Placebo-controlled randomised trial of tecovirimat in non-hospitalised Mpox patients (PLATINUM)

Background: Mpox is an acute febrile rash illness caused by the monkeypox virus. Since its first human identification in 1970, the majority of cases have been reported from Africa. Historically, there have been sporadic travel associated cases in countries outside of Africa, with very limited onward transmission.

Following notification from the United Kingdom to WHO on the 15th of May 2022, of two confirmed and one probable case of mpox, person-to-person transmission of mpox has been observed in multiple countries outside of Africa.

Several investigational antivirals demonstrate activity against monkeypox virus in vitro and in animal models, but none has been evaluated in a clinical trial. The most promising is tecovirimat, which is an oral anti-viral drug developed by SIGA Technologies, Inc. and approved by the US Food and Drug Administration (FDA) for the treatment of smallpox and by the European Medicines Agency (EMA) and Medicines and Healthcare products Regulatory Agency (MHRA), under an exceptional circumstances rule, for the treatment of smallpox, cowpox and mpox.

Eligibility and randomisation: This protocol describes a double-blind, placebo-controlled, randomised trial among non-hospitalised adults and children with laboratory-confirmed mpox. Patients will be identified following clinical assessment and laboratory confirmation of mpox infection as part of usual clinical care. All eligible and consenting patients will be randomly allocated (1:1) to receive tecovirimat or matching placebo for 14 days, each to be given in addition to the usual standard of care.

Study endpoints: The primary clinical efficacy endpoint is the time to resolution of active lesions. Secondary efficacy endpoints are time to complete lesion resolution, and the time to negative cultures for monkeypox virus in throat and lesion swabs. Safety data will also be collected. For the main analyses, follow-up will be censored at 28 days after randomisation. Additional information on longer term outcomes may be collected through review of medical records or linkage to medical databases (such as those managed by NHS Digital and other health care organisations). Additional assessments may be conducted following the end of the main assessment period of the study (28 days) to assess complete resolution of mpox symptoms.

Safety: All adverse events, and reasons for stopping study treatment will be recorded and will be reviewed by medical staff at the Central Coordinating Office. Suspected Unexpected Serious Adverse Reactions (SUSARs) to study medication (e.g., Stevens-Johnson syndrome, anaphylaxis, aplastic anaemia, etc.) will be reported in an expedited fashion.

Data collection: To facilitate patient isolation and infection control, and participation by clinicians and patients, data collection and all other trial procedures are streamlined and focused on those aspects critical to participant safety and the reliability of the study results. Informed consent, randomisation and follow up will be conducted remotely by telephone call or video call and data will be recorded by electronic methods by participants and trial staff.

Numbers to be randomised: The rates of clinical and microbiological resolution are uncertain for mpox in general, and in particular for the current epidemiological context.

Sample size estimates using data on the natural history of clade 1 (Congo Basin clade) mpox indicate that randomisation of 500 individuals would provide at least 85% power and a two-sided α of 0.05 to detect a 40% improvement in the rate of lesion resolution at day 28 (account for one interim analysis and approximately 10% losses to follow-up). Monitoring of blinded event rates will be used to re-estimate sample size requirements as data from the trial accrue.

Study organisation: The study is led by researchers at the University of Oxford (the regulatory trial sponsor) and includes experts in infectious disease at the Pandemic Sciences Institute and experienced clinical trialists applying methods established in the RECOVERY and PANORAMIC trials of treatments for COVID-19. Chelsea and Westminster Hospitals NHS Trust is providing sexual health expertise. The University of Liverpool is providing laboratory expertise. The study is coordinated by the Clinical Trial Service Unit in the Nuffield Department of Population Health.

To enquire about the trial, contact the PLATINUM Central Coordinating Office

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1 BACKGROUND AND RATIONALE

1.1 Mpox

Mpox is an acute febrile rash illness caused by the monkeypox virus. The clinical features of human mpox closely resemble those of smallpox, although mpox is typically milder than smallpox.(1)

Two distinct clades of mpox have previously been characterized: Clade 1 (Congo Basin) and Clade 2 (West African). Clade 2 has a reported mortality of approximately 1-4%. Clade 1 is associated with higher mortality (up to 10%) and seems to transmit more frequently between humans.(2) After a 5 to 21-day incubation period, a prodromal illness with fever, malaise, and painful swollen lymph nodes is observed in most patients. The prodromal period generally lasts 1–3 days before the occurrence of the typical vesiculo-pustular rash, which lasts 2 to 4 weeks. Skin lesions are characteristic of the disease with uniform progression from macules to papules, vesicles, pustules, umbilication, crusting and finally desquamation. In addition to skin lesions, extracutaneous manifestations, such as secondary skin and/or soft-tissue infection (19% of cases), pneumonitis (12%), ocular complications (4%–5%), and encephalitis (<1%) can be observed in patients infected with mpox. Death, when it occurs, generally occurs during the second week of the lesional stage of the disease. Subclinical infection and asymptomatic cases have also been reported with an estimated rate of approximately 30%.(3)

Mpox case numbers have been increasing in Central and West Africa over recent years, possibly due to waning of population immunity derived from the smallpox eradication program.(4-7) Historically, there have been sporadic imported cases to the UK with limited onward transmission. (8, 9)

Following notification from the United Kingdom to WHO on the 15th of May 2022, of two confirmed and one probable case of mpox, many countries are reporting a growing number of mpox cases without a travel history, indicating person-to-person transmission of mpox. The viruses associated with these cases are most closely related to clade 2 but have some genetic differences and has been tentatively named Clade 3.

The epidemiology and clinical characteristics of the current outbreak are atypical. From 1 January to 22 June 2022, 3413 laboratory confirmed cases and one death have been reported to WHO from 50 countries/territories in five WHO Regions. The majority of laboratory confirmed cases (2933/3413; 86%) were reported from the WHO European Region. As of 11 July, there were 1,735 confirmed cases in the UK, of which 1,660 are in England. The majority of the cases identified to date have been among men who have sexual activity with men (https://www.gov.uk/government/publications/monkeypox-outbreak-technical-briefings/investigation-into-monkeypox-outbreak-in-england-technical-briefing-4). However, there have also been cases in other groups. There has been a preponderance of genital, perianal and mucosal lesions, rather than the centrifugal rash classically described for mpox. Some of the lesions have persisted for a long period and some patients have required hospitalisation for pain management or treatment of secondary skin infections.

1.2 Treatment Options

To date, most of the patients affected by mpox receive only supportive and symptomatic care as standard treatment. However, several investigational antivirals demonstrate activity

against monkeypox virus in vitro and in animal models, but none has been evaluated in a clinical trial. The most promising is tecovirimat, which is an oral anti-viral drug developed by SIGA Technologies, Inc.(10-18) In 2018, the FDA granted SIGA Technologies, Inc. approval of tecovirimat for the treatment of human smallpox disease in adults and paediatric patients weighing at least 13 kg (for the oral formulation) under the Animal Rule (SIGA NDA 208627 and SIGA IND 69019).(19) In June 2022, the MHRA granted marketing authorisation (under an 'exceptional circumstances' rule) for tecovirimat for the treatment of mpox and other orthopoxvirus diseases including vaccinia complications in adults and children of at least 13 kg body weight.(20)

1.3 Design Considerations

The PLATINUM trial protocol describes an overarching trial design to provide reliable evidence on the efficacy of tecovirimat for laboratory-confirmed mpox in patients presenting to healthcare services and managed as outpatients. Since patients hospitalised for complications of mpox treatment may be prescribed tecovirimat for clinical indications, the trial is restricted to outpatients.

