A randomized, placebo-controlled, double-blinded trial of the safety and efficacy of tecovirimat for the treatment of adult and pediatric patients with monkeypox virus disease

Protocol

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Title: A randomized, placebo-controlled, double-blinded trial of the safety and efficacy of tecovirimat for the treatment of adult and pediatric patients with monkeypox virus disease

Investigational Agents:

Drug Name:	tecovirimat (TPOXX®)
Manufacturer:	Catalent Pharma Solutions and SIGA Technologies, Inc.
Drug Sponsor:	SIGA Technologies, Inc.

Study Sponsors: National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), United States of America, and Institut National de la Recherche Biomédicale (INRB), Democratic Republic of the Congo (DRC)

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Study sites:
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Institutional Review Board (IRB)/EC:
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1 PROTOCOL SUMMARY

1.1 Synopsis

Title:	A randomized, placebo-controlled, double-blinded trial of the safety and efficacy of tecovirimat for the treatment of adult and pediatric patients with monkeypox virus disease
Study Description:	This is a randomized, placebo-controlled, double-blind study to test the safety and efficacy of the antiviral drug tecovirimat in adults and children with laboratory-confirmed monkeypox virus (MPXV) disease at study sites in the DRC. Participants will be randomly assigned to receive oral tecovirimat or placebo (1:1 via block randomization, stratified by study site and days from onset of prodromal symptoms ≤7 days or >7 days), each administered in the hospital with standard-of-care (SOC) treatment for 14 days. Participants will be followed for 28 days with an optional visit at Day 59 for long-term assessment.
Objectives:	Primary Objective: 1. To evaluate the clinical efficacy, as assessed by time to lesion resolution, of tecovirimat plus SOC versus placebo plus SOC for patients with mpox. Secondary Objectives: 1. To evaluate the clinical efficacy, as assessed by time to lesion resolution, of tecovirimat plus SOC versus placebo plus SOC for patients with mpox, according to duration of symptoms (≤7 days or >7 days). 2. To evaluate the virologic efficacy, as assessed by PCR separately of blood, skin lesion, and oropharynx samples, of tecovirimat plus SOC relative to placebo plus SOC 3. To evaluate the clinical efficacy of tecovirimat plus SOC versus placebo plus SOC in patients with mpox as assessed by mortality, clinical severity, and duration of symptoms. 4. To evaluate the safety of tecovirimat plus SOC relative to placebo plus SOC in patients with mpox. Exploratory Objectives: 1. To evaluate the frequency and characteristics of persistent residual lesions. 2. To describe lesion progression longitudinally over the study period. 3. To evaluate exposure history of confirmed mpox cases

	and to identify risk factors for MPXV infection. 4. To develop a baseline disease severity metric for mpox. 5. To evaluate the potential impact of the presence of anti-orthopoxvirus (OPXV) antibodies on the course of disease and the clinical efficacy of tecovirimat. 6. To evaluate persistence of MPXV PCR positivity in blood, skin lesions, and the oropharynx. 7. To evaluate the trajectory of MPXV immunoglobulin (Ig) M and IgG over time during infection. 8. To assess genomic variability in MPXV isolated from participants based on geographic and clinical differences. 9. To assess whether viral resistance develops due to selective pressure by treatment. 10. To assess the effect of HIV infection on mpox clinical outcomes and treatment effect. 11. To measure tecovirimat drug levels in a real-world scenario. 12. To describe clinically and virologically any cases of recrudescent disease as defined by the protocol (see section 9.1.2).
Endpoints:	Primary Endpoint: Time to lesion resolution, defined as the first day on which all lesions on the total body are scabbed or desquamated or a new layer of epidermis has formed (see section 8.4.1), up to 28 days after randomization. Secondary Endpoints: 1. Time to lesion resolution, as defined in the primary endpoint, according to stratification by time from onset of illness as ≤ 7 days or > 7 days. 2. Proportions with negative PCR results separately by blood, oropharyngeal swab, and lesion swab samples 14 days after randomization. 3. Mortality within the first 28 days after randomization. 4. Time to death up to 28 days after randomization. 5. Frequency and duration of clinical symptoms (including nausea, vomiting, abdominal pain, diarrhea, anorexia, cough, lymphadenopathy, dysphagia, sore throat, muscle aches, fatigue/lack of energy, fever, chills, night sweats, headache, ocular lesions, eye pain, change in vision, buccal ulcers, nasal congestion,

	cough, joint pain, pain with urination, painful skin lesions, pruritic skin lesions). 6. Incidence of serious adverse events (SAEs), adverse events (AEs) requiring drug discontinuation, and incidence of other AEs. 7. Incidence of bacterial infections. Bacterial infections will be defined clinically with laboratory and radiographical confirmation when possible. 8. Automated image analysis of lesion counts and characteristics over time. Exploratory Endpoints: 1. Presence, location, and duration of persistent residual lesions, defined as any lesion (in any area of the body) unresolved after all assessment-region lesions are scabbed or desquamated. 2. Longitudinal description of lesion progression over the study period. 3. Number and percentage of confirmed mpox cases reporting exposure to animals, symptomatic humans, or with no known exposures. 4. Associations between measures of baseline disease severity (including lesion counts, duration of symptoms, and comorbidities) and efficacy endpoints. 5. Differences in outcomes based on the presence of anti-OPXV antibodies. 6. Viral load and proportion with negative PCR results in blood, oropharyngeal swab, and open lesion swab samples over time and time to the first negative PCR result in each of these specimens up to 28 days after randomization. 7. Change in antibody titer over time. 8. Sequencing differences between virus isolated from participants from different geographic areas and with differing clinical trajectories and responses to tecovirimat. 9. Sequencing differences between virus isolated prior to and after treatment. 10. Differences in severity and duration of MPXV infection and treatment effect by HIV status and HIV viral load. 11. Pre-dose concentration in all participants and 4h post-dose concentration only in participants ≥18 years of age of

	tecovirimat in blood measured on day 7. 12. Incidence of recrudescent disease and description of clinical and virologic characteristics of recrudescent disease cases.
Study Population:	Patients of any age with laboratory-confirmed MPXV infection. **Sample Size:** N=600 **Accrual Ceiling:** 1000 screened participants, in order to enroll up to 600 participants.
Phase:	3
Description of Study Intervention:	Tecovirimat capsules or placebo capsules will be administered orally to participants for 14 days as follows: • ≥120 kg: three capsules three times a day (total daily tecovirimat dose: 1,800 mg). • 40 to <120 kg: three capsules twice a day (total daily tecovirimat dose: 1,200 mg). • 25 to <40 kg: two capsules twice a day (total daily tecovirimat dose: 800 mg). • 13 to <25 kg: one capsule twice a day (total daily tecovirimat dose: 400 mg). • 6 to <13 kg: ½ the contents of a capsule twice daily (total daily tecovirimat dose: 200 mg). • 3 to <6 kg: ¼ the contents of a capsule twice daily (total daily tecovirimat dose: 100 mg).
Study Duration:	Up to 5 years, but could be shortened depending on the pace of enrollment
Participant Duration:	Up to 59 days

1.2 Schema

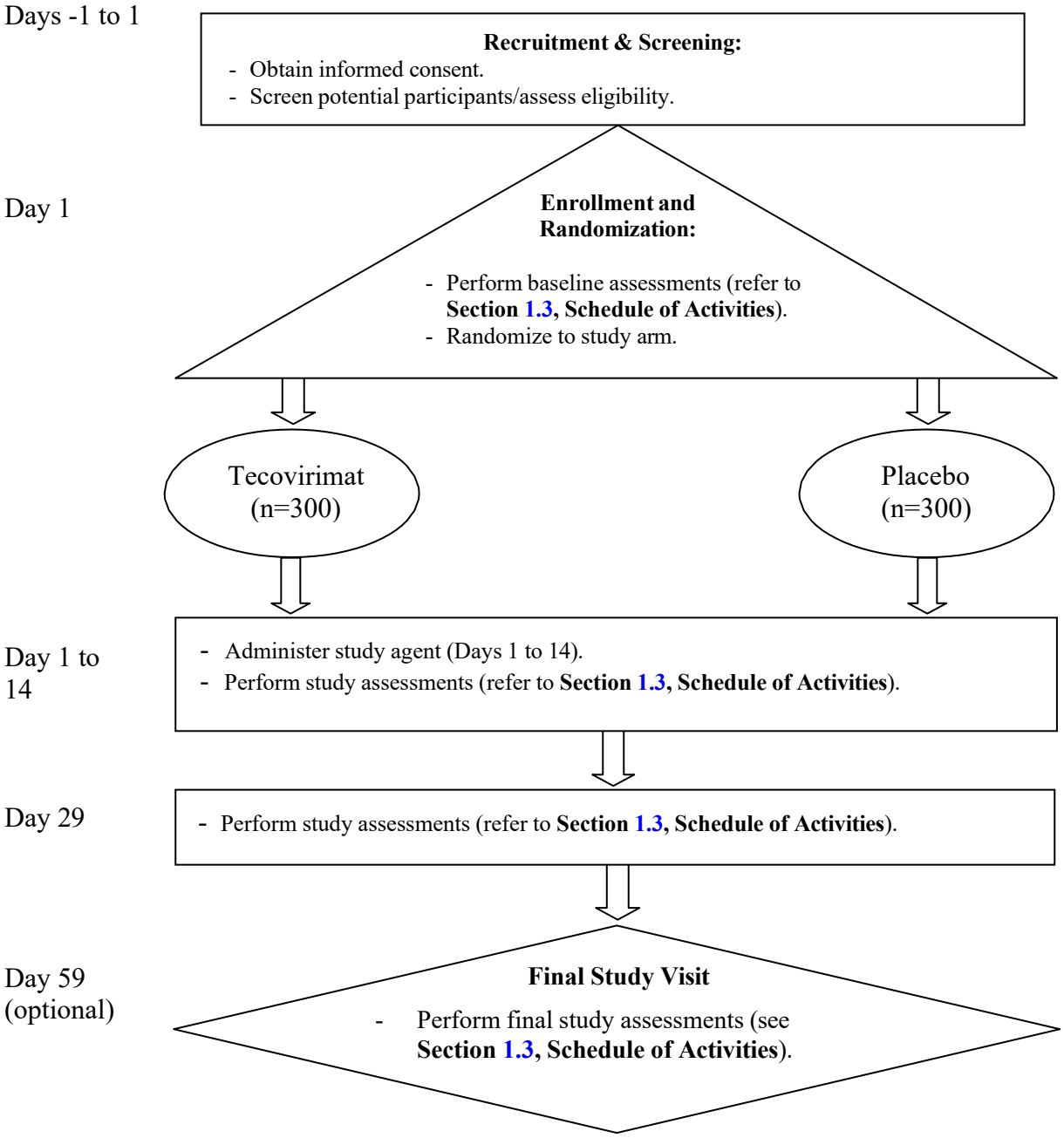


Figure 1. Study Schema.

1.3 Schedule of Activities

Evaluation/Procedure	Screen	Baseline	Follow-Up										Sick visit[n]	Pregnancy outcome follow-up (optional)
Day +/- Window	−1 or 1	1	2	3	4	5	6	7[p]	8	9+ while hospitalized[d]	29±7[a]	59±7[b]		
OPERATIONAL AND CLINICAL ASSESSMENTS														
Informed consent[l]	X	X												
Eligibility (inclusion/exclusion) assessment	X													
Demographics		X[k]												
Medical history		X[k]												
Medication review	X	X	X	X	X	X	X	X	X	Daily until discharge	X		X	
Weight	X	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	Daily through last day of study drug administration[c]			X	
Height	X												X	
Arm circumference (age 3 months to ≤ 5 years)	X												X	
Pregnancy test (serum or urine; females of childbearing potential)		X												
Randomization		X												
Vital Signs		X	X	X	X	X	X	X	X	Daily until discharge	X	X	X	
Lesion Assessment[e]		X	X	X	X	X	X	X	X	Daily until resolution of lesions	X[e]		X[o]	
Current symptoms		X	X	X	X	X	X	X	X	Daily until discharge	X	X	X	
Assessment of AEs/SAEs		X	X	X	X	X	X	X	X	Daily until discharge	X	X	X	
Completion of pregnancy outcome case report form														X
STUDY DRUG ADMINISTRATION														
Study drug administration		Tecovirimat or placebo daily orally for 14 days												

Evaluation/Procedure	**Screen**	**Baseline**	**Follow-Up**										Sick visit[n]	Pregnancy outcome follow-up (optional)
Day +/- Window	−1 or 1	1	2	3	4	5	6	7[p]	8	9+ while hospitalized[d]	29±7[a]	59±7[b]		
RESEARCH LABORATORY EVALUATIONS[m]														
MPXV PCR (blood) with CT	X[f]	X[g]		X		X		X		Every other day until negative x2			X	
Blood for storage		X						X		Day 13	X	X	X	
Oropharyngeal swab	X[f]	X[g]		X		X		X		Every other day until negative x2			X	
Skin lesions swab	X[f]	X[g]		X		X		X		Every other day until negative x2			X	
CLINICAL LABORATORY EVALUATIONS[m]														
HIV antibody test[i]		X												
HIV viral load[i]		X												
Varicella zoster virus PCR[j]		X											X	
Malaria rapid test[j]		X											X	
Glucose (mg/dl)		X[h]		X		X		X		Every other day until discharge	X		X	
Hemoglobin (g/dL)	X	X[h]		X		X		X		Every other day until discharge	X		X	
Hematocrit (L/L)		X[h]		X		X		X		Every other day until discharge	X		X	
Creatinine (mg/dL)		X[h]		X		X		X		Every other day until discharge	X		X	
Potassium (mmol/L)		X[h]		X		X		X		Every other day until discharge	X		X	
Sodium (mmol/L)		X[h]		X		X		X		Every other day until discharge	X		X	
eGFR (mL/min/1.73m^2)		X[h]		X		X		X		Every other day until discharge	X		X	
AST (U/L)		X[h]		X		X		X		Every other day until discharge	X		X	
ALT (U/L)		X[h]		X		X		X		Every other day until discharge	X		X	

Evaluation/Procedure	**Screen**	**Baseline**	**Follow-Up**										Sick visit[n]	Pregnancy outcome follow-up (optional)
Day +/- Window	−1 or 1	1	2	3	4	5	6	7[p]	8	9+ while hospitalized[d]	29±7[a]	59±7[b]		
BUN (mg/dL)		X[h]		X		X		X		Every other day until discharge	X		X	
CBC with differential (c/mm^3)		X[h]		X		X		X		Every other day until discharge	X		X	
Calcium (mg/dL)		X[h]		X		X		X		Every other day until discharge	X		X	
Total protein (g/dL)		X[h]		X		X		X		Every other day until discharge	X		X	
C-reactive protein (ug/mL)		X[h]						X		Day 13	X		X	
Creatinine kinase (U/L)		X[h]		X		X		X		Every other day until discharge	X		X	
Total CO_2 (mEq/L)		X[h]		X		X		X		Every other day until discharge	X		X	
Chloride (mEq/L)		X[h]		X		X		X		Every other day until discharge	X		X	
Alkaline phosphatase (IU/L)		X[h]		X		X		X		Every other day until discharge	X		X	
t-Bilirubin (mg/dL)		X[h]		X		X		X		Every other day until discharge	X		X	
Amylase (U/L)		X[h]						X		Day 13	X		X	
Albumin (g/dL)		X[h]		X		X		X		Every other day until discharge	X		X	
PT (sec)/INR		X[h]						X		Day 13				
Urinalysis, dipstick		X[h]		X		X		X		Every other day until discharge	X		X	

Abbreviations: AE, adverse event; ALT, alanine transaminase; activated partial thromboplastin time; AST, aspartate transaminase; BUN, blood urea nitrogen; CBC, complete blood count; cluster of differentiation 4 count; CO_2, carbon dioxide; CT, cycle threshold; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; INR, international normalized ratio; MPXV, monkeypox virus; PCR, polymerase chain reaction; PT, prothrombin time; SAE, serious adverse event.

[a] This study visit will include a +/- 7-day visit window for participants discharged prior to Day 29. For participants who remain inpatient through Day 29, the visit should take place exactly on Day 29, but clinical and research labs will not be collected if already collected on Day 28. For participants who are discharged prior to Day 29 but within the visit window (i.e., Day 22 to Day 28), the Day 29 visit will be the day of discharge.

[b] The Day 59 visit is optional and may be completed in person or by phone. Failure to complete a Day 59 visit will not result in a protocol deviation. Some procedures may not be able to be performed if the visit takes place over the phone.

[c] Only for participants who weigh <40 kg. For these participants, weight will be taken each morning before breakfast and used to calculate the study drug dose for that day.

[d] After completion of the 14-day treatment period, participants are eligible for discharge at the discretion of the treating physician only after all mpox lesions on the total body are scabbed or desquamated and they have received two consecutive negative results on the blood PCR test. The date of discharge will be documented.

[e] During daily lesion assessments, photographs may be taken of the body, which may include different part of the body and the face, including the eyes. While the participant still has unresolved lesions in the target region, assessment of whether there are unresolved lesions on other areas of the body will be optional but preferred. Once all lesions in the target region are resolved, a simplified full body lesion assessment will be done daily until all lesions are resolved (or Day 29, whichever comes first).

[f] Any positive MPXV PCR from blood, oropharynx, or skin lesion collected up to 48 hours prior to informed consent may be used to establish eligibility.

[g] The baseline specimen will ideally be collected within 24 hours prior to randomization. If the specimen cannot be collected within 24 hours and there is a specimen available that was collected within 48 hours prior to randomization, the 48-hour specimen may be used as the baseline sample.

