lackemeyer, Kelly Stuthman, Sean Van Tongeren, Ginger Donnelly, Cary Retterer, Jacqueline Benko, and Shannon Mort; we also thank Dr. Jay-anand Vasudevan for his insightful comments, Dr. Ryszard Kole for his thoughtful review of an early version of the manuscript, and Dr. Diane Mould of Projections Research for completing the Monte Carlo simulations.

REFERENCES


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