It is anticipated that such patients will be seen initially in healthcare facilities where the provisional diagnosis will be made and lesion and/or throat swabs taken for measurement of monkeypox virus DNA by PCR in biosecure clinical laboratories run or authorised by the Health Security Agency (HSA). Thus the identification of eligible cases is considered to be part of routine NHS clinical care.

The protocol is suitable for a wide range of settings, allowing a broad range of patients to be enrolled, potentially in large numbers. The trial has been designed so that it could accommodate patients who may be assessed in a variety of medical settings (e.g. genito-urinary medicine clinics, accident & emergency departments, primary care, or through public health services). The approach to recruitment is strongly informed by the experience of the PRINCIPLE and PANORAMIC trials of treatments for COVID-19 and is designed to be readily integrated into standard clinical and public health workflows for this disease.

Confirmed cases may be geographically widely distributed and the settings in which cases are diagnosed may change over time. To recruit patients diagnosed through multiple clinical and public health sites and settings without the need for numerous clinical trial agreements, the trial will be conducted as a "remote" trial without research sites or participant identification centres. In accordance with Health Research Authority (HRA) guidance*, research participants will be identified through normal clinical activity (e.g. a routine clinic) and referred to the research study in order to gain access to the clinical intervention. Trial activities will be being overseen by the Chief Investigator who will delegate trial duties to other appropriately trained and qualified staff and formally record such delegation.

At the time of starting this trial, most cases are young or middle aged adults who do not require hospital care and will be managed at home but who do require strict isolation for infection control purposes. Therefore, the protocol is designed to be implemented through a mixture of patient self-assessment, video or telephone call assessment by trial team members, and self-swabbing. Although the vast majority of patients are adults, the protocol includes a provision for the recruitment of children weighing ≥13kg.

* https://www.myresearchproject.org.uk/help/hlpsitespecific.aspx#PIC

Since the assessment of symptoms and lesions status, and compliance with trial procedures may be influenced by knowledge of treatment allocation, a placebo controlled trial design (rather than open label) is necessary in order to reliably assess the effects of the treatment. Accurate quantification of any clinical benefit or impact on infectiousness is particularly important for a drug such as tecovirimat, where availability and cost may limit the extent to which its use is recommended, especially in people with mild disease.

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2 STUDY DESIGN

2.1 Study aims

The PLATINUM trial aims to provide reliable evidence about the efficacy and safety of oral tecovirimat in the treatment of acute mpox infection among patients who do not require admission to hospital. The trial will evaluate whether a two-week course of tecovirimat increases the rate of resolution of mpox skin and mucosal lesions, and/or increases the rate of viral clearance as defined by viral culture of throat and lesion swabs. PLATINUM will use a remote design, combining online forms for self-assessment of lesion resolution and calls from staff at the Central Coordinating Office. Couriers will deliver tecovirimat or matching placebo to participants who are self-isolating because of their infection, and will also collect self-taken follow-up swabs for analysis at a central laboratory. The trial aims to recruit 500 participants with confirmed mpox, who will followed-up for 28 days following trial entry.

2.2 Eligibility

Patients are *eligible* for the study if **all** of the following are true:

(i) Laboratory-confirmed mpox infection
(ii) The presence of active skin or mucosal lesion(s)*
(iii) Patient is appropriate to be managed without hospitalisation
(iv) Women with reproductive potential† are willing to use effective contraception‡ from the time of enrolment through study day 28.

Patients are to be *excluded* if **any** of the following are true:

(i) Weight <13 kg (children weighing more than this are eligible)
(ii) Planned use of contraindicated treatment (see section 2.5.5) during study period
(iii) Current or past use of tecovirimat
(iv) Lack of capacity to provide informed consent
(v) The referring doctor considers there to be a definite indication for tecovirimat
(vi) Hypersensitivity to tecovirimat or any excipients in the study treatment
(vii) Current pregnancy or breastfeeding
(viii) Clinically determined severe renal impairment i.e., under the care of a nephrologist
(ix) Clinically determined severe hepatic impairment i.e. under the care of a hepatologist
(x) Diagnosis of epilepsy

Other considerations:

(i) Patients who have received an orthopoxvirus vaccination may be included.
(ii) Limited safety trials including an elderly population (up to the age of 79 years) suggest no clinically important effects of age on the safety of tecovirimat. Therefore, there is no upper age limit on participation in the trial.(18)

* An active lesion is a skin lesion that is not scabbed or desquamated or a mucosal lesion that has not healed.
† Female reproductive potential is defined as the time following menarche until becoming post-menopausal, unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
‡ Acceptable methods of effective contraception include the following: intrauterine devices; progestogen-only injections, pill or implant; combined hormonal contraception (pill, patch or vaginal ring); male or female condom; diaphragm or cervical cap with a spermicide.

(iii) There is no upper time limit for days since symptom onset. However, the Trial Steering Committee will monitor this aspect of recruitment and may introduce an upper time limit to ensure that a substantial proportion of participants are enrolled early in the disease (when the anti-viral effects of tecovirimat are most likely to be greater).

2.2.1 Pregnancy and breastfeeding

Background: No adequate and well-controlled studies of tecovirimat in pregnant women have been conducted. Therefore, there are no human data to establish the presence or absence of tecovirimat-associated benefit or risk in pregnancy. In animal reproduction studies, no developmental toxicity was observed in mice during the period of organogenesis at tecovirimat exposures (area under the curve) up to 23 times higher than human exposure at the recommended human dose. In rabbits, no developmental toxicity was observed during organogenesis at tecovirimat exposures less than human exposures at the recommended human dose. 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 recommended human dose.

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.(19) The developmental and health benefits of breastfeeding should be weighed against the mother's clinical need for tecovirimat and any potential adverse effects on the breastfed child from tecovirimat or from the underlying maternal condition.

Pregnant women may be at risk for more severe disease and possible congenital mpox disease.(21) It remains unclear what the risk of severe mpox is in breastfeeding women. Pregnant women will be excluded from this trial. Non-pregnant women with reproductive potential must agree to use effective means of contraception when engaging in sexual activities that can result in pregnancy, from the time of enrolment through study day 28. Acceptable methods of contraception include the following: intrauterine devices; progestogen-only injections, pill or implant; combined hormonal contraception (pill, patch or vaginal ring); male or female condom; diaphragm or cervical cap with a spermicide. If a woman becomes pregnant during the trial treatment period, she will discontinue the study drug.

Women who are breastfeeding will need to stop breastfeeding to be eligible for enrolment. The benefits and risks of this decision will be made between the patients' treating clinician and the patient.

2.2.2 Immunocompromised Patients

Background: The safety of tecovirimat in immunocompromised individuals has not yet been established. No clinical studies of tecovirimat in immunocompromised patients have been performed. Studies in immunocompromised animal models demonstrated a potential for reduced efficacy, but no increased safety concern.(25)

Given that immunocompromised patients may be at risk for more severe disease or death, the potential benefits of receiving tecovirimat may outweigh potential risks. Therefore, immunocompromised patients will be eligible for enrolment.

2.2.3 Older adults

Background: A randomized, double-blind, safety trial involving healthy volunteers had a median age of tecovirimat recipients (n=359) of 38 years, an age range of 18 to 79 years and 10% of participants were aged 65 years or older.(18) This study did not identify any age-related safety concerns and the EU SmPC for tecovirimat does not have an upper age for use in the clinic.