[h] Any laboratory tests obtained within 1 day prior to randomization do not need to be repeated on day 1.

[i] Participants may opt out of HIV testing. HIV viral load may be performed for HIV-infected individuals only. Tests will be performed retrospectively.

[j] Although collection is highly desirable, these labs may be waived if not feasible, per investigator discretion. Varicella zoster virus PCR may be done retrospectively.

[k] Clinical and demographic information collected within 48 hours of randomization may be collected for study purposes.

[l] A signed screening consent will be obtained prior to performing screening procedures; once eligibility is confirmed, consent for study participation will be obtained using a main study consent prior to performing Day 1 procedures.

[m] Research and clinical labs at all time points, though highly desirable, may be waived if not feasible (e.g., due to blood draw volume concerns related to participant weight or hemoglobin or due to site logistics), per investigator discretion.

[n] If a participant reaches full body lesion resolution but subsequently develops at least one new lesion consistent with mpox after discharge but while still enrolled in the study, they will be eligible to make an optional “Sick Visit” and they will be offered standard of care for mpox.

[o] Full body lesion count will be performed.

[p] An additional voluntary/optional blood sample will be obtained from all participants ≥18 years of age at 4 hours after receiving their first dose of study drug on day 7 to be used for PK analysis.

2 INTRODUCTION

2.1 Background

2.1.1 Monkeypox Virus

Monkeypox virus belongs to the family of *Poxviridae* and the genus of *Orthopoxvirus*, which comprises 10 species, of which *Monkeypox*, *Variola*, *Vaccinia*, and *Cowpox viruses* represent pathogens of medical interest for humans.[1] *Monkeypox virus* is antigenically related to *Variola*, the causative agent of smallpox, and *Vaccinia viruses*. The *Monkeypox virus* is a brick-shaped, enveloped virus of 200-250 nm, with characteristic surface tubules and a dumbbell-shaped core component.[2] Its genome consists of linear double-stranded DNA, and the virion is composed of 4 major elements (core, lateral bodies, outer membrane, and the outer lipoprotein envelope) that intervene at different steps of the virus' life cycle.[3] *Monkeypox virus* was first identified as the cause of pox-like illness in captive monkeys in a laboratory at the Institute of Copenhagen in 1958.[4] Since its first human identification in 1970 in the DRC, the majority of subsequent cases were mainly reported from rain forest areas of Central Africa and sporadic other cases from West Africa.[5] Genetic evolution of the virus revealed the existence of two *Monkeypox virus* clades, the Congo Basin (CB) and the West African (WA) clade, presenting nucleotide changes in their sequences[6] with different clinical expressions and geographic locations. The WA clade was reported to be less severe than the CB clade with a case-fatality rate of 0-6%; while the CB clade presented a mortality estimated to be 11%, with a higher percentage observed in children (~17%).[6,7]

2.1.2 Epidemiology

Although mpox disease has clinical similarities with smallpox disease, the human epidemiology of the disease differs significantly. Mpox surveillance is not well established, and limited information is available on the prevalence and incidence of the disease in the countries most affected. Early epidemiological data came from investigations of outbreaks in Central and Western Africa and depicted different epidemiology profiles of the disease depending on the surveillance period.[8] Furthermore, data collected during the first outbreak of mpox in United States (US, 2003), due to imported wild animals from West Africa, have added to what is known about the disease epidemiology, even though no inter-human transmission was reported.[9-11]

2.1.3 Transmission

Several animal reservoirs have been implicated in the primary transmission of MPXV infection.[4,12] However, epidemiological investigations have defined a close link with forest-dwelling rodents (Gambia pouched rat, rope squirrel).[13] The initial transmission mode described was a primary transmission from animal to human.[8] Direct contact with infected animals or possible ingestion of inadequately cooked meat are the main modes of primary contamination. Secondary contamination does occur, and during the 1996-1997 outbreak in the DRC, 8-15% of contacts reported respiratory droplets, direct contact with muco-cutaneous lesions, or fomites as modes of secondary transmission.[8]

2.1.4 Clinical Manifestations

The clinical features of the disease are typical of an acute febrile rash illness and are preceded by a viral incubation period from 4 to up to 21 days and is characterized by two phases: the

prodromal and rash phases. The prodromal phase includes general signs like fever, headache, chills, sweats, sore throat, myalgias, prostration, and lymphadenopathy (cervical, sub-mandibular, axillary, inguinal). Lymphadenopathy represents the pathognomonic sign of the disease and contributes to clinically differentiate mpox from variola (smallpox) and other viral rash illnesses (chickenpox).[2] The rash phase can last between 2 and 4 weeks. Skin lesions are characteristic of the disease with uniform progression from macules to papules, vesicles, pustules, umbilication, crusting, and finally desquamation. Lesions have a centrifugal distribution starting from the head and the face of the patient with extension to the trunk and the extremities of the body.[2] Other extra-cutaneous findings include gastro-intestinal symptoms. Two types of complications are frequently described and may be related to bacterial superinfection (bronchopneumonia, encephalitis, sepsis, ocular infection) and dehydration.[14] Subclinical infection and asymptomatic cases have also been reported with an estimated rate of approximately 30%.[15]

2.1.5 Recent Outbreak

Among the cases reported worldwide, the DRC has the highest number of cases with more than 1000 cases reported each year since 2005. Data reported from week 1 to 21 in 2021 by the DRC's Ministry of Health epidemiological surveillance showed that 20% (104/516) of health zones in the country, including Boende and Kole, have reported cases clinically compatible with mpox disease. On December 9, 2021, the World Health Organization (WHO) reported an outbreak that was declared by the Congolese authorities in the Tunda health district in Kibombo territory in Maniema province. The index case was reported in Tunda health district the week of October 03, 2021. The epidemic continues to spread geographically in the province of Maniema with evidence of sustained human-to-human transmission in 7 health zones including Tunda, Kindu, Obokote, Samba, Kibombo, Kunda, and Lubutu. The Ministry of Health epidemiological report of week 1 to 18 in 2022 listed 513 clinically confirmed cases and 39 deaths. Additional Health Zones have identified suspected cases in Kibombo and Kindu with epidemiological links.[16,17] As the frequency of mpox cases has been increasing over the last decades, and because of the significant morbidity it causes to individuals in areas with limited-resources, research efforts to find a cure against this disease is more relevant than ever.

2.1.6 Vaccination Against MPXV

Smallpox vaccines induce cross-reactive antibodies that protect against infection from other *Orthopoxvirus* species. Live vaccinia virus vaccine (first generation), which was used during the smallpox eradication program, was estimated to be 85% effective against MPXV infection.[18] The vaccination program was discontinued after smallpox eradication was declared in 1980, causing the proportion of the unvaccinated population to rise. Furthermore, this first generation of vaccinia vaccine can cause SAEs and is contradicted in pregnant women, immunocompromised people, and people with a history of eczema.[18] Improved manufacturing procedures allowed the development of the second (ACAM2000), third (JYNNEOS), and fourth generation vaccinia vaccines with reduced side effects and simplified administration. New generation vaccine effectiveness (JYNNEOS), immunogenicity, and safety are also being evaluated in healthcare personnel at risk of MPXV infection in the Boende area in DRC[18] where an Ebola vaccine clinical trial with a modified vaccinia virus Ankara (MVA) vector was also performed.

2.1.7 Treatment

To date, most of the patients in remote regions affected by mpox receive only supportive and symptomatic care as standard treatment. However, several investigational antivirals, initially developed against smallpox, demonstrate activity against MPXV and other *Orthopoxviruses* in vitro and in animal models,[19] but none has been evaluated in a clinical trial. The most promising is tecovirimat, which is a drug developed by SIGA Technologies, Inc. (SIGA)[20] and approved by the US Food and Drug Administration (FDA) for the treatment of smallpox.[21] The FDA initially granted SIGA approval of tecovirimat for the treatment of human smallpox disease in adults and pediatric patients weighing at least 13 kg under the Animal Rule (SIGA New Drug Application 208627 and SIGA Investigational New Drug [IND] application 69019), and has since expanded the approval to individuals weighing at least 3 kg. Tecovirimat is also authorized by the European Medicines Agency for the treatment of smallpox, mpox, and cowpox.[22] Tecovirimat inhibits the exit of viral particles from an OPXV-infected cell, thereby inhibiting systemic spread of infection. The p37 protein target of tecovirimat is highly conserved in all species of *Orthopoxviruses* and is similarly targeted by tecovirimat with equivalent efficiency. There are no mammalian homologs to p37, and no orthologous genes exist outside the *Poxviridae* family. Therefore, no off-target activity has been observed. The pharmacology of tecovirimat has been evaluated in nonclinical in vitro and in vivo studies designed to assess the activity and mechanism of action of tecovirimat. In vivo efficacy studies were conducted in non- human primates and rabbits; numerous additional exploratory studies were also conducted in different animal models.[23] The clinical pharmacological and safety results from these studies are encouraging. Also, safe administration of tecovirimat has been recently reported in some of the confirmed cases identified in the US and Europe.[24]

2.2 Risk/Benefit Assessment

2.2.1 Known Potential Risks

Tecovirimat: The safety of oral tecovirimat was evaluated in 359 healthy adult participants ages 18-79 years in a Phase 3 clinical trial. The most frequently reported adverse reactions (occurring in at least 5% of participants) were headache and nausea. Abdominal pain and vomiting each occurred in 2% of participants. A total of 6 participants discontinued drug due to mild adverse reactions and one abnormal electroencephalogram change. Additional details on less common adverse reactions and the adverse reactions that led to drug discontinuation are found in the TPOXX prescribing information.[21]

Tecovirimat is a weak inducer of cytochrome P450 (CYP) 3A and a weak inhibitor of CYP2C8 and CYP2C19. However, the effects are not expected to be clinically relevant for most substrates of those enzymes based on the magnitude of interactions and a 14-day duration of tecovirimat administration, with the exception of repaglinide and midazolam as follows.

Co-administration of repaglinide and tecovirimat may cause mild to moderate hypoglycemia. In a drug interaction study, 10 of 30 healthy participants experienced mild (6 participants) or moderate (4 participants) hypoglycemia following co-administration of repaglinide (2 mg) and tecovirimat. Symptoms resolved in all participants after intake of food and/or oral glucose. Due to the risk of hypoglycemia, individuals with concomitant use of a meglitinide (repaglinide,

nateglinide) are excluded from enrollment in this study; similarly, use of these drugs is prohibited during study participation.

Tecovirimat decreased the concentration of midazolam when the drugs were co-administered in a drug interaction study. Therefore, individuals with concomitant use of midazolam are excluded from enrollment in this study; similarly, use of this drug is prohibited during study participation. Refer to the TPOXX prescribing information for additional information on drug interactions.[21]

Phlebotomy: The primary risks of phlebotomy include local discomfort, occasional bleeding or bruising of the skin at the site of needle puncture, hematoma, and, rarely, infection or fainting. Because ongoing clinical care of participants may require frequent blood draws independent of actual study-related assessments, it will be important that study teams ensure that research blood draws do not exceed the guidelines set forth by each institution's safety regulations.

Swabs: Collection of the swab samples may be uncomfortable but should not be painful.

Photography: Taking pictures of the face (including eyes) and body may be embarrassing to some people. These photographs may be used for teaching or education purposes, as well as for future research projects by the study team or other researchers. They may also be published in medical journals, without identifying the participant. We will attempt to preserve the anonymity of the participant as much as possible, while providing the information needed to support the research being published. Photographs will be stored securely, but there is a slight risk of loss of confidentiality.

Confidentiality: We will maintain participants' samples and data securely and confidentially to the extent possible, but there is a slight risk that someone will gain unauthorized access to samples and/or data, resulting in a loss of confidentiality.

2.2.2 Known Potential Benefits

All participants may benefit from the supportive care and clinical oversight provided by participation in the study and free of charge.

There is also significant benefit for the local community. Training will be provided to local hospitals and health care workers, and the study sites will benefit from logistic and material support. In addition, the knowledge gained from this study will provide important information about treatment options for MPXV infection, which currently has no approved treatment options, and thus this will be of great benefit for both the local and international community.

Alternatives to participation: Individuals who do not participate in this study may continue to receive SOC treatment or discuss other treatment options with their personal health care provider.

2.2.3 Assessment of Potential Risks and Benefits

Mpox disease is associated with significant morbidity but has no approved treatments in the DRC. Tecovirimat, developed for the treatment of smallpox, has a well-defined safety profile and has been recommended by the US Centers for Disease Control and Prevention (CDC) for control

of mox outbreaks;[25,26] however, this is currently stockpiled by the Strategic National Stockpile and may only be administered with an IND. It is approved by the European Medicines Agency (EMA) for the treatment of mpox disease, and although it has not been studied for the indication of mpox disease in humans, animal and human safety data have not raised significant safety concerns. Therefore, the risks of tecovirimat treatment are reasonable given its potential benefit as an effective treatment. Risks associated with tecovirimat treatment in this study will be minimized by following the approved dosing for smallpox for individuals who weigh at least 13 kg and following dosing based on PK modeling for those weighing <13 kg. We will be excluding individuals who may be at increased risk of AEs from treatment. All participants will be hospitalized for at least 14 days to allow for close supervision. In addition, study procedures will be limited to minimize risks and collect only the information needed to assess the study objectives. Participants will be provided a limited insurance to cover injury as the resultant of his participation to study activities.

2.3 Study Rationale

Human mpox cases have been increasing in sub-Saharan Africa since 2000,[27] and sporadic outbreaks outside of Africa have occurred.[9,28] Cessation of routine smallpox vaccination in the late 1970s has resulted in the eruption of susceptible populations to other *Orthopoxviruses*. The similarity between MPXV and the variola virus, coupled with the high comorbidity on affected individuals from areas with limited resources, have placed mpox treatments at the forefront of public health and scientific research agendas in many countries.

In the US, while one vaccine, JYNNEOS (also known as Imvamune or Imvanex), has been licensed to prevent mpox, there are no approved treatment options for mpox. Symptomatic and supportive treatments are currently the only options for clinical management. However, pre-clinical evidence for the efficacy of several compounds against MPXV infection is encouraging. ST-246 (USAN tecovirimat, used under compassionate use and sold under the brand name TPOXX), developed by SIGA for treatment of smallpox, may present an attractive option for the treatment of mpox. Phase 1 clinical trials have demonstrated a reasonable safety profile of tecovirimat in healthy volunteers.[29,30] Additionally, current US CDC guidance recommends that tecovirimat, currently administered under an IND, can be used for control of mpox outbreaks. In January 2022, the EMA approved SIGA's Marketing Application for oral tecovirimat to be administered for 14 days. However, no randomized controlled clinical trial has yet evaluated the efficacy of tecovirimat for treatment of human mpox. A lack of understanding about mpox and the need for effective, proven outbreak control measures necessitate further research activities. This effort should include clinical trials to evaluate potential medical countermeasures against mpox.

3 OBJECTIVES AND ENDPOINTS

Primary Objective:

1. To evaluate the clinical efficacy, as assessed by time to lesion resolution, of tecovirimat plus SOC versus placebo plus SOC for patients with mpox.

Secondary Objectives:

1. To evaluate the clinical efficacy, as assessed by time to lesion resolution, of tecovirimat plus SOC versus placebo plus SOC for patients with mpox, according to duration of symptoms (≤7 days or >7 days).
2. To evaluate the virologic efficacy, as assessed by PCR separately of blood, skin lesion, and oropharynx samples, of tecovirimat plus SOC relative to placebo plus SOC for patients with mpox.
3. To evaluate the clinical efficacy of tecovirimat plus SOC versus placebo plus SOC in patients with mpox as assessed by mortality, clinical severity, and duration of symptoms.
4. To evaluate the safety of tecovirimat plus SOC relative to placebo plus SOC in patients with mpox.

Exploratory Objectives:

1. To evaluate the frequency and characteristics of persistent residual lesions.
2. To describe lesion progression longitudinally over the study period.
3. To evaluate exposure history of confirmed mpox cases and to identify risk factors for MPXV infection.
4. To develop a baseline disease severity metric for mpox.
5. To evaluate the potential impact of the presence of anti-OPXV antibodies on the course of disease and the clinical efficacy of tecovirimat.
6. To evaluate persistence of MPXV PCR positivity in blood, skin lesions, and the oropharynx.
7. To evaluate the trajectory of MPXV IgM and IgG over time during infection.
8. To assess genomic variability in MPXV isolated from participants based on geographic and clinical differences.
9. To assess whether viral resistance develops due to selective pressure by treatment.
10. To assess the effect of HIV infection on mpox clinical outcomes and treatment effect.
11. To determine tecovirimat drug levels in a real-world scenario.
12. To describe clinically and virologically any cases of recrudescent disease as defined by the protocol (see section 9.1.2).

Primary Endpoint: Time to lesion resolution, defined as the first day on which all lesions on the total body are scabbed or desquamated or a new layer of epidermis has formed (see section 8.4.1), up to 28 days after randomization.

Secondary Endpoints:

1. Time to lesion resolution, as defined in the primary endpoint, according to stratification by time from onset of illness as ≤ 7 days or > 7 days.

2. Proportions with negative PCR results separately by blood, oropharyngeal swab, and lesion swab samples 14 days after randomization.
3. Mortality within the first 28 days after randomization.
4. Time to death up to 28 days after randomization.
5. Frequency and duration of clinical symptoms (including nausea, vomiting, abdominal pain, diarrhea, anorexia, cough, lymphadenopathy, dysphagia, sore throat, muscle aches, fatigue/lack of energy, fever, chills, night sweats, headache, ocular lesions, eye pain, change in vision, buccal ulcers, nasal congestion, cough, joint pain, pain with urination, painful skin lesions, pruritic skin lesions).
6. Incidence of SAEs, AEs requiring drug discontinuation, and incidence of other AEs.
7. Incidence of bacterial infections. Bacterial infections will be defined clinically with laboratory and radiographical confirmation when possible.
8. Automated image analysis of lesion counts and characteristics over time.

