Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Oral Tecovirimat for the Treatment of Smallpox

Online Appendix – Supplemental Materials

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ANIMAL MODELS

Monkeypox/NHPs

During the first round of studies characterizing the MPXV infection model in NHPs, respiratory inoculation routes (intratracheal, intranasal, aerosol)[1,2] were able to produce a lethal infection in some animals with lethality primarily due to lung complications. However, the intravenous infection model[3] which generated a systemic disease similar to late stage smallpox was most reproducible and consistently lethal. Since the development of a therapeutic countermeasure relies on the state of the disease at time of treatment, and the intravenous model, in contrast to respiratory challenge models, resembles the infection at late stage human smallpox SIGA has used this model for product evaluation. Intravenous (IV) inoculation of NHPs with 5×10^7 pfu monkeypox virus produces a systemic lesional disease with mortality rates essentially ~100%.

The IV challenge model in NHPs represents a severe challenge model that resembles a natural smallpox infection beginning at the prodromal, or virus dissemination stage (Figure S9). Disease onset is rapid following IV inoculation with virus seeding the reticuloendothelial system to establish productive infection. Obvious clinical symptoms appear between Day 3 and 4 post-infection with animals exhibiting a generalized vesiculopustular rash and small numbers of distinct lesions appearing on the head, legs and mouth. Lesions appear on other parts of the body by Day 5 and increase in number over time. Other characteristics of disease include fever, elevated white blood cell count, lymphadenopathy, splenomegaly, and pulmonary edema. The disease progresses rapidly with death occurring between 7-15 days post-infection in greater than 99% of the animals. On average, the viral DNA copy number in the blood following monkeypox infection increased from 10^3 copies/mL at Day 1 post-infection to a peak of ~10^7 copies/mL by Day 12 post-infection. Both viral DNA copy number in the blood and lesion number correlated with mortality ($P < 0.001$). Higher Viral DNA copy number in the blood ($P < 0.001$) (but not higher lesion count) correlates with a shorter time to death. Lesions are detected by Day 3 or 4 post-inoculation and increased over time reaching a peak (Average >1500 lesions per animal) by Day 11. Moreover, viral DNA copy number in the blood correlated with lesion total ($R = 0.77$; $P < 0.001$) providing quantifiable endpoints to predict disease severity. Hematological abnormalities and changes in blood chemistry become evident by Day 7 post-infection. While changes in these values were consistent with severe orthopoxvirus infection, variability from animal to animal and between experiments, made these values less reliable predictors of disease severity.

Lesion Formation – Skin lesions are the hallmark of human smallpox infection and formed the basis of clinical diagnosis. Skin lesions or pocks, are formed by infection of the capillary epithelium of the dermal layer of the skin by circulating virus during the secondary viremia phase of infection. The lesions that develop are similar in appearance in humans infected with smallpox and non-human primates (NHP) infected with monkeypox virus providing a link between human disease and NHP models of orthopoxvirus infection.

A comparison of the pathophysiology of skin lesion formation from smallpox patients, a monkeypox patient, and NHPs infected with MPXV reveals a remarkable similarity in the histological changes associated with lesion formation. The process of lesion development in all cases begins with the productive infection of endothelial cells in the blood vessels within the papillary dermis. Infection leads to dilatation of the capillaries followed by endothelial swelling of the dermal blood vessel walls. Virus spreads to the overlying epithelium and replication in this

tissue initiates the characteristic rash associated with orthopoxvirus infection. This process results in the formation of a papule that is characterized by swollen, degenerating cells in the middle layer of the epidermis. Virus-induced inclusion bodies or Guarnieri bodies can be detected in the cytoplasm of degenerating cells. The nuclei of these cells condense and ultimately disappear due to lysis. The cell membranes rupture giving rise to multiloculated vesicles, which increase in size as more cells become involved. The basal layers of the surrounding vesicles proliferate and may be twice the size of the unaffected epidermis giving rise to the elevated border surrounding the vesicle. This appears as a raised area on the skin surrounded by unaffected skin.

The pustule is formed by infiltrating polymorphonuclear granulocytes that degenerate within the vesicle and their nuclei fragment, forming a cavity at the center of the lesion. Umbilication, a hallmark of orthopoxvirus lesions, is thought to be caused by swelling of the cells surrounding the cavity through edema and reticulation and proliferation of the basal layers surrounding the vesicles. The proliferating cells surrounding the lesion encroach upon the cavity to form the raised edges of the lesion with a depression in the center as fluid drains from the cavity. During the healing stage, proliferating cells from the surrounding lesion encroach upon the cavity to form a parakeratotic cell layer which upon desiccation of the cavity initiates the encrustation process. The parakeratotic cell layer increases in density as the lesion heals. Finally the scab is shed revealing newly formed epidermis.

The appearance and extent of lesion formation provides a useful marker of orthopoxvirus disease severity and links human smallpox to orthopoxvirus disease in NHP. Lesion development requires systemic virus spread and productive infection of the capillary epithelia. Antiviral therapies that reduce lesion formation in NHP models of orthopoxvirus disease will likely be effective treatments for human smallpox.

Viremia – In the monkeypox/NHP model, the level of circulating viral DNA genomes in the blood, measured by qPCR, correlates with disease severity[4,5]. While plaque assay can be used to measure infectious virus, interfering substances found in the blood complicate the technical steps required to accurately measure infectious virus making PCR a more reproducible and reliable assay to measure viremia by the presence and number of viral genomes. In humans, information regarding the level of variola virus DNA in blood from smallpox patients is unavailable since PCR technology did not exist prior to the eradication. However, infectious virus has been cultured from the oral mucosa of smallpox patients during the prodromal phase of infection prior to the onset of lesions suggesting that patients contained high levels of circulating virus[6]. Thus, quantifying viral DNA copy number in the blood by qPCR is a good surrogate of active viremia and of disease severity in animal models of orthopoxvirus infection and provides an indirect link to smallpox in humans.

Mortality - Death is often a primary endpoint in animal models of severe orthopoxvirus disease. The cause of death in these experimental systems is not well understood and has been attributed to severe bronchopneumonia, multi-organ failure, and septic shock syndrome. In humans, mortality due to smallpox has been attributed to bronchopneumonia and toxemia, a poorly defined clinical syndrome that resembles bacterial septicemia[6]. The systemic nature of the viral infection suggests that many causes may contribute to mortality since replicating virus can be isolated from many tissues late in infection. The preponderance of data, in both animal models and human experience, suggest that the severity of the disease is a product of the level of viral replication and any therapy that can reduce that viral replication may improve patient outcome.

In SIGA sponsored efficacy studies, nearly all MPXV-infected untreated NHPs succumbed to disease (95%, 19/20), highlighting the robustness of this model used in our studies. The intravenous MPXV challenge model results in a systemic infection that imposes a severe challenge on many organ systems. In the interest of humane treatment most animals are euthanized prior to actual death by disease. Criteria for early euthanasia in moribund animals were based on the severity of the clinical observations (level of moribundity/lethargy, inability to eat/drink) in combination with significant weight loss, severity of pock lesions, sustained elevated body temperature or hypothermia.

Trigger for Therapeutic Intervention - In evaluating which NHP model for human smallpox is most appropriate for demonstrating the efficacy of antiviral therapeutics, a number of parameters have to be considered: First, it is important to determine the stage of disease progression during the course of human smallpox at which treatment would no longer be considered prophylactic, but rather is considered therapeutic. Since SIGA is developing tecovirimat for a therapeutic indication, the biomarkers and triggers used for medical intervention in the animal model to the appropriate corresponding symptoms in human smallpox that are definitive of disease must be linked. Since smallpox was eradicated from the human population prior to the development of diagnostics using modern molecular biology, physicians relied on years of observation and clinical experience to diagnose the disease. The most distinctive and unambiguous identification of smallpox was the appearance of a synchronous, centrifugal rash that progressed from an enanthema/exanthema to pustules beginning a few days after severe fever. The nature and progression of this rash was used to clinically differentiate smallpox from other rash-like diseases such as chicken pox. In the intravenous challenge NHP model, lesions containing virus appear 3-4 days post-challenge and continue to increase in number and progress through stages typical of human smallpox until death. This symptom provides the most direct and obvious link between MPX disease in NHPs and smallpox disease in humans. Considering the striking similarity between human smallpox lesions and monkeypox lesions and the likelihood that, at least for index cases in a human smallpox outbreak, smallpox would not be diagnosed until the presentation of lesions, it is entirely fitting that in this model, the trigger for treatment would be the first appearance of lesions.

In the event of a suspected outbreak of smallpox it is likely that index cases would not be diagnosed or treated until after pock formation. With the development of modern technologies, a definitive diagnosis of smallpox could be made (particularly in those suspected of exposure) prior to pock formation and probably as early as the prodromal fever (when secondary viremia would be easily detected by qPCR). This suggests that by current standards, treatment started any time post-diagnosis should then be considered “therapy”. This argument is made in order to suggest that in evaluating anti-smallpox therapeutics in animals, therapy could be initiated with the onset of fever when viremia is detectable by qPCR but certainly after the development of pock lesions. This also highlights that an acceptable animal model must be characterized by post-exposure fever and viremia and preferably followed by the development of a significant number of skin lesions.

Rabbitpox/Rabbit

The 16 week old rabbit infected intradermally with 1000 pfu is a very robust model with 100% mortality, if untreated, in all SIGA-sponsored studies. Following infection, the time to death ranges from 6 to 10 days post-inoculation. Clinical signs consistent with rabbitpox infection (see Figure S10) are observed including changes in respiration rates and redness, edema, scabbing

and necrosis at the injection site. Individual body temperatures relative to baseline established in quarantine are significantly increased typically beginning on Day 3 or 4 and remain elevated until just prior to death/euthanasia at which point animals experience a rapid drop in temperature and many become hypothermic. Infected animals may display secondary lesions at some time between 4 and 10 days post-inoculation, with back lesions being the most prevalent from days 5 through 10 post-infection. Ear lesions may be observed prior to death but only in a fraction of animals. In SIGA and BARDA sponsored studies, weight loss is variable following infection as some animals may maintain or gain weight while others may lose weight. Rabbitpox infection was confirmed post-mortem by pathological analysis (gross and histological) and by qPCR amplification of rabbitpox DNA in nine tissues (spleen, kidneys, heart, lungs, liver, brain, skin, tongue, and ear) examined from days 6 through 10 post-challenge. Histological findings included necrosis, inflammation, hemorrhage, and/or edema. The timing of disease onset, magnitude of the symptoms, and time to death were very similar in both 9 and 16 week old rabbits.

Lesion Formation – Natural history studies to characterize the course of disease in the intradermal challenge model showed that the disease course was similar to human smallpox with an initial primary infection, fever and virus dissemination in the blood, and a systemic infection characterized by external lesions distributed widely. The use of uninfected controls demonstrated that pock lesions associated with infection could be detected as early as day 4 on the shaved backs of rabbits. Seventy-five to ninety-five percent of the rabbits developed back lesions by Day 6 post-infection. Because of the rapid disease course in rabbits the majority of the animals (67-94%) did not exhibit back lesions until day 5 post-challenge, approximately one day prior to death. Not all of the RPXV-infected rabbits develop back lesions before death. Secondary lesions were identified on other body sites such as the eye, nose, mouth, and ano-genital area but were not detected in the majority (50-59%) until Day 6 post-infection. The rapid progression of the disease also meant that most, but not every, rabbit developed easily detectable secondary lesions prior to death. Although lesions could be used as a trigger for treatment, the observation that most, but not all rabbits display lesions means group sizes would have to substantially larger to evaluate efficacy with this trigger.

Viral Load – Another aspect of the intradermal RPXV model in rabbits that is consistent with the pathogenesis of variola virus in human smallpox is the pattern of virus replication and spread within the host. As illustrated in Figure S9, the onset of the pre-eruptive fever and headache in smallpox is associated with a secondary viremia, which is followed a few days later by the development of a focal eruption on the mucous membranes and skin. Similarly, SIGA-sponsored studies have demonstrated that at the time fever is evident following intradermal RPXV infection, viral DNA is detectable in the blood by qPCR. Blood draws for qPCR analysis demonstrated that 100% of the rabbits had detectable levels of RPXV DNA above the LOD (limit of detection) at the time of fever became evident. In all the studies, viral copy number continued to rise as the disease progressed and high levels of quantifiable RPXV DNA (10^5 - 10^9 genome copies/mL or blood) was observed in all RPXV-infected rabbits at the time of death. Importantly, no mock-infected animals showed levels of RPXV DNA above the LOD at any time throughout the studies. These studies clearly demonstrate the consistency and reproducibility of the correlation between the onset of a clinical sign of disease (i.e., fever) and a biomarker (viral load) in the intradermal RPXV model.

Mortality – The cause of death or humane euthanasia in RPXV-infected rabbits is generally attributed to severe respiratory distress. Respiratory symptoms are first evident as a decrease in the resting respiration rate of the animals. This coincides with observations of constriction and

frank lung sounds. At 7 or 8 days p.i., most animals exhibit severe respiratory symptoms, including profuse mucopurulent discharge from the nostrils, often tinged with blood, and very slow labored breathing. At this stage, the animals frequently exhibited open-mouth breathing. Upon necropsy, the lungs of most RPVV-infected rabbits were dark and marbled, displaying large hemorrhagic regions. In SIGA sponsored studies, RPXV was 100% lethal in all untreated animals (100%, 18/18). Although the intradermal challenge model causes a systemic disease with virus present in many organs, the humane treatment of animals requires the development of euthanasia criteria predictive of outcome to shorten the suffering of the infected animals. The same criteria applied to the NHP are not transferrable to the rabbits as they are not as interactive and some criteria for clinical scoring (i.e., interaction with veterinarian staff) are not readily transferrable. Observations made during the natural history studies to develop the model determined that specific observations provide a quantifiable measure of animal distress. These were used to prospectively define criteria for pre-emptive euthanasia for each study. The criteria were continually refined to include those most predictive of outcome, reproducible, and quantifiable.