Given the lack of any safety concerns in healthy adults up to the age of 79 years and the possibility (but unknown) risk for more severe disease in older adults, there is no upper age limit for inclusion in the trial.

2.2.4 Children and Adolescents

Background: The safety of tecovirimat in children and adolescents below 18 years of age has not yet been established. Paediatric subjects have not been studied in clinical trials with tecovirimat. Safety data are available for young adults and these show no clinically important effects of age on the safety of tecovirimat.(18)

Historically, mpox has been a disease that affects children as well as adults. Given that paediatric patients commonly experience more severe disease than adults that routinely requires intensive care, the potential benefits of receiving tecovirimat may outweigh potential risks. Therefore, children weighing ≥13 kg will be eligible for enrolment.

2.2.5 Contraindications due to other treatments.

The Summary of Product Characteristics provides cautions for tecovirimat use with several concomitant medications. Patients taking these medications during the study period will not be eligible for enrolment. Discussions regarding whether it is appropriate to temporarily discontinue or replace of one of these medications for an alternative will need to occur (and be documented) with their usual treating clinician before a patient is considered eligible for enrolment.

- Bupropion
- Repaglinide
- Voriconazole
- Rilpirivine
- Maraviroc
- Midazolam
- Atorvastatin
- Tacrolimus
- Methadone
- Flurbiprofen
- Phosphodiesterase type 5 inhibitors (sildenafil, tadalafil, vardenafil)
- Darunavir
- Proton pump inhibitors (lansoprazole, omeprazole, rabeprazole)

2.2.6 Comorbidities

Use in people with epilepsy: The potential for tecovirimat to lower seizure threshold is unknown and so persons with a diagnosis of epilepsy will not be eligible for enrolment.

Renal and hepatic impairment: There is limited clinical data regarding tecovirimat use in patients with severe renal or hepatic impairment, and there is a risk of higher unbound drug and metabolites. Biological sampling for drug plasma concentrations cannot be undertaken in this trial and so patients with

a) clinically determined severe renal impairment (defined as being under the treatment of a nephrologist); or
b) clinically determined severe hepatic impairment (defined as being under the care of a hepatologist)

will not be eligible for enrolment.

2.3 Treatment comparisons

Eligible individuals who have provided and consent will be allocated to tecovirimat or placebo using a minimised randomisation program that helps maximise balance between the allocated treatment groups with respect to important prognostic variables (including age [<18, ≥18-<40, ≥40], sex at birth [male/female], previous orthopoxvirus vaccination [yes/no/not known], severity [localised vs disseminated rash (defined as >1 area, e.g. groin & head)], and days since lesion onset [≤7 days or >7 days]).

Randomised participants will be issued with a supply of tecovirimat capsules (200mg) or placebo capsules to be taken orally with food as follows:

- Adults aged 18 years or older: three capsules twice a day for 14 days (total daily tecovirimat dose: 1200 mg
- Children and adolescents aged <18 years:
    - Estimated body weight ≥13 to <25 kg: one capsule twice a day for 14 days (total daily tecovirimat dose: 400 mg).
    - Estimated body weight ≥25 to <40 kg: two capsules twice a day for 14 days (total daily tecovirimat dose: 800 mg).
    - Estimated body weight ≥40 kg: three capsules twice a day for 14 days (total daily tecovirimat dose: 1200 mg).

Although PK/PD modelling suggest that higher doses may be preferable in adult patients weighing ≥120 kg, all adults allocated to active tecovirimat will receive the current standard dose (as above) without adjustment for weight.

2.4 Study endpoints

2.4.1 Primary endpoint

(i) **Time (days) to active lesion resolution**, defined as the first day on which all skin lesions are scabbed or desquamated (and mucosal lesions healed), up to 28 days after randomisation.

2.4.2 Secondary endpoints

(i) **Time (days) to complete lesion resolution**, defined as the first day on which all lesions are completely resolved (all scabs dropped off and intact skin remains underneath, and mucosal lesions healed), up to 28 days after randomisation.

(ii) **Time to negative throat swab viral culture**, defined as time to consistently negative culture for monkeypox virus on throat swab at Days 7, 14, 21, and 28.*
(iii) **Time to negative skin or mucosa swab viral culture**, defined as time to consistently negative culture for monkeypox virus on swab of most recent active skin or mucosa lesion at Days 7, 14, 21, and 28.

2.4.3 Subsidiary outcomes

To evaluate the efficacy of tecovirimat versus placebo in patients with mpox:

(i) **Clinical status** on day 7, 14, 21 and 28 according to an ordinal scale. The ordinal scale is a) all lesions completely resolved (all scabs dropped off and intact skin remains underneath, and all mucosal lesions healed), b) active lesions resolved (all skin lesions scabbed or desquamated, but not fully resolved), c) active lesions persist but no new lesions in last 24 hours, d) new active lesion(s) in last 24 hours.
(ii) **Throat swab monkeypox virus DNA levels:** Change from baseline in monkeypox virus DNA concentration in throat swabs at Days 7, 14, 21, 28
(iii) **Number (%) of patients admitted to hospital for a complication of mpox** (overall and by type)
(iv) **Time to sustained absence of use of analgesia**, defined as time to consistently reporting no use of analgesia, up to 28 days after randomisation.

Justification of trial endpoints: To date there have been no studies of mpox therapeutics in humans to inform the design of the present trial and there is little clinical experience of their use in non-hospitalised patients. As such, there are no standards for study endpoints.

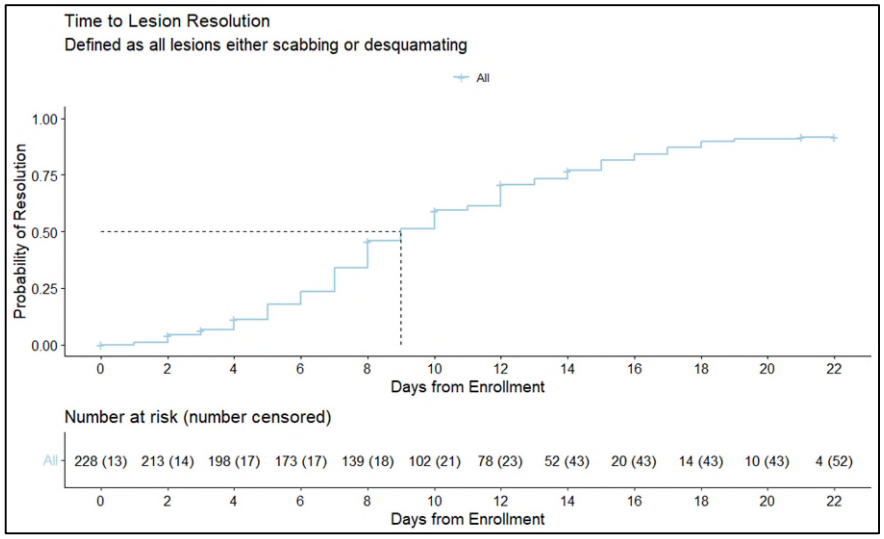
Mpox lesions are painful and are known to contain high concentrations of monkeypox virus. Therefore, lesion status is both a clinically relevant outcome and an epidemiologically relevant proxy for infectiousness. Self-reported assessment of skin and mucosal lesions can be done daily, allowing a time-to-event analysis.