Exploratory Endpoints:

1. Presence, location, and duration of persistent residual lesions, defined as any lesion (in any area of the body) unresolved after all assessment-region lesions are scabbed or desquamated.
2. Longitudinal description of lesion progression over the study period.
3. Number and percentage of confirmed mpox cases reporting exposure to animals, symptomatic humans, or with no known exposures.
4. Associations between measures of baseline disease severity (including lesion counts, duration of symptoms, and comorbidities) and efficacy endpoints.
5. Differences in outcomes based on the presence of anti-OPXV antibodies.
6. Viral load and proportion with negative PCR results in blood, oropharyngeal swab, and open lesion swab samples over time and time to the first negative PCR result in each of these specimens up to 28 days after randomization.
7. Change in antibody titer over time.
8. Sequencing differences between virus isolated from participants from different geographic areas and with differing clinical trajectories and responses to tecovirimat.
9. Sequencing differences between virus isolated prior to and after treatment.
10. Differences in severity and duration of MPXV infection and treatment effect by HIV status, including HIV viral load.
11. Pre-dose concentration in all participants and 4h post-dose concentration only in participants ≥18 years of age of tecovirimat in blood measured on day 7.
12. Incidence of recrudescent disease and description of clinical and virologic characteristics of recrudescent disease cases.

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, placebo-controlled, double-blind study to test the antiviral drug tecovirimat for the treatment of adults and children with laboratory-confirmed MPXV disease at participating sites in DRC. Study sites will be in geographic locations where cases of mpox were reported and previous surveillance activities related to this disease have been carried out, namely, in the health zones of Boende in Tshuapa, Kole in Sankuru, and Tunda in Maniema. We anticipate that those 3 health zones will ensure the completion of the study accrual in the 5 years of the study duration. Sites will be opened one after another to ensure correct workflow of activities within a site and synchronization of activities between sites later on.

Eligible and consented participants (N=600) will be randomized 1:1 to receive either tecovirimat or placebo; all participants will also receive SOC treatment standardized at each site according to local/site practice and outlined in a manual of operations. Randomization will be stratified according to time since prodromal symptom onset (≤7 days or >7 days) and study site. A participant will be considered enrolled beginning from when the informed consent form is signed and randomization to an assigned treatment has occurred. Once enrolled, study drug administration will begin according to study group assignment. Tecovirimat will be administered as described below (section 6.2). Study drug and placebo administration will be for 14 days.

Participants will be hospitalized throughout the period of study treatment for free and will undergo frequent clinical and laboratory assessments for safety and efficacy evaluations (see section 1.3 for a detailed schedule of assessments). Participants and up to 2 accompanying family members will receive a daily stipend (section 5.9). Participants will be eligible for discharge at the discretion of the treating physician when all mpox lesions on the total body are scabbed with no residual inflammation or desquamated or new layer of epidermis and the participant has received two consecutive negative blood PCR results, but not before day 14 when study drug administration is complete. If a participant reaches full body lesion resolution but subsequently develops at least one new lesion consistent with mpox after discharge but while still enrolled in the study, they will be eligible to make a “Sick Visit” as defined in the Schedule of Activities and will be offered standard of care for mpox. Day 29 is the final required study visit, but participants may return for an optional visit at Day 59 for long-term clinical and laboratory evaluations. Interim monitoring of study safety and integrity will be performed by a data and safety monitoring board (DSMB). The DSMB may recommend stopping the study early for efficacy if there is clear and substantial evidence of a treatment benefit, or for evidence of harm or futility.

4.2 Scientific Rationale for Study Design

Data from an observational study on mpox, carried out in the Sankuru province of the DRC between 2007 and 2011 as part of a joint effort involving the DRC National Institute of Biomedical Research (Institut National de Recherche Biomédicale; INRB) and the US Army Medical Research Institute of Infectious Diseases (USAMRIID), have considerably contributed to the development of the study design. Data were available on 228 patients with PCR-confirmed MPXV disease and included a limited set of baseline characteristics and demographics, longitudinal vital signs, longitudinal MPXV PCR, and daily lesion counts classified by lesion

stage (macule, papule, vesicle, pustule, umbilication, scabbing, or desquamating). The primary endpoint is designed to quantify the resolution of mpox illness. Specifically, the primary endpoint is "time to lesion resolution," defined as the time for all lesions to reach a scabbed or desquamating stage. Faster resolution of painful lesions is meaningful to the patient and lesion scabbing and desquamation coincides with resolution of viremia and clinical symptoms.

Additionally, a patient is no longer considered infectious when all lesions are desquamated. Time to one or two negative PCR results were deemed to be of less clinical importance to the patient and are considered as secondary endpoints.

Randomization will be used to eliminate the selection bias, to balance the groups with respect to many known and unknown confounding or prognostic variables. A placebo control group will be incorporated in order to fully understand whether the drug under investigation is effective. Furthermore, to avoid any disclosure related to the administration of the drug from the study's investigator or participants and to preclude any influence by the study investigators, the study was designed to be double blinded.

4.3 Justification for Dose

Tecovirimat will be administered at the FDA-approved dose (for individuals weighing ≥13 kg) for the treatment of smallpox, which is caused by another *Orthopoxvirus* (variola virus) that is closely related to MPXV. The approved treatment duration for smallpox is 14 days, which did not result in severe or serious AEs; accordingly, under this protocol, study drug will be administered for 14 days. For participants weighing <13 kg, oral rather than intravenous dosing (as indicated under the FDA approval) will be used; SIGA provided oral tecovirimat dosing for these participants based on population pharmacokinetic (PK) modeling.

5 STUDY POPULATION

5.1 Inclusion Criteria

Individuals must meet all the following criteria to be included in the study:

1. Laboratory-confirmed MPXV infection as determined by PCR obtained from blood, oropharynx, or skin lesion within 48 hours of screening.
2. Mpox illness of any duration provided that the patient has at least one active, not yet scabbed, lesion.
3. Weight ≥3 kg.
4. Men and non-pregnant women of reproductive potential must agree to use effective means of contraception when engaging in sexual activities that can result in pregnancy, from the time of enrollment through the end of study participation. Acceptable methods of contraception include the following:
    - Hormonal contraception.
    - Male or female condom.
    - Diaphragm or cervical cap with a spermicide.
    - Intrauterine device.

5. Stated willingness to comply with all study procedures (including required inpatient stay) and availability for the duration of the study.
6. Ability to provide informed consent personally or by a legally or culturally acceptable representative if the patient is unable to do so.

5.2 Exclusion Criteria

Individuals meeting any of the following criteria are not eligible for enrollment in the study:

1. Current or planned use of a meglitinide (repaglinide, nateglinide).
2. Planned use of midazolam while on study drug.
3. Severe anemia, defined as hemoglobin <7 g/dL.
4. Current or planned use of another investigational drug at any point during study participation.
5. Patients who, in the judgement of the investigator, will be at significantly increased risk as a result of participation in the study.
6. Participants who are unable to safely swallow oral medications, such as those who are at risk of aspiration.

5.3 Pregnant or Breastfeeding Women

No adequate and well-controlled studies in pregnant women have been conducted; therefore, there are no human data to establish the presence or absence of tecovirimat-associated risk in pregnancy. Given that pregnant women may be at risk for more severe disease and possible congenital mpox disease, pregnant women will be enrolled in this study if the principal investigator agrees that the benefits of receiving TPOXX outweigh its risks. If possible, long-term outcomes will be assessed in pregnant participants.

In animal reproduction studies, no embryofetal developmental toxicity was observed in mice during the period of organogenesis at tecovirimat exposures (area under the curve [AUC]) up to 23 times higher than human exposure at the recommended human dose (RHD). In rabbits, no embryofetal developmental toxicity was observed during organogenesis at tecovirimat exposures (AUC) less than human exposures at the RHD. In a mouse pre-/post-natal development study, no toxicities were observed at maternal tecovirimat exposures up to 24 times higher than human exposure at the RHD.

Similarly, there are no data to assess the effect on milk production, the presence of the drug in human milk, and/or the effects on the breastfed child. When administered to lactating mice, tecovirimat was present in the milk.[21] The developmental and health benefits of breastfeeding should be weighed against the mother's clinical need for TPOXX and any potential adverse effects on the breastfed child from TPOXX or from the underlying maternal condition.

5.4 Inclusion of Vulnerable Participants

Children: Tecovirimat is approved in the US for the treatment of smallpox disease in children weighing at least 3 kg, and in the European Union for the treatment of smallpox, mpox, and

smallpox in children weighing at least 13 kg. This study will enroll all children who meet eligibility if they weigh at least 3 kg. Using population PK modeling, SIGA has provided dosages that will allow for oral dosing in participants weighing <13 kg. The incidence of mortality from mpox in children is higher than in adults,[31] so inclusion of this population is particularly important for this study. Since tecovirimat has potential benefit as a treatment for mpox disease, which can cause significant morbidity and has no currently approved treatments in the DRC, children who meet the weight requirements will be allowed to enroll in this study.

Adults who lack capacity to consent to research participation: Adults who are unable to consent are eligible for enrollment in this protocol because mpox may cause severe disease, and data obtained from these individuals are necessary to answer important scientific questions about this disease and possible treatments. Similarly, enrolled participants who lose the ability to provide ongoing consent during study participation may continue in the study. The risks and benefits of participation for adults unable to consent should be the same as those described for less vulnerable participants. The process for obtaining consent for these individuals is described below (section 11.1.1).

5.5 Lifestyle Considerations

During this study, participants are asked to refrain from use of any of the following throughout study participation:

- Meglitinides (repaglinide, nateglinide)
- Midazolam.
- Another investigational drug.

Men and women participants of childbearing age will be required to use an accepted form of contraception outlined in section 5.1.

5.6 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a modifiable factor may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.7 Community Engagement

Community-level meetings before the start of the study will be conducted in order to improve the understanding of the research by potential study participants. Community-level consultations will be implemented by the social mobilization group of the study team in the form of community sensitizations, which is a process by which research staff hold meetings to make

research information available in the community from which potential research participants can be recruited. These pre-study activities will be organized in collaboration with the Ministry of Health staff and international nongovernmental organizations working in the health system of the study region. The survey team will oversee outreach activities and assess the messages to be communicated to the community to avoid any misunderstanding or miscommunication. Community residents will be invited to a central meeting place where the study is explained, and questions can be asked. At the end of this process, the authorization to carry out the research in the community can be given by the leader of the community or a representative in the event of their absence. Although such authorization can in no way replace the consent of individuals, it represents the engagement of the community. The study team will attempt to identify hotspots of resistance in the community to the study and will present adequate solutions during the study to mitigate or eliminate mistrust.

5.8 Strategies for Recruitment and Retention

Patients with MPXV infection at participating health centers will be approached by a member of the study team and offered potential participation in this study. All participants enrolled in the study will be hospitalized during the study treatment period to avoid missed or delayed study activities during this critical period. Special dispositions will be put in place to offer accommodation at the hospital for family members who will accompany study participants. Phone calls will be established with the participant after their discharge to remind them of the follow-up visit.

5.9 Costs

There will be no costs to participants for participating in this study. Hospitalization and treatment will be free of charge. Meals will be provided daily to the participant and up to two individuals accompanying the participant during the participant's hospitalization with an approximate value of $8, equivalent in local currency to 16,000 CDF, per person per day.

5.10 Compensation

Study participants and up to two individuals accompanying the participant will receive US$15, equivalent of 30,000 Congolese francs in local currency, to compensate for their time and inconvenience at study screening. If they qualify and are enrolled in the study, the participant and up to two individuals accompanying them will also receive US$15 for Day 29 and for Day 59. An additional stipend of $4, equivalent in local currency to 8,000 CDF, will be provided daily to the participant and up to two individuals accompanying the participant while the participant is hospitalized. Round trip travel to the study site for screening and for each study visit (Days 29 and 59) will be provided for the participant and up to two individuals accompanying the participant. If a participant develops new lesions consistent with mpox after discharge but while still enrolled in the study, travel will be provided for at least one sick visit for the participant and up to two individuals accompanying the participant.

If a participant does not sign a screening consent but is eligible to join the study and signs the main study consent, the participant and up to two others will receive $15, equivalent in local currency to 30,000 Congolese francs (CDF), for the first study visit. Travel will also be provided as outlined above.

6 STUDY INTERVENTION

6.1 Study Intervention Description

Tecovirimat is an antiviral drug against variola (smallpox) virus that is manufactured by Catalent Pharma Solutions and distributed by SIGA Technologies, Inc. under the brand name TPOXX. It is approved by the US FDA for the treatment of human smallpox disease in adults and pediatric patients weighing at least 3 kg. It works by inhibiting the OPXV VP37 envelope-wrapping protein, which is encoded by and highly conserved in all members of the *Orthopoxvirus* genus. Its effects on the VP37 protein ultimately prevent the formation of egress-competent enveloped virions necessary for virus transmission. See the TPOXX prescribing information for additional details.[21]

6.2 Dosing and Administration

Tecovirimat capsules or placebo capsules will be administered orally to participants for 14 days as follows.

- ≥120 kg: three capsules three times a day (total daily tecovirimat dose: 1,800 mg).
- 40 to <120 kg: three capsules twice a day (total daily tecovirimat dose: 1,200 mg).
- 25 to <40 kg: two capsules twice a day (total daily tecovirimat dose: 800 mg).
- 13 to <25 kg: one capsule twice a day (total daily tecovirimat dose: 400 mg).
- 6 to <13 kg: ½ the contents of a capsule twice daily (total daily tecovirimat dose: 200 mg).
- 3 to <6 kg: ¼ the contents of a capsule twice daily (total daily tecovirimat dose: 100 mg).

For participants who weigh <40 kg, weight will be taken each day before breakfast and used to determine the tecovirimat dose or equivalent number of placebo capsules for that day. The study agent should be taken within 30 minutes after a full meal of moderate or high fat, defined as 600 calories and 25g of fat. Infants and small children who are unable to will not be required to consume the calorie and fat requirement.

No dose adjustments will be made for pregnant women.

Preparation instructions for pediatric participants and participants who are unable to swallow capsules are provided in section 6.3.4.

6.2.1 Dose Modifications

No dosage adjustment is required for patients with mild, moderate, or severe renal or hepatic impairments at baseline. See section 9.4 for pausing rules.

Missed doses
If a participant misses:

1. less than 24 hours of therapy: restart regular dosing schedule.

2. between 24-48 hours of therapy, may restart the regular dosing schedule at the physician's discretion.
3. more than 48 hours of therapy, discontinue the study drug.

6.3 Preparation/Handling/Storage/Accountability

6.3.1 Acquisition and Accountability

Acquisition: Tecovirimat and placebo will be shipped from the US to the study site where administration will take place, in compliance with all applicable transport guidelines.

Accountability: The study pharmacist will be responsible for maintaining an accurate record of the study arm codes, inventory, and an accountability record of study agent supplies.

6.3.2 Formulation, Appearance, Packaging, and Labelling

Tecovirimat is available as immediate-release capsules containing tecovirimat monohydrate equivalent to 200 mg of tecovirimat for oral administration. The capsules are imprinted in white ink with "SIGA" followed by the SIGA logo followed by "®" on an orange body, and a black cap imprinted in white ink with "ST-246®." The capsules include the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The capsule shell is composed of gelatin, FD&C blue #1, FD&C red #3, FD&C yellow #6, and titanium dioxide.

The placebo product is identical to the tecovirimat in all aspects except it contains no active drug.

The capsules will be stored at 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F).

6.3.3 Product Storage and Stability

Tecovirimat capsules may be stored up to 84 months in the original container at 20°C to 25°C (68°F to 77°F), with excursions permitted from 15°C to 30°C (59°F to 86°F).

6.3.4 Preparation

For participants who cannot swallow capsules, study drug can be prepared by carefully mixing the required contents in 30 mL of liquid (e.g., milk, chocolate milk) or soft food (e.g., apple sauce, yogurt). The entire mixture should be administered within 30 minutes of its preparation.

6.4 Measures to Minimize Bias: Randomization and Blinding

6.4.1 Randomization

Once eligibility has been confirmed, participants will be eligible for randomization. Randomization will be performed onsite by the site pharmacist. Regardless of whether the randomization process occurs online or offline, participants will be randomized via permuted block randomization in a 1:1 ratio to tecovirimat or placebo within randomization strata of days from onset of prodromal symptoms (≤7 days or >7 days) and study site.

Because of the rural location of study sites, a consistent and strong internet connection is not guaranteed. While randomization using a secure online portal is preferred, a backup procedure for randomization via sequentially numbered secure envelope will be in place at study sites. Backup randomization envelopes for each stratum will be shipped to the site in advance of study start in secure boxes and stored in an access-controlled location.

A randomization procedure document will be developed prior to study start to provide details on the randomization process and procedures for maintaining the integrity of the randomization. The treatment allocation table and the program used to generate the treatment allocation table will be maintained by the data coordinating center on secure servers. The block size or sizes used to create the treatment allocation table will not be revealed to anyone outside the unblinded team responsible for creating the table.

6.4.2 Blinding/Unblinding

Study team members, including the pharmacovigilance team, and participants will be blinded to treatment arm assignment throughout the duration of the study. To preserve blinding, after preparation, the drug or placebo will be placed outside the pharmacy for pick-up. The pharmacist will alert the responsible study team member that the treatment is ready to be picked up. The unblinded pharmacy staff is responsible for maintaining security of the study treatment assignments.