Trigger for Therapeutic Intervention - The three most reproducible biomarkers associated with infection were fever (usually first observed by day 3-4 post-challenge), rabbitpox virus genomes in the blood (usually detected by qPCR by day 2-3 post-challenge) and lesions (first observed day 5 post-challenge or after). The drawbacks to using lesions as a trigger were discussed above. The studies supported by SIGA to evaluate tecovirimat used the combination of significant increase in body temperature (SIBT), and viremia (positive quantitative polymerase chain reaction (qPCR) detection of RPXV genomes in blood) as a reliable and conservative indicator of established disease following a challenge with a lethal dose of RPVX Utrecht. Fever was defined for each animal as a temperature (^{o}F) reading equal to or greater than two standard deviations above baseline as established prior to viral challenge. Once an animal is identified as having a fever, the fever temperature reading was confirmed by a second reading taken approximately one hour later. Blood samples were then collected within one hour of fever confirmation and analyzed by qPCR assay for confirmation of viremia. In SIGA sponsored pivotal efficacy studies (SR13-025F and SR14-008F), all animals were confirmed qPCR positive coincident with fever confirmation. Given that fever and qPCR positivity is always observed in all RPXV-infected rabbits by Day 4 post-challenge, tecovirimat treatment initiation was synchronized for all animals on Day 4 regardless of earlier observations of fever. That is, even if an animal exhibited fever prior to Day 4, it did not start tecovirimat treatment until Day 4. In SIGA sponsored studies the typical spike in temperature (i.e. fever) that was observed as the first clinical sign of systemic RPXV disease by Day 4 post-infection was used as a therapeutic trigger since it is: 1) objective (measured by subcutaneous transponders), 2) specific (only RPXV-infected, not mock-infected, animals experience fever), 3) uniform (100% of animals experience fever), 4) reproducible (always observed by at least Day 4 post-infection), 5) robust (demonstrated by different investigators at different institutions). SIGA also believes this is a reasonable trigger for therapeutic intervention because it correlates with clinically relevant symptoms seen in human smallpox and considering that disease establishment was additionally confirmed by qPCR detection of viral DNA in the blood, represents a conservative clinical trigger for intervention compared to what will be practiced during a smallpox emergency.

Drug Metabolism and Toxicology in Animals

Drug Metabolism

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Interspecies differences in ADME were considered in determining the human dose. Data from animal and human studies have been compiled and analyzed. When administered orally in both animals and humans, tecovirimat appears to be readily absorbed and the absorption is enhanced in the presence of food. The absolute bioavailability (F_{ab}) values obtained from mice and monkeys were 45% and 50%, respectively. Although no F_{ab} values were determined in humans, tecovirimat was readily absorbed to achieve the C_{max} within 4-6 hours of oral administration and then declined in a bi-phasic profile with an elimination half-life of approximately 19-24 hours. Data in both animals and humans indicate that drug exposures are enhanced in the presence of food. The drug exposure (AUC_{0-24h}) at 30 mg/kg dose was increased by approximately 75% from 14,704 to 25,742 ng.hr/mL while the C_{max} was increased by approximately 160% from 1,148 to 2,983 ng/mL in monkeys which is the species used to support the clinical dose. Similarly, the AUC_{0-24h} at 600 mg twice daily dose in humans was increased by approximately 60% from 21,088 to 34,056 ng.hr/mL. Multiple-day dosing in humans results in drug accumulation with the steady state drug exposures at approximately 50% (AUC_{0-24h}) and 40% (C_{max}) higher from those of the first dose. However, no or slight accumulation of drug has been observed in monkeys.

Drug distribution utilizing radioactive labeling has been investigated in mice. Tecovirimat appears to be systemically distributed in mice and radioactivity was eliminated within 168 hours (the last time point observed) from most of the tissues with only a trace amount detected in the bone marrow and liver.

In vitro metabolic stability studies using cDNA expressed human cytochrome P450 (CYP) enzymes, human hepatocytes, and liver microsomes showed that tecovirimat was not a substrate of major CYP enzymes. This is supported by human studies, demonstrating that tecovirimat is extensively metabolized by amide hydrolysis into metabolites M4 and tri-fluoromethyl benzoic acid (TFMBA). Based on clinical data, M4 is presumably metabolized further via deamination process to form the metabolite M5. Tecovirimat and M4 are further metabolized by direct glucuronide conjugation prior to excretion in urine. At steady state, TFMBA constitutes the highest level of exposure in plasma (AUC of 70% of total exposure), whereas the M4 exposure was 10% of total exposure. M5 constitutes only a minor fraction of total exposures (6%). The metabolites M4, M5, and TFMBA, were also identified in mice and monkeys following oral administration of tecovirimat at 1,000 and 300 mg/kg once daily, respectively, for 14 days. Although the plasma ratios are different in different species, these metabolites appear well tolerated in both animals and humans. Unlike tecovirimat, *in vitro* data demonstrates that these metabolites do not possess the pharmacological activity (i.e. they do not have anti-orthopoxvirus activity). Therefore the presence of these metabolites should not interfere with the extrapolation of the dose-response between animals and humans.

Excretion data from a human study showed that approximately 95% of the radiolabeled material was recovered in urine and feces over the 192 hour post dose period, with approximately 73% of the radioactivity administered being recovered in urine and 23% being recovered in feces. In urine, tecovirimat glucuronide and M4 glucuronide conjugates were the most abundant

radioactive components accounting for approximate means of 30% and 34% of the dose, respectively. Only a trace amount of unchanged tecovirimat and M4 were detected in urine. In feces, tecovirimat was the predominant component of the excreted radioactive material and accounted for approximately 16% of the dose. The fact that only a limited amount of tecovirimat is being excreted in feces and a large portion of drug is excreted in urine as metabolites indicates that the metabolic clearance is the major route of tecovirimat elimination in humans.

PROTEIN BINDING CHARACTERISTICS

Differences in protein binding characteristics between animals and humans also should be considered, because only free drug, or the unbound fraction, is pharmacologically active. If the protein binding characteristics in the selected species differ from those in humans, comparison of free drug exposures will be relevant for dose selection.

Plasma protein binding of tecovirimat in animals and human ranged from 87 to 96% and 77 to 82%, respectively. Based on this data, more unbound drug will be available for pharmacological activity in humans compared to that in animals (Table 2.1.2-1). Because rabbit and NHP models are being used for efficacy support of human clinical dose, the unbound fractions of tecovirimat in rabbits, NHPs, and humans are relevant for dose selection and need to be considered under the Animal Rule. Data indicate that the unbound fraction of tecovirimat in NHP is approximately 11% higher than that in rabbits. The unbound fraction of tecovirimat in humans is approximately 62% and 80% higher compared to that in NHPs and rabbits, respectively.

DRUG-DRUG INTERACTION POTENTIAL

Based on in vitro results, tecovirimat is not metabolized by major CYP P450 enzymes but is conjugated by several human uridine diphosphate glucuronosyltransferases (UGT). In addition, tecovirimat is not a substrate for common transporters such as P glycoprotein (P-gp), organic anion transporting polypeptide (OATP) 1B1 and OATP1B3, and breast cancer resistance protein (BCRP). This is unlikely to impact tecovirimat dosing in humans.

Tecovirimat did not show inhibition potentials toward major CYP enzymes and common transporters except BCRP in *in vitro* drug-drug interaction (DDI) potential assays. However, tecovirimat may induce certain CYP enzymes including CYP3A4, CYP2B6, CYP2C8, CYP2C9, and CYP2C19. A DDI clinical study was subsequently conducted to evaluate the CYP induction potential. The results of the study indicated that tecovirimat, when administered to subjects, did not have an impact on CYP2B6 and CYP2C9. However it was found to be a weak inducer of CYP3A4 and a weak inhibitor of CYP2C8 and CYP2C19.

Animal Toxicology

The safety margin analysis shows that the highest Cmax values are at least 29.4-fold in mouse and 2.4-fold in monkeys, and the highest AUC values are at least 28.0-fold in mouse and 2.5-fold in monkeys higher than that observed corresponding values after oral administration of a human clinical dose of 600 mg twice daily. These AUC and Cmax levels have not resulted in any significant toxicity across species.

The presence of the three metabolites in humans (M4, M5, and TFMBA) was observed in both mice and monkeys. M4 and M5 exposures in mice and M5 exposure in monkeys exceeded that

in humans at the recommended clinical dose. TFMBA exposure in humans exceeds those in mice and monkeys; however, this exposure level did not result in any significant adverse events.

The C_{max} ceiling is defined at 5,575 ng/mL based on the central nervous system signals such as salivation, licking and twitching observed in a dog study. This toxic level in dogs is well above the maximum C_{max} value of 4,460 ng/mL obtained in humans from the clinical dose of 600 mg twice daily.

Overall, the nonclinical toxicology of tecovirimat has been well characterized. Sufficiently large safety margins were established between the NOAELs/NOELs generated in animal studies and the recommended human clinical dose. The dog is considered to be more sensitive to tecovirimat than any other species tested. Due to the toxicity signal observed in dogs, the proposed human clinical dose exposure is well below the exposure that caused the safety signal in dogs. Therefore, the evidence supports that orally administered tecovirimat at 600 mg twice daily for 14 days is not considered a safety concern in humans.

ANIMAL STUDY METHODS

NHP studies

STUDY AP-09-026G

Title: Double Blind, Randomized, Placebo-Controlled, Repeat-Dose Efficacy Study of the Minimum Effective Therapeutic Dose of Oral ST-246® Polyform I in Cynomolgus Monkeys Infected with Monkeypox Virus

This was a double blind, randomized, placebo-controlled, repeat dose efficacy study of tecovirimat Polyform I in cynomolgus monkeys conducted according to GLP regulations. The study was conducted at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). The statistician randomly selected 27 healthy male cynomolgus monkeys of Mauritius descent (crab-eating macaques – *Macaca fascicularis)* from the USAMRIID colony that had successfully completed quarantine. Animals were screened prior to placement on study to ensure all animals randomized onto study were free of detectable orthopoxvirus-neutralizing antibody levels. Animals were randomized into two iterations (five treatment groups per iteration with three monkeys per group in iteration 1 and two monkeys per group in iteration 2) (Table S1). Two monkeys (one per iteration) were infected to serve as potential replacements and were assigned to the placebo group. Cynomolgus monkeys not previously exposed to any orthopoxvirus were intravenously infected with 5.0×10^7 pfu of Zaire 79 strain of monkeypox on Day 0. Monkeys received tecovirimat at 0 (placebo), 0.3, 1, 3, and 10 mg/kg once daily by orogastric gavage beginning on the day lesions first appeared on an animal (Day 4) and continued every 24±2 hours for 14 consecutive days. This study evaluated a series of decreasing doses (10, 3, 1, and 0.3 mg/kg) plus placebo to determine the non-protective dose of tecovirimat. At least five animals/group were infected. Exposure levels of tecovirimat in the blood that corresponded to the lowest protective dose were evaluated. Survival was evaluated statistically for up to 23 days after infection (although survivors were monitored for up to 48 days) as the primary endpoint. Secondary endpoints included viral DNA levels (measured as time-weighted average, rate of increase and maximum), total lesions (measured as time-weighted

average, rate of increase, and maximum), clinical observations (vital signs, body weights, food consumption, and signs of illness), hematology and clinical chemistry, and gross and microscopic anatomic pathology.

STUDY FY10-087

Title: Evaluation of the Pharmacokinetics of ST-246 in Cynomolgus Macaques Infected Intravenously with Monkeypox Virus

This study was a GLP study designed to evaluate the pharmacokinetics of tecovirimat in cynomolgus macaques (crab-eating macaques, *Macaca fascicularis)* infected via intravenous injection with monkeypox virus. The study was conducted at the Lovelace Respiratory Research Institute (LRRI). All animals were randomized into 4 groups (3 males and 3 females per group) (Table S2). Animals were screened prior to placement on study to ensure all animals randomized onto study were free of detectable orthopoxvirus-neutralizing antibody levels. Tecovirimat (3, 10, or 20 mg/kg) or vehicle was administered by oral gavage beginning 4 days following intravenous MPXV Zaire 79 strain infection (5×10^7 pfu), for a total of 14 days. Animals also received a single dose of tecovirimat or vehicle on Day -10 as a comparator for the pharmacokinetics during infection. Pathogen load analyses, pox lesion enumeration and photography, and clinical observations (including temperature monitoring) were performed to monitor the progression of the monkeypox infection and changes associated with tecovirimat or vehicle administration.