Primary and secondary endpoints were 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 Institut National pour la Recherche Biomedicale ("National Institute for Biomedical Research" - INRB) in collaboration with the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) between 2007 and 2011.(22) Note, however, that these data are from mpox caused by the Congo Basin clade, which is generally thought to be more severe than the West African clade, which is the cause of the current outbreak outside of Africa.

Data from the Democratic Republic of Congo suggest that the median time to all lesions being scabbed or desquamated is around study day 9, with around 77% having all lesions scabbed or desquamated by day 22 (see Figure 1). This provides sufficient data to estimate sample size requirements.

Although all lesions being scabbed or desquamated likely indicates less infectivity than active lesions, scabs do contain virus and all lesions healed (all scabs have dropped off, and intact skin remains underneath) is a more complete measure of lack of infectivity. Therefore, complete resolution of lesions will be a key secondary outcome.

Figure 1. Time to lesion resolution among a cohort of 228 patients with laboratory-confirmed mpox in the 2007-2011 INRB/USAMRIID observational study *



Time to loss of infectiousness is best assessed by conducting viral culture of daily lesion and throat swabs. However, daily swabbing is not likely to be feasible in the outpatient setting due to logistical and infection control constraints on collecting, transporting and testing such a large volume of monkeypox virus specimens. Therefore, swabbing will be intermittent, with interval censored statistical analysis.

Pain, sometime severe, is very commonly reported in clade 3 associated mpox and pain management is a major reason for admission to hospital. Therefore, alleviation of pain is an important outcome for patients.

2.4.4 Safety assessments

To evaluate the safety and tolerability of tecovirimat relative to placebo in patients with mpox:

(i) Number (%) of patients suffering serious adverse events (overall and by type) within 28 days of randomisation
(ii) Number (%) of patients suffering adverse events of special interest (overall and by type) within 28 days of randomisation
(iii) Number (%) of patients suffering death, overall and by cause

2.4.5 Exploratory analyses

Other analyses may be conducted to explore the effects of tecovirimat vs. placebo on clinical efficacy, safety and microbiological outcomes, including in subsets of patients defined by baseline characteristics and medical history (with appropriate caution in the interpretation of the exploratory nature of these analyses and the multiple number of such comparisons).

2.5 Statistical analysis

A more detailed statistical analysis plan will be developed by the investigators and published on the study website whilst still blind to any analyses of aggregated data on study outcomes

by treatment allocation. All analyses for reports, presentations and publications will be prepared by statisticians and data management staff at University of Oxford.

2.5.1 Methods of analysis

Comparisons will be made between all participants randomised to the different treatment arms, irrespective of whether they received their allocated treatment ("intention-to-treat" analyses).

Primary and first secondary outcome: For time-to-event analyses of the primary and first secondary outcome, the tecovirimat group will be compared with the placebo group using a stratified log-rank test (days since symptom onset ≤7, >7 days). Kaplan-Meier estimates for the time to event will also be plotted (with associated log-rank p-values). The log-rank 'observed minus expected' statistic (and its variance) will also be used to estimate the average event rate ratio (and its confidence interval) for those allocated to treatment group versus the placebo group.

Other secondary outcomes: Time to consistently negative culture for monkeypox virus on throat swab and on swab of most recent active skin or mucosa lesion at Days 7, 14, 21, and 28 will be analysed using an interval censored Weibull model. A negative culture will be considered 'consistently negative' if it is not followed by a positive culture on the same type of swab during subsequent assessments.

Subsidiary and safety outcomes: Clinical status on an ordinal scale will be compared between tecovirimat and placebo groups using a proportional odds model.(23) Howard's method will be used if the proportional odds assumption is not satisfied.(24) Monkeypox virus DNA concentration will be compared between groups using the Wilcoxon rank-sum test. Data on hospital admissions and safety will be analysed using Fisher's exact test. For time-to-event analyses of the subsidiary outcome of need for analgesia, the tecovirimat group will be compared with the placebo group using a stratified log-rank test (days since lesion onset ≤7, >7 days).

Adjustment for multiple testing: A step-down approach will be used to control the family-wise error rate across the primary and three secondary outcomes: Hypothesis testing will first be conducted for the primary (time to active lesion resolution). Only if the null hypothesis is rejected at a 2-tailed p=0.0476, confirmatory analysis of the three secondary endpoints will be performed at a 2-tailed p=0.0476. To account for multiplicity of testing of the three secondary endpoints, the Benjamini-Hochberg method will be used.(25) For all other assessments (including those of subsidiary, safety, and exploratory assessments and any subgroup assessments) due allowance will be made in their interpretation for multiple comparisons.

Subgroup analyses: Pre-specified subgroup analysis will be conducted for the primary outcome using the statistical test for interaction (or test for trend where appropriate) for the following: age (<18, ≥18<40, ≥40), sex, orthopoxvirus vaccination status, and time since onset of first lesion (≤7 days or >7 days]).

2.6 Planned sample size

For the log-rank test of the primary endpoint 'time to active lesion resolution', the two key determinants of power are the total number of active lesion resolution events and the treatment-to-control ratio of the rate of active lesion resolution.

Table 1 displays the power of this test for various scenarios. In total, 318 patients with lesion resolution by day 28 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 instead of death; values greater than one indicate improved outcomes) with at least 85% power and a two-sided α of 0.05. Conservatively assuming that the observed event rate of 77% from the 2007-2011 INRB/USAMRIID observational study will apply to the combined time to event data of experimental and control groups yields a total targeted sample size of 413 participants. **A total sample size of 500 is planned** to account for one interim analysis and approximately 10% losses to follow-up.

Table 1. Number of events needed to have 80% and 85% power at 2P=0.05 to detect an improvement in the primary outcomes.

Rate Ratio	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*
1.30	457	594	522	678
1.40	278	362	318	413
1.50	191	249	219	285

* Assumes that 77% of patients will experience the event and does not account for potential dropout. In the 2007-2011 INRB/USAMRIID observational study, 77% of patients reached lesion resolution (as defined above) within 22 days.

2.7 Sample Size Re-estimation

Since the event rate is uncertain, the sample size will be reviewed and revised based on blinded data (i.e. with time to event data for the experimental and control groups combined), when about 50% of the originally planned number of participants have reached determination of the primary endpoint.

2.8 Data and safety monitoring

The study will collect information on:

(i) **Serious Adverse Events (SAE)**: A SAE is any adverse event that:
- results in death
- is life-threatening*
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

The MHRA SmPC will be the source of Reference Safety information (RSI).

(ii) **Non-serious Adverse Events (NSAE):** This includes any new symptoms reported by the participant. Participants will be specifically asked about AEs of special interest, including headache, sore eyes, cough, shortness of breath, nausea, vomiting, diarrhoea, muscle aches, joint pain.

rm "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe

(iii) **Reasons for prematurely stopping allocated study treatment.**

These will be ascertained from the weekly review calls with the participant by a study clinician (up to day 28), and spontaneous reports from healthcare professionals caring for the participant. In addition, participants (and their parents or carers if under 16) will be provided with a dedicated 24-hour phone support line for any trial-related queries, and with a wallet card containing details of the trial that they should carry with them during the 28 day follow-up period. These safety outcomes will be collected up to day 28 (i.e. 14 days after the completion of study treatment). Study staff that become aware of a potential SAE will report this within 24 hours to the Chief Investigator or their designee.

