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ST-246 Antiviral Efficacy in a Nonhuman Primate Monkeypox Model: Determination of the Minimal Effective Dose and Human Dose Justification▽

Robert Jordan,[1] Arthur Goff,[2] Annie Frimm,[3] Michael L. Corrado,[3] Lisa E. Hensley,[2] Chelsea M. Byrd,[1] Eric Mucker,[2] Josh Shamblin,[2] Tove' C. Bolken,[1] Carly Wlazlowski,[2] Wendy Johnson,[2] Jennifer Chapman,[2] Nancy Twenhafel,[2] Shanthakumar Tyavanagimatt,[1] Adams Amantana,[1] Jarasvech Chinsangaram,[1] Dennis E. Hruby,[1]* and John Huggins[2]

SIGA Technologies, Corvallis, Oregon[1]; U.S. Army Medical Research Institute of Infectious Diseases, Frederick, Maryland[2]; and INC Research, Raleigh, North Carolina[3]

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Therapeutics for the treatment of pathogenic orthopoxvirus infections are being sought. In the absence of patients with disease, animal models of orthopoxvirus disease are essential for evaluation of the efficacies of antiviral drugs and establishment of the appropriate dose and duration of human therapy. Infection of nonhuman primates (NHP) by the intravenous injection of monkeypox virus has been used to evaluate a promising therapeutic drug candidate, ST-246. ST-246 administered at 3 days postinfection (which corresponds to the secondary viremia stage of disease) at four different doses (from 100 mg/kg of body weight down to 3 mg/kg) once a day for 14 days was able to offer NHP 100% protection from a lethal infection with monkeypox virus and reduce the viral load and lesion formation. In NHP, the administration of ST-246 at a dose of 10 mg/kg/day for 14 days resulted in levels of blood exposure comparable to the levels attained in humans administered 400 mg in the fed state. These results suggest that administration of an oral dosage of 400 mg once daily for 14 days will be effective for the prevention or treatment of smallpox or monkeypox infections in humans.

Variola virus (VAR), the etiological agent of smallpox, has been eliminated from the environment by a successful worldwide vaccination campaign coordinated by the World Health Organization. Recent concerns over the potential use of VAR as a biological weapon have prompted new interest in the development of small-molecule therapeutics for the prevention and treatment of smallpox. Since VAR is no longer found in nature, human clinical trials designed to link antiviral efficacy to clinical outcome have been supplanted by antiviral efficacy evaluations with animal models of orthopoxvirus disease. The development of animal models that link efficacy end points with clinical correlates predictive of human disease outcome are necessary for the evaluation of new antiorthopoxvirus therapeutics.

VAR and monkeypox virus (MPX) cause severe systemic lesional disease in humans. Humans are the only known natural host for VAR, while monkeypox is primarily a zoonotic disease transmitted to humans through contact with infected rodents. The courses of natural orthopoxvirus infections in humans infected by the respiratory route and in nonhuman primates (NHP) experimentally infected by intravenous (i.v.) injection of virus are similar, especially during the later stages of disease progression, when lesional disease predominates. Virus enters the respiratory tract and establishes infection of the mucosal epithelium. Virus is carried by monocytes to the regional lymph nodes, where replication produces a primary viremia that seeds the spleen and other components of the reticuloendothelial system (9). Replication in the reticuloendothelial system produces a secondary viremia that disseminates virus to the skin and other major organs, causing the characteristic rash and potentially other end organ damage (1). Clinical illness begins during or shortly after this secondary viremia, with high fever and constitutional symptoms occurring (1, 5). In fatal cases, death occurs in the second week of illness (4). The majority of cases succumb to profound shock, generally attributed to viral toxemia (1). MPX infection in both humans and NHP is also characterized by marked lymphadenopathy, which is typically absent or significantly diminished in patients with smallpox (11). Due to the potential threat of either virus (VAR or MPX) being deliberately or accidentally introduced into our environment, the absence of an active vaccination campaign, and the risks associated with the current vaccine, there is a need for a safe and effective antiviral drug for use as a countermeasure against poxvirus.