STUDY SR10-037F

Title: Double-Blind Placebo Controlled Study to Evaluate Effect of Delayed ST-246 Treatment on Efficacy Following Lethal Monkeypox Virus Challenge in Cynomolgus Macaques

The study design was a randomized, double blinded, placebo-controlled study of tecovirimat administered orally to cynomolgus monkeys infected intravenously with monkeypox virus (MPXV). The study was conducted at Southern Research Institute (SR). Twenty-one (21) randomly selected healthy male and female cynomolgus monkeys (crab-eating macaqes, *Macaca fascicularis)* were assigned to four groups according to weight and sex (Table S3). Animals were screened prior to placement on study to ensure all animals randomized onto study were free of detectable orthopoxvirus-neutralizing antibody levels. The monkeys were intravenously infected with 5.0×10^7 PFU of Zaire 79 strain of MPXV on Day 0. Animals received tecovirimat at 10 mg/kg by oral gavage beginning on Day 4 (Group 2), 5 (Group 3), and 6 (Group 4) after inoculation and continued to received once-daily doses for 14 consecutive days. To accommodate blinding, Groups 2, 3, and 4 were administered placebo on non-tecovirimat dosing days during the treatment period. Group 1 received placebo only. Throughout the study, clinical observations (depression, weakness, recumbency, dehydration, dyspnea, cough, eating, nasal discharge, ocular discharge, and edema), lesion development, body weight, and body temperature were monitored. Blood was drawn for clinical chemistry, and hematology. Viral load in the blood was evaluated by qPCR at regular intervals throughout the study. Blood for tecovirimat bioanalysis was drawn from each monkey on Day -7 (baseline), approximately 4 hours post-dose on Days 4, 9, and 19. Survival was evaluated statistically for up to 56 days after infection as the primary endpoint. Secondary endpoints include viral DNA levels (measured as time-weighted average, rate of increase and maximum), total lesions (measured as time-weighted

average, rate of increase, and maximum), and clinical observations (vital signs, body weights, food consumption, and signs of illness).

STUDY SR10-038F

Title: Double-Blind, Placebo-Controlled Study to Evaluate Effect of Duration of ST-246 Treatment on Efficacy Following Lethal Monkeypox Virus Challenge in Cynomolgus Macaques

The study design was a randomized, double blinded, placebo-controlled study of tecovirimat administered orally to cynomolgus monkeys (crab-eating macaques, *Macaca fascicularis)* infected intravenously with MPXV. The study was conducted at Southern Research Institute (SR). Twenty-five (25) randomly selected healthy male and female cynomolgus monkeys were assigned to five groups according to weight and sex (Table S4). Animals were screened prior to placement on study to ensure all animals randomized onto study were free of detectable orthopoxvirus-neutralizing antibody levels. The monkeys were intravenously infected with 5.0 x 10^7 PFU of Zaire 79 strain of MPXV on Day 0. Animals received tecovirimat at 10 mg/kg by oral gavage for 3, 5, 7, or 10 consecutive days beginning on Day 4 after inoculation. To accommodate blinding, Groups 2, 3, and 4 were administered placebo on non-tecovirimat dose days during the treatment period. Group 1 received placebo only. Throughout the study, clinical observations (depression, weakness, recumbency, dehydration, dyspnea, cough, eating, nasal discharge, ocular discharge, and edema), lesion development, body weight, and body temperature were monitored. Blood was drawn for clinical chemistry, and hematology. Viral load in the blood was evaluated by qPCR at regular intervals throughout the study. Blood for tecovirimat bioanalysis was drawn from each monkey on Day -7 (baseline), approximately 4 hours post-dose on Days 4, 7, 9, and 11, and on Day 14 (approximately 24 hours after the final dose administration on Day 13). Survival was evaluated statistically for up to 28 days after infection as the primary endpoint. Secondary endpoints include viral DNA levels (measured as time-weighted average, rate of increase and maximum), total lesions (measured as time-weighted average, rate of increase, and maximum), and clinical observations (vital signs, body weights, food consumption, and signs of illness).

Rabbit studies

STUDY SR14-008F

Title: Evaluation of the Dose-Response Relationship between Tecovirimat Plasma Exposure and Therapeutic Efficacy in NZW Rabbits Intradermally-Infected with a Lethal Dose of Rabbitpox Virus

This study was a blinded, placebo-controlled, repeat ascending dose efficacy study conducted following GLP regulations. The study was conducted at Southern Research Institute (SR). Fifty (50, 25 male/25 female) 16-week old New Zealand White rabbits were randomized into 5 groups of 10 animals based on gender and body weight (Table S5). Animals were screened prior to placement on study to ensure all animals randomized onto study were free of detectable orthopoxvirus-neutralizing antibody levels. On Day 0, all animals were challenged intradermally with RPXV at a target dose of 1,000 PFU. On Day 4 post-challenge (a day by which all RPXV-infected animals were exhibiting fever as a therapeutic trigger), all animals started once daily dosing by oral gavage of tecovirimat corresponding to each group's dose level as outlined in Table S5. The daily dosing continued for 14 consecutive days. Following infection and for the duration of the study, animals were monitored for clinical signs of disease, including temperature

and weight changes and appearance of secondary lesions, and survival for up to 30 days. Tecovirimat exposure was determined by plasma bioanalysis on blood samples collected approximately at T_{max} (2 hours ± 15 minutes post-dosing) and at T_{min} (24 hours ± 30 minutes post-dosing) on Days 4, 10, and 17 (sparse sampling corresponding to the 1st, 7th and 14th doses). Blood viral load was determined by real-time qPCR in blood samples collected at the time of fever confirmation, prior to treatment initiation on Day 4, and at regular intervals throughout the study. At any time during the study, animals that display disease symptoms satisfying the prospectively defined euthanasia criteria were euthanized. All surviving animals were euthanized at the end of the study starting on Day 30. At necropsy, gross pathology examination was performed and lung and spleen tissue sections were harvested to evaluate viral load in the tissues by qPCR. In addition, viral load was assessed by plaque assay on blood, lung, and spleen samples collected at the time of unscheduled/scheduled euthanasia.

STUDY SR13-025F

Title: Evaluation of the Impact of Rabbitpox Virus Infection on Oral Pharmacokinetics of Tecovirimat in Male and Female New Zealand White Rabbits

This study was conducted blinded and following GLP regulations. The study was conducted at Southern Research Institute (SR). Twenty-four (24) fifteen (15) week old NZW rabbits were randomized into 3 groups of 8 animals each based on gender and body weight. Animals were screened prior to placement on study to ensure all animals randomized onto study were free of detectable orthopoxvirus-neutralizing antibody levels. On Day -7 (7 days prior to virus infection day), all animals will received a single treatment dose of tecovirimat corresponding to each dose group as illustrated in Table S6. Lithium-heparin blood was collected from all animals once prior to dosing and seven time points following dosing at target time points of 1 hour, 2, 3, 4, 8, 12 (± 15 min) and 24 hours (± 30 min) post-dose. On Day 0, all animals were intradermally injected with 200 uL of DPBS containing 1,000 PFU of RPXV. On Day 4 post-challenge, all animals started once daily dosing by oral gavage of tecovirimat corresponding to each dose group (Table S6). The daily dosing continued for 14 consecutive days. Following infection and for the duration of the study, animals were monitored for clinical signs of disease, including temperature and weight changes and appearance of secondary lesions, and survival for up to 19 days. Blood viral load by real-time qPCR was determined in samples collected at the time of fever observation, immediately following infection and at regular intervals throughout the study. For PK sampling a series of lithium-heparin blood collections were made on the first day of treatment (Day 4 post-challenge); middle of treatment regimen (Day 10 post-challenge), and on the last day of treatment (Day 17 post-challenge). At each PK bleeding day, blood was collected approximately at the following time points: 1hr ± 15 min prior to dosing and 1 hr ± 15 min, 2 hrs ± 15 min, 3 hrs ± 15 min, 4 hrs ± 15 min, 8 hrs ± 15 min, 12 hrs ± 15 min and 24 hrs ± 30 min following dosing. At any time during the study, animals that satisfy prospectively defined euthanasia criteria were euthanized. All surviving animals were euthanized at the end of the study on Day 18 or Day 19. At necropsy, gross pathology examination was performed and lung and spleen tissue sections were harvested to evaluate viral load in the harvested tissues by qPCR. In addition, viral load was assessed by plaque assay on blood, lung, and spleen samples collected at the time of unscheduled/scheduled euthanasia.

SIGA-246-008 INCLUSION-EXCLUSION CRITERIA

Subject Inclusion Criteria

Subjects must meet all of the following criteria:
18 to 80 years old, inclusive
Available for clinical follow-up for the duration of the study
Able and willing to give written informed consent
In good general health without clinically significant medical history; have not been hospitalized for a chronic medical condition in the last 2 years
Able to comply with dietary requirements throughout the study drug dosing period
Adequate venous access for those individuals participating in PK testing
PE and laboratory results without clinically significant findings within the 14 days before receipt of study drug
Agree not to drink alcohol from the beginning of the Screening Period through the completion of the Day 28 (+ 2 days) Follow-up Visit
Agree not to use any nicotine products, including electronic vapor cigarettes, nicotine patches, or nicotine gum, for at least 30 days before the Day 1 Randomization Visit and through completion of the Day 15 Dosing Complete/Early Termination Visit
Agree not to consume caffeine during all study visits, including overnight stays for those subjects participating in the PK testing; sodas, coffee, and tea designated as caffeine-free or non-caffeinated may be consumed on study days; caffeine may be consumed while at home and between study visits
Agree not to receive any immunizations/vaccinations starting from 4 days before study drug dosing on Day 1 through completion of the Day 15 Dosing Complete/Early Termination Visit
Agree not to take herbal products from the beginning of the Screening Period through 7 days after the last dose of study drug; vitamins, antacids, low-dose aspirin, acetaminophen, ibuprofen, and iron supplements are allowed
For Lead-in cohort(s) only: Able and willing to refrain from taking any prescription and nonprescription medications, including herbal products, antacids, vitamins, and iron supplements for a period of 14 days before first dosing and for 7 days after the last dose of study drug
Exceptions: Oral contraceptives, spermicides, non-systemic medications, and medications to alleviate AEs will be allowed. The INC medical monitor should be consulted for use of other drugs.
For women of childbearing potential, a negative β-HCG pregnancy test (serum) at the Screening Visit and a confirmatory negative urine pregnancy test at the Day 1 Visit before randomization and before receipt of the first dose of study drug
If male, subjects must agree not to donate sperm from the beginning of the Screening Period through 90
Meet 1 of the following criteria:
The subject or his or her partner has undergone surgical sterilization
The subject is postmenopausal, defined as 12 consecutive months with no menses without an alternative medical cause
The subject agrees to be abstinent (i.e., heterosexually inactive or women in a religious order)
The subject agrees to consistently use 1 of the following methods of contraception from the beginning of the Screening Period (which he or she has been consistently using for at least 30 days before the first dose) through 30 days after the last dose of study drug:
Condoms, male or female, with a spermicide

Diaphragm or cervical cap with spermicide
Intrauterine device with spermicide
Oral contraceptives or other hormonal methods
Male sexual partner who has undergone a vasectomy at least 3 months before Screening
NOTE: The subject is to be withdrawn from the study if the result of any pregnancy test is positive. A female subject who becomes pregnant during study participation must be promptly withdrawn from the trial. She will be asked for consent to allow her treating physician to provide the sponsor or its designee with any follow-up information regarding the pregnancy and its outcome. If the partner of a male subject becomes pregnant, the partner will be asked for consent to allow her treating physician to provide the sponsor or its designee with any follow-up information regarding the pregnancy and outcome of the pregnancy.