2.9 Central assessment of SAEs and onward reporting of SUSARs

All serious adverse events (SAEs) will be documented and their causal relationship to the study treatment will be assessed by the Chief Investigator or designee. Serious Adverse Events that are believed with a reasonable probability to be due to the study treatment will be considered a Suspected Serious Adverse Reaction (SSAR) (https://database.ich.org/sites/default/files/E2A_Guideline.pdf).

Clinicians at the Central Coordinating Office are responsible for expedited review of reports of SSARs received. Additional information (including relevant medical and medication history) will be sought from relevant healthcare teams. An assessment made of whether the event is "expected" or not (assessed against the relevant Reference Safety Information*). Any SSARs that are not expected would be considered a Suspected Unexpected Serious Adverse Reaction (SUSAR).

All confirmed SUSARs will be reported to the Chair of the DMC, the trial sponsor, and to MHRA and the ethics committee, in an expedited manner in accordance with regulatory requirements.

2.10 Interim analyses: role of the Data Monitoring Committee

A Data Monitoring Committee (DMC) Charter will be approved by the Trial Steering Committee prior to it considering any unblinded data from the trial. This will affirm that members of the DMC are free from any conflicts of interest regarding the study intervention. During the study, interim analyses of unblinded study data (including information on the pre-specified primary, secondary and safety outcomes) will be supplied in strict confidence to the independent Data Monitoring Committee (DMC). The DMC will request such analyses at a frequency relevant to the stage of the study and the speed and volume of new information (typically every 6 months with a Chair's review at 3 months) or in response to emerging information from other studies.

The DMC will independently evaluate these analyses and any other information considered relevant. The DMC will review the analyses among children (age <18 years) both separately and combined with the adult data. The DMC is expected to advise the Chief Investigator and Chair of the Trial Steering Committee if, in the view of the DMC, there is compelling evidence of *hazard* that seems likely to outweigh any potential benefit (either overall or in a particular subgroup of participants).

* MHRA SmPC

A single interim assessment for *benefit* is to take place when 50% of the originally planned number of participants have reached determination of the primary endpoint (i.e. experienced active lesion resolution before or at day 28 or reached 28 days of follow-up). A group sequential design was used to generate asymmetric two-sided boundaries based on Hwang-Shih-DeCani alpha and beta spending functions for efficacy and non-binding futility assessments (Table 2).

Table 2. DMC guidance for interim analysis of benefit

		Lower bounds (futility assessment)		**Upper bounds (efficacy assessment)**	
Analysis	**N**	Z-statistic	P-value*	Z-statistic	P-value*
Interim	216	0.42	0.6616	2.75	0.0030
Final	432	1.98	0.9762	1.98	0.0238

*One-sided p-values; the one-sided p-value of the final analysis of 0.0238 corresponds to a two-sided p-value of 0.0476.
Boundaries estimated using R package gsDesign

The DMC will assess the effect of tecovirimat vs. placebo on the primary outcome against these criteria and advise the Chief Investigator accordingly. In considering its recommendations, the DMC should also take account of the totality of the evidence from the trial data (including effects on secondary and other outcomes and in key participant subgroups) and any other information from external sources that it considers relevant (e.g. results from other trials, emerging information on the nature of the disease and its epidemiology).

The Chief Investigator is responsible for considering the advice of the DMC in discussion with members of the Trial Steering Committee, amending the protocol accordingly, and making the information available to the public. Unless this happens, the Trial Steering Committee, Chief Investigator, study staff, investigators, study participants, funders and other partners will remain blind to the treatment allocation for individual participants and to the interim results until 28 days after the last patient has been randomised (at which point unblinded analyses may be conducted).

2.11 Blinding and Emergency Unblinding

This is a placebo-controlled trial in order to avoid knowledge about the treatment allocation impacting (or being perceived to impact) the assessment of clinical outcomes and adverse events or adherence to the study procedures (e.g. completion of questionnaires or collection of samples). While the study is in progress, access to the treatment allocation for individual participants and tabular results of study outcomes by allocated treatment allocation will not be available to anyone other than the DMC and the statistical team responsible for preparing analyses for the DMC.

There are two exceptions in which unblinding of the treatment allocation (tecovirimat or placebo) for an individual participant may be warranted:

- When knowledge of the treatment allocation could materially influence the immediate medical management (e.g. after overdose); and
- When the Chief Investigator (or delegated clinician) reviews a report of a SSAR.

An unblinding service is available on a 24-hour basis via the CCO telephone service. The treatment allocation will be provided promptly to any clinician treating a patient in the trial who requests the treatment allocation assignment in emergency circumstances.

2.12 Development Safety Update Report

The CI will submit (in addition to the expedited reporting above) Development User Safety Reports once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee, HRA (where required), and Sponsor..

3 STUDY PROCEDURES

PARTICIPANT IDENTIFICATION

- Patient attends NHS service where diagnostic swabs are taken. If possible the study is discussed with the patient and PIS handed to the patient at the consultation or emailed to the patient on the same day as the consultation.
- UKHSA informs attending clinician of positive monkeypox virus result and at same time informs/reminds clinician of availability of PLATINUM trial.
- Attending clinician contacts patient to inform them of their diagnosis and self-isolation requirements as part of routine NHS care.
- Attending clinician also informs patient of the PLATINUM trial and seeks verbal permission to share contact details with Clinical Coordinating Office (CCO) team via secure NHS email.
- Attending clinician confirms fact of diagnosis via email and that there is no current plan to manage as an inpatient or start tecovirimat treatment
- Patient is given a link to Participant Information Sheet on the PLATINUM website by their attending clinician or is emailed this by the CCO.

RANDOMISATION (DAY 0)

- CCO Team contacts the patient by phone call (or video call if preferred) to discuss participation and answer questions.
- If a patient does not wish to join the study, their personal details will be deleted from the secure shared mailbox, and will not have been recorded anywhere else.
- If patient wishes to join the study, CCO performs eligibility screening and conducts consent discussions, with signed consent provided to the trial team and participant using an online form.
- CCO performs baseline assessments.
- Minimised randomisation performed by CCO.
- Allocated study treatment and sampling kits dispatched to participant's home by next-day courier from the central pharmacy.

FOLLOW-UP (DAYS 1-28)

- Study treatment pack and self-swabbing kits delivered on day 1.
- Participant takes study medication on days 1-14.
- Participant completes daily online symptom diary on days 1-28 via text or email link sent by CCO
- Weekly follow-up calls by CCO nurse or doctor on days 7, 14, 21 and 28 to collect further information on symptoms, adverse events, and treatment adherence. At this call any participant concerns will be addressed and the procedure for self-swabbing explained, with reference to the participant self-swabbing instructions.
- Participants collect throat and lesion swabs on days 7, 14, 21 and 28, which are picked up by courier and delivered to central testing laboratory at the University of Liverpool.
- All participants can contact the CCO via email or phone at any time.
- Active participant involvement is completed on day 28. For participants that consented to further record linkage, additional data on safety and efficacy outcomes is obtained by linkage to NHS datasets for up to 1 year.
- Additional contact after day 28 may be conducted to assess complete resolution of mpox symptoms if these have not resolved by the final follow-up call.

3.1 Identification and invitation

The diagnosis of suspected mpox will be made as part of routine NHS clinical care where lesion and throat swabs will be taken for measurement of monkeypox virus DNA by PCR in clinical laboratories run or authorised by the Health Security Agency. Thus the assessment of eligible cases is considered to be part of routine clinical care. No trial procedures will be conducted until the diagnosis is confirmed. The proposed patient flow is outlined in the flowchart above.