To that end, SIGA is developing a new orally bioavailable drug, ST-246, for the treatment of pathogenic orthopoxviruses, including VAR. Previous work has shown that ST-246 is extremely potent, inhibiting orthopoxvirus replication in vitro at nM concentrations (2, 13, 16). The compound has been demonstrated to protect multiple animal species from lethal challenge with a variety of different orthopoxviruses, including

* Corresponding author. Mailing address: SIGA Technologies, Inc., 4575 SW Research Way, Suite 230, Corvallis, OR 97333. Phone: (541) 753-2000. Fax: (541) 753-9999. E-mail: dhruby@siga.com.
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VAR and MPX (7, 10, 12–14, 16). Preclinical safety pharmacology studies with mice and NHP indicate that ST-246 is readily absorbed and well tolerated. Commercial-scale synthetic routes have been established and validated. Human phase I clinical trials have shown that ST-246 is safe and well tolerated by healthy human volunteers, with the levels of plasma drug exposure being consistent with once-per-day dosing and drug levels being in the range predicted to be antiviral on the basis of data from efficacy studies with animal models of orthopoxvirus disease (8).

Because there are currently no patients with smallpox and because it would be unethical to deliberately infect volunteers, the regulatory approval of ST-246 will depend on demonstration of antiviral efficacy in appropriate animal models and the use of these models to construct pharmacokinetic arguments to support the dose for use by humans and the course of therapy. Although a large number of different animal models are available for pathogenic orthopoxviruses, infection of NHP with MPX is undoubtedly the most relevant due to the evolutionary relatedness of the hosts and the pathology and time course of the disease induced.

Infection of cynomolgus macaques via i.v. injection, a step that mimics the secondary viremia of smallpox, with 5×10^7 PFU of virus produces a uniformly lethal disease similar to the lesional disease observed in humans with MPX or VAR infection (6). Following i.v. challenge with MPX, the animals develop a generalized vesiculopustular rash, with other characteristics of disease including fever, elevated white blood cell count, lymphadenopathy, splenomegaly, and pulmonary edema (6). The disease progresses rapidly, with death occurring between 7 and 15 days postinfection (dpi) (6).

We have previously conducted two MPX challenges of NHP to test the efficacy of ST-246 (J. Huggins et al., submitted for publication). In both cases, the drug was shown to completely protect the NHP from death and lesional disease and to dramatically lower the viral load. However, the previous experiments were done with a high drug level, 300 mg/kg of body weight, which would be difficult to achieve in humans, and therapy was initiated at early times postinfection (0 or 1 day). The study reported here was designed to evaluate and compare the therapeutic effects of lower doses of ST-246 in cynomolgus monkeys which had been infected 3 days earlier with MPX. This represents a time point at which the NHP should be fully symptomatic and on the verge of lesion development.

MATERIALS AND METHODS

Virus preparation. MPX strain Zaire 79 (V79-I-005), originally isolated from the scab of a fatally infected human, was obtained from J. Esposito at the Centers for Disease Control and Prevention, Atlanta, GA, and propagated in MA-104 cells. A clarified lysate of infected cells was used to make the challenge stock of virus.

Study design. The study was designed as a randomized, placebo-controlled, parallel-group, longitudinal study of oral ST-246 in cynomolgus monkeys (*Macaca fascicularis*) infected i.v. with MPX. Fifteen NHPs were infected with 5×10^7 PFU of the Zaire 79 strain of MPX by i.v. injection and were randomized into five treatment arms of three NHP each that were administered vehicle or ST-246 at 3 mg/kg, 10 mg/kg, 30 mg/kg, and 100 mg/kg orally once per day followed by 5 ml/kg of a 30% suspension of hydrated homogenized monkey biscuits. Treatment was started on day 3 postinfection and was continued once daily for 14 days.

The infected animals were observed at least twice each day for up to 33 days to examine them for signs of illness. Blood samples were collected from the infected animals for virological, hematological, immunological, and chemical analyses. A full necropsy was performed on animals that died during the study to collect tissues for pathological examination. To determine the extent of infection, three animals were euthanized on day 3 and their tissues were processed to determine the virus levels in tissues. The organs were freeze-thawed, and a 10% tissue homogenate was produced and analyzed by quantitative PCR. The number of MPX genomes per milliliter of blood was determined by the extraction of DNA with a Qiagen QIAmp DNA minikit and quantitative TaqMan-MGB PCR, as described previously (3). Monkeypox lesions were enumerated daily. All USAMRIID animal facilities and animal programs are accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International. All animal use was approved by the USAMRIID Animal Care and Use Committee and was conducted in accordance with federal animal welfare act regulations.