Scheduled unblinding:
After all participants have completed the final study visit (or in the event that the study is stopped early), the study will be unblinded and participants will be informed about their study treatment assignment by the study team.

Unscheduled unblinding:
Intentional:
By the Medical Monitor (MM) or other pharmacovigilance/safety/oversight/regulatory entity to clarify a potential safety signal or comply with a regulatory requirement.

NOTE: This specifically does NOT cover an urgent need to know at the site level for subject treatment imperative, which is covered in the next section, after that immediately below:

- The DSMB may unblind itself at any time, and for any data and number of cases if indicated in keeping with its charter and its oversight and safety role. Action will proceed at the discretion of the DSMB chair and will be documented confidentially and internally by the DSMB Executive Secretary. The DSMB may work directly with the unblinded data and statistical team that supports it to accomplish this. The impacted data and outcome of such non routine review should be confidentially and internally documented through the DSMB Executive Secretary. Disclosure of this review should be at the discretion of the DSMB in a manner that does not unduly compromise the study blind or integrity. Should the review indicate an action is needed for subject safety or study integrity, etc., that action will be taken at the direction of the DSMB and chair in a

discrete manner that accomplishes the study imperative while minimally impacting the study blind or integrity.

- The MM, pharmacovigilance committee, or protocol level Principal Investigator/Chair, may request unblinded review of an event or series of events or other study data by the DSMB (general process outlined above) to clarify a potential safety signal or to comply with a regulatory requirement such as Safety Oversight or Event Reporting. Such a request is made in writing, specifying the impacted data/study records, the concern or requirement being met, and any other information that will help define, facilitate, but also limit the review to help preserve study integrity and blind. The request is made through the DSMB Executive Secretary. As outlined above, the DSMB will conduct the review as narrowly as possible, utilizing unblinded study team members such as the unblinded data and statistical staff, and will issue a summary statement as it sees fit, to balance the request against the need to maintain the study blind and study integrity.
- **At all times, and in all manners, the human subject protection priority will be met in a way that maximally protects study and data integrity, while avoiding or else strictly limiting to 'need to know,' the breadth and the degree of any unblinding.**
- A summary record of the names, roles, and unblinded records disclosed to parties who become unblinded is maintained by the study staff who reveal blinded data. This is documented, and forwarded WITHOUT FURTHER UNBLNDING INFORMATION, to the unblinded study statistician and the clinical trials monitors.

By a study site investigator to meet an urgent need to know at the site level for subject treatment imperative:

- An emergency request for unblinding of treatment assignment at the site level is permitted ONLY when knowledge of the treatment will clearly and urgently impact subject protection, e.g. by **significantly** altering treatment choices or clinical options.
- Such requests may be made directly by or through (in the case of a request from outside the study, e.g. by a clinician) a site investigator to the site pharmacist, who provides the required information directly and in the most limited manner possible to the site investigator.
- **At all times, and in all manners, the human subject protection priority will be met in a way that maximally protects study and data integrity, while avoiding or else strictly limiting to 'need to know,' the breadth and the degree of any unblinding.**
- If there is disagreement at the site level the decision is urgently (phone or other timely and reliable method) elevated to the MM and/or study clinical leadership for a decision.

Unintentional: If unintentional unblinding of study agent assignment occurs, the site principal investigator will create a plan for ongoing management of the participant(s) involved and for preventing the recurrence of a similar incident, as appropriate. If the protocol team determines that the unintentional unblinding may have a significant impact on the study plan (e.g., if the treatment codes for multiple participants were accidentally revealed), the need for a protocol amendment will be addressed as soon as possible.

Intentional and unintentional unscheduled unblinding will be documented in the appropriate source and/or research record and will include the reason for the unscheduled unblinding, the date it occurred, who approved the unblinding, who was unblinded, who was notified of the unblinding, and the plan for the participant. The site principal investigator will report all cases of intentional and unintentional unscheduled unblinding to the DSMB in writing within 1 business day after site awareness via email to the DSMB outlining the reason for the unblinding and the date it occurred. The report will also be submitted to the MM. If the unblinding meets the definition of a reportable event, it will be reported to the IRB/EC according to their respective procedures.

If an SAE has resulted in unblinding, this information will be included in the SAE report.

6.5 Study Intervention Compliance

The pharmacist will monitor the inventory of investigative products through the distribution log, which will record entries and exits, quarantines, transfers between sites, and the conditions of storage, as well as any comments useful to inform about the quality of the product. During the dispensing of the product, the dispensing log will be completed with participant number, quantity (mg) of product received, day, date, batch of medication, and initials of the pharmacist and the preparer.

The pharmacist will perform the randomization and keep a randomization log to document the link between the participant number and the product assigned.

Study drug will be administered to participants under direct observation by a member of the study team.

A quality log will be kept documenting any temperature excursions affecting the study agents (less than 15°C and more than 30°C). Temperature excursions outside of this range will be reported, and the log will be made available to the principal investigator, pharmaceutical company, and study pharmacist to establish whether the affected product can be used. All critical issues/conditions relating to the quality of the product will be documented.

A destruction log will be available at the site to document the destruction of all expired or damaged product batches.

6.6 Concomitant Therapy

All concomitant prescription and nonprescription (including over-the-counter, herbal, or traditional) medications taken during study participation will be recorded. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician.

6.7 Prohibited Medications

Participants who are currently or plan to use a meglitinide (repaglinide, nateglinide) or midazolam will be excluded from this study. If the need to use one of these drugs arises after

enrollment into the study, the participant will not be allowed to continue study drug administration.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Study intervention may be discontinued for an individual participant or groups of participants (i.e., pausing), or it may be discontinued for all participants and enrollment suspended (i.e., halting). Pausing and halting rules and procedures are described in sections 9.4 and 9.5.

7.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request. Criteria and procedures for withdrawal and replacement of a participant by the investigator are provided in section 9.2.

7.3 Lost to Follow-up

If a patient cannot be located or contacted (i.e., the patient lost to follow-up) between the time of discharge and Study Day 59, their completion date will be considered the last known date of contact with them by study personnel.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Personnel for Study Procedures

Assessments and study procedures may be performed by members of the investigative team and clinical team as assigned.

The study will be conducted in accordance with the protocol, Good Clinical Practice (GCP), and all applicable US and host country ethical and regulatory requirements.

8.2 Site-Specific Considerations

Due to the remote area in which the study will be implemented, participating sites in this study may face significant resource challenges. Therefore, the SOC regimen will not be set by the protocol. Rather, SOC will be standardized at each site according to local/site practices and availability of resources. Furthermore, sites should make every effort to comply with the study evaluations outlined below; however, the inability of a site to collect the full frequency of research assessments due to unavoidable resource limitations, and despite best efforts, will not constitute a protocol deviation.

8.3 Study Schedule

See section 1.3 for a detailed schedule of procedures. The day when the participant is randomized to their assigned treatment arm is denoted as Study Day 1. Screening procedures will occur in the day prior to or the same day as (but prior to) randomization (Study Day -1 to 1). Note that there is no Study Day 0. Study Day -1 is the 24-hour day prior to the day of randomization. The first day after randomization is Study Day 2. Subsequent days will be

numbered chronologically through Day 59 of study. Therefore, the Day 29 visit occurs 28 days after randomization and the Day 59 visit occurs 58 days after randomization.

8.4 Study Evaluations and Procedures

8.4.1 Operational and Clinical Assessments

Informed Consent
The investigator or a qualified and previously designated member of the study team will review the informed consent documents with the participant. If a participant is incapable of reading the informed consent, the study procedures will be explained in the local language preferred by the participant. Each consent will be attended by a witness in addition to the investigator or previously designated study team member, and the witness will also sign the informed consent. The date that informed consent was obtained will be documented on the informed consent form. A signed screening consent will be obtained prior to performing screening procedures; once eligibility is confirmed, consent for study participation will be obtained using a main study consent prior to performing Day 1 procedures.

Demographics
The following information should be recorded from the participant or surrogate:

- Age
- Sex
- Geographic region (health zone) of residence

Medical History
The following information should be recorded:

- Focused medical history regarding mpox and confirmation of at least one active, not yet scabbed, mpox lesion (to be recorded as part of eligibility determination).
- Current symptoms (nausea, vomiting, abdominal pain, anorexia, cough, lymphadenopathy, dysphagia, fever, headache, ocular lesions, and buccal ulcers).
- Current comorbidities (HIV, tuberculosis, malaria, hypertension, diabetes mellitus, asthma, hepatitis, hyperlipidemia, cancer, heart failure, renal disease, liver disease, chronic obstructive pulmonary disease (COPD), COVID-19, neoplasm, obstructive sleep apnea, obesity, immunosuppressive disorder other than HIV, sickle cell anemia, concurrent bacterial infections such as urinary tract, ear nose and/or throat, pulmonary, central nervous system, skin or gastrointestinal infection, bacteremia/sepsis or other. Bacterial infections will be defined clinically with laboratory and radiographical confirmation when possible.
- Smallpox vaccination status or presence of vaccination scar.
- Risk factors for MPXV infection such as questions related to: recent contact with known mpox case including type of contact, residing or visiting an area with an active mpox outbreak, animal handling.

Medication Review
All concomitant prescription and nonprescription (including over-the-counter, herbal, or traditional) medications taken during study participation will be recorded. All medications taken by the participant up to one week prior to enrollment will be recorded.

Vital signs
Temperature, heart rate, respiratory rate, and blood pressure will be measured, with oxygen saturation measured if possible.

Weight
Weight will be measured at screening for all participants and used to determine study drug dose throughout the treatment period for participants ≥40 kg. For participants <40 kg, weight will be taken every day before breakfast during the treatment period and used to determine daily study drug dose.

Height
Height will be obtained for all participants at screening.

Arm circumference
Arm circumference will be obtained at screening for participants aged 3 months to ≤ 5 years.

Pregnancy Testing
Serum or urine pregnancy testing will be performed for females of childbearing potential only.

HIV Testing
HIV testing will be performed retrospectively on blood collected at Day 1 for participants who agree to be tested. If possible, all HIV-infected participants, whether with previously known or newly diagnosed infection, will be contacted by a study staff member for referral to a local HIV treatment center or contacted by a health zone official in charge of coordinating activities related to the HIV program. Viral load may be performed for HIV-infected participants.

Malaria testing
Rapid malaria testing may be done at Day 1 for all participants. Although collection is highly desirable, malaria testing may be waived if not feasible, per investigator discretion.

Varicella zoster virus (VZV) testing
VZV PCR testing may be done retrospectively on blood collected at Day 1 for all participants. Although collection is highly desirable, VZV PCR may be waived if not feasible, per investigator discretion.

Determination of Eligibility
Once the screening procedures are complete, eligibility will be determined based on the inclusion and exclusion criteria. Participants that are found to be ineligible will be informed during the screening evaluation, and the reason for their ineligibility will be discussed and documented.

Lesion Assessments

- Target region assessment: Total number of lesions in the assessment region will be counted and recorded until all lesions in the assessment region are scabbed or desquamated ("resolved"). A lesion is considered 'scabbed' when the pustule has resolved, the lesion no longer appears inflamed, and scab (keratotic crust or eschar) is the only remaining component of the lesion. Desquamation refers to loss of the scab and the presence of intact epidermis at the site of previous involvement.

  In order to be considered "resolved," a lesion must fit into one of last stages of lesion evolution:

  1. Scab formation of entire lesion/lesion is otherwise flat with no residual inflammation
  2. Desquamation (loss of scab)
  3. New layer of epidermis (scar)

- Consensus guidelines on lesion characteristics will be developed to standardize the manual count. Photographs of the assessment region and other parts of the body will be collected and later analyzed using a computer-vision algorithm to determine lesion counts. These counts will be compared to the manual count to evaluate the accuracy of the manual count. A protocol standardizing the collection of assessment region photographs will be developed.

- The target assessment region is composed of the right leg (including the front and back of the foot) and right arm (including the front and back of the hand). In the event that a participant is missing a part of a right limb, the left leg (including the front and back of the foot) and left arm (including the front and back of the hand) may be used as the target assessment region. The target assessment region will be undefined for any participants who do not have either a) both a right leg and right arm or b) both a left leg and left arm. In the event that such participants are enrolled in the study, target region assessment will not be performed (e.g., no counts will be performed since the assessment region would be ill-defined). Full body assessments described below would still be performed so that determination of the primary endpoint can still occur.

- Full body assessment: After resolution of lesions in the target region, assessment of lesion counts will progress to a simplified full-body evaluation, not requiring lesion counting, will record whether all lesions are resolved ("yes/no"). This assessment will continue until all lesions are resolved (or Day 29, whichever comes first), at which point the primary endpoint is met. Photography of residual lesions not in the assessment region will be taken as well as of the entire body once all of the lesions have resolved.

- If a participant reaches full body lesion resolution but subsequently develops at least one new lesion consistent with mpox after discharge but while still enrolled in the study, they will be eligible to make a "Sick Visit" as defined in the Schedule of Activities and will be offered standard of care for mpox.

Randomization
Randomization defines Study Day 1. Randomization will only occur when a given individual has met all eligibility criteria as outlined above (sections 5.1 and 5.2).

Study Drug Administration
Study drug administration will begin on Day 1 and continue for 14 days, as described in section 6.

SOC Received
SOC will be outlined in a manual of operations and treatments will be recorded.

Assessment of AEs/SAEs
See section 9.

8.4.2 Research Laboratory Evaluations

Blood will be collected via venipuncture for MPXV PCR with CT, and blood will be stored for antibody titer measurements, viral sequencing, and other future research testing. Swabs will be collected from the oropharynx and open skin lesions for viral load and sequencing assessments. All collected specimens will be stored for later assessment. An additional voluntary/optional blood sample will be obtained from all participants ≥18 years of age at 4 hours after receiving their first dose of study drug on day 7 to be used for PK analysis (Appendix D). The blood volume to draw will be specified in the Laboratory Manual.

8.4.3 Clinical Laboratory Evaluations

Laboratory testing, including urinalysis, will be performed as described in section 1.3, and results will be shared with participants if they want them. While every effort should be made to obtain these laboratories as indicated, note that the frequency and volume of blood draws is always subject to the clinical judgment of the site investigator as to safety and logistical considerations. Hence, though highly desirable, these evaluations may be waived if not feasible (e.g., due to blood draw volume concerns related to participant weight or due to site logistics), per investigator discretion. The blood volume to draw will be specified in the Laboratory Manual.

9 SAFETY AND OTHER ASSESSMENTS

Assessment of AEs/SAEs: Information about AEs/SAEs will be assessed via appropriate questioning and examination at each study contact. Additional procedures may be performed (e.g., clinical laboratory evaluations) as needed to further characterize events.

9.1 Safety Definitions, Management, and Reporting

9.1.1 Definitions

Adverse Event: An AE is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the research.

Adverse Reaction (AR): An AR means any AE caused (see "Causality" below) by a study agent. ARs are a subset of all suspected adverse reactions (SARs; defined below) where there is reason to conclude that the study agent caused the event.

Suspected Adverse Reaction (SAR): SAR means any AE for which there is a reasonable possibility that the study agent caused the AE. "Reasonable possibility" means there is evidence to suggest a causal (see "Causality" below) relationship between the study agent and the AE. A SAR implies a lesser degree of certainty about causality than an AR, which means any AE caused by a study agent.

Serious Adverse Event (SAE): An SAE

- is an AE that results in death.
- is an AE that is life-threatening event (places the subject at immediate risk of death from the event as it occurred).
- is an AE that requires inpatient hospitalization or prolongs an existing hospitalization. NOTE:
    - Hospitalization is considered required if outpatient treatment would generally be considered inappropriate.
    - Same-day surgical procedures that are required to address an AE are considered hospitalizations, even if they do not involve an overnight admission.
    - Hospitalization due to a condition that has not worsened and that pre-dates study participation (e.g., elective correction of an unchanged baseline skin lesion), or due to social circumstance (e.g., prolonged stay to arrange aftercare), or that is planned/required "per protocol" AND that proceeds without prolongation or complication, is NOT considered an SAE by this criterion.
- is, or results in, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- is a congenital anomaly/birth defect/miscarriage/stillbirth.
- is a medically important event.

NOTE: Medical and scientific judgment should be exercised. Events that significantly jeopardize the subject and/or require intervention to prevent one of the SAE outcomes listed above are generally considered medically important and are thus SAEs.

Unexpected Adverse Event (UAE): A UAE is unexpected if it is not listed in the investigator's brochure or package insert (for marketed products) at the frequency, AND specificity, AND severity that has been observed.

- Such events should also be evaluated for possible reporting as unanticipated problems (UPs) (see section 9.1.2.3.2).
- Unexpected, as used in this definition, also refers to AEs or SARs that are mentioned in the investigator's brochure as occurring with a class of drugs/biologics, or as anticipated

from the pharmacological properties of the study agent but are not specifically mentioned as occurring with the particular study agent under investigation.

Serious and Unexpected Suspected Adverse Reaction (SUSAR): A SUSAR is a SAR (defined above) that is both serious and unexpected.

Unanticipated Problem (UP): A UP is any event, incident, experience, or outcome that is:

1. **unexpected** in terms of nature, severity, or frequency in relation to:
    a. the research (including but not limited to risks) as described in the IRB/EC-approved research protocol and informed consent document, investigator's brochure, or other study documents; **and**
    b. the characteristics of the subject population being studied; **and is**
2. possibly, probably, or definitely related (see "Causality" below) to participation in the research; **and**
3. suggests the research places subjects or others at a **greater risk** of harm (including physical, psychological, economic, or social harm) than was previously known or recognized, per the documents currently approved by the IRB/EC.