Information about the trial will be provided online (accessible via a computer, smartphone or tablet) in both written format and in a video with subtitles. These materials will initially be developed in English and, if need, in other languages used commonly in the patient group.

Consenting patients will be contacted (ideally within 24 hours of a positive swab result) by a member of the Clinical Coordinating Office (CCO) Clinical Team working. The CCO Clinical Team will comprise registered doctors and nurses with appropriate trial-specific training who have been delegated to fulfil this role by the Chief Investigator.

3.2 Consent

Informed consent will be sought from each patient aged 16 years or older before enrolment into the study. Due to infection control risks, consent will be obtained remotely. All interested patients will have a two-way discussion by telephone or video call with a member of the CCO Clinical Team. Interested patients will be required to confirm they have reviewed the patient information leaflet and consent materials and will be given an opportunity to ask any questions. They will be asked for verbal consent for use of the electronic consent system, and will then provide their written (electronic) informed consent to enter the trial in accordance with regulatory guidance (in particular, the joint MHRA/HRA statement on electronic consent in Clinical Trials of Investigational Medicinal Products: https://s3.eu-west-2.amazonaws.com/www.hra.nhs.uk/media/documents/hra-mhra-econsent-statement-sept-18.pdf). Participants will be sent an electronic copy of their consent form, and a physical copy as well if they wish. A validated e-consent system will be used that provides a full audit trail of the consent process.

For children aged less than 16 years, consent will be sought from a parent or legal guardian. Where possible, children aged between 10 and 15 years old will also be asked for assent. This will use participant information written for the parent or legal guardian, and for children aged 10-15, but will otherwise use the same processes of participant identification, telephone discussion and online consent as for adult participants.

Patients who lose mental capacity whilst in the trial may continue to have data collected compliant with the CTIMP regulations on consent enduring loss of capacity. This eventuality is covered in the informed consent.

3.3 Baseline information

After informed consent has been given, a CCO Clinician (doctor or nurse with appropriate training) will record the following information on a web-based form:

- Participant details (name, date of birth, sex at birth, self-reported weight for adults, measured weight for children, NHS/CHI number)
- Medical history (diabetes mellitus, HIV infection, other immunosuppression (e.g. solid organ transplant), known chronic kidney or liver disease)
- Orthopoxvirus vaccination history
- Symptom onset date (fever onset, lesion onset)
- Pregnancy and breastfeeding status (to confirm eligibility)
- Relevant medications (including current use of repaglinide, systemic corticosteroids, HIV medications, immunosuppressants including cancer treatments)
- Clinical signs and symptoms of mpox (e.g. rash, mouth lesions, breathlessness)

3.4 Randomised allocation of treatment

Once eligibility has been confirmed and consent obtained, the person completing the form for the CCO will be asked to confirm that they wish to randomise the patient. Participants will be randomised in a 1:1 ratio to tecovirimat or placebo using a minimisation algorithm that ensures appropriate balance for key prognostic features (specified in section 2.2).

3.5 Supply of allocated treatment to randomized participants

Study treatment will be couriered to the participant (with confirmation of its delivery provided to the trial team) and will include instructions on dosing for the participant.

3.6 Collecting follow-up information

Follow-up information is to be collected on all study participants, irrespective of whether or not they complete the scheduled course of allocated study treatment. The processes are designed so that they can be conducted remotely without the need for patients to attend a clinical or research facility or to be seen by a member of study staff. If a patient is not able to perform the relevant activities for themselves (e.g. for young children or those with a relevant disability), then they may be assisted by a relative or carer. And reasons for stopping study treatment (if applicable).

3.6.1 Microbiological sampling

Participants will be asked to self-collect swabs from themselves of the oropharynx (throat) and most recent active skin or mucosal lesion at days 7, 14, 21, and 28 (each ±2 days). Kits will be provided along with instructions for obtaining high quality samples and for safe packaging and return (by courier) to a central laboratory. If available, residual material from swab samples used to diagnose mpox may be retained and transferred to the trial laboratory. For schedule of events see appendix 2. Samples from participant who provide consent will be retained for possible use in future research, and will otherwise be destroyed at the end of the trial.

3.6.2 Electronic and other sources of health information

Study staff may seek additional follow-up information (e.g. to clarify potentially serious safety issues) through various means including by contacting medical staff, reviewing information from medical notes, or obtaining data from routine healthcare systems and registries.

3.7 Duration of follow-up

All randomised participants are to be followed up for 28 days after randomisation. Longer term (up to 1 year) follow-up may be sought through linkage to electronic healthcare records and medical databases including those held by NHS Digital, Health Safety Agency and equivalent bodies. Additional follow-up calls may be conducted following the end of the main assessment period of the study (28 days) to assess complete resolution of mpox symptoms and other relevant adverse events.

3.8 Treatment discontinuation

Study treatment may be permanently or temporarily discontinued under the following circumstances:

- A participant becomes pregnant
- A participant wishes to breastfeed
- Suspected Serious Adverse Reaction
- Clear indication or contraindication to tecovirimat (in accordance with relevant UK licensing and NHS guidance)
- At the request of the participant or their doctors (for whatever reason) or any other situation where continuing study treatment is not considered to be in the participant's best interests by their own doctors or the study clinical team.

Cessation of study medication (temporary or permanent) is not, on its own, considered to be withdrawal from the trial (see section 3.9).

3.9 Withdrawal of consent

A decision by a participant that they no longer wish to continue receiving study treatment should **not** be considered to be a withdrawal of consent for follow-up. However, participants are free to withdraw consent for some or all aspects of the study at any time if they wish to do so (including withdrawal of consent for the retention of samples for future research). In accordance with regulatory guidance, de-identified data that have already been collected and incorporated in the study database will continue to be used (and any identifiable data will be destroyed).

4 QUALITY MANAGEMENT

4.1 Quality By Design Principles

In accordance with the principles of Good Clinical Practice and the recommendations and guidelines issued by regulatory agencies, the design, conduct and analysis of this trial is focussed on issues that might have a material impact on the wellbeing and safety of study participants (patients with confirmed mpox) and the reliability of the results that would inform the care for future patients.

The critical factors that influence the ability to deliver these quality objectives are:

- to provide information on the study to patients and clinicians in a timely and readily digestible fashion but without impacting adversely on other aspects of the trial or the patient's care
- to ensure that suitable patients have access to the trial medication without delay
- to minimise the burden on patients and health care staff and avoid disruption of healthcare facilities
- to minimise risk of onward transmission of mpox
- to collect relevant information on disease status

4.2 Training and monitoring

The focus will be on those factors that are critical to quality (i.e. the safety of the participants and the reliability of the trial results). Remedial actions would focus on issues with the potential to have a substantial impact on the safety of the study participants or the reliability of the results.

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP), Good Participatory Practice, the Good Clinical Trials Collaborative Guidelines for Good Randomised Trials, and relevant local, national and international regulations. Any serious breach of GCP in the conduct of the clinical trial will be handled in accordance with regulatory requirements. Members of the CCO Clinical Team will be qualified by qualifications, training and experience for their role. In particular, they will be doctors or nurses on the GMC or NMC register who have completed training in relevant aspects of GCP and the trial and been delegated to their role by the Chief Investigator.

4.3 Data management

Data will be held in central databases located at the University of Oxford or on secure cloud servers. CCO staff will use be responsible for provision of the relevant web-based applications and for generation of data extracts for analyses.