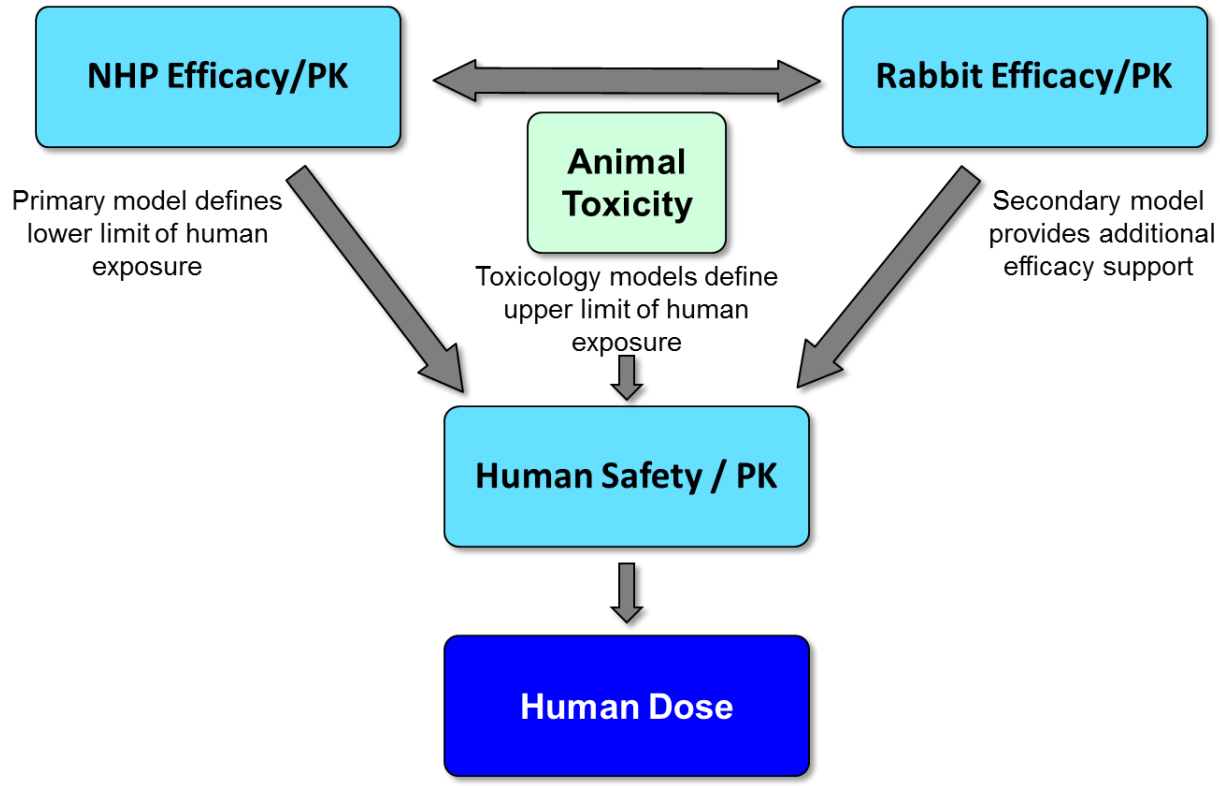
Subject Exclusion Criteria

For inclusion in the study, none of the following exclusion criteria must be met:
Pregnant or breast-feeding or planning to become pregnant before 3 months after the last dose of study drug
Have a history of any clinically significant conditions including:
Asthma treated with oral systemic steroids within the past 6 months
Serious angioedema episodes within the previous 3 years or requiring medication in the previous 2 years
Hypertension that is poorly controlled (repeat readings > 140 mmHg systolic and/or > 90 mmHg diastolic)
History of head trauma resulting in a diagnosis of traumatic brain injury other than concussion
Family history of idiopathic seizures
Have any limitation of activity because of cardiac disease
Have bleeding disorder diagnosed by a doctor (e.g., factor deficiency, coagulopathy, or platelet disorder requiring special precautions) or history of significant bruising or bleeding difficulties with intramuscular injections or blood draws
Be currently (within 7 days [or 5 half-lives, whichever is longer] before study drug administration on Day 1 through the Day 28 (+ 2 days) Follow-up Visit) using any of the following: insulin, anticoagulants, anticonvulsants, methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan, atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, dronedarone, eplerenone, felodipine, nisoldipine, ticagrelor, vardenafil, sildenafil, budesonide, conivaptan, darifenacin, eletriptan, fluticasone, sirolimus, tolvaptan, triazolam, dihydroergotamine, ergotamine, probenecid, or quinidine
Have a malignancy that is active, or a treated malignancy for which there is no reasonable assurance of sustained cure, or a malignancy that is likely to recur during the period of the study
Have a history of seizure, excluding febrile seizures
Have an EEG result graded as an E2 or higher, as determined by the central reader
Have a blood dyscrasia determined to be clinically significant by the investigator
Have a history of drug allergy that, in the opinion of the investigator, contraindicates participation in the trial
Have any medical, psychiatric, or social condition, or any occupational reason, or any other responsibility that, in the judgment of the investigator, would jeopardize the safety or rights of a subject participating in the trial or would render the subject unable to comply with the protocol (includes homelessness)
Have an inability to swallow medication
Have a clinically significant abnormal ECG finding at the Screening Visit, as interpreted by the site investigator

Have an ECG result of QTcF > 450 msec at the Screening Visit
Have participated in a clinical trial within 30 days of study entry or be planning to participate in any experimental treatment study during the study period
Have a history of current drug or alcohol abuse within 1 year. Drug abuse screening will be performed for ethanol, amphetamines, methamphetamines, cannabinoids, opiates, cocaine, and barbiturates
Have received immunizations/vaccines administered starting from 4 days before study drug dosing at Day 1 through Day 14
Have a current clinically significant acute bacterial, fungal, or mycobacterial infection requiring the administration of systemic antibiotics
Have known chronic bacterial, mycobacterial, fungal, parasitic, or protozoal infection with the exception of clinically insignificant dermal infections
Have known hepatitis B or hepatitis C infection, or positive test result for hepatitis B or C at the Screening Visit
Have known human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) illness, or a positive test result for HIV at the Screening Visit regardless of CD4 count
Have a current clinically significant viral infection
Have known clinically significant chronic viral infection (e.g., human T-cell lymphotropic Virus I or II)
Have received treatment with > 20 mg prednisone or equivalent dose or any immunosuppressant or immunomodulatory medication, within the 3 months before Screening; subjects receiving a single instance of treatment for seasonal allergies using a tapering dose of prednisone are exempt from this restriction
Have any of the following laboratory test results within 14 days before the first scheduled dose of study drug:
For Lead-in cohort(s) only: Estimated serum creatinine clearance (Cockcroft-Gault) < 80 mL/min
Estimated serum creatinine clearance (Cockcroft-Gault) < 30 mL/min
Creatinine in males > 1.7 mg/dL and in females > 1.4 mg/dL (1.3 times the upper central laboratory reference range)
Hemoglobin ≤ 10% of the lower central laboratory reference range
White blood cell (WBC) count not within the central laboratory reference range
Absolute neutrophil count < 1,000 cells/mm^3
Platelets not within ± 10% of central laboratory reference range
Alanine aminotransferase (ALT) > 2 times above the upper central laboratory reference range
Aspartate aminotransferase (AST) > 2 times above the upper central laboratory reference range
Alkaline phosphatase > 20% above the upper central laboratory reference range
For all subjects, hemoglobin A1c (HbA1c) ≥ 7.0% (for diabetic subjects, this includes those whose diabetes is diet controlled or who are taking oral hypoglycemics)
Cholesterol ≥ 300 mg/dL and low-density lipoprotein (LDL) ≥ 190 mg/dL
Have a ≥ 20% risk of suffering a major cardiovascular event in the next 10 years based on the National Cholesterol Education Program cardiovascular risk calculator, which can be found on the internet at http://cvdrisk.nhlbi.nih.gov/calculator.asp.
Have been previously enrolled in this or any clinical trial involving tecovirimat.

FIGURES

Figure S1. Human dose selection strategy



Legend: Lower limit of human exposure was delineated based on animal efficacy data in a "Triangulation" process, recommended by an FDA Advisory Committee. Two animal models (monkeypox/NHP and rabbitpox/rabbit) - accepted by FDA for smallpox countermeasure evaluation - were used to evaluate tecovirimat efficacy. PK/PD models for NHP and rabbit species were generated and used to select the primary model (i.e. the model that requires higher exposure of tecovirimat for successful treatment). Upon analysis, the monkeypox/NHP model was designated as the primary model and an extrapolating PK/PD analysis was performed with NHP and human data to define the lower limit of human exposure. Based on the FDA guidance, the acceptable human exposure levels need to exceed those of the NHP model by multiples, yet not approaching exposure levels that may trigger safety concerns. The upper limit of human exposure was delineated based on toxicology safety data. The human dose of 600 mg twice a day was selected as it provides the exposure levels well within the defined upper and lower limits.

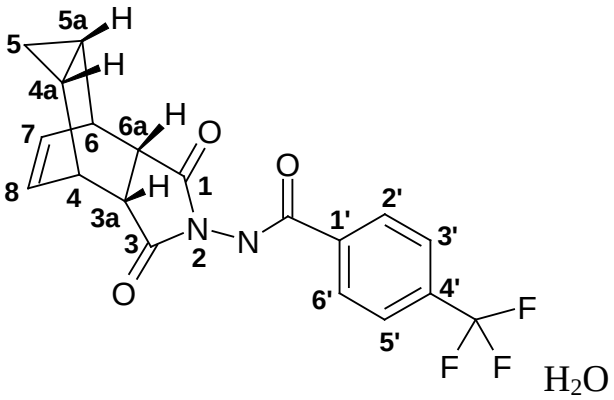
Figure S2. Structure and properties of tecovirimat

Chemical name: Benzamide, *N*-[(3a*R*,4*R*,4a*R*,5a*S*,6*S*,6a*S*)-3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[*f*]isoindol-2(1*H*)-yl]-4-(trifluoromethyl), *rel*-(monohydrate)

CAS #: 1162664-19-8

USAN: Tecovirimat

Molecular Structure:



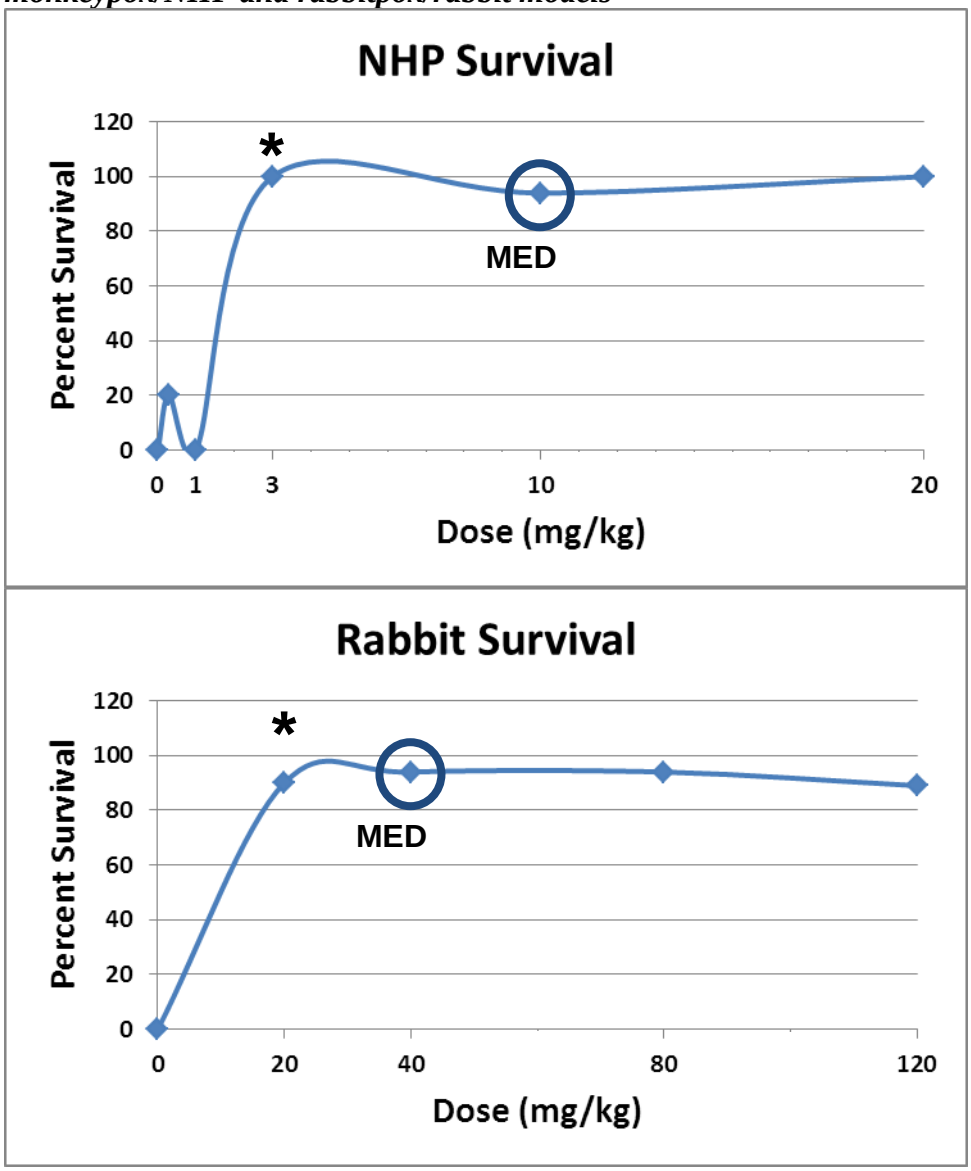
Molecular Formula: $C_{19}H_{15}F_3N_2O_3 \cdot H_2O$

Molecular Weight: 394.33 g/mol

Physical Description: white to off-white powder

pKa: 7.77

Figure S3. Determination of the minimum effective dose (MED) of tecovirimat in the monkeypox/NHP and rabbitpox/rabbit models

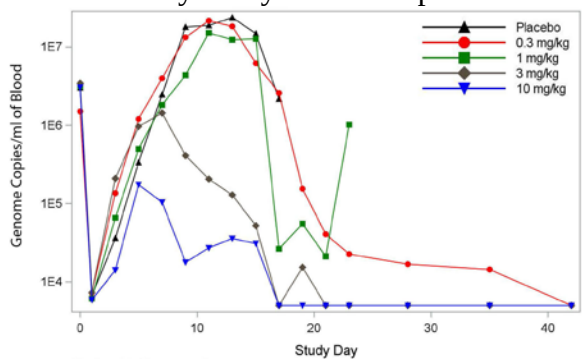


Legend: Crab-eating macaques (NHP) and New Zealand White rabbits were lethally infected with monkeypox virus ($5x10^7$ pfu intravenously) or rabbitpox virus (1000 pfu intradermally), respectively. Tecovirimat treatment, at doses indicated on the "x" axis for each graph, was initiated at four days post-infection when disease was well-established in all animals. Percent survival for each dose is indicated on the "y" axis.

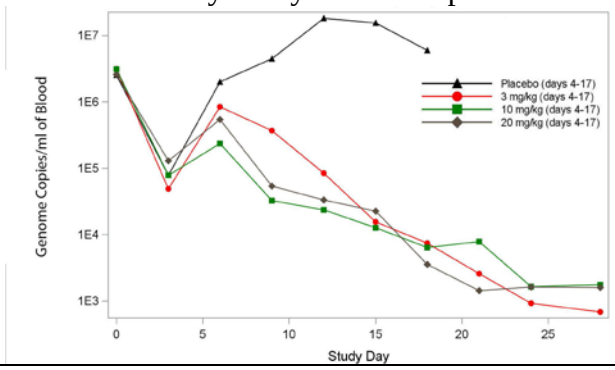
*****Based on the Animal Rule Guidance, a dose of 3 mg/kg in the monkey and 20 mg/kg in the rabbit could be considered the MED. SIGA and FDA have taken a more conservative approach and considered the next higher dose in each species to be the MED for modeling human dose requirements.