    NOTE:

    - An SAE always meets this "greater risk" criterion.
    - An incident, experience, or outcome that meets the definition of a UP generally will warrant consideration of changes to the protocol or informed consent form, or to study procedures (e.g., the MOP for the study), in order to protect the safety, welfare, or rights of participants or others. Some UPs may warrant a corrective and preventive action plan (CAPA) at the discretion of the oversight entities.

Unanticipated Problem that is not an Adverse Event (UPnonAE): A UPnonAE belongs to a subset of UPs that:

- meets the definition of a UP, AND
- does NOT fit the definition of an AE or an SAE.

    NOTE: Examples of UPnonAEs include, but are <u>not limited to</u>:

    - a breach of confidentiality
    - prolonged shedding of a vaccine virus beyond the anticipated timeline
    - unexpectedly large number of pregnancies on a study
    - subject departure from an isolation unit prior to meeting all discharge criteria
    - accidental destruction of study records
    - unaccounted-for study agent
    - overdosage, underdosage, or other significant error in administration or use of study agent or intervention, even if there is no AE/SAE

- development of an actual or possible concern for study agent purity, sterility, potency, dosage, etc.

  NOTE: A decision to temporarily quarantine, or to permanently not use all or part of study agent supply due to an unexpected finding or event (e.g., particulate, cloudiness, temperature excursion), even if there is no known or proven issue (i.e., out of an "abundance of caution"), is considered a UPnonAE.

Non-compliance: Failure of investigator(s) to follow the applicable laws, regulations, or institutional policies governing the protection of human subjects in research, or the requirements or determinations of the IRB/EC, whether intentional or not.

1. **Serious non-compliance:** Non-compliance, whether intentional or not, that results in harm or otherwise materially compromises the rights, welfare and/or safety of the subject. Non-compliance that materially affects the scientific integrity or validity of the research may be considered serious non-compliance, even if it does not result in direct harm to research subjects.
2. **Continuing non-compliance:** A pattern of recurring non-compliance that either has resulted, or, if continued, may result in harm to subjects or otherwise materially compromise the rights, welfare and/or safety of subjects, affect the scientific integrity of the study or validity of the results. The pattern may comprise repetition of the same non-compliant action(s), or different noncompliant events. Such non-compliance may be unintentional (e.g., due to lack of understanding, knowledge, or commitment), or intentional (e.g., due to deliberate choice to ignore or compromise the requirements of any applicable regulation, organizational policy, or determination of the IRB/EC).

Protocol Deviation (PD): Any change, divergence, or departure from the IRB-approved research protocol.

- **Major Deviations:** Deviations from the IRB/EC-approved protocol that have, or may have the potential to negatively impact, the rights, welfare, or safety of the participant, or to substantially negatively impact the scientific integrity or validity of the study.

- **Minor Deviations:** Deviations that do not have the potential to negatively impact the rights, safety, or welfare of participants or others, or the scientific integrity or validity of the study.

9.1.2 Documenting, Assessing, Recording, and Reporting Events

ALL AEs, including those that may appear to have a non-study cause (see "Causality" below) and including any baseline condition (with the exception of mpox lesions) that worsens by at least 1 grade (see Section 9.1.2.1.1 Severity Grading below), will be documented (e.g., on the clinical chart/progress notes/clinical laboratory record) and recorded (e.g., in the study-specified case report form [CRF]/research database), and all Grade 3 and above AEs will be reported (e.g., cumulatively from the research database, or according to protocol-specified expedited reporting mechanism) to the pharmacovigilance committee from the time informed consent is obtained through the timeframe specified below. At each contact with the participant, information

regarding AEs will be elicited by open-ended questioning and examinations. AEs indicating the presence of infections including urinary tract; ear, nose, and/or throat; ocular; pulmonary; central nervous system; skin or gastrointestinal infection; bacteremia/sepsis; or other will be defined clinically with laboratory and radiographical confirmation when possible. In participants with recrudescent disease, defined as the appearance of at least one new lesion consistent with mpox in a participant still enrolled in the study who has previously reached full body lesion resolution, the mpox lesion(s) and mpox diagnosis themselves will not be an AE but other symptoms or diagnoses will be considered AEs.

AEs and SAEs will generally be recorded, assessed, and reported according to the timeframes outlined in Table 1.

Table 1. Standard event recording, assessment, and reporting timeframes.

Event type	Record, assess, and report through	Timeline for reporting
Related SAEs	End of subject participation in study, or if study personnel become aware thereafter	• Deaths and life-threatening SAEs: no later than the first business day following the day of study personnel awareness • All other SAEs: no later than the third business day following the day of study personnel awareness
Unrelated SAEs	End of subject participation in study	
Related and unrelated non-serious AEs	End of subject participation in study	Record in research database no less than every week

9.1.2.1 Investigator Assessment of Adverse Events

The principal investigator and/or designee will review all data on each participant on a regular basis (at least weekly) to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff. The investigator will assess all AEs with respect to **seriousness** (according to SAE definition above), **severity** (intensity or grade, see below), and **causality** (relationship to study agent and relationship to participation in the research, see below).

9.1.2.1.1 Severity Grading

The investigator will grade the severity of each AE, including laboratory and testing abnormalities and results, as follows. Chemistry, hematology (with the exception of hemoglobin), and coagulation parameters will be graded according to the table in APPENDIX A. Hemoglobin

values will be graded according to the table in APPENDIX B. Any values/events not included in Appendices A or B will be graded according to the "Common Terminology Criteria for Adverse Events (CTCAE)" (v 5.0) which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Laboratory values that are not graded in Appendices A or B or the CTCAE v5.0 will be evaluated by the clinician, and if clinically significant, the resulting clinical diagnosis will be considered an AE, recorded in the database, and reported as an AE as described below (section 9.1.2.1.2).

Events that are NOT gradable using the above specified tables will be graded as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
- Grade 4: Life threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

NOTE: A participant death should always be reported as grade 5.

9.1.2.1.2 Laboratory Value Assessment and Clinical Significance Criteria

ALL abnormal lab values of grade 3 or above are REPORTABLE unless present at baseline. Abnormal lab values not included in CTCAE v5.0 (with the exception of hemoglobin, see Appendices A and B) are considered CLINICALLY SIGNIFICANT, and are to be recorded in the research database, and reported, if they meet ONE or more of the criteria below.

- result in a study agent dosage adjustment, interruption, or discontinuation
- are accompanied by clinically abnormal signs or symptoms that are likely related to the laboratory abnormality (e.g., clinical jaundice)
- indicate a possible organ toxicity (e.g., elevated serum creatinine)
- result in additional/repeat testing or medical intervention (procedures/treatments) (e.g., EKG to evaluate arrhythmia potential with a high serum potassium; one or more EKGs to assess an elevated troponin level; potassium supplementation for hypokalemia)
- indicates possible over-dosage
- are considered clinically significant by the investigator or pharmacovigilance committee.

9.1.2.1.3 Causality

Causality (likelihood that the event is caused by the study agent) will be assessed by the principal investigator considering the factors listed under the following categories:

Definitely Related

- reasonable temporal relationship
- follows a known response pattern
- clear evidence to suggest a causal relationship
- there is no alternative etiology

Probably Related

- reasonable temporal relationship
- follows a suspected response pattern (based on similar agents)
- no evidence of a more likely alternative etiology

Possibly Related

- reasonable temporal relationship
- little evidence for a more likely alternative etiology

Unlikely Related

- does not have a reasonable temporal relationship and/or
- there is good evidence for a more likely alternative etiology

Not Related

- does not have a temporal relationship and/or
- is definitely due to an alternative etiology

Note: Other factors (e.g., dechallenge, rechallenge, if applicable) should also be considered for each causality category when appropriate. Causality assessment is based on available information at the time of the assessment of the AE. The investigator may revise the causality assessment as additional information becomes available.

Causality assessment will be reviewed by the sponsor. The sponsor may make the final determination on the "reasonable possibility" that the event was "related" (comprising definitely, probably, and possibly related) or "unrelated" (comprising unlikely and not related) to the study agent.

9.1.2.2 Recording of Events

AEs will be promptly recorded in the research database no less than every week, regardless of possible relationship to study interventions. If a diagnosis is clinically evident (or subsequently determined), the diagnosis rather than the individual signs and symptoms or laboratory abnormalities will be recorded as the AE. The investigator will review events regularly to ensure they have been captured correctly and to perform assessment of events individually and cumulatively to assess possible safety trends.

9.1.2.3 Investigator Reporting Responsibilities

The site principal investigator and/or equally qualified designee will check daily for events that may require expedited reporting.

The site principal investigator and/or equally qualified designee will also monitor all accumulating data no less than weekly, or according to study site procedures, whichever is more frequent.

Data will be reviewed by the site principal investigator/designee on a regular basis for accuracy and completeness.

Data will be submitted to the pharmacovigilance committee in keeping with all applicable agreements and when requested, such as for periodic safety assessments, and preparation of final study reports.

The principal investigator, protocol chair, and/or other study designee will ensure prompt reporting to safety oversight bodies (e.g., pharmacovigilance committee, DSMB), regulatory entities, and stakeholders as specified below, and according to any additional requirements or agreements.

9.1.2.3.1 Serious Adverse Events (Expedited Reporting)

Unless otherwise specified above, all SAEs (regardless of relationship and whether or not they are also UPs) must be reported to the DRC pharmacovigilance committee as specified by the pharmacovigilance committee (e.g., research electronic data capture [REDCap] system; use email if REDCap is not available). If the preferred/indicated mechanism for reporting is not available, the pharmacovigilance committee/MM should be contacted by telephone, fax, or other reasonable mechanism to avoid delays in reporting.

Unless otherwise specified above, deaths and immediately life-threatening SAEs must be reported to the pharmacovigilance committee promptly, and no later than the **first business day** following the day of study personnel awareness.

All other SAEs must be reported to the pharmacovigilance committee no later than the **third business day** following the day of study personnel awareness.

If an individual participant experiences multiple SAEs in a closely timed/overlapping “cause-and-effect” (cascade) sequence, the site investigator, after careful evaluation, will report ONLY

primary/precipitating event(s) individually. SAEs that are determined to be definitely secondary to other SAEs will be detailed in the narrative portion of the report of the relevant primary/precipitating SAE. A clinical rationale and findings to support such reporting should be part of the narrative.

For each SAE report, the research database entry MUST match the corresponding entries on the SAE report (e.g., start and stop dates, event type, relationship, and grade), and **must be updated if necessary** (e.g., if the SAE report was generated after the corresponding AE was entered in the research database).

Unless otherwise specified above, SAEs that have not resolved by the end of the per-protocol follow-up period for the participant are to be followed until final outcome is known (to the degree permitted by the IRB/EC-approved informed consent form). If it is not possible to obtain a final outcome for an SAE (e.g., the participant is lost to follow-up), and to update the pharmacovigilance committee, the last known status and the reason a final outcome could not be obtained will be recorded by the investigator on an SAE report update and the CRF.

9.1.2.3.2 Unanticipated Problems

UPs (as defined in this protocol, or as defined by the IRB/EC of record, whichever definition is more conservative) must be reported to the Data Coordinating Center and local IRB/EC as per local institutional requirements. UPs may include problems with protocol implementation, participant safety, and/or concerns regarding informed consent. Initial reports must be communicated no later than 7 calendar days of site awareness of the event.

All UPs that are also SAEs will be reported via the SAE CRF to the pharmacovigilance committee no later than when they are due to be reported to the Data Coordinating Center and local IRB/EC.

9.1.2.3.3 Non-compliance and Protocol Deviations

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations and/or noncompliance to the IRB/EC as described in the MOP. All deviations must be addressed in study source documents and reported to the INRB and the Data Coordination Center.

9.1.2.3.4 Pregnancy

Participants found to be pregnant during the study will not be excluded from the study. When possible, they will be followed to determine the outcome of the pregnancy. Pregnancy itself is not an AE, but events that meet AE or SAE criteria in relation to pregnancy, delivery, or the conceptus/neonate (see section 9.1.1) are reportable.

9.1.2.4 Sponsor's Reporting Responsibilities

SUSARs, as defined in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 5.17 guideline, will be reported to all participating country regulatory authorities, and all participating Investigators as Safety Reports.

The Sponsor (INRB) will also submit an Annual Report of the progress of the investigation to all participating country regulatory authorities.

AEs that are also UPs will be summarized by the Sponsor (INRB) and distributed to investigators if they are relevant to other sites.

9.2 Withdrawal Criteria for an Individual Participant

An individual participant will be withdrawn from the study for any of the following:

- An individual participant's decision. (The investigator should attempt to determine the reason for the participant's decision.)
- Non-compliance with study procedures to the extent that it is potentially harmful to the participant or to the integrity of the study data.
- The investigator determines that continued participation in the study would not be in the best interest of the participant.

9.2.1 Re-enrollment and Unplanned Procedure Repetition

Unless otherwise specified within this protocol, each person who is a participant in this study may be enrolled and may pass through each step and process outlined in the protocol only **ONCE** (i.e., participants may not "go back" and repeat a protocol step already completed). On a case-by-case basis a request for re-enrollment or for repetition of a protocol step or procedure already completed may be submitted to, reviewed by, and approved by the MM in writing. The MM may also recommend or require consultation of the IRB/EC and/or DSMB.

9.2.2 Replacement of Withdrawn Participants or Participants Who Discontinue Study Agent

Participants who are withdrawn from the study or discontinue study drug will not be replaced.

All participants exposed to study agent MUST be included in the safety dataset.

9.3 Additional Safety Oversight

9.3.1 Pharmacovigilance Committee

A pharmacovigilance committee will conduct safety oversight for this study. The DRC National Pharmacovigilance Centre is located at the University of Kinshasa. It receives all reports of AE/SAEs, analyses them, and sends monthly reports to the Directorate of Pharmacy and Medicine (Direction de la Pharmacie et du Médicament; DPM) and Congolese Pharmaceutical Regulatory Authority (Autorité Congolaise de Réglementation Pharmaceutique; ACOREP).

9.3.2 Medical Monitor

A MM in the DRC has been appointed for oversight of safety in this clinical study. The MM will be responsible for performing oversight and review of safety assessments.

9.3.3 Oversight Committees

9.3.3.1 Data and Safety Monitoring Board

The NIAID intramural DSMB includes independent experts that do not have direct involvement in the conduct of the study and have no significant conflicts of interest as defined by NIAID policy. The DSMB will be supplemented with local subject matter experts at the chair's discretion. The DSMB will review the study protocol, consent document(s), and investigator brochure prior to initiation and twice a year thereafter, or as may be determined by the DSMB. The DSMB may convene additional reviews as necessary. The DSMB will review the study data as needed to evaluate the safety, efficacy, study progress, and conduct of the study.

All deaths, SAEs, UPs, pregnancies, and safety reports will be reported to the DSMB at the same time they are submitted to the IRB and pharmacovigilance committee unless otherwise specified herein. Any other study documents requested by the DSMB will be submitted for periodic scheduled DSMB reviews.

All cases of intentional or unintentional unblinding will be reported to the DSMB not later than one business day from the time of study personnel awareness.

The principal investigator will notify the DSMB at the time pausing or halting criteria are met and obtain a recommendation concerning continuation, modification, or termination of the study. The principal investigator will submit the written DSMB summary reports with recommendations to the IRB/EC.

The DSMB is the primary entity charged with NON-EMERGENCY, FIREWALLED ad hoc review of unblinded data, as may be indicated, to facilitate safety/pharmacovigilance team assessment of potential signals or to fulfill regulatory/oversight body requirements or requests. See section 6.4.2.

9.4 Pausing Rules

"Pausing" is discontinuation of study intervention/treatment/dosing (agent/placebo/procedure, etc.) in a single participant or, at the discretion of the MM in consultation with the pharmacovigilance committee, a protocol-defined group or "arm," until a decision is made to either resume or permanently discontinue such activity. Participants continue to be followed for safety during a pause.

The pausing criteria for individual participants in this study include any one or more of the following:

- A participant experiences an SAE that is unexpected (per the product label) and possibly, probably, or definitely related to a study agent;
- The development of an unexpected lab toxicity of grade 3 or greater that is deemed by the investigator to be possibly, probably, or definitely related to a study agent will trigger a review by the MM that may result in pausing the study drug.

- A participant has a hemoglobin level <7 g/dL. This would only lead to the cessation of blood draws until the hemoglobin level stabilizes and the clinician at bedside judges it to be safe to resume blood draws.
- A participant with signs or symptoms thought to be resulting from anemia at any hemoglobin level. This would only lead to the cessation of blood draws until the hemoglobin level stabilizes and the clinician at bedside judges it to be safe to resume blood draws.

The principal investigator/study chair(s) or the MM in consultation with the pharmacovigilance committee may also pause dosing/study interventions for one or more participants for any safety issue. The DSMB may recommend a pause to the MM and pharmacovigilance committee. The IRB/EC may also recommend a pause.

9.4.1 Reporting a Pause

If a pausing criterion is met, a description of the AE(s) or safety issue must be reported by the principal investigator/study chair(s) within 1 business day to the MM and pharmacovigilance committee and the IRB/EC according to their requirements. The principal investigator/study chair(s) will also notify the DSMB. In addition, the MM or designee, in consultation with the pharmacovigilance committee, will notify all other site investigators by email or through the specified pathway.