All data access will be controlled by unique usernames and passwords, and any changes to data will require the user to enter their username and password. Staff will have access restricted to the functionality and data that are appropriate for their role in the study.

4.4 Laboratory assays

Swabs will be placed in virus transfer medium (VTM). The presence of infectious virus from clinical samples will be assessed using two parallel methods:

(i) **Cell culture**: Mpox patient sample suspended in VTM will be applied to monolayers of BSC-1, or equivalent suitable cell line, for virus culture. After 3 days incubation supernatant will be removed and stained with crystal violet to visualise monkeypox virus plaques.

(ii) **Quantitative PCR**: Mpox patient sample in VTM will be analysed by qPCR to determine viral genome copy number at culture day 0. Quantitative PCR may be used to determine whether samples are cultured, if it becomes clear that PCR can reliably predict culture results in certain circumstances (for example if a negative PCR result reliably predicts culture negativity).

4.5 Source documents and archiving

Source documents for the study constitute the records held in the study main database and the results of laboratory assays. These will be retained for at least 25 years from the completion of the study, with the exception of children for whom such data must be stored until they reach 21 years old (due to the statute of limitations). Consent forms will be retained for at least five years, in line with clinical trials regulations, and for the lifetime of any retained samples as required for HTA traceability purposes. Other identifiable data will be retained only for so long as it is required to maintain linkage with routine data sources. The sponsor and regulatory agencies will have the right to conduct confidential audits of such records in the CCO (but should mindful of the infection control and privacy requirements).

5 OPERATIONAL AND ADMINISTRATIVE DETAILS

5.1 Sponsor and coordination

The University of Oxford will act as the trial Sponsor. The study is led by researchers with expertise in infectious disease at the Pandemic Sciences Institute and experienced clinical trialists applying methods established in the RECOVERY and PANORAMIC trials of treatments for COVID-19. Chelsea and Westminster Hospitals NHS Trust is providing sexual health expertise. The University of Liverpool is providing laboratory expertise. The study is coordinated by a Central Coordinating Office within the Nuffield Department of Population Health staffed by members of the two registered clinical trials units (the Clinical Trial Service Unit and the National Perinatal Epidemiology Unit Clinical Trials Unit). The data will be collected, analysed and published independently of the source of funding.

5.2 Funding

The trial is funded by a grant from National Institutes for Health and Care Research (NIHR135639).

5.3 Indemnity

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).

5.4 Delegation of responsibilities

It is anticipated that the majority of patients will be managed at home following initial assessment and diagnosis at an NHS organization (e.g. genito-urinary medicine clinic). Genitourinary medicine clinics will identify potential research participants through normal clinical activity and refer these individuals to the research study in order to gain access to the clinical intervention. Therefore, in accordance with the Health Research Authority guidance, this trial will be conducted as a "remote" trial without local research sites.[*] We do not expect this model to require any contracting with the NHS organisations or payment as there are no additional non-clinical services. Trial activities will be overseen by the Chief Investigator, who will delegate trial duties to other staff (including clinical staff) at the CCO and to UK Health Security Agency staff (including clinicians and laboratory staff). Such delegation will be recorded formally. Service contracts will be established with any third party organisations involved in the trial (e.g. laboratories, drug supply organisations, IT providers).

Participants and other healthcare professionals will have access to the study Freephone number at any time. CCO study clinicians, or research nurses, will be available to respond to queries from participants or their doctors. CTSU runs an after-hours on-call rota for our ongoing trials, staffed by trained CCO study clinicians. If the participant has provided consent, their GP will be informed of their participation and information about the trial, including contact details for the CCO in case of any trial-related questions. Throughout the trial, clinical management, will remain the responsibility of the participant's usual doctors.

[*] https://www.myresearchproject.org.uk/help/hlpsitespecific.aspx#PIC

5.5 Supply of study treatments

Tecovirimat and placebo is donated by SIGA pharmaceuticals. Tecovirimat or placebo will be packaged and shipped to patients' home addresses by a commercial suppliers on the instruction of the CCO.

5.6 End of trial

The end of the scheduled treatment phase is defined as the date of the last follow-up visit of the last participant. The follow-up period may be extended for a year or more beyond the final study visit through linkage to routine medical records and central medical databases. The end of the study is the date of the final data extraction from NHS Digital (anticipated to be 1 year after the last patient is enrolled) or additional assessments if required to assess complete resolution of mpox symptoms.

5.7 Information security

All personal data, including names and addresses, will be protected against unauthorised access, unlawful use, accidental loss, corruption or destruction in line with University of Oxford and departmental Information Governance policies. All such data will remain encrypted, with access limited to essential CCO staff, and identifiable data will be replaced with a unique study ID and held separately from research data wherever possible. Secure methods, such as encrypted email, will be used for any transfer of personal data.

5.8 Publications, reports and data sharing for health research in the public interest

The Central Coordinating Office will be responsible for drafting the main reports from the study and for review of any other reports. In general, papers initiated by the Central Coordinating Office (including the primary manuscript) will be written in the name of the PLATINUM Collaborative Group, with individual contributors named personally at the end of the report (or, to comply with journal requirements, in web-based material posted with the report).

The Central Coordinating Office will also establish a process by which proposals for additional publications (including from independent external researchers) are considered by the Trial Steering Committee. The Central Coordinating Office will facilitate the use of the study data for health research in the public interest and approval will not be unreasonably withheld. However, the Central Coordinating Office will need to be satisfied that any proposed publication is of high quality, honours the commitments made to the study participants in the consent documentation and ethical approvals, and is compliant with relevant legal and regulatory requirements (e.g. relating to data protection and privacy). The Trial Steering Committee will have the right to review and comment on any draft manuscripts prior to publication.

5.9 Substudies

Proposals for substudies must be approved by the Trial Steering Committee and by the relevant ethics committee and competent authorities (where required) as a substantial amendment or separate study before they begin. In considering such proposals, the Trial Steering Committee will need to be satisfied that the proposed substudy is worthwhile and will not compromise the main study in any way (e.g. by impairing recruitment).

6 INVESTIGATIONAL MEDICINAL PRODUCT

6.1 Name and description of the investigational medicinal product

The active study treatment in PLATINUM is oral tecovirimat in the form of 200mg capsules. The control will be matching placebo capsules. Study treatment will be provided by SIGA Technologies, Netherlands B.V. Oral tecovirimat is licensed by the MHRA and EMA for the treatment of mpox, smallpox and cowpox, and by the US FDA for the treatment of smallpox.

6.2 IMP preparation, storage, labelling and supply

SIGA will be responsible for providing packs of finished IMP in accordance with GMP standards.

The trial's UK-based contract distributer will be responsible for labelling and Qualified Person release. Under the instruction of the CCO the contract distributer will be responsible for:

- Storage of packaged IMP
- Selection and preparation for dispatch of specified bottles of packaged IMP assigned to specified study participants
- Providing UK-based QP oversight in line with MHRA requirements

IMP labels will be designed in accordance with Annex 13 of the EU GMP Guide. The CCO will maintain an inventory and audit trail of all bottles of study IMP on the trial IT system. All bottled study IMP will be labelled with an expiry date beyond which it should not be used, and will only be issued to participants with due allowance for the remaining shelf life.

6.3 Mail-out of study treatment

All packs of study IMP assigned to study participants will be delivered by same-day or next-day courier on instruction from the CCO. At the point of dispatch of packs of study treatment by the UK-based contract distributer, a participant identifier ancillary label will be applied to each pack. The courier will confirm delivery of study medication to participants, and the CCO will monitor whether these have been received within an acceptable time following randomisation. Once IMP is received by the participant, no further accountability will be recorded.