Figure S4. Geometric Mean Viral Load in the Blood after MPXV Infection and Treatment with Placebo or Tecovirimat

A. NHP Efficacy Study – Dose Exploration

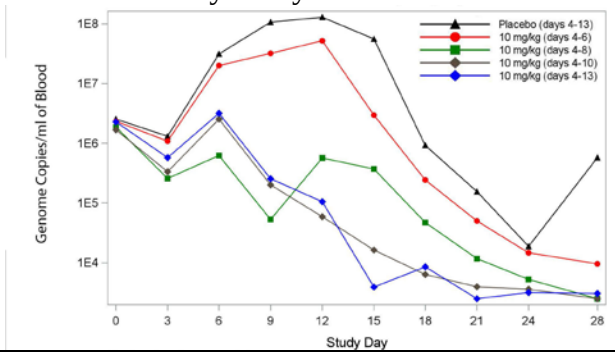


B. NHP Efficacy Study – Dose Exploration/PK



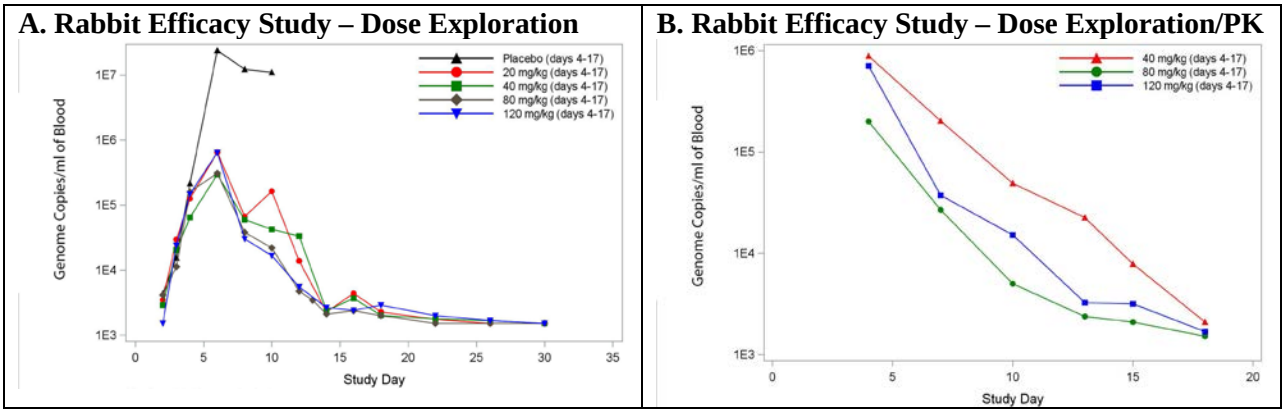
C. NHP Efficacy Study – Dose Delay
Data previous published by Berhanu et al[7]

D. NHP Efficacy Study – Dose Duration



Legend: NHPs were infected with MPXV and treated with placebo or tecovirimat as outlined in Animal Study Methods above and in Figure 1 of the manuscript (Figure 1A-D). Viral load in the blood was assessed by quantitative PCR to determine genome copies per mL of blood for each study day as indicated on the graphs. On Day 0, viral load was assessed immediately following intravenous inoculation to demonstrate infection as intended.

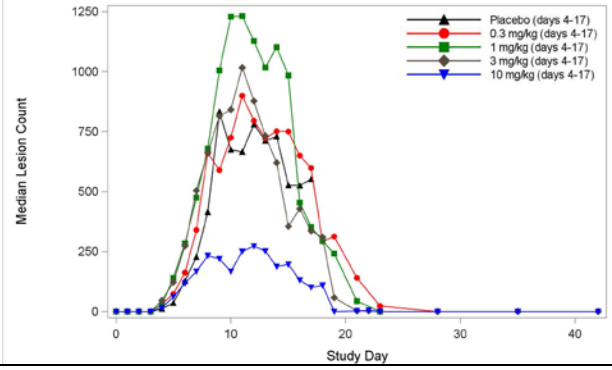
Figure S5. Geometric Mean Viral Load in the Blood after RPXV Infection and Treatment with Placebo or Tecovirimat



Legend: Rabbits were infected with RPXV and treated with placebo or tecovirimat as outlined in Animal Study Methods above and in Figure 1 of the manuscript (Figure 1C and D). Viral load in the blood was assessed by quantitative PCR to determine genome copies per mL of blood for each study day as indicated on the graphs.

Figure S6. Median Lesion Count after MPXV Infection and Treatment with Placebo or Tecovirimat

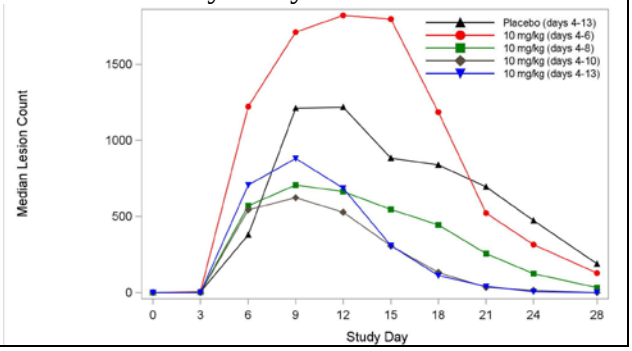
A. NHP Efficacy Study – Dose Exploration



B. NHP Efficacy Study – Dose Exploration/PK (Lesion count was only estimated for this study)

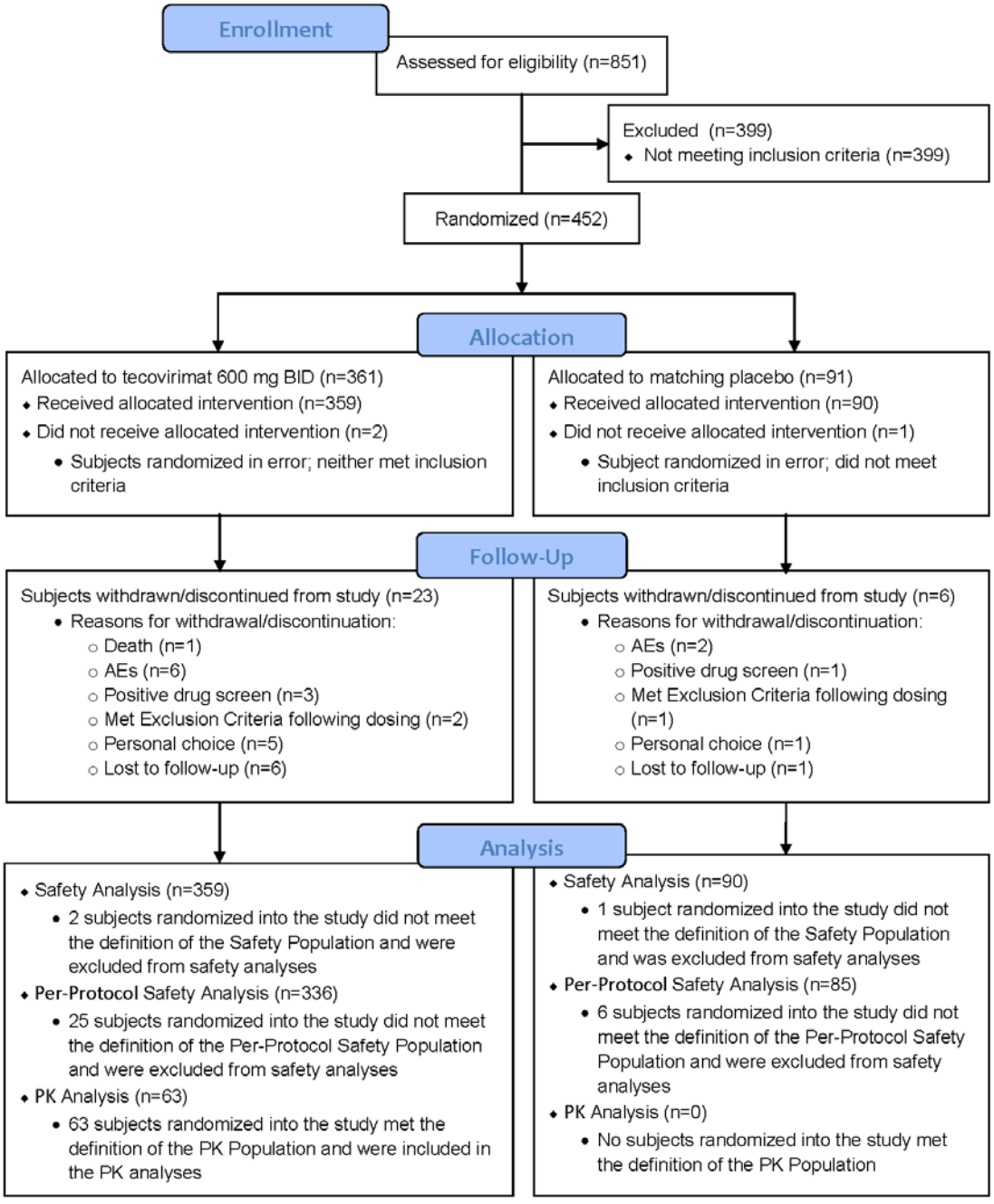
C. NHP Efficacy Study – Dose Delay
Data previous published by Berhanu et al[7]

D. NHP Efficacy Study – Dose Duration



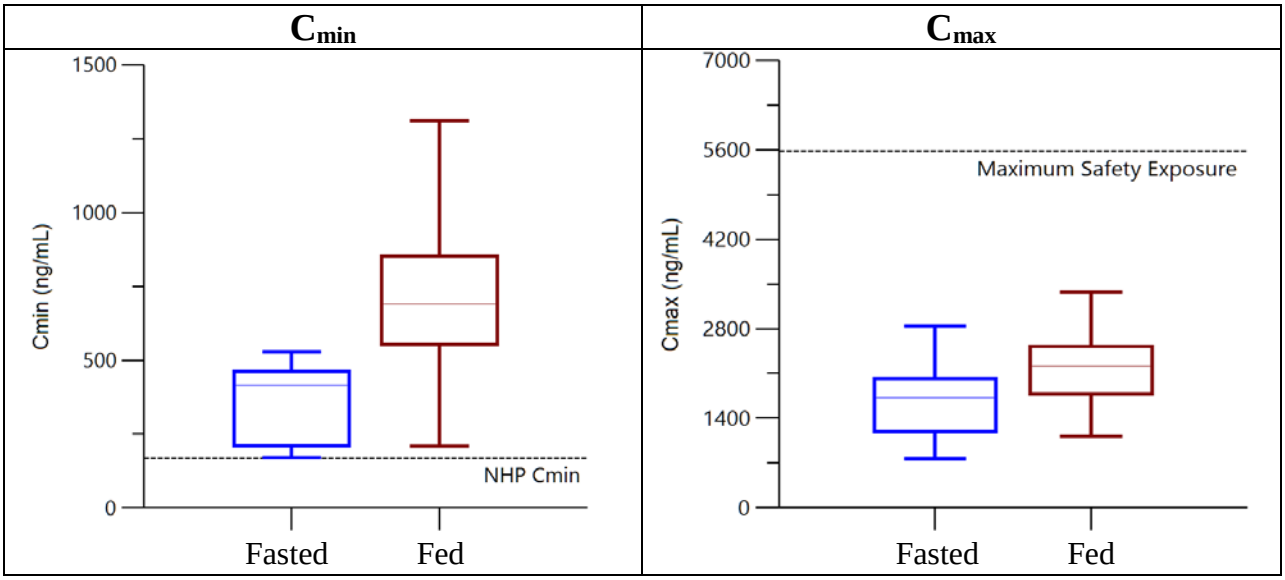
Legend: NHPs were infected with MPXV and treated with placebo or tecovirimat as outlined in Animal Study Methods above and in Figure 1 of the manuscript (Figure 1A and B). Viral load in the blood was assessed by quantitative PCR to determine genome copies per mL of blood for each study day as indicated on the graphs. On Day 0, viral load was assessed immediately following intravenous inoculation to demonstrate infection as intended.

Figure S7. Enrollment and Randomization



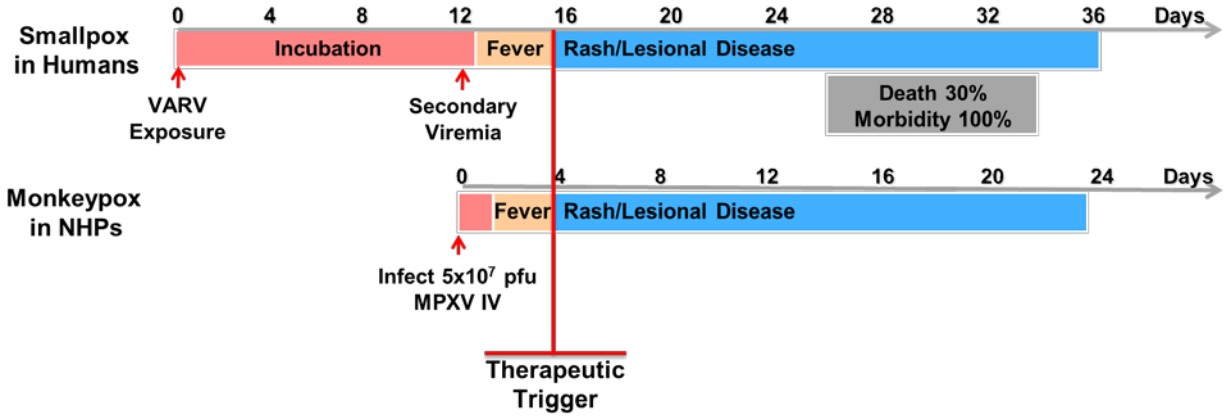
Population Definitions:
Study populations are defined as the following:
1. Intent-To-Treat (ITT) Population: all subjects who were randomly assigned (i.e., a randomization number and randomization date are present in the database).
2. Safety Population: all subjects who received at least 1 dose of study drug.
3. Per-Protocol Safety Population: all subjects who have taken at least 23 of the 28 doses of study drug.
4. PK Population: all subjects who have taken at least 23 of the 28 doses of study drug with at least the last 2 doses of study drug in sequence, have sufficient drug concentrations in plasma, and have no protocol deviations or other circumstances that would exclude the subject from analysis.