Pharmacokinetic analysis of ST-246 in cynomolgus monkeys (NHP). The NHP were administered ST-246 at 10, 20, and 30 mg/kg by oral gavage under fed conditions. On the dosing days, all animals were administered a primate biscuit slurry immediately prior to dose administration. The biscuit slurry contained one can (8 oz) of Ensure or other liquid diet, approximately 36 g of fluid and electrolyte replacement formula (Prang), approximately 94 g of infant formula, 1 jar (2.5 oz) of strained fruit, five monkey chow biscuits, and approximately 2 oz of water blended together to achieve a uniform consistency. The biscuit slurry was administered via oral gavage at a dose volume of 10 ml/kg. After each dose of the test article was administered and prior to the removal of the gavage tube, the tube was flushed with 10 ml of tap water. The dosing formulations were stirred with a magnetic stir bar and stir plate prior to and throughout the administration. Individual doses were based on the most recent body weights. Except for the 20-mg/kg dose group, each dose group contained three male and three female NHP; the 20-mg/kg dose group contained four male and four female NHP. The NHP in the 10- and 30-mg/kg dose groups received ST-246 for 14 consecutive days, and those in the 20-mg/kg dose group received a single dose of ST-246. Blood samples were collected from the femoral artery/vein pretesting (0 h) (prior to dosing) and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 h postdosing on days 1, 7, and 14 for determination of the plasma concentrations of ST-246. ST-246 was quantified from monkey plasma specimens (50 ml) by a validated liquid chromatography-tandem mass spectrometry method by using an analog of ST-246 as an internal standard (8). A noncompartmental module was applied to the plasma concentration values for the individual NHP to determine the peak concentration of the drug in plasma (C_{max}) and the level of systemic exposure to the drug (the area under the concentration-time curve for each dosing interval measured from time zero to 24 h [$AUC_{0\text{-}24}$]).

Human subjects. Research with human subjects was conducted in compliance with federal and state statutes and regulations relating to the protection of human subjects. All data and human subjects research were gathered and conducted for this publication under protocols approved by the institutional review boards of the authors' institutions.

Survival. Survival was analyzed by the product limit (Kaplan-Meier) method, and curves were compared by the log-rank test (two tailed) for three NHP per group.

Maximum values. The maximum viral load (log converted) and the maximum total lesion count for each animal were summarized for each study arm as means and were used to compare the log-transformed maximum viral loads and maximum total lesion counts for the group to which vehicle was administered to those for the groups to which ST-246 was administered by use of a one-way analysis of variance (ANOVA) with Tukey's multiple-comparison test (two tailed, three NHP per group).

Repeated-measures analysis. Repeated-measures analysis for viral load and total lesion count over the study period in which censored values from animals that died were replaced with the last observed value to allow for the evaluation of the complete disease course (last value carried forward). Repeated-measures analysis was used to compare the viral loads and lesion counts of the placebo group and those of the ST-246 dosing groups. Since viral loads are expected to be lognormal in distribution, these analyses were log transformed to normalize the data prior to analysis by two-way ANOVA (two tailed, three NHP per group).

RESULTS

Evaluation of ST-246 efficacy in cynomolgus monkey model of monkeypox. The study described here was a randomized, placebo-controlled, parallel-group, longitudinal study of oral ST-246 in NHP infected i.v. with MPX. The animals exhibited