9.4.2 Resumption Following a Pause

The MM in consultation with the pharmacovigilance committee, and in collaboration with the principal investigator/study chair(s) and DSMB, will determine if study activities including study agent administration and/or other study interventions may be resumed, and any additional modifications or requirements that may apply, for the impacted participant(s), or whether the events that triggered the pause require expansion to a study halt (see below).

The MM or designee, in consultation with the pharmacovigilance committee will notify the principal investigator/study chair(s) of the decision. The principal investigator/study chair(s) will notify the IRB/EC of the decision according to the IRB's/EC's processes.

9.4.3 Discontinuation of Study Agent

A participant who does not resume study agent/intervention/treatment will continue to be followed for protocol-specified safety assessments or as clinically indicated, whichever is more conservative.

9.5 Halting Rules for the Protocol

"Halting" is discontinuation of study intervention/treatment/dosing (agent/placebo/procedure, etc.) for all participants in a study and suspension of enrollment until a decision is made to either resume or permanently discontinue such activity. Participants continue to be followed for safety during a halt.

The halting rules are:

- The MM, in consultation with the pharmacovigilance committee may recommend to halt the study if a pattern of AEs emerges which elevates the concern for study related toxicity.
- Any safety issue that the principal investigator/study chair(s) or the MM, in consultation with the pharmacovigilance committee determines should halt the study. The DSMB may recommend a halt to the MM and pharmacovigilance committee.

In addition, any regulatory body having oversight authority may halt the study at any time. The IRB/EC may halt the study at their sites. Country-specific regulatory authorities may halt the study for sites under their jurisdiction. The DSMB may recommend a study halt.

9.5.1 Reporting a Study Halt

If a halting criterion is met, a description of the AE(s) or safety issue must be reported by the principal investigator/study chair(s), within 1 business day to the MM and pharmacovigilance committee and the IRB/EC according to their requirements. The principal investigator/study chair(s) will also notify the DSMB. In addition, the MM and/or pharmacovigilance committee or designee will notify all other site investigators by email or through the specified pathway.

9.5.2 Resumption of a Halted Study

The MM and pharmacovigilance committee, in collaboration with the principal investigator/study chair(s) and DSMB, will determine if study activities, including enrollment, study agent administration, and/or other study interventions, may be resumed and any additional modifications or requirements that may apply.

The MM and/or pharmacovigilance committee or designee will notify the principal investigator/study chair(s) of the decision. The principal investigator/study chair(s) will notify the IRB/EC of the decision according to the IRB's/EC's processes.

9.5.3 Discontinuation of Study Agent

Participants who do not resume study agent/study intervention will continue to be followed for protocol-specified safety assessments or as clinically indicated, whichever is more conservative.

9.6 IRB/EC and Institutional Reporting Procedures

As a general statement, safety and other reportable events will be reported per the institutional requirements of each participating entity.

10 STATISTICAL CONSIDERATIONS

10.1 Design Overview

This is a randomized, placebo-controlled, double-blind trial to test superiority of the antiviral drug tecovirimat, as described above. Figure 1 provides a study schema of the trial design.

To date there have been no studies of mpox therapeutics in humans to inform the design of the present trial. As such, there are no standards for study endpoints. The primary endpoint was largely informed by subject matter experts with experience treating mpox and secondary analysis of data generated from an observational study of mpox patients in DRC carried out by the DRC's INRB in collaboration with the USAMRIID between 2007 and 2011.

The present trial design reflects the major clinical characteristics of mpox disease and includes multiple secondary endpoints ordered by importance as well as a sample size re- estimation procedure described in section 10.4.1.

10.2 Populations for Analyses

The primary analysis and secondary efficacy analyses will be based on an intention-to-treat (ITT) population consisting of all randomized participants and described in detail in the statistical analysis plan (SAP). Safety analyses including 28-day mortality, incidence of SAEs, incidence of AEs requiring drug discontinuation, and incidence of other AEs will be based on an as-treated population consisting of all participants who received at least one dose of tecovirimat or placebo.

10.3 Study Endpoints and Statistical Analyses

10.3.1 General Approach

This is a randomized, placebo-controlled, double-blind trial testing a superiority hypothesis with a two-sided type I error rate of 5%. Secondary endpoints have been ordered according to relative importance.

A statistical analysis plan will be developed prior to unblinding of the study and database lock.

10.3.2 Endpoints

10.3.2.1 Primary Endpoint

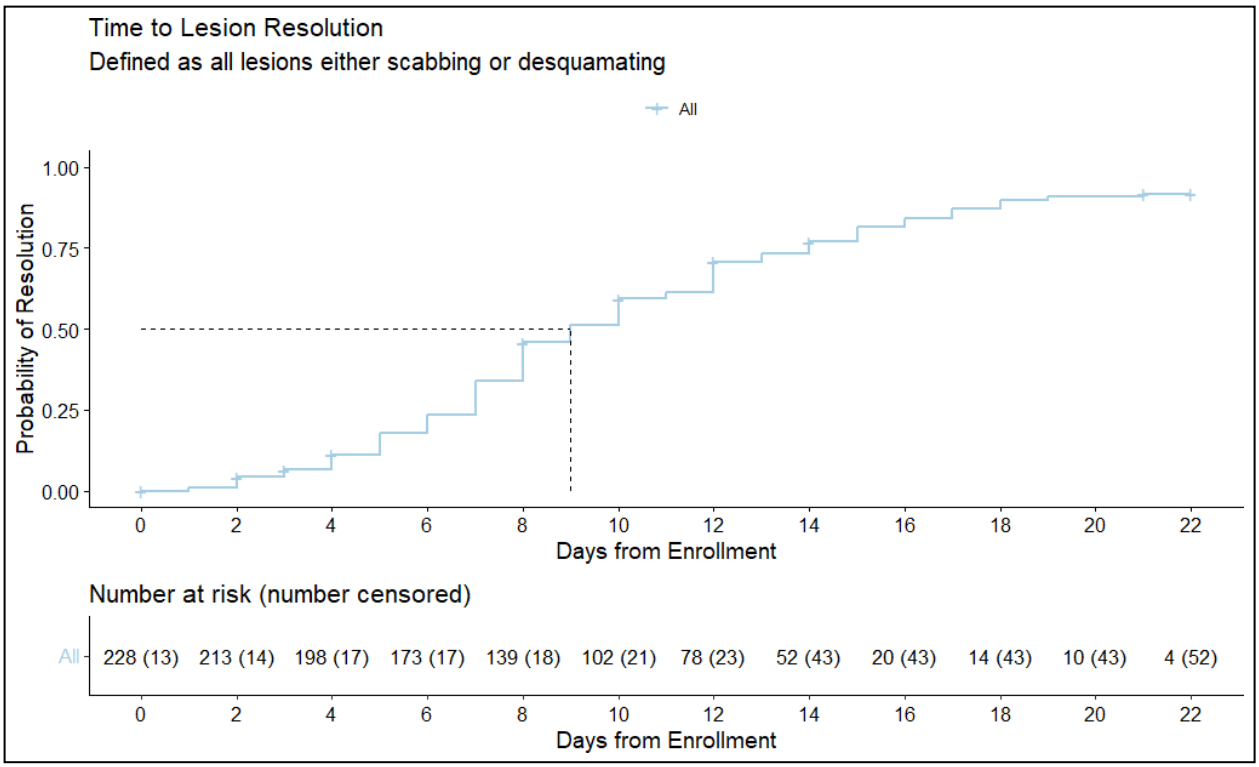
The primary endpoint is time (days) to lesion resolution, defined as the first day on which all lesions on the total body are scabbed or desquamated or a new layer of epidermis has formed (see section 8.4.1), up to 28 days after randomization.

Justification

The primary endpoint emphasizes the clinical relevance of lesion resolution for patients with mpox. Mpox lesions are painful and reduce patients' ability to carry out ordinary tasks such as swallowing. Lesions progress through discrete stages at roughly the same rate starting with macules (flat lesions) and moving on to papules (raised), vesicles (raised and filled with clear fluid), pustules (filled with opaque fluid), and finally scab and fall off (desquamate). Lesion scabbing and desquamation generally coincides with resolution of other symptoms and is an important criterion for discharge in clinical practice (in addition to blood PCR negativity, which is included as a secondary endpoint). Therefore, demonstration of an improvement in time to lesion resolution would provide a direct clinical benefit to patients.

Figure 2 displays time to lesion resolution (as defined for this primary endpoint) for N=228 patients with laboratory-confirmed mpox from the aforementioned 2007-2011 INRB/USAMRIID observational study. The median time to lesion resolution was 9 days. In addition to the clinical significance noted above, part of the motivation for this primary endpoint is that this leaves sufficient room to observe a potential treatment effect of tecovirimat. Note also that the study duration for the observational trial was 22 days and 176/228 (77.2%) were observed to meet the endpoint. Thus, we expect that the 28-day duration planned for the present trial will provide ample time to observe events. Section 10.4 describes the power and sample size calculations for the trial in detail. The trial is designed to achieve 85% power to detect a lesion resolution event rate ratio of 1.40, which requires 318 overall resolution events. Extrapolating the 77% event rate from the observational study provides a conservative estimate of the required sample size and still results in a reasonable sample size. NOTE: Updated power and sample size calculations based on the sample size re-estimation plan described below are provided in APPENDIX C.

Figure 2. Time to lesion resolution among a cohort of N=228 patients with laboratory-confirmed mpox in the 2007-2011 INRB/USAMRIID observational study.



Finally, note that similar primary endpoints have been used for studies of other diseases with characteristic skin lesions. For example, time to 100% crusting has been employed as a primary endpoints in trials of oral acyclovir for treatment of varicella (chickenpox).[32]

Hypothesis

The primary null hypothesis is that time to lesion resolution does not differ between study arms.

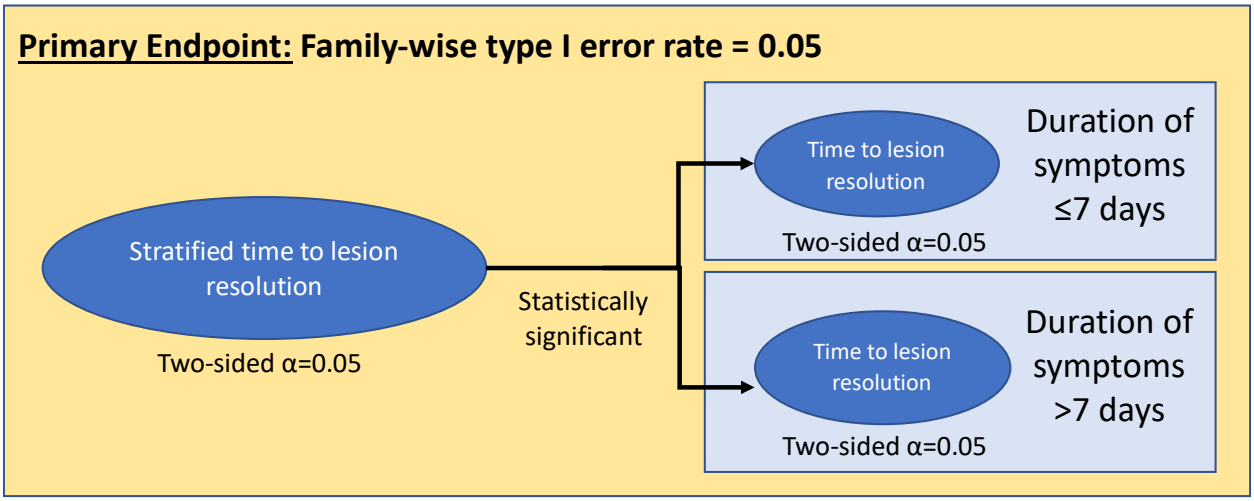
10.3.2.2 Secondary and Exploratory Endpoints

Secondary and exploratory endpoints are listed in Section 3. Brief analysis plans for these endpoints are contained in Section 10.3.2.4 and 10.3.2.5. Full details will be contained in the SAP.

10.3.2.3 Primary Endpoint Analysis

The primary analysis of time to lesion resolution will be assessed using a Fine-Gray competing risks model[33] and will be stratified by days from onset of symptoms to randomization (≤7 days vs >7 days; Figure 3). The statistical significance of the primary endpoint will be assessed using Gray's test with a two-sided type I error rate of α=0.05. Gray's test is analogous to the log-rank test comparing Kaplan-Meier curves (and results in the same sample size calculations) but is specific to the competing-risk setting.

Figure 3. Primary analysis.



There is no validated measure of baseline disease severity for mpox. Stratification by duration of symptoms aligns with the prevailing knowledge that antivirals are most efficacious when administered early in the course of infection and on data from the INRB/USAMRIID observational study showing that the correlation between days from symptom onset and time to lesion resolution was higher than both the correlation between baseline lesion count and time to resolution and between baseline viral load and time to resolution. Of note, development and validation of a baseline disease severity metric is an exploratory aim of this study.

The statistical analysis plan will include procedures for handling missing data as well as provide technical details for how analyses will be performed.

10.3.2.4 Secondary Endpoint Analyses

- The primary analysis will be repeated within the two randomization strata (≤ 7days or > 7 days from symptom onset to randomization), reporting 95% confidence intervals rather than p-values.
- The proportion with negative blood, oropharyngeal swab, and lesion swab PCR results 14 days after randomization will be summarized with point estimates and 95% confidence intervals (CIs). The difference in proportions and 95% CIs for the difference will be presented for each compartment.
- Time to death will be assessed using a Cox proportional hazards models, with estimates and 95% CIs for the hazard ratio for death within 28 days reported for an overall stratified model and within each stratum.
- Mortality within the first 28 days by study arm will be summarized by proportions with 95% CIs and the difference in proportions with a 95% CI.
- Frequency of clinical symptoms by symptom and study arm will be summarized as proportions at baseline and selected timepoints described in the SAP. Duration of clinical symptoms will be summarized according to median days and interquartile range.
- Incidence of SAEs, AEs requiring drug discontinuation, and other AEs will be summarized by proportions and differences in proportions with 95% CIs where appropriate. AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Each AE will be graded by severity and relationship to underlying disease or study intervention. AEs will be presented by System Organ Class, severity, and causality. AEs leading to premature discontinuation from the study intervention will be presented in tables as described above and listed. Listings will be prepared of all AEs and all SAEs.
- Incidence of bacterial infections by study arm will be summarized by proportions and differences in proportions with 95% CIs as appropriate.

10.3.2.5 Exploratory Endpoint Analyses

- Frequency and location of persistent residual lesions by location and study arm will be provided.
- Lesion progression over the study period will be compared using descriptive analyses of lesion count trajectories. An automated image analysis algorithm will be trained using longitudinal photographs of lesions. Lesion counts and characteristics from photographs will be assessed and compared to evaluate the performance of the algorithm relative to a human rater.
- Number and percentage of confirmed mpox cases reporting exposure to animals, symptomatic humans, or with no known exposures will be provided.
- Viral persistence in blood, oropharyngeal swabs, and skin lesion swabs will be summarized by the proportion with negative results for each sample type (out of those positive at baseline) at timepoints specified in the SAP. . Viral load from all sample types will be shown longitudinally by study arm as medians and interquartile ranges.

- Time to the first negative blood, oropharyngeal swab, and open lesion swab PCR result will be summarized using the Fine-Gray procedure as described above. Treatment effect rate ratios and accompanying 95% CIs as well as plots of the cumulative incidence function for each event will be provided.
- Antibody titers will be summarized with geometric means and geometric standard deviations by study arm. Change from baseline at selected timepoints will be provided.
- Pre-dose concentration of tecovirimat in blood measured on day 7 will be reported for the tecovirimat arm using the minimum value, 25th percentile, median, 75th percentile, maximum, mean, and standard deviation.
- Incidence of recrudescent disease and description of clinical and virologic characteristics of recrudescent disease cases will be provided.

10.3.2.6 Subgroup Analyses

Planned subgroup analyses will evaluate the treatment effect across the following subgroups: duration of symptoms prior to randomization (≤7 days or >7 days), study site (if more than one site enrolls participants), age, sex, baseline lesion burden according to a scale developed for smallpox by WHO (see Table 2 below), baseline viral load (≤ median or > median), HIV status, virus clade (if available), and presence/absence of anti-OPXV antibodies. A forest plot will display point estimates and 95% CIs for the lesion resolution rate ratio by subgroup. Interaction tests will be conducted to determine whether the effect of treatment varies by subgroup. Additional subgroups may be identified and evaluated. Full details of planned subgroup analyses will be provided in the statistical analysis plan.

Table 2. WHO smallpox baseline lesion severity categories

WHO smallpox baseline lesion severity category	**Number of lesions**
Subclinical	0 – 4
Mild	5 – 25
Moderate	26 – 100
Severe	101 – 250
Grave	>250

10.3.2.7 Additional Planned Analyses

Efforts will be made to develop a baseline disease severity metric for use in future studies of human mpox. Risk classification models will be implemented to summarize the strength of the relationships between baseline characteristics (including age, sex, baseline lesion count, type and duration of symptoms, viral load, and selected comorbidities) and the primary and secondary endpoints.

10.3.3 Baseline Descriptive Statistics

Baseline characteristics will be summarized by treatment arm. For continuous measures the mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum value will be provided. Categorical variables will be described by the number and proportion in each category. The proportion of missingness for each variable will be provided.

10.4 Power and Sample Size

This section describes the original power and sample size calculations. Updated power and sample size calculations based on the sample size re-estimation plan described below are provided in APPENDIX C.

For the test of the primary endpoint, the two key determinants of power are the total number of lesion resolution events, E, and the treatment-to-control ratio of the rate of lesion resolution, θ. The number of events required to achieve power $1-\beta$ to detect a rate ratio of θ using a two-tailed test with type I error rate α=0.05 is approximately

$$E = \frac{4\left(1.96 + z_{\beta}\right)^2}{\{\ln(\theta)\}^2},$$

where z_{β} is the $100(1-\beta)$th percentile of the standard normal distribution.