Figure S8. C_{min} and C_{max} steady state exposures in humans dosed in the fed or fasted state at 600 mg twice daily for 14 days



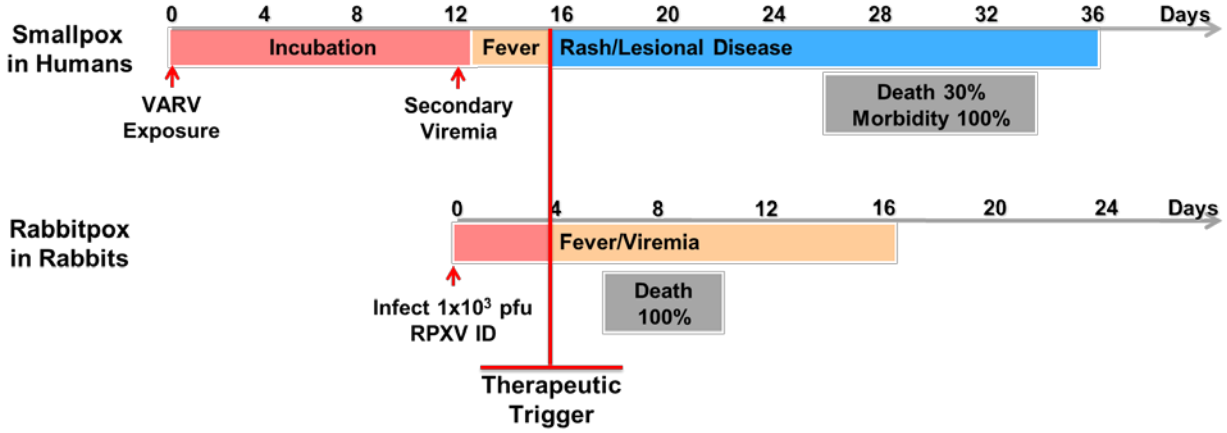
Legend: Shown are the minimum exposure (Cmin) and maximum exposures (Cmax) at steady state in humans dosed in the fed (n=48) or fasted (n=15) state who received 600 mg tecovirimat twice a day at 12 hour intervals. For C_{min}, the average effective minimal concentration (NHP C_{min} of 169 ng/ml) as determined by NHP studies is depicted as a straight line across the graph. The C_{min} was identified as the most critical PK parameter for prediction of efficacy based on NHP PK/PD analysis. For C_{max}, the maximum allowable exposure (Maximum Safety Exposure) as determined in animal toxicology studies (C_{max} of 5575 ng/ml) is depicted as a straight line across the graph.

Figure S9. Comparison of Disease Course in Human Smallpox and NHP Monkeypox



Legend: Disease course is plotted from the day of exposure (day post-infection). Intravenous infection of NHPs with 5 x 10^7 pfu of MPXV results in monkeypox disease that mimics human smallpox very closely from the stage of secondary viremia.

Figure S10. Comparison of Disease Course in Human Smallpox and Rabbitpox in Rabbits



Legend: Disease course is plotted from the day of exposure (day post-infection). Intradermal infection of rabbits with 1 x 10^3 pfu of RPXV results in rabbitpox disease characterized by fever and viremia that mimics human smallpox from the stage of secondary viremia. Lesions are an unreproducible feature of rabbitpox as some animals will die of disease prior to the formation of lesions

TABLES

Table S1. Non-Human Primate Study AP-09-026G Design Overview

Group	Treatment[a] Group	Number of Animals/group (All Male)	MPXV IV Challenge Dose[c]
1	Tecovirimat 10 mg/kg/day, Day 4 – 17 (14 doses)	5	$5X10^7$ PFU
2	Tecovirimat 3 mg/kg/day, Day 4 – 17 (14 doses)	5	$5X10^7$ PFU
3	Tecovirimat 1 mg/kg/day, Day 4 – 17 (14 doses)	5	$5X10^7$ PFU
4	Tecovirimat 0.3 mg/kg/day, Day 4 – 17 (14 doses)	5	$5X10^7$ PFU
5	Placebo Day 4 – 17[b] (14 daily doses)	7	$5X10^7$ PFU

[a]Group 5 received only vehicle (Placebo) from Days 4 – 17. Groups 1 to 4 were administered tecovirimat by oral gavage from Days 4 - 17.
[b] All days listed are relative to monkeypox virus challenge day on Day 0.
[c]All animals were intravenously injected with $5X10^7$ PFU of monkeypox virus in 1 ml volume on Day 0.

Table S2. Non-Human Primate Study FY10-087 Design Overview

Group	Treatment[a] Group	Number of Animals/group (Male/Female)	MPXV IV Challenge Dose[c]
1	Placebo Day 4 – 17[b] (14 daily doses)	6 (3/3)	$5X10^7$ PFU
2	Tecovirimat 3 mg/kg/day, Day 4 – 17 (14 doses)	6 (3/3)	$5X10^7$ PFU
3	Tecovirimat 10 mg/kg/day, Day 4 – 17 (14 doses)	6 (3/3)	$5X10^7$ PFU
4	Tecovirimat 20 mg/kg/day, Day 4 – 17 (14 doses)	6 (3/3)	$5X10^7$ PFU

[a]Group 1 received only vehicle (Placebo) from Days 4 – 17. Groups 2 to 5 were administered tecovirimat by oral gavage from Days 4 - 17.
[b] All days listed are relative to monkeypox virus challenge day on Day 0.
[c]All animals were intravenously injected with $5X10^7$ PFU of monkeypox virus in 1 ml volume on Day 0.

Table S3. Non-Human Primate Study SR10-037F Design Overview

Group	Treatment[a] Group	Number of Animals/group (Male/Female)	MPXV IV Challenge Dose[c]
1	Placebo Day 4 – 19[b] (16 daily doses)	3 (1/2)	$5X10^7$ PFU
2	Tecovirimat 10 mg/kg/day, Day 4 – 17 (14 doses)	6 (3/3)	$5X10^7$ PFU
3	Tecovirimat 10 mg/kg/day, Day 5 – 18 (14 doses)	6 (3/3)	$5X10^7$ PFU
4	Tecovirimat 10 mg/kg/day, Day 6 – 19 (14 doses)	6 (3/3)	$5X10^7$ PFU

[a]Group 1 received only vehicle (Placebo) from Days 4 – 19. Groups 2 to 5 were administered tecovirimat by oral gavage on the days indicated here. To accommodate blinding, on non-tecovirimat treatment days, animals were treated with Placebo to complete 16 total days of dosing.
[b] All days listed are relative to monkeypox virus challenge day on Day 0.
[c]All animals were intravenously injected with $5X10^7$ PFU of monkeypox virus in 1 ml volume on Day 0.

Table S4. Non-Human Primate Study SR10-038F Design Overview

Group	Treatment[a] Group	Number of Animals/group (Male/Female)	MPXV IV Challenge Dose[c]
1	Placebo Day 4 – 13[b] (10 daily doses)	4 (2/2)	$5X10^7$ PFU
2	Tecovirimat 10 mg/kg/day, Day 4 – 6 (3 doses)	4 (2/2)	$5X10^7$ PFU
3	Tecovirimat 10 mg/kg/day, Day 4 – 8 (5 doses)	6 (3/3)	$5X10^7$ PFU
4	Tecovirimat 10 mg/kg/day, Day 4 – 10 (7 doses)	6 (3/3)	$5X10^7$ PFU
5	Tecovirimat 10 mg/kg/day, Day 4 – 13 (10 doses)	5 (2/3)	$5X10^7$ PFU

[a]Group 1 received only vehicle (Placebo) from Days 4 – 13. Groups 2 to 5 were administered tecovirimat by oral gavage on the days indicated here. To accommodate blinding, after cessation of tecovirimat treatment, animals continued on Placebo to complete 10 total days of dosing.
[b]All days listed are relative to monkeypox virus challenge day on Day 0.
[c]All animals were intravenously injected with $5X10^7$ PFU of monkeypox virus in 1 ml volume on Day 0.

Table S5. Rabbit Study SR14-008F Design Overview

Group	Treatment[a] Group	Number of Animals/group (Male/Female)	RPXV ID Challenge Dose[c]
1	Placebo	10 (5/5)	1,000 PFU
2	Tecovirimat 20 mg/kg/day, Day 4 – 17[b]	10 (5/5)	1,000 PFU
3	Tecovirimat 40 mg/kg/day, Day 4 – 17	10 (5/5)	1,000 PFU
4	Tecovirimat 80 mg/kg/day, Day 4 – 17	10 (5/5)	1,000 PFU
5	Tecovirimat 120 mg/kg/day, Day 4 – 17	10 (5/5)	1,000 PFU

[a]All animals will be treated with the specified dose once daily for 14-consecutive days from Day 4 to Day 17 post-infection.
[b]All days listed are relative to rabbitpox virus challenge day on Day 0.
[c]All animals were intradermally injected with 1,000 PFU of rabbitpox virus on Day 0. The virus dose in 200 uL volume was given by intradermal injections bilaterally, one injection of 100 uL in each shaved thigh using 2 syringes of 100 uL each.

Table S6. Rabbit Study SR13-025F Design Overview

Group	Treatment[a] Group	Number of Animals/group (Male/Female)	RPXV ID Challenge Dose[c]
1	Tecovirimat 40 mg/kg, Day 4 – 17[b]	8 (4/4)	1,000 PFU
2	Tecovirimat 80 mg/kg, Day 4 – 17	8 (4/4)	1,000 PFU
3	Tecovirimat 120 mg/kg, Day 4 – 17	8 (4/4)	1,000 PFU

[a]All animals will be treated with the specified dose once daily for 14-consecutive days from Day 4 to Day 17 post-infection.
[b]All days listed are relative to rabbitpox virus challenge day on Day 0.
[c]All animals were intradermally injected with 1,000 PFU of rabbitpox virus on Day 0. The virus dose in 200 uL volume was given by intradermal injections bilaterally, one injection of 100 uL in each shaved thigh using 2 syringes of 100 uL each.

Table S7. Pooled survival outcomes[a] data for NHPs and rabbits lethally infected with MPXV and RPXV, respectively, and treated with various doses of tecovirimat after onset of clinically evident disease.

Animal Species	**Virus**	**Tecovirimat Dose**	**Survival Outcome (%)**
Crab-Eating Macaque (*Macaca fascicularis*)	Monkeypox, Zaire '79 Strain (IV injection $5x10^7$ pfu)	0 mg/kg	1/20 (5%)
		0.3 mg/kg	1/5 (20%)
		1 mg/kg	0/5 (0%)
		3 mg/kg	10/10 (100%)[a]
		10 mg/kg	31/33 (94%)[a]
		20 mg/kg	6/6 (100%)
New Zealand White Rabbits (*Oryctolagus cuniculus)*	Rabbitpox, Utrecht Strain (ID injection 1000 pfu)	0 mg/kg	0/9 (0%)
		20 mg/kg	9/10 (90%)
		40 mg/kg	16/17 (94%)[c]
		80 mg/kg	15/16 (94%)[c]
		120 mg/kg	16/18 (89%)

[a]Six monkeypox/NHP and two rabbitpox/rabbit studies were conducted according to methods described in the text and further detailed in this Online Appendix - Supplemental Materials.
[b]One animal excluded from analysis due to cause of death other than MPXV or RPXV infection.
[c]Two animals excluded from analysis due to cause of death other than RPXV infection.