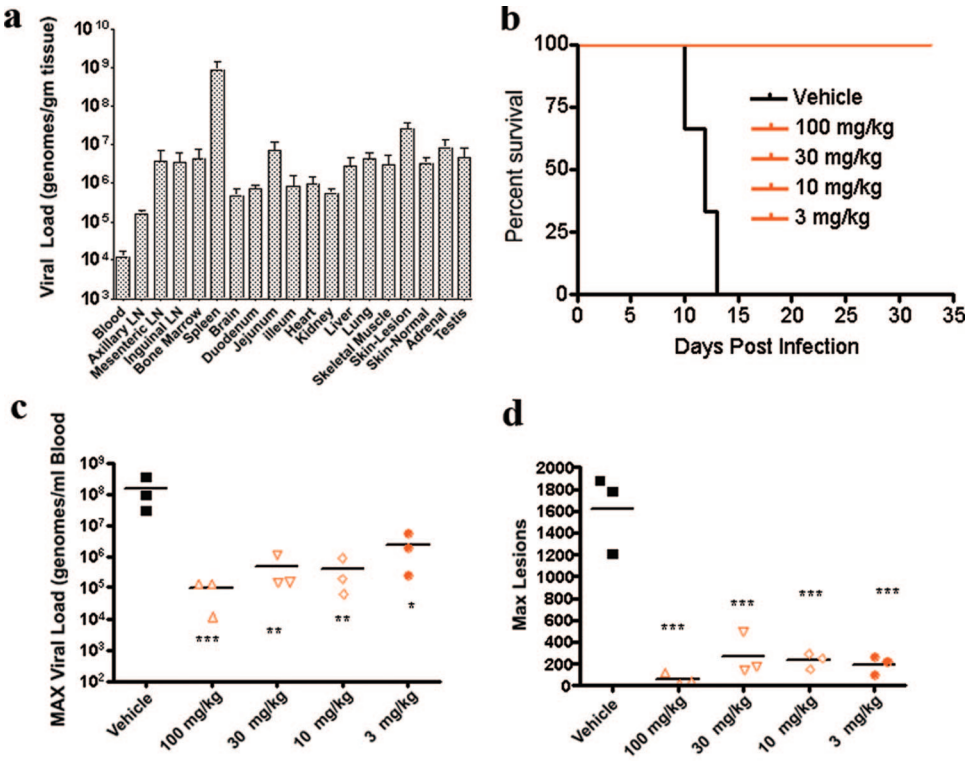

FIG. 1. Disease outcomes for NHP (three NHP per treatment group) infected with 5×10^7 PFU of MPX and treated with either vehicle alone or ST-246 administered at 3, 10, 30, or 100 mg/kg/day starting at day 3 postinfection. (a) Virus level in tissues 3 dpi and just prior to initiation of drug treatment. (b) Kaplan-Meier survival curve (log-rank test, all ST-246 groups, $P < 0.001$). (c) Maximum viral DNA by treatment and day postinfection. Bars, means; triangle, individual values (for 100-mg/kg ST-246-treated group, $P < 0.001$; for 30- and 10-mg/kg ST-246-treated groups, $P < 0.01$; for 10-mg/kg ST-246-treated group, $P < 0.05$). (d) Maximum lesion count by treatment group. Bars, means; triangles, individual values (for all ST-246-treated groups, $P < 0.001$).

extensive MPX infection of major tissues, as demonstrated by the level of virus in tissues 3 dpi (Fig. 1a). At the time of ST-246 treatment, one-third of the NHP had viral lesions.

All animals receiving vehicle alone either died or required euthanasia because they were moribund during the study period of 33 days, while all animals receiving ST-246 survived. A Kaplan-Meier survival curve (Fig. 1b) showed a significant difference between the vehicle-treated group and all dosing groups ($P < 0.001$); the maximum viral loads and the maximum poxvirus lesion counts per treatment dose for the NHP infected with MPX were significantly reduced compared to those for the NHP in the vehicle-treated group (Fig. 1c and d). One of the NHP in the vehicle-treated group died on day 11 postinfection, while the other two NHP in the vehicle-treated group were euthanized on days 13 and 14 postinfection, respectively, because they became moribund. Each of the animals receiving ST-246 survived the full study.