Table 3 displays the power of this test for various scenarios. In total, 318 patients with lesion resolution up to 28 days after randomization are needed to detect a 40% improvement in the rate of lesion resolution as measured by the rate ratio (akin to a "hazard ratio" but for a positive outcome; values greater than one indicate improved outcomes) with 85% power and a two-sided type one error rate of α=0.05. Extrapolating the observed event rate of 77% from the 2007-2011 INRB/USAMRIID observational study yields a total targeted sample size of 413 participants. Although every effort will be made to eliminate patient dropout, a total sample size of 450 is planned to account for potential dropout.

Note that the 77% event rate used to determine the sample size is derived from an observational cohort and thus is most likely to correspond to the event rate on the control arm in this trial. Assuming the hypothesized rate ratio of 1.40 is accurate, the event rate on the tecovirimat arm (and therefore the overall event rate) will be higher than 77%. A higher rate of events will increase the power of the trial. Therefore, if the overall event rate is higher than expected, the power of the trial will be higher than 85%. One could argue that the planned sample size could be decreased and the trial could still expect to enroll sufficient participants to hit the 318 events necessary to achieve 85% power. However, one benefit of the somewhat conservative approach to sample size taken here is that by enrolling more participants, the power for subgroup and secondary analyses will be improved.

Table 3. Number of events needed for 80% and 85% power. The shaded region represents the rate ratio, number of events, and projected sample size for the trial before accounting for potential drop out.

Rate Ratio (θ)	Scenario for 80% Power (β=0.20)		Scenario for 85% Power (β=0.15)	
	Number of Events Needed	Number of Patients Needed*	Number of Events Needed	Number of Patients Needed*
1.15	1608	2089	1839	2389
1.20	945	1228	1081	1404
1.25	631	820	722	938
1.30	457	594	522	678
1.35	349	454	399	519
1.40	278	362	318	413
1.45	228	297	261	339
1.50	191	249	219	285
1.55	164	213	187	243
1.60	143	186	163	212
1.65	126	164	144	188

* Assumes that 77% of patients will experience the event and does not account for potential dropout. Seventy-seven percent was the observed percentage of patients who reached lesion resolution (as defined above) within 22 days in the 2007-2011 INRB/USAMRIID observational study.

Updated power and sample size calculations based on the sample size re-estimation plan described below are provided in APPENDIX C.

10.4.1 Sample Size Re-estimation

A blinded sample size re-estimation will be conducted at the midpoint of the trial when 159 lesion resolution events have occurred (i.e., at 50% information). The blinded overall rate of events will be computed and provided to a sample size re-estimation committee. The committee will be tasked with assessing whether the sample size should be increased either in response to a lower than expected event rate (which may lead to more than 450 participants required to achieve 318 resolutions) or in order to increase the overall power of the study (i.e., to target greater than 318 events, which may be desirable if enrollment allows). Results of the re-estimation are provided in APPENDIX C.

10.5 Planned Interim Monitoring

A DSMB will monitor ongoing results to ensure the well-being and safety of participants as well as study integrity. The DSMB will be asked to recommend stopping the study early for efficacy only when there is substantial evidence of a treatment benefit. Similarly, the DSMB will be asked to recommended stopping early for futility only when there is substantial evidence to make such a recommendation.

10.5.1 Interim Monitoring for Efficacy and Futility

The Lan-DeMets spending function analog of the O'Brien-Fleming boundaries will be used to monitor the primary endpoint as a guide for the DSMB for an overall two-sided type-I error rate of 0.05. The original study design called for interim efficacy analyses to be conducted at approximately 33%, 67%, and 100% of total information. Updated interim monitoring considerations based on the sample size re-estimation plan described above are provided in APPENDIX C.

The statistical analysis plan will provide a more detailed description of the stopping boundaries used for interim analyses.

Conditional power will be presented as an additional guide to the DSMB at interim efficacy analyses. If conditional power is less than 20% under the original trial assumptions, consideration should be given to stopping the trial.

The unblinded statistical team will prepare these closed reports for DSMB review and recommendations. Analyses will be presented with blinded codes for treatment arms to protect against the possibility that the DSMB report may fall into the wrong hands. A DSMB charter will further describe procedures and membership.

11 REGULATORY AND OPERATIONAL CONSIDERATIONS

11.1 Informed Consent Process

11.1.1 Consent/Assent Procedures and Documentation

Informed consent is a process where information is presented to enable persons to voluntarily decide whether or not to participate as a research participant. It is an ongoing conversation between the human research participant and the researchers which begins before consent is given and continues until the end of the participant's involvement in the research. Discussions about the research will provide essential information about the study and include purpose, duration, experimental procedures, alternatives, risks, and benefits. Coercion and undue influence will be minimized by informing participants that their decision to join the study will not affect any medical care they are currently receiving, or their eligibility to participate in other research studies. Participants will be given as much time as they need to read the consent forms and ask questions of the investigators. Participants will also be given time to discuss their participation with family members, friends, and other healthcare providers.

The informed consent procedure will be conducted in the native or preferred language of the patients by a qualified person formally identified by the principal investigator. Written information and consent forms will be provided to the patients for their review in language spoken in the study area and understood by the participant.

Informed consent will be obtained in person by a study team member authorized to obtain consent. The privacy of the participant will be maintained. The consenting investigator and participant will be located in a private area (e.g., clinic consult room). Participants over 18 years of age will sign the informed consent documents (in a language understood by the participant)

prior to any procedures being done specifically for the study. The signature of a culturally acceptable representative of the potential participant will be obtained for adults who are impaired and unable to provide informed consent. In the case of adults whose ability to consent is uncertain, capacity to consent will be evaluated by the principal or associate investigator(s).

Parental/guardian permission and minor assent for children through 17 years of age will be obtained according to local standards and country-specific requirements. In DRC an assent must be obtained for children aged 12 to 17 years. Children that are too young to sign an assent form can be enrolled provided informed consent is signed/marked by a parent or guardian. If a minor participant expresses reluctance to participate in the study during the assent process, he or she will not be enrolled, notwithstanding consent from his or her parents/guardians.

A copy of the informed consent documents will be given to the participants for their records. The consenting investigator will document the signing of the consent forms in the participant's study record. The investigator will confirm that written legally effective consent has been obtained prior to initiating any study interventions.

The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. The participants may withdraw consent at any time throughout the course of the trial.

11.1.2 Consent for Minors When They Reach the Age of Majority

When a pediatric participant reaches age 18, continued participation (including ongoing interactions with the participant or continued analysis of identifiable data) will require that consent be obtained from the now adult with the standard protocol consent document to ensure legally effective informed consent has been obtained.

If reconsent is not feasible, we request waiver of informed consent to continue to use data and/or specimens for those individuals who become lost to follow up or who have been taken off study prior to reaching the age of majority.

Requirements for waiver of consent consistent with 45 CFR 46.116(f)(3):

(1) The research involves no more than minimal risk to the subjects.

   a. Analysis of samples and data from this study involves no additional risks to subjects.

(2) The research could not practicably be carried out without the waiver or alteration.

   a. Considering the potential length of time between the minor's last contact with the research team and their age of majority, it may be very difficult to locate them again. A significant reduction in the number of samples analyzed is likely to impact the quality of the research.

(3) As the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format.

a. Though the purpose of future studies cannot yet be known, they often involve the correlation of clinical outcomes and clinical interventions with laboratory studies. Such information would be unavailable if access to medical record numbers was unavailable.

(4) The waiver or alteration will not adversely affect the rights and welfare of the subjects.

a. Retention of these samples or data does not affect the welfare of subjects.

(5) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

a. We only request a waiver of consent for those subjects who have been lost to follow-up or who have completed study participation prior to reaching the age of majority.

11.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification documenting the reason for study suspension or termination will be provided by the suspending or terminating party to the principal investigators, pharmacovigilance committee, and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the study participants, IRB/EC, pharmacovigilance committee, and relevant regulatory authorities, as applicable, and will provide the reason(s) for the termination or suspension. Study participants will be informed of changes to study visit schedule, if applicable.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Demonstration of efficacy that would warrant stopping.
- Insufficient compliance to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Determination that the primary endpoint has been met.
- Determination of futility.

In the case of a temporary suspension, the study may resume once concerns about safety, protocol compliance, and/or data quality are addressed and satisfy the IRB/EC, pharmacovigilance committee, and regulatory authorities, as applicable.

11.3 Confidentiality and Privacy

All records will be kept confidential to the extent provided by federal, state, and local laws in the jurisdictions in which the study is conducted. Study monitors and other authorized individuals may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records. Records will be kept locked and data will be coded. Any personally identifiable information maintained for this study will be kept on restricted-access computers and networks. Personally identifiable information will only be shared with individuals authorized to receive it under this protocol. Individuals not authorized to receive personally identifiable information will be provided with coded information only, as needed. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the IRB/EC, NIAID, local regulatory agencies, the pharmaceutical supporter, or other authorized individuals.

11.4 Future Use of Stored Specimens and Data

Coded data and specimens will be stored indefinitely for future research related to mpox and other infectious diseases after the study is complete. Plans for future use of data and specimens will be described in the informed consent document. Case report forms will be retained in secure facilities at the study sites. Coded data will be retained in the data management system on secure, password-protected servers maintained by the Data Coordinating Center at NIAID. Coded specimens will be stored in secure facilities. The key to the participant codes will be maintained securely at the study sites.

Other investigators (at NIH, at INRB, and elsewhere) may wish to study these data and/or specimens. In that case, the principal investigators and the steering committee will review the request. If the planned research falls within the category of "human subjects research" on the part of the investigators, IRB/EC review(s) and approval(s) will be obtained as appropriate. This includes the investigators sending out coded and linked specimens or data and getting results that they can link back to their participants.

11.5 Safety Oversight

Safety oversight for this study is described in section 9.3.

11.6 Data Management and Monitoring

11.6.1 Data Management Responsibilities

The site investigator is responsible for assuring that the data collected is complete, accurate, and recorded in a timely manner. Source documentation (the point of initial recording of information) should support the data transferred to the electronic data system and, when possible, should be signed and dated by the person recording and/or reviewing the data. All data should be reviewed by the Investigator and co-signed as required.

11.6.2 Data Capture Methods

Study data collected at the bedside at study sites will later be recorded on paper CRFs. CRFs will be scanned and submitted to an electronic system provided by NIAID and managed by the CTRS Data Management Team. The INRB Data Management team will have access to these scanned

images, and they will enter the data in the REDCap clinical data management system (CDMS) provided by NIAID. The data system includes password protection and internal quality checks, to identify inconsistent, incomplete, or inaccurate data. Any corrections to the electronic data systems will be tracked electronically (password protected and through an audit trail) with time, date, individual making the correction, and what was changed. AEs and concomitant medications will be coded according to the most current versions of MedDRA and WHODrug, respectively. The CTRS Data Management team, in collaboration with the INRB's Coordinating Center Data Management team, will be responsible for data management, data entry review, quality review, analysis, and reporting of the study data.

11.6.3 Types of Data

Source documents may include, but are not limited to, the participant's medical records, laboratory reports, ECG tracings, x-rays, radiologist's reports, participant's diaries, biopsy reports, ultrasound photographs, progress notes, pharmacy records, and any other similar reports or records of procedures performed during the subject's participation in the study.

11.6.3.1 Source Documents and Access to Source Data/Documents

Source documents include all recordings of observations or notations of clinical activities, and all reports and records necessary for the evaluation and reconstruction of the clinical trial.

11.6.4 Record Retention

The protocol team is responsible for retaining all essential documents listed in the ICH Good Clinical Practice Guideline. All essential documentation for all study participants is to be maintained by the investigators in a secure storage facility for a minimum of 3 years per NIAID policies or per in-country local or federal regulatory requirements (whichever is longer). These records are also to be maintained in compliance with IRB/EC and local medical records retention requirements, whichever is longest. All stored records are to be kept confidential to the extent required by applicable laws in the jurisdiction in which they are stored.

11.6.5 Site Monitoring Plan

As per ICH-GCP 5.18, clinical protocols are required to be adequately monitored by the study sponsor. This study monitoring will be conducted according to the "NIAID Intramural Clinical Monitoring Guidelines." If feasible, monitors under contract to the NIAID/Office of Clinical Research Policy and Regulatory Operations (OCRPRO) or their designee may visit the clinical research site to monitor aspects of the study in accordance with the appropriate regulations and the approved protocol. The objectives of a monitoring visit would be: 1) to verify the existence of signed informed consent documents and documentation of the Informed Consent Form process for each monitored participant; 2) to verify the prompt and accurate recording of all monitored data points, and prompt reporting of all SAEs; 3) to compare data abstracts with individual participants' records and source documents (participants' charts, laboratory analyses and test results, medical progress notes, nurses' notes, and any other relevant original participant information); and 4) to help ensure investigators are in compliance with the protocol. The monitors also may inspect the clinical site regulatory files to ensure that regulatory requirements (Office for Human Research Protections [OHRP]) and applicable guidelines (ICH-GCP) are

being followed. During the monitoring visits, the investigator (and/or designee) and other study personnel should be available to discuss the study progress and monitoring visit.

11.7 Data Sharing Plan

11.7.1 Human Data Sharing Plan

At the completion of the trial, a comprehensive study report will be prepared in concert with the DRC and will be made available to the DSMB and study partners. . The relevant primary and secondary outcome data from this trial will also be entered into ClinicalTrials.gov for access by other researchers. In addition, it is the intention of the extended protocol team that de-identified data from this trial will be made available upon request to outside investigators upon scientific review of the merits of their proposed research plan. This availability will be in accordance with the WHO Joint statement on public disclosure of results from clinical trials. To facilitate this, a Presentations and Publications subcommittee (which will include full representation of the DRC and any additional institution who may join the study as well as representation from the extended protocol team) will be created to receive, review for scientific merit, and, if appropriate, approve these requests for use of de-identified data arising from the trial.

11.8 Collaborative Agreements

11.8.1 Agreement Type

Agreements for each participating site will be executed as needed.

11.9 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with NIAID has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

12 ABBREVIATIONS

ADL	activities of daily living
AE	adverse event
ALT	alanine transaminase
aPTT	activated partial thromboplastin time
AR	adverse reaction
AST	aspartate transaminase
AUC	area under the curve
BRB	Biostatistics Research Branch
BUN	blood urea nitrogen
CAPA	corrective and preventive action plan
CB	Congo Basin

CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CMRPD	Clinical Monitoring Research Program Directorate
CT	cycle threshold
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CYP	cytochrome P450
DCR	Division of Clinical Research
DNA	deoxyribonucleic acid
DRC	Democratic Republic of Congo
DSMB	Data and Safety Monitoring Board
EC	ethics committee
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
Ig	immunoglobulin
IND	investigational new drug (application)
INR	international normalized ratio
INRB	Institut National de Recherche Biomédicale
IRB	institutional review board
mITT	modified intention-to-treat
MM	medical monitor
MOP	manual of procedures
MPXV	monkeypox virus
MVA	modified vaccinia virus Ankara
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OCRPRO	Office of Clinical Research Policy and Regulatory Operations
OHRP	Office for Human Research Protections
OPXV	orthopoxvirus
PCR	polymerase chain reaction
PK	pharmacokinetic
PT	prothrombin time
REDCap	research electronic data capture
RHD	recommended human dose
RPR	Rapid Plasma Reagin
SAE	serious adverse event
SAR	suspected adverse reaction
SOC	standard of care
SUSAR	serious and unexpected suspected adverse reaction

UP	unanticipated problem
UPnonAE	unanticipated problem that is not an adverse event
USAMRIID	US Army Medical Research Institute of Infectious Diseases
USAN	United States adopted name
US	United States
VZV	Varicella zoster virus
WA	West African
WHO	World Health Organization

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APPENDIX A: Chemistry, Hematology, and Coagulation Parameter Grading Scale

CHEMISTRY PARAMETER	Qualifier	NORMAL LIMITS	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE THREATENING
Albumin (g/dL): Low		3.3-5.5 g/dL	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated
Alkaline phosphatase (IU/L): High	male	53-128 U/L	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
	female	42-141 U/L	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Amylase (U/L): High		14-97 U/L	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 x ULN and with signs or symptoms
AST (U/L): High		<=38 U/L	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
ALT (U/L): High		<=47 U/L	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Bilirubin, Blood, High		0.2-1.6 mg/dL	>ULN - 1.5 x ULN if baseline was normal; >1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal

				was abnormal	was abnormal	
BUN (mg/dL)		7-22 mg/dL	No AE grading reference range available. If abnormal, clinician to determine if abnormal lab is clinically significant.			
Calcium (mg/dL): High		8.0-10.3 mg/dL	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences
Calcium (mg/dL): High		8.0-10.3 mg/dL	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences
Chloride (mEq/L)		98-108 mmol/L	No AE grading reference range available. If abnormal, clinician to determine if abnormal lab is clinically significant.			
C-reactive protein (ug/mL)		< 7.5 mg/L	No AE grading reference range available. If abnormal, clinician to determine if abnormal lab is clinically significant.			
Creatinine (mg/dL): High		≤1.2	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline - 1.5 - 3.0 x ULN	>3.0 x baseline; 3.0 -- 6.0 x ULN	>6.0 x ULN
eGFR (mL/min/1.73m^2)		>=90	No AE grading reference range available. If abnormal, clinician to determine if abnormal lab is clinically significant.			
Creatinine kinase (U/L): High	male	39-380 U/L	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN
	female	30-190 U/L	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN
Glucose (mg/dL): High			Use grading for clinical diagnosis "hyperglycemia"			

Glucose (mg/dL): Low			<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures
Potassium (mmol/L): High		3.6-5.1	> ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences
Potassium (mmol/L): Low		3.6-5.1	<LLN-3.0mmol/L	Symptomatic with <LLN-3.0 mmol/L; intervention indicated	<3.0-2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences
Sodium (mmol/L): High		130-145	146-150	>150-155; intervention indicated	155-160; hospitalization indicated	≥ 160; life-threatening consequences
Sodium (mmol/L): Low		130-145	<130	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms	≤ 120; life-threatening consequences
Total CO_2 (mEq/L)		18-33 mmol/L	No AE grading reference range available. If abnormal, clinician to determine if abnormal lab is clinically significant.			
Total protein (g/dL)		6.4-8.1 g/dLb	No AE grading reference range available. If abnormal, clinician to determine if abnormal lab is clinically significant.			
HEMATOLOGY PARAMETER	**Qualifier**	**NORMAL LIMITS**	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE THREATENING**
Hematocrit (L/L): low		32.5 – 46.2	No AE grading reference range available. If abnormal, clinician to determine if abnormal lab is clinically significant.			
Lymphocytes %		13.9 – 44.4	No AE grading reference range available. If abnormal, clinician to determine if abnormal lab is clinically significant.			
Lymphocytes #: Low		1.0 – 3.4 x $10^3/\mu l$	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L
MCV			No AE grading reference range available. If abnormal, clinician to determine if abnormal lab is clinically significant.			
Neutrophils %		49.1 – 76.9	No AE grading reference range available. If abnormal, clinician to determine if abnormal lab is clinically significant.			