Table S8: Survival Time Analyses for Tecovirimat Studies

Study Number	**Species/Strain**	**Dose and Treatment Regimen**	**Survival %** (# Survived/ #Treated)	**Wilcoxon exact P-value[1]**
FY10-087	Monkey/ cynomolgus	Placebo (days 4-17)	0% (0/6)	NA
		3 mg/kg (days 4-17)	100% (6/6)	0.0011*
		10 mg/kg (days 4-17)	100% (6/6)	0.0011*
		20 mg/kg (days 4-17)	100% (6/6)	0.0011*
AP-09-026G	Monkey/ cynomolgus	Placebo (days 4-17)	0% (0/7)	NA
		0.3 mg/kg (days 4-17)	20% (1/5)	0.1654
		1 mg/kg (days 4-17)	0% (0/5)	0.4394
		3 mg/kg (days 4-17)	80% (4/5)	0.0354
		10 mg/kg (days 4-17)	80% (4/5)	0.0341
SR10-037F	Monkey/ cynomolgus	Placebo (days 4-19)	0% (0/3)	NA
		10 mg/kg (days 4-17)	83% (5/6)	0.0119*
		10 mg/kg (days 5-18)	83% (5/6)	0.0238*
		10 mg kg (days 6-19)	50% (3/6)	0.0238*
SR10-038F	Monkey/ cynomolgus	Placebo (days 4-13)	25% (1/4)	NA
		10 mg/kg (days 4-6)	50% (2/4)	0.1000
		10 mg/kg (days 4-8)	100% (6/6)	0.0333
		10 mg kg (days 4-10)	100% (6/6)	0.0333
		10 mg kg (days 4-13)	80% (4/5)	0.1270
SR13-025F	Rabbit/NZW	40 mg/kg (days 4-17)	100% (8/8)	NA[2]
		80 mg/kg (days 4-17)	100% (8/8)	NA[2]
		120 mg/kg (days 4-17)	100% (8/8)	NA[2]
SR14-008F	Rabbit/NZW	Placebo (days 4-17)	0% (0/10)	NA
		20 mg/kg (days 4-17)	90% (9/10)	<0.0001*
		40 mg/kg (days 4-17)	90% (9/10)	<0.0001*
		80 mg/kg (days 4-17)	80% (8/10)	<0.0001*
		120 mg/kg (days 4-17)	80% (8/10)	<0.0001*

[1]One-sided p-value, comparison to control

[2]NA result for study SR13-025F is due to the absence of a placebo comparator in this study.

*Denotes statistical significance at the 0.025 level.

Table S9: PK parameters of tecovirimat in fed subjects after the first dose (PK Day 1) and at steady state after the last dose (PK Day 14)

PK Day		T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (ng.hr/mL)	Half-life (hr)	Clearance (CL/F) (L/hr)
1	Mean (n)	11 (48)	1591 (48)	25876 (48)	-	-
	SD	7.2	516	7480	-	-
	CV%	66.2	32.4	28.9		
14	Mean (n)	5 (48)	2209 (48)	30632 (45)	23 (14)	41 (16)
	SD	3.3	726	10668	6	13
	CV%	64.3	33	35	25	30

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Subjects with at Least One TEAE		30 (33.3)	68	134 (37.3)	318	164 (36.5)	386
Overall	1	22 (24.4)	56	104 (29.0)	278	126 (28.1)	334
	2	7 (7.8)	11	26 (7.2)	36	33 (7.3)	47
	3	1 (1.1)	1	3 (0.8)	3	4 (0.9)	4
	4	0	0	0	0	0	0
	5	0	0	1 (0.3)	1	1 (0.2)	1
	>=3	1 (1.1)	1	4 (1.1)	4	5 (1.1)	5
NERVOUS SYSTEM DISORDERS	Total	15 (16.7)	24	70 (19.5)	123	85 (18.9)	147
	1	10 (11.1)	18	60 (16.7)	111	70 (15.6)	129
	2	5 (5.6)	6	8 (2.2)	10	13 (2.9)	16
	3	0	0	2 (0.6)	2	2 (0.4)	2
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	2 (0.6)	2	2 (0.4)	2
Headache	Total	13 (14.4)	19	61 (17.0)	104	74 (16.5)	123
	1	9 (10.0)	14	52 (14.5)	93	61 (13.6)	107
	2	4 (4.4)	5	7 (1.9)	9	11 (2.4)	14
	3	0	0	2 (0.6)	2	2 (0.4)	2
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	2 (0.6)	2	2 (0.4)	2

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Dizziness	Total	3 (3.3)	3	9 (2.5)	9	12 (2.7)	12
	1	2 (2.2)	2	9 (2.5)	9	11 (2.4)	11
	2	1 (1.1)	1	0	0	1 (0.2)	1
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Migraine	Total	0	0	4 (1.1)	4	4 (0.9)	4
	1	0	0	4 (1.1)	4	4 (0.9)	4
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Somnolence	Total	2 (2.2)	2	2 (0.6)	2	4 (0.9)	4
	1	2 (2.2)	2	2 (0.6)	2	4 (0.9)	4
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Disturbance in attention	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Dysgeusia	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Paraesthesia	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Syncope	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	0	0	0	0
	2	0	0	1 (0.3)	1	1 (0.2)	1
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
GASTROINTESTINAL DISORDERS	Total	7 (7.8)	13	54 (15.0)	87	61 (13.6)	100
	1	6 (6.7)	12	47 (13.1)	77	53 (11.8)	89
	2	1 (1.1)	1	7 (1.9)	10	8 (1.8)	11
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Nausea	Total	5 (5.6)	5	20 (5.6)	29	25 (5.6)	34
	1	4 (4.4)	4	18 (5.0)	27	22 (4.9)	31
	2	1 (1.1)	1	2 (0.6)	2	3 (0.7)	3
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Diarrhoea	Total	3 (3.3)	4	11 (3.1)	13	14 (3.1)	17
	1	3 (3.3)	4	9 (2.5)	11	12 (2.7)	15
	2	0	0	2 (0.6)	2	2 (0.4)	2
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Vomiting	Total	0	0	9 (2.5)	10	9 (2.0)	10
	1	0	0	8 (2.2)	9	8 (1.8)	9
	2	0	0	1 (0.3)	1	1 (0.2)	1
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Abdominal pain upper	Total	0	0	6 (1.7)	7	6 (1.3)	7
	1	0	0	6 (1.7)	7	6 (1.3)	7
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Constipation	Total	2 (2.2)	2	5 (1.4)	5	7 (1.6)	7
	1	2 (2.2)	2	4 (1.1)	4	6 (1.3)	6
	2	0	0	1 (0.3)	1	1 (0.2)	1
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Dry mouth	Total	0	0	5 (1.4)	5	5 (1.1)	5
	1	0	0	5 (1.4)	5	5 (1.1)	5
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Dyspepsia	Total	1 (1.1)	1	3 (0.8)	3	4 (0.9)	4
	1	1 (1.1)	1	2 (0.6)	2	3 (0.7)	3
	2	0	0	1 (0.3)	1	1 (0.2)	1
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Abdominal distension	Total	0	0	2 (0.6)	2	2 (0.4)	2
	1	0	0	2 (0.6)	2	2 (0.4)	2
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Abdominal discomfort	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Abdominal pain	Total	1 (1.1)	1	1 (0.3)	1	2 (0.4)	2
	1	1 (1.1)	1	1 (0.3)	1	2 (0.4)	2
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Abdominal pain lower	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	0	0	0	0
	2	0	0	1 (0.3)	1	1 (0.2)	1
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Chapped lips	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	0	0	0	0
	2	0	0	1 (0.3)	1	1 (0.2)	1
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Dental caries	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	0	0	0	0
	2	0	0	1 (0.3)	1	1 (0.2)	1
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Epigastric discomfort	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Eructation	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Food poisoning	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Hypoaesthesia oral	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Paraesthesia oral	Total	0	0	1 (0.3)	2	1 (0.2)	2
	1	0	0	1 (0.3)	2	1 (0.2)	2
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Toothache	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Uvulitis	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
INFECTIONS AND INFESTATIONS	Total	2 (2.2)	3	19 (5.3)	20	21 (4.7)	23
	1	1 (1.1)	2	13 (3.6)	14	14 (3.1)	16
	2	1 (1.1)	1	6 (1.7)	6	7 (1.6)	7
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Nasopharyngitis	Total	1 (1.1)	1	6 (1.7)	6	7 (1.6)	7
	1	0	0	4 (1.1)	4	4 (0.9)	4
	2	1 (1.1)	1	2 (0.6)	2	3 (0.7)	3
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Acute sinusitis	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	0	0	0	0
	2	0	0	1 (0.3)	1	1 (0.2)	1
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Bacterial vaginosis	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Bronchitis	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Conjunctivitis	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Fungal infection	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Gastroenteritis viral	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	0	0	0	0
	2	0	0	1 (0.3)	1	1 (0.2)	1
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Influenza	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	0	0	0	0
	2	0	0	1 (0.3)	1	1 (0.2)	1
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Kidney infection	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Pharyngitis	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Sinusitis	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	0	0	0	0
	2	0	0	1 (0.3)	1	1 (0.2)	1
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Tooth abscess	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Upper respiratory tract infection	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Urinary tract infection	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Viral infection	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Folliculitis	Total	1 (1.1)	1	0	0	1 (0.2)	1
	1	1 (1.1)	1	0	0	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Gastroenteritis	Total	1 (1.1)	1	0	0	1 (0.2)	1
	1	1 (1.1)	1	0	0	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Total	5 (5.6)	5	13 (3.6)	18	18 (4.0)	23
	1	4 (4.4)	4	9 (2.5)	14	13 (2.9)	18
	2	1 (1.1)	1	4 (1.1)	4	5 (1.1)	5
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Fatigue	Total	4 (4.4)	4	5 (1.4)	5	9 (2.0)	9
	1	3 (3.3)	3	4 (1.1)	4	7 (1.6)	7
	2	1 (1.1)	1	1 (0.3)	1	2 (0.4)	2
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Pyrexia	Total	0	0	4 (1.1)	4	4 (0.9)	4
	1	0	0	3 (0.8)	3	3 (0.7)	3
	2	0	0	1 (0.3)	1	1 (0.2)	1
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Pain	Total	0	0	3 (0.8)	3	3 (0.7)	3
	1	0	0	3 (0.8)	3	3 (0.7)	3
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Chills	Total	0	0	2 (0.6)	2	2 (0.4)	2
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	1 (0.3)	1	1 (0.2)	1
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Asthenia	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Malaise	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Oedema peripheral	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	0	0	0	0
	2	0	0	1 (0.3)	1	1 (0.2)	1
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Thirst	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Peripheral swelling	Total	1 (1.1)	1	0	0	1 (0.2)	1
	1	1 (1.1)	1	0	0	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Total	3 (3.3)	4	12 (3.3)	16	15 (3.3)	20
	1	2 (2.2)	3	12 (3.3)	16	14 (3.1)	19
	2	0	0	0	0	0	0
	3	1 (1.1)	1	0	0	1 (0.2)	1
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	1 (1.1)	1	0	0	1 (0.2)	1

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Rash	Total	0	0	3 (0.8)	4	3 (0.7)	4
	1	0	0	3 (0.8)	4	3 (0.7)	4
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Pruritus	Total	1 (1.1)	1	2 (0.6)	3	3 (0.7)	4
	1	1 (1.1)	1	2 (0.6)	3	3 (0.7)	4
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Alopecia	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Dermatitis contact	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Erythema	Total	1 (1.1)	1	1 (0.3)	1	2 (0.4)	2
	1	1 (1.1)	1	1 (0.3)	1	2 (0.4)	2
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Hyperhidrosis	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Palpable purpura	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Pruritus generalised	Total	1 (1.1)	1	1 (0.3)	1	2 (0.4)	2
	1	1 (1.1)	1	1 (0.3)	1	2 (0.4)	2
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Rash pruritic	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Skin hypertrophy	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Swelling face	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Hidradenitis	Total	1 (1.1)	1	0	0	1 (0.2)	1
	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	1 (1.1)	1	0	0	1 (0.2)	1
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	1 (1.1)	1	0	0	1 (0.2)	1

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Total	6 (6.7)	7	11 (3.1)	12	17 (3.8)	19
	1	5 (5.6)	6	9 (2.5)	10	14 (3.1)	16
	2	1 (1.1)	1	1 (0.3)	1	2 (0.4)	2
	3	0	0	1 (0.3)	1	1 (0.2)	1
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	1 (0.3)	1	1 (0.2)	1
Arthralgia	Total	1 (1.1)	1	2 (0.6)	2	3 (0.7)	3
	1	1 (1.1)	1	2 (0.6)	2	3 (0.7)	3
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Myalgia	Total	1 (1.1)	1	2 (0.6)	2	3 (0.7)	3
	1	1 (1.1)	1	1 (0.3)	1	2 (0.4)	2
	2	0	0	1 (0.3)	1	1 (0.2)	1
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Back pain	Total	2 (2.2)	2	1 (0.3)	1	3 (0.7)	3
	1	2 (2.2)	2	1 (0.3)	1	3 (0.7)	3
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Muscle tightness	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Musculoskeletal pain	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Neck pain	Total	1 (1.1)	1	1 (0.3)	1	2 (0.4)	2
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	1 (1.1)	1	0	0	1 (0.2)	1
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Osteoarthritis	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	1 (0.3)	1	1 (0.2)	1
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	1 (0.3)	1	1 (0.2)	1
Pain in jaw	Total	0	0	1 (0.3)	2	1 (0.2)	2
	1	0	0	1 (0.3)	2	1 (0.2)	2
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Tendonitis	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Joint swelling	Total	1 (1.1)	1	0	0	1 (0.2)	1
	1	1 (1.1)	1	0	0	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Musculoskeletal stiffness	Total	1 (1.1)	1	0	0	1 (0.2)	1
	1	1 (1.1)	1	0	0	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	Total	1 (1.1)	1	9 (2.5)	10	10 (2.2)	11
	1	1 (1.1)	1	6 (1.7)	6	7 (1.6)	7
	2	0	0	3 (0.8)	4	3 (0.7)	4
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Muscle strain	Total	0	0	4 (1.1)	4	4 (0.9)	4
	1	0	0	3 (0.8)	3	3 (0.7)	3
	2	0	0	1 (0.3)	1	1 (0.2)	1
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Ligament sprain	Total	0	0	2 (0.6)	2	2 (0.4)	2
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	1 (0.3)	1	1 (0.2)	1
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Head injury	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	0	0	0	0
	2	0	0	1 (0.3)	1	1 (0.2)	1
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Skin abrasion	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Sunburn	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Upper limb fracture	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	0	0	0	0
	2	0	0	1 (0.3)	1	1 (0.2)	1
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Fall	Total	1 (1.1)	1	0	0	1 (0.2)	1
	1	1 (1.1)	1	0	0	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
PSYCHIATRIC DISORDERS	Total	3 (3.3)	3	7 (1.9)	9	10 (2.2)	12
	1	2 (2.2)	2	6 (1.7)	8	8 (1.8)	10
	2	1 (1.1)	1	1 (0.3)	1	2 (0.4)	2
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Depression	Total	0	0	2 (0.6)	2	2 (0.4)	2
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	1 (0.3)	1	1 (0.2)	1
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Nervousness	Total	0	0	2 (0.6)	2	2 (0.4)	2
	1	0	0	2 (0.6)	2	2 (0.4)	2
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Dysphoria	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Insomnia	Total	1 (1.1)	1	1 (0.3)	2	2 (0.4)	3
	1	1 (1.1)	1	1 (0.3)	2	2 (0.4)	3
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Irritability	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Panic attack	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Libido increased	Total	1 (1.1)	1	0	0	1 (0.2)	1
	1	1 (1.1)	1	0	0	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Nightmare	Total	1 (1.1)	1	0	0	1 (0.2)	1
	1	0	0	0	0	0	0
	2	1 (1.1)	1	0	0	1 (0.2)	1
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Total	2 (2.2)	5	7 (1.9)	8	9 (2.0)	13
	1	2 (2.2)	5	6 (1.7)	7	8 (1.8)	12
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	1 (0.3)	1	1 (0.2)	1
	>=3	0	0	1 (0.3)	1	1 (0.2)	1