Viral load and lesion development were quantified daily (Fig. 2). All doses of ST-246 significantly decreased ($P < 0.001$, ANOVA) the amount of viral DNA present compared to that in the vehicle-treated animals beginning on 5 dpi. At the end of the 14-day treatment, the viral loads in the ST-246-treated groups showed a linear dose-response, with all treatment groups showing a significant reduction in the level of virus replication of more than 1,000-fold compared to that in the vehicle-treated group. There was some variability in the viral DNA levels in the blood of the ST-246-treated animals, especially later in the infection process. The reason for this variability is not known but could be caused by the presence of circulating noninfectious DNA shed during immune-mediated clearance of the infected tissue. Lesions were first observed on days 3 to 4 following inoculation with MPX for all animals. Lesions were observable first in the mouth and on the head and spread to the remainder of the body by 5 to 8 dpi. Animals treated with all doses of ST-246 had significantly fewer ($P < 0.001$, ANOVA) poxvirus lesions than animals treated with vehicle did.

Determination of ST-246 oral dose equivalency between cynomolgus monkeys and adult humans. To estimate the human dose required to achieve a similar systemic exposure in NHP, the pharmacokinetics of ST-246 in cynomolgus monkeys under fed conditions were evaluated following single and repeat oral dosing daily for 14 consecutive days. A noncompartmental analysis was applied to the plasma concentration values of the individual NHP to determine the C_{max} of the drug and the level of systemic exposure to the drug (AUC_{0-24}). The estimated pharmacokinetic parameters are presented in Table 1. These data were used to select the proposed human dose, as described below.

Ethical and other logistical constraints prevent assessment of the efficacy of ST-246 in humans. The dose selected for use in the animal efficacy and safety assessments was based upon