Neutrophils #: Low		2.4 – 7.5 x 10^3/µl	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L
Platelets: Low		136 – 388	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L
WBC: High		4-11.5x10^3/µl			>100x 10^3/µl	
WBC: Low		4-11.5x10^3/µl	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L
COAGULATION PARAMETER	**Qualifier**	**NORMAL LIMITS**	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE THREATENING**
INR: high		<1.2	>1.2 - 1.5; >1 - 1.5 x baseline if on anticoagulation; monitoring only indicated	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated	>2.5; >2.5 x baseline if on anticoagulation; bleeding	
PT (sec); not on anticoagulation: High		11-13 sec	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN

Adapted from Common Terminology Criteria for Adverse Events (CTCAE)" (v 5.0). Available from: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

APPENDIX B: Hemoglobin Laboratory Value Grading Scale

PARAMETER	QUALIFIER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE THREATENING
Hemoglobin (g/dL): Low, ≥ 13 years of age	Male	10.0 to 10.9	9.0 to < 10.0	7.0 to < 9.0	< 7.0
	Female	9.5 to 10.4	8.5 to < 9.5	6.5 to < 8.5	< 6.5
Hemoglobin (g/dL): Low, 57 days of age to < 13 years of age	Male and Female	9.5 to 10.4	8.5 to < 9.5	6.5 to < 8.5	< 6.5
Hemoglobin (g/dL): Low, 36 to 56 days of age	Male and Female	8.5 to 9.6	7.0 to < 8.5	6.0 to < 7.0	< 6.0
Hemoglobin (g/dL): Low, 22 to 35 days of age	Male and Female	9.5 to 11.0	8.0 to < 9.5	6.7 to < 8.0	< 6.7
Hemoglobin (g/dL): Low, 8 to ≤ 21 days of age	Male and Female	11.0 to 13.0	9.0 to < 11.0	8.0 to < 9.0	< 8.0
Hemoglobin (g/dL): Low, ≤ 7 days of age	Male and Female	13.0 to 14.0	10.0 to < 13.0	9.0 to < 10.0	< 9.0

From the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

APPENDIX C: Sample Size Updates

1. Original Power and Sample Size Calculations

The original study design anticipated requiring 450 participants to achieve 318 lesion resolution events, an implied event rate of approximately 70%. 318 events are sufficient to provide 85% power to detect a 40% improvement in the rate of lesion resolution as measured by the subdistribution hazard ratio. Details for the original sample size calculations are provided in section 10.4 and in the statistical analysis plan.

The study protocol also pre-specified a blinded sample size re-estimation procedure to occur at 50% information under the original design (i.e., after 159 lesion resolution events; see section 10.4.1).

1.1. Size Re-Estimation Procedure Details

The sample size re-estimation committee meeting occurred on 29 August 2023 and included data on 165 total events. The blinded report reviewed by the committee and the meeting minutes were archived to serve as documentation of the considerations made by the committee and their decisions regarding the sample size and interim monitoring plan, detailed below. These changes to the study protocol will be accompanied by a corresponding update to the statistical analysis plan.

1.2. Updated Power and Sample Size Calculations – Protocol Version 3.0

This section describes the updated power and sample size calculations which formed the basis for protocol version 3.0. Protocol version 3.0 increased the target number of lesion resolution events to 440. A subsequent sample size increase later increased the target number of events to 550.

The sample size re-estimation committee determined that the study design should be updated to target 440 lesion resolution events rather than the 318 specified by the original design. This decision reflects a higher-than-anticipated event rate and steady enrollment, the combination of which presents an opportunity to increase statistical power without changing the target enrollment of 450 participants. In addition to providing greater statistical power for the primary endpoint, statistical power for secondary and exploratory endpoints (including subgroup analyses) will also be increased. Given the operational difficulty imposed by the study setting, the committee felt it appropriate to maximize the resources currently deployed and attempt to provide the most definitive evidence possible. Table 4 describes the revised power calculations for the trial. The hypothesized subdistribution hazard ratio of 1.40 used to estimate power (indicating a 40% improvement in the rate of lesion resolution, accounting for the competing risk of death) remains unchanged. The assumed split for stratification by days from symptom onset to randomization (75% ≤7 days; 25% >7 days) is based on current trial data as of 29 August 2023.

Table 4. Revised Power Calculations

Overall			Days from symptom onset to randomization ≤7 days, 75% of overall			Days from symptom onset to randomization >7 days, 25% of overall		
N	**N Events**	**Power**	**N**	**N Events**	**Power**	**N**	**N Events**	**Power**
450	440	94.2%	338	331	86.5%	112	109	41.9%

Calculations assume a 98% event rate and a true subdistribution hazard ratio of 1.40 overall and within each stratum.

1.3. Updated Interim Monitoring Plan – Protocol Version 3.0

This section describes the updated interim monitoring plan for protocol version 3.0, which targeted 440 total lesion resolution events. Protocol version 4.0 increases the target number of events to 550, which necessitates further updates to the interim monitoring plan. Refer to Appendix C section 1.4 for the current interim monitoring plan.

Adjusting the target number of events midtrial requires an update to the interim monitoring plan. Interim analysis boundaries for statistical monitoring will still be based on the information time of the analysis (i.e., the proportion of events observed thus far), but the calculations will assume that 440 events will be represented in the final data rather than 318.

The higher-than-anticipated overall event rate reviewed by the sample size re-estimation committee suggested that the first interim analysis (scheduled for 19 October 2023) would contain approximately 200-220 events, substantially more events than intended under the original design. To address this and due to the rapid enrollment that resulted in the first interim analysis occurring at 50% information, the committee determined that the interim monitoring plan should reduce the number of planned interim analyses from 3 (at 1/3, 2/3, and full information) to 2 (at approximately 1/2 and full information). This was initially approved by the DSMB. However, later the DSMB requested updating the interim monitoring plan to add an interim analysis at approximately 75% information (330 events), midway between the first interim and the final analysis. Table 5 outlines the Z score boundaries and p-value thresholds for significance under the original and updated strategies for interim efficacy analyses using the Lan-DeMets spending function analog of the O'Brien-Fleming boundaries, as described in the original protocol and statistical analysis plan.

Table 5. Interim Analysis Boundaries for the Original and Updated Designs

Strategy	Information Time	Z Score Boundary	Nominal Alpha (p-value threshold for significance)
Original design Target 318 events Perform 3 analyses	0.33 (106 events)	±3.71	0.0002
	0.67 (212 events)	±2.51	0.0120
	1 (318 events)	±1.99	0.0463
Updated design Target 440 events Perform 3 analyses	0.50 (220 events)	±2.96	0.0031
	0.75 (330 events)	±2.36	0.0183
	1 (440 events)	±2.01	0.0440

1.4. Updated Interim Monitoring Plan – Protocol Version 4.0

Protocol version 4.0 further increases the target number of lesion resolution events from 440 to 550. This decision was made by the blinded study team based on multiple motivating factors. Given the logistical complexities of operating the trial and the unpredictable nature of outbreak settings, the study team anticipates limited opportunity for other randomized trials to enroll large numbers of cases of clade I monkeypoxvirus. Therefore, the study must aim to provide definitive evidence not only relating to the primary endpoint but extending to secondary and exploratory endpoints as well as subgroup analyses. Absent definitive evidence of efficacy or futility (which may trigger a DSMB recommendation to stop the trial early), there is a scientific benefit in continuing to enroll participants while the outbreak is ongoing and there remains enough study product to randomize and treat participants. An internal pharmacy inventory estimated that there is currently enough study product available in country to randomize and treat up to 600 total participants. We will therefore target enrolling up to 600 participants, with the expectation that this will provide data on approximately 550 lesion resolution events.

Note – at the time protocol version 4.0 was drafted, talks had already begun for scheduling the second interim analysis review, expected to contain data on 330 lesion resolution events. This was initially expected to represent 75% information time. However, given the revised target of 550 events, the analysis will take place at approximately 60% information time. This has a small impact on the thresholds for declaring statistical significance, described in Table 6.

Table 6. Interim monitoring strategies for protocol versions 3 and 4

	Information Time	**Z Score Boundary**	**Nominal Alpha (p-value threshold for significance)**
Version 3.0 (target 440 total events)	0.50 (220 events)	±2.96	0.0031
	0.75 (330 events)	±2.36	0.0183
	1 (440 events)	±2.01	0.0440
Version 4.0 (target 550 total events)	0.40 (220 events)*	±3.36	0.0008
	0.60 (330 events)	±2.68	0.0074
	1 (550 events)	±1.98	0.0476

*Because the first interim analysis has already occurred at the time of this update, the nominal alpha spent on the interim was approximately 0.0031 (the amount spent at that analysis according to the active protocol at that time, 3.0). The remaining alpha is distributed over the next two planned analyses as a function of the true information time and will be calculated by the unblinded statistics team when performing the analyses).

APPENDIX D: Pharmacokinetics (PK) Sampling Specifications Plan

Summary: An additional voluntary/optional blood sample will be obtained from all participants ≥18 years of age at 4 hours after receiving their first dose of study drug on day 7 to be used for PK analysis.

Purpose: There are no published data to establish therapeutic levels of tecovirimat in humans infected with monkeypox virus. Absorption of the drug may be affected by certain parameters like sex, age, metabolism, and the bioavailability the drug is optimal when the drug is administered in a fed state. Given the unknowns regarding tecovirimat concentrations in the setting of mpox, an exploratory objective was included in the PALM007 protocol to measure tecovirimat levels at day 7, when steady-state drug concentrations are expected to be achieved. The addition of the post-4-hour blood draw is necessary to calculate the Cmax or peak concentration of drug. This additional blood draw from participants receiving placebo will be stored for future research and may be used as quality controls in the PK analysis.

Risk to participants: The risks of phlebotomy are like those with other blood draws in the study. There is a risk of anemia with the additional blood draw. The blood draw will be deferred if the participant has a hemoglobin level ≤ 7 g/dL or signs thought to be resulting from anemia at any hemoglobin level below the normal range.

Procedure: Adult participants will be informed of the reason for the intended blood draw and will have the option to decline the draw via checkboxes to opt in or opt out in the informed consent document. For those who agree, up to 4 mL of additional blood for PK assessment will be drawn 4 hours after the first dose of tecovirimat is administered on day 7.

Summary of protocol changes

PALM007: A randomized, placebo-controlled, double-blind trial of the safety and efficacy of tecovirimat for the treatment of adult and pediatric patients with monkeypox virus disease

Version 1.0, dated 19 August 2022, approved on 7 Sept 2022

Version 2.0, dated 28 November 2022, approved on 9 December 2022

1. Clinical labs and mpox PCR will be obtained every other day throughout the hospitalization.
2. All PCR sample collections will be stopped after there are negative results x2 for each individual sample.
3. The discharge criteria no longer include the 24-hour limit. We just consider a negative result x 2 according to the laboratory schedule which is every other day.
4. The paragraph stating that all laboratory samples should be collected prior to randomization has been removed (we agree as long as they were obtained on day 1)
5. Paragraphs have been added to indicate that the baseline specimen will ideally be collected within 24hours prior to randomization. If the specimen cannot be collected within 24 hours and there is a specimen available that was collected within 48 hours prior to randomization, the 48-hour specimen may be used as the baseline sample.
6. The subscript "m" has been modified to add the bolded text: "Although strongly desirable, research laboratory and clinical tests at all stages may be disregarded at the discretion of the investigator if not feasible (e.g., due to problems with blood collection volume related to the participant's weight or hemoglobin or due to site logistics)
7. The following wording has been added to section 9.4 regarding hemoglobin. "A participant with a hemoglobin level <7 g/dl. This would lead to the cessation of blood draws until the hemoglobin level stabilizes and the bedside clinician judges it is safe to resume blood draws." "A participant with signs or symptoms thought to be the result of anemia at any hemoglobin level. This would lead to the cessation of blood draws until the hemoglobin level stabilizes and the bedside clinician feels it is safe to resume blood draws."
8. Section 5.9 (Costs) has been amended to read: "There will be no cost to participants to participate in this study. Hospitalization and treatment will be free of charge. Meals will be provided daily to the participant and to a maximum of two persons accompanying the participant during the participant's hospitalization of an approximate value of $8, equivalent in local currency to 16,000 Congolese francs, per person per day.
9. Section 5.10 (Compensation): "Study participants and up to two accompanying persons will receive US$15, equivalent to 30,000 Congolese francs in local currency, to compensate for their time and inconvenience during the study. The participant will be required to pay a fee at the time of registration for the study and at each subsequent study visit (days 29 and 59). If a selected participant does not meet the study criteria, $15, equivalent to 30,000 Congolese francs in local currency, will be provided to the participant and two accompanying persons to compensate for their time and inconvenience. An additional allowance of $4, equivalent to 8,000 Congolese francs in local currency, will be paid daily to the participant and up to two accompanying persons during the hospitalization. A round trip to the study site for registration and for each study visit will be provided. A trip to the study site for registration and each study visit (days 29 and 59) will be provided to the participant and up to two accompanying persons. If a participant does not sign a screening consent but is eligible to join the study and signs the consent for the main study, the participant and up to two other

accompanying persons will receive $15 American, equivalent in local currency to 30,000 Congolese francs, for the first study visit. Travel will also be provided as indicated above. The screening form and informed consent form have been edited accordingly."

10. Section 9.3.3.1 NON EMERGENCY has been replaced with "NON URGENT"; it was a recommendation for change from the DSMB.
11. The first secondary endpoint was changed to: Time to first negative blood PCR result until 28 days after randomization. The STATS section has been modified to reflect this change.
12. The third secondary evaluation criterion has been removed. The STATS section has been modified to reflect this change.

Version 3.0, dated 1 September 2023, approved on 6 Oct 2023

1. Monkeypox disease was changed to "mpox" throughout the protocol. When referring to viral
infection or the virus itself, the term monkeypox virus is used.
2. A row was added to the schedule of activities for "pregnancy outcome."
3. An additional visit was added to the Schedule of Activities for sick visits post discharge to be able to capture data from participants who may present with recrudescent mpox lesions after
whole body lesion resolution (we have had two such participants). If this occurs, PCR of blood, OP and skin lesions will be obtained as well as clinical labs and total lesion count. An exploratory objective and endpoint were added to reflect this.
4. The lab AE grading table adapted from the CTCAE v5.0 was added as an appendix. Another appendix was added for hemoglobin grading based off the DAIDS v2.1 grading document.
5. Edits made to say that clinical labs or events that cannot be graded according to CTCAE will be evaluated by the clinician and if considered clinically significant (definition provided in protocol), the resulting clinical diagnosis will be considered an AE and reported.
6. Several Stats edits from Tyler including: 1) Proportion PCR negative in each compartment at Day 15 added as secondary with no formal testing 2) Designation of key objectives removed.
7. We have decided against collecting conjunctival swabs, csf and amniotic fluid as part of this study. These had been added to previous revisions but have since been removed.
8. Due to testing/work load constraints, CRP and amylase will only be tested on days 1, 7, 13, 29. CK will be done retrospectively.
9. CD4 count was taken out of the protocol since these cannot be measured retrospectively.
10. Edits to Exploratory objective #6: Viral persistence was changed to persistent PCR positivity.

Version 4.0, dated 15 December 2023, approved on 24 Jan 2024

1. Pharmacokinetic (PK) sampling specifications: Appendix D:
    a. Addition of Appendix D describing an additional voluntary/optional blood sample to be collected from all participants aged fi 18 years 4 hours after receiving their first dose of study drug on day 7 to be used to calculate Cmax or maximum drug concentration.
    b. Exploratory objective 10 was modified to add measurement of concentration 4 hours after administration and this was also added to the schedule of activities.

2. Increase sample size and update power and sample size calculations based on sample size re-estimation plan. Appendix C: Sample Size Updates added.
3. Update of the provisional monitoring plan for the protocol: Appendix C
4. Added wording compensation to indicate that the trip will be covered for at least one sickness visit for the participant and up to two accompanying.