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Nasal congestion	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Oropharyngeal pain	Total	2 (2.2)	2	1 (0.3)	1	3 (0.7)	3
	1	2 (2.2)	2	1 (0.3)	1	3 (0.7)	3
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Pulmonary embolism	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	1 (0.3)	1	1 (0.2)	1
	>=3	0	0	1 (0.3)	1	1 (0.2)	1

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Respiratory tract congestion	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Rhinorrhoea	Total	1 (1.1)	1	1 (0.3)	1	2 (0.4)	2
	1	1 (1.1)	1	1 (0.3)	1	2 (0.4)	2
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Sputum retention	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Vasomotor rhinitis	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Wheezing	Total	1 (1.1)	1	1 (0.3)	1	2 (0.4)	2
	1	1 (1.1)	1	1 (0.3)	1	2 (0.4)	2
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Cough	Total	1 (1.1)	1	0	0	1 (0.2)	1
	1	1 (1.1)	1	0	0	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
INVESTIGATIONS	Total	0	0	5 (1.4)	6	5 (1.1)	6
	1	0	0	5 (1.4)	6	5 (1.1)	6
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Blood pressure systolic increased	Total	0	0	2 (0.6)	2	2 (0.4)	2
	1	0	0	2 (0.6)	2	2 (0.4)	2
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Electroencephalogram abnormal	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Haematocrit decreased	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Haemoglobin decreased	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Heart rate increased	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
EAR AND LABYRINTH DISORDERS	Total	2 (2.2)	2	3 (0.8)	3	5 (1.1)	5
	1	2 (2.2)	2	3 (0.8)	3	5 (1.1)	5
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Ear pain	Total	0	0	2 (0.6)	2	2 (0.4)	2
	1	0	0	2 (0.6)	2	2 (0.4)	2
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Vertigo	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Hearing impaired	Total	1 (1.1)	1	0	0	1 (0.2)	1
	1	1 (1.1)	1	0	0	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Tinnitus	Total	1 (1.1)	1	0	0	1 (0.2)	1
	1	1 (1.1)	1	0	0	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Lymphadenopathy	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
CARDIAC DISORDERS	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Ventricular extrasystoles	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
EYE DISORDERS	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Eye irritation	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
RENAL AND URINARY DISORDERS	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Dysuria	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Menstruation irregular	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
VASCULAR DISORDERS	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
Peripheral coldness	Total	0	0	1 (0.3)	1	1 (0.2)	1
	1	0	0	1 (0.3)	1	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0
METABOLISM AND NUTRITION DISORDERS	Total	1 (1.1)	1	0	0	1 (0.2)	1
	1	1 (1.1)	1	0	0	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S10. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity Safety Population (Continued)

SYSTEM ORGAN CLASS Preferred Term	Grade	Placebo N=90 n (%)	E	Tecovirimat 600 mg N=359 n (%)	E	Total N=449 n (%)	E
Dehydration	Total	1 (1.1)	1	0	0	1 (0.2)	1
	1	1 (1.1)	1	0	0	1 (0.2)	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	>=3	0	0	0	0	0	0

Note: Adverse events are coded by using MedDRA version 18.0 or later.
Note: Treatment-emergent adverse events include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.
Note: Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experiences will be counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term.
Note: n = no. of subjects; E = no. of TEAEs.

Table S11. Treatment-related adverse events in the Expanded Safety Trial

Adverse Event by Preferred Term	**Placebo (N = 90) n = 32**	**Tecovirimat (N = 359) n = 176**	**Total (N = 449) n = 208**
Headache	11	80	91
Dizziness	1	4	5
Migraine	0	3	3
Somnolence	1	2	3
Disturbance in attention	0	1	1
Dysgeusia	0	1	1
Paraesthesia	0	1	1
Nausea	4	22	26
Diarrhoea	2	9	11
Vomiting	0	8	8
Abdominal pain upper	0	7	7
Dry mouth	0	3	3
Constipation	2	2	4
Dyspepsia	0	2	2
Abdominal discomfort	0	1	1
Chapped lips	0	1	1
Eructation	0	1	1
Paraesthesia oral	0	2	2
Abdominal pain	1	0	1
Fatigue	3	3	6
Pyrexia	0	2	2
Chills	0	1	1
Malaise	0	1	1
Pain	0	1	1
Thirst	0	1	1
Palpable purpura	0	1	1
Pruritus	1	2	3
Pruritus generalised	1	1	2
Rash	0	1	1
Rash pruritic	0	1	1
Erythema	1	0	1
Electroencephalogram abnormal	0	1	1
Haematocrit decreased	0	1	1
Haemoglobin decreased	0	1	1
Heart rate increased	0	1	1
Depression	0	1	1
Dysphoria	0	1	1
Irritability	0	1	1
Panic attack	0	1	1
Insomnia	1	0	1
Nightmare	1	0	1
Arthralgia	0	1	1
Osteoarthritis	0	1	1
Oropharyngeal pain	0	0	1
Hearing impaired	1	0	1
Tinnitus	1	0	1

N = number of subjects in treatment group; n = instance of treatment-related treatment emergent adverse event

Table S12. Treatment-emergent Adverse Events with a Maximum Intensity of Grade 3 or Higher by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Placebo (N = 90)		Tecovirimat 600 mg (N = 359)		Total (N = 449)	
	n (%)	E	n (%)	E	n (%)	E
Subjects with at least 1 TEAE of Grade 3 or higher	1 (1.1)	1	4 (1.1)	4	5 (1.1)	5
Nervous system disorders	0	0	2 (0.6)	2	2 (0.4)	2
Headache	0	0	2 (0.6)	2	2 (0.4)	2
Skin and subcutaneous tissue disorders	1 (1.1)	1	0	0	1 (0.2)	1
Hidradenitis	1 (1.1)	1	0	0	1 (0.2)	1
Musculoskeletal and connective tissue disorders	0	0	1 (0.3)	1	1 (0.2)	1
Osteoarthritis	0	0	1 (0.3)	1	1 (0.2)	1
Respiratory, thoracic and mediastinal disorders	0	0	1 (0.3)	1	1 (0.2)	1
Pulmonary embolism	0	0	1 (0.3)	1	1 (0.2)	1

Key: AE = adverse event; E = number of events; TEAE = treatment-emergent adverse event.

Notes: Treatment-emergent AEs included any newly occurring event or previous condition that increased in severity or frequency since administration of the first dose of study drug. Subjects who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the subject experienced was counted for the overall summaries. The total rows are the total number of subjects for the system organ class or preferred term. Adverse events were coded by using the Medical Dictionary for Regulatory Activities, version 18.0.

Table S13. Adverse Events Leading to Discontinuation of Study Drug

Subject No (S/R/A)[a]	System Organ Class/ Preferred Term/ Verbatim Term	Onset Day	Stop Day	Severity/ Relationship to Study Drug	Actions	Outcome
Placebo						
106-162 (F/B/39)	*Gastrointestinal disorders/* *Nausea/* *Nausea*	1	3	Moderate/ Definitely related	None	Recovered/ Resolved
	General disorders and administration site conditions/ Fatigue/ Fatigue	1	6	Moderate/ Definitely related	None	Recovered/ Resolved
	Psychiatric disorders/ Nightmare/ Nightmares	4	5	Moderate/ Definitely related	None	Recovered/ Resolved
109-141[b] (F/W/68)	Nervous system disorders/ Dizziness Dizziness	8	8	Mild/ Not related	None	Recovered/ Resolved
	General disorders and administration site conditions/ Fatigue/ Fatigue	10	10	Mild/ Possibly related	None	Recovered/ Resolved
Tecovirimat 600 mg						
101-164 (M/W/21)	*Investigations/* *Electroencephalogram abnormal/* *Abnormal EEG result – Grade 3*	2	14	Mild/ Possibly related	Other: dosing was stopped permanently	Recovered/ Resolved
	Gastrointestinal disorders/ Nausea/ Nausea	9	10	Mild/ Possibly related	None	Recovered/ Resolved
	General disorders and administration site conditions/ Fatigue/ Fatigue	11	12	Mild/ Possibly related	None	Recovered/ Resolved

Subject No (S/R/A)[a]	System Organ Class/ Preferred Term/ Verbatim Term	Onset Day	Stop Day	Severity/ Relationship to Study Drug	Actions	Outcome
103-151 (F/W/60)	*Gastrointestinal disorders/ Abdominal discomfort/ Slight upset stomach*	3	5	Mild/ Possibly related	None	Recovered/ Resolved
	Gastrointestinal disorders/ Dry mouth/ Dry mouth	3	5	Mild/ Possibly related	None	Recovered/ Resolved
	Psychiatric disorders/ Dysphoria/ Dysphoric	3	5	Mild/ Possibly related	None	Recovered/ Resolved
	Nervous system disorders/ Disturbance in attention/ Decreased concentration	3	6	Mild/ Possibly related	None	Recovered/ Resolved
104-110 (M/W/47)	*General disorders and administration site conditions/ Pyrexia/ Fever*	2	4	Mild/ Definitely related	Con med	Recovered/ Resolved
	Gastrointestinal disorders/ Diarrhoea/ Diarrhea	2	6	Moderate/ Definitely related	None	Recovered/ Resolved
	Gastrointestinal disorders/ Nausea/ Nausea	2	6	Mild/ Definitely related	None	Recovered/ Resolved
	Nervous system disorders/ Headache/ Headache	2	6	Severe/ Definitely related	Con med	Recovered/ Resolved
106-138 (F/W/58)	*Skin and subcutaneous tissue disorders/ Palpable purpura/ Palpable purpura*	2	16	Mild/ Definitely related	Other: dosing was stopped permanently	Recovered/ Resolved

Subject No (S/R/A)[a]	System Organ Class/ Preferred Term/ Verbatim Term	Onset Day	Stop Day	Severity/ Relationship to Study Drug	Actions	Outcome
106-151 (M/W/56)	*Gastrointestinal disorders/* *Nausea/* *Nausea*	8	13	Mild/ Definitely related	Other: dosing interrupted	Recovered/ Resolved
	General disorders and administration site conditions/ *Chills/* *Chills*	12	13	Mild/ Unlikely related	None	Recovered/ Resolved
	General disorders and administration site conditions/ *Pyrexia/* *Fever*	12	13	Mild/ Unlikely related	None	Recovered/ Resolved
109-114 (F/W/37)	*Skin and subcutaneous tissue disorders/* *Erythema/* *Facial redness*	2	5	Mild/ Not related	None	Recovered/ Resolved
	Skin and subcutaneous tissue disorders/ *Pruritus/* *Pruritus*	2	5	Mild/ Not related	None	Recovered/ Resolved
	Skin and subcutaneous tissue disorders/ *Swelling face/* *Facial swelling*	2	5	Mild/ Not related	None	Recovered/ Resolved

Key: AE = adverse event; B = Black or African American; Con med = concomitant medication; EEG = electroencephalogram; F = female; M = male; TEAE = treatment-emergent adverse event; W = White.

Notes: Onset/Stop Day was the day relative to the date of the first dose of study drug.
Drug withdrawal was not an action captured on the AE case report form. Subjects were identified from the End of Dosing case report form where the primary reason for not completing dosing was AE. All TEAEs experienced by these subjects are listed, and the TEAE(s) leading to study drug discontinuation are shown in *italics*.
Treatment-emergent AEs included any newly occurring event or previous condition that increased in severity or frequency since administration of the first dose of study drug.
Adverse events were coded by using the Medical Dictionary for Regulatory Activities, version 18.0.

[a] S/R/A indicates sex/race/age at randomization (years).

[b] Subject 109-141 is indicated as discontinuing study drug because of an AE; however, the listing also notes that the subject was unable to meet the dosing times because of her work schedule and does not specify which (if any) TEAE led to discontinuation.

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