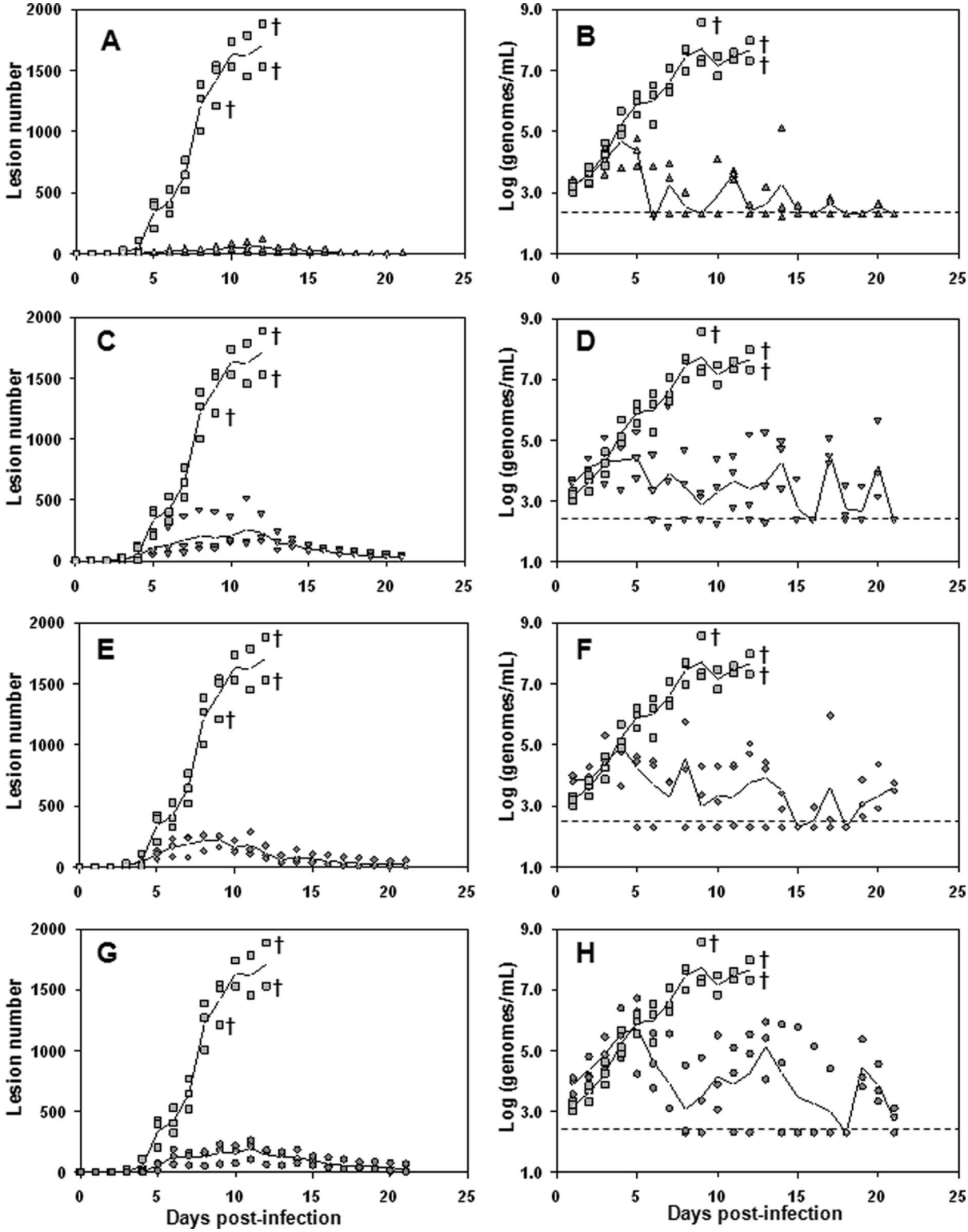

FIG. 2. Average lesion number and viral load of NHP (three NHP per treatment group) infected with 5×10^7 PFU of MPX and treated with either vehicle alone or ST-246 administered once per day for 14 days starting at day 3 postinfection. Viral lesion numbers (A, C, E, and G) and DNA levels (B, D, F, and H) were measured for animals treated with vehicle (squares) or ST-246 at 100 mg/kg (A and B; triangles), 30 mg/kg (C and D; inverted triangles), 10 mg/kg (E and F; diamonds), or 3 mg/kg (G and H; circles). Each symbol represents the data for an individual animal. The data from the vehicle-treated animals is included in each panel for comparison purposes. The geometric mean is shown as a solid line through the data points. The lower limit of quantification for DNA levels measured by quantitative PCR assay is shown as a black dashed line. All vehicle-treated animals either died or were euthanized (daggers) due to MPX infection between day 11 and 14 postinfection. A one-way ANOVA model generated a P value of <0.001 for all treatment groups compared to the results for the vehicle-treated control group.

TABLE 1. Estimated pharmacokinetic parameters in NHP following single and repeat oral administration of ST-246 under fed conditions

Dose (mg/kg)	Dose (mg/m^2)	Day	C_{max} (ng/ml)		AUC_{0-24} (ng · h/ml)	
			Mean ± SD	Range	Mean ± SD	Range
10	120	1	1,011 ± 367	734–1,700	13,736 ± 3,733	8,952–20,218
		7	1,025 ± 295	644–1,550	12,640 ± 5,040	7,110–21,627
		14	1,081 ± 143	888–1,260	13,504 ± 2,312	9,325–15,817
20	240	1	1,265 ± 172	1,070–1,480	18,358 ± 2,444	14,864–20,527
		7	NA[a]	NA	NA	NA
		14	NA	NA	NA	NA
30	360	1	1,152 ± 506	746–1,880	18,064 ± 8,513	10,273–29,466
		7	1,508 ± 611	978–2,670	20,736 ± 8,079	12,247–32,801
		14	1,191 ± 374	669–1,740	15,803 ± 6,453	7,756–27,027

[a] NA, repeat dosing was not conducted at this dose level.

the pharmacology and toxicology data from nonclinical studies. The process used to select the dose (including dose escalation) for humans in the phase 1 clinical safety study was based on the no observed-adverse-effect level (NOAEL) for the NHP, which was used to determine the equivalent dose in humans by the common body surface area dose conversion factors, in accordance with FDA draft guidance for establishing the safe starting dose for humans. In NHP, a dose of 10 mg/kg/day (120 mg/m^2) for 14 days resulted in levels of blood exposure comparable to the levels attained in humans administered a 400-mg (240-mg/m^2) dose in the fed state in the two phase 1 studies that have been completed (8). These dose levels are well below the multiple-dose NOAEL of 2,000 mg/kg/day (6,000 mg/m^2) in mice and the multiple-dose no-observed effect level of 300 mg/kg/day (3,600 mg/m^2) in NHP (8).