Participants will be advised to take any expired or unused study IMP to a local pharmacy for safe disposal at the end of treatment. Due to the design of PLATINUM, in which participants will not attend sites, it is considered overly complex and prone to unacceptable risk to expect study participants to securely return study IMP via the postal system or other courier service.

6.4 Use of IMP in line with the Summary of Product Characteristics

Use of tecovirimat in PLATINUM will be in line with the MHRA summary of product characteristics, including indication, dose (described in section 2.3), and contraindicated medicinal products. Further information about the pharmacology, formulation and stability of tecovirimat is in Appendix 1.

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8 VERSION HISTORY

Version number	Date	Brief Description of Changes
1.0	08_Aug-2022	Initial version
2.0	17-Aug- 2022	Revisions following MHRA review (including exclusion of pregnant and breastfeeding women)
2.1	15-Sep-2023	Monkeypox disease renamed mpox. Update to laboratory assay section following assay validation.

9 APPENDICES

9.1 Appendix 1: Tecovirimat (TPOXX®)

Pharmacology
Tecovirimat inhibits the exit of viral particles from an infected cell, thereby inhibiting systemic spread of infection. The VP37 protein target of tecovirimat is highly conserved in all species of Orthopoxviruses and is similarly targeted by tecovirimat with equivalent efficiency. Tecovirimat specifically inhibits all orthopoxviruses tested, including the human pathogenic viruses, variola, vaccinia, cowpox virus and, importantly for this proposed expanded access protocol, monkeypox virus (1). There are no mammalian homologs to VP37, 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 a program of 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 (NHPs) and rabbits; numerous additional exploratory studies were also conducted in different animal models. SIGA Technologies Netherlands (SIGA), the applicant of the FDA, EMA and MHRA approvals, have conducted twelve clinical trials evaluating the safety and pharmacokinetics of tecovirimat; ten Phase 1 studies, one Phase II study and one Phase III study.

Tecovirimat is generally well tolerated. The approved human dose of 600 mg twice daily results in exposures that exceed efficacious exposures in the mpox/non-human primate models. At the approved dose, the incidence of adverse events (AEs) was similar to the incidence of AEs among subjects receiving placebo in human trials. Most AEs were mild or moderate and resolved without sequelae.

There are no known instances of naturally occurring tecovirimat resistant orthopoxviruses, although tecovirimat resistance may develop under drug selection. Tecovirimat has a relatively low resistance barrier, and certain amino acid substitutions in the target VP37 protein can confer large reductions in tecovirimat antiviral activity.

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. In animal reproduction studies, no embryofetal developmental toxicity was observed.

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

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 maximum 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 subjects experienced mild (6 subjects) or moderate (4 subjects) hypoglycemia following co-administration of repaglinide (2 mg) and tecovirimat. Symptoms resolved in all subjects after intake of food and/or oral glucose.

Co-administration of midazolam and tecovirimat may reduce the effectiveness of midazolam. Effectiveness of midazolam should be monitored when administering tecovirimat with midazolam.

Refer to the tecovirimat prescribing information for additional information on drug interactions.(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.

Tecovirimat capsules are supplied in 75-cc high-density polyethylene bottles fitted with a heat induction seal and child-resistant screw cap closure system.

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

Product Storage and Stability

Tecovirimat drug bottles must be stored in a secure location out of direct sunlight, and out of reach of children and pets, at a temperature below 25°C.

1. Grosenbach DW, Honeychurch K, Rose EA, Chinsangaram J, Frimm A, Maiti B, et al. Oral Tecovirimat for the Treatment of Smallpox. N Engl J Med. 2018;379(1):44-53.
2. SIGA Technologies Inc. TPOXX Prescribing Information. 2018.

9.2 Appendix 2: Schedule of events

	B	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15-20	D21	D22-27	D28
Consent	X																		
Demographics	X																		
Comorbidities	X																		
Concomitant medicines	X																		
Clinical review (remote)*	X							X							X		X		X
Patient self-assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Treatment administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Lesion swab+	X§							X							X		X		X
Throat swab	X§							X							X		X		X

* Clinical review will be conducted remotely (telephone call/video call) by study clinicians or study nurses

+ Swab most recent active skin or mucosal lesion

§ Diagnostic samples taken prior to baseline assessment

9.3 Appendix 3: Organisational Structure and Responsibilities

Chief Investigator
The Chief Investigator has overall responsibility for:

(i) Design and conduct of the Study in collaboration with the Steering Committee;
(ii) Preparation of the Protocol and subsequent revisions;

Steering Committee
The Steering Committee (see Section 9.4 for list of members) is responsible for:

(i) Agreement of the final Protocol and the Data Analysis Plans;
(ii) Reviewing progress of the study and, if necessary, deciding on Protocol changes;
(iii) Review and approval of study publications and substudy proposals;
(iv) Reviewing new studies that may be of relevance.

Data Monitoring Committee
The independent Data Monitoring Committee is responsible for:

(i) Reviewing unblinded interim analyses according to the Protocol;
(ii) Advising the Steering Committee if, in their view, the randomised data provide evidence that may warrant a change in the protocol (e.g. modification or cessation of one or more of the treatment arms).

Central Coordinating Office (CCO)
The CCO is responsible for the overall coordination of the Study, including:

(i) Study planning and organisation of Steering Committee meetings;
(ii) Ensuring necessary regulatory and ethics committee approvals;
(iii) Development of Standard Operating Procedures and computer systems
(iv) Monitoring overall progress of the study;
(v) Monitoring and reporting safety information in line with the protocol and regulatory requirements;
(vi) Dealing with technical, medical and administrative queries

UK Health Security Agency (HSA)
The HSA Lead and HSA Staff are responsible for:

(i) Informing clinicians who are caring for patients newly diagnosed with mpox about the trial.
(ii) Providing a daily line list of laboratory confirmed mpox cases to the CCO.
(iii) Providing scientific advice to the Chief Investigator and CCO.

9.4 Appendix 4: Organisational Details

Chief Investigator	Peter Horby
Clinical Coordinator	Leon Peto
Clinical Trial Unit Leads	Richard Haynes, Ly-Mee Yu
Co-investigators	Martin Landray (clinical trials), Chris Butler (clinical trials), Marian Knight (Maternal Health Lead), Tommy Rampling (HSA clinical), Meera Chand (HSA laboratory), Jake Dunning (clinical), Piero Olliaro (clinical trials), Miles Carroll (virology), Calum Semple (Paediatrics / ID), Ashleigh Cheyne (PPIE), Amanda Rojek (clinical), Ruth Byrne (sexual health), Marta Boffito (sexual health)

STEERING COMMITTEE

(Major organisational and policy decisions, and scientific advice; blinded to treatment allocation)

Chair	Shunmay Yeung
Members	Placide Mbala, Michael Jacobs, Lori Dodd, Ian Muchamore, Peter Horby

DATA MONITORING COMMITTEE

(Interim analyses and response to specific concerns)

Chair	David Lalloo
Members	Anton Pozniak Laura Waters Angela Crook
Statisticians (non-voting)	Ly-Mee Yu, Nicola Williams

To enquire about the trial, contact the PLATINUM Central Coordinating Office

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(copies of this protocol and related forms and information can be downloaded here)