In addition to this nonclinical safety and efficacy information, the dose ranges for use in future clinical studies are selected on the basis of the safety and pharmacokinetic results from completed single- and repeat-dose phase 1 studies with ST-246 and humans. A single oral dose of 500 mg (AUC_{0-24}, 9,879 ng · h/ml), 1,000 mg (AUC_{0-24}, 21,088 ng · h/ml), and 2,000 mg (AUC_{0-24}, 24,548 ng · h/ml) in fasted subjects and 1,000 mg (AUC_{0-24}, 34,056 ng · h/ml) in fed subjects was generally well tolerated by a total of 31 actively treated male and female healthy volunteers (8). The single-dose plasma pharmacokinetic data suggest drug accumulation with the administration of a single daily dose to humans. Hence, the dose levels (250 mg, 400 mg, and 800 mg) selected for use in the second multiple-ascending-dose study with humans were chosen to estimate the accumulation index and to bracket potential therapeutic doses (Table 2). The pharmacokinetic parameters from this study revealed that steady-state concentrations were achieved by day 6, with 16% to 21% drug accumulation; saturable absorption occurred at the 800-mg/day dose level; and the urinary excretion of ST-246 was very low (<0.03% of the dose) (unpublished data). In addition, the levels of exposure in a single child (age, 28 months) receiving ST-246 under an emergency investigational new drug application approval based on body surface area calculations proportional to the body surface area for adults were monitored and have yielded preliminary information (15).

By comparing the plasma exposure data obtained from NHP and human clinical pharmacokinetics, as shown in Tables 1 and 2, respectively, the level of exposure achieved with a 10-mg/kg (120-mg/m^2) dose in NHP is comparable to the level of exposure achieved with a 400-mg (248-mg/m^2) dose in humans under fed conditions, as shown in Table 3.

TABLE 2. Estimated pharmacokinetic parameters in humans following single and repeat administration of oral doses of ST-246 under fed conditions

Dose (mg/day)	Dose (mg/kg)[a]	Dose (mg/m^2)	Day	C_{max} (ng/ml)	AUC_{0-24} (ng · h/ml)
250	4.2	155	1	985	9,101
			6	1,212	11,892
			21	1,101	10,083
400	6.7	248	1	1,392	13,146
			6	1,298	15,432
			21	1,457	16,182
800	13.3	492	1	2,279	20,959
			6	2,337	23,352
			21	2,437	22,684

[a] A 60-kg human was assumed.

DISCUSSION

On the basis of the data from the study of the efficacy of ST-246 against MPX by use of a model with NHP and survival as the primary end point, an oral dose of approximately 3 mg/kg/day (36 mg/m^2) given for a period of 14 days starting at 3 dpi in nonfasted NHP conferred 100% protection from death, while an oral dose of approximately 10 mg/kg/day (120 mg/m^2) not only protected the animals from death but also significantly reduced the levels of viremia and the lesion counts.

TABLE 3. Comparison of NHP and human pharmacokinetic parameters for ST-246 under fed conditions after administration of a single dose

Species	Dose (mg/kg)[a]	Dose (mg/m^2)	C_{max} (ng/ml)	AUC_{0-24} (ng · h/ml)
Monkey	10	120	1,011	13,736
Human	6.7	248	1,392	13,146

[a] A 60-kg human was assumed.

Because 3 mg/kg was the minimum efficacious dose in NHP and on the basis of the plasma exposure in NHP and humans, the extrapolated dose in humans is about 80 mg. Given the variability in exposure levels in NHP and humans in the fed and fasted states and also the variation in interindividual human weights, the proposed human therapeutic dose of 400 mg/day (233 mg/m^2) in the fed or fasted state is anticipated to provide exposure levels comparable to those achieved with a dose of 10 mg/kg (a dose threefold higher than the minimum efficacious dose of 3 mg/kg) in NHP that was protective in the model of orthopoxvirus disease in NHPs. The primate equivalent of the proposed human ST-246 dose provides protection in a monkeypox primate model and suggests that ST-246 will be an effective oral treatment for smallpox and monkeypox after a clinical diagnosis is made on the basis of the presence of pox lesions.

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