World Health Organization

SOLIDARITY PARTNERS

Platform Adaptive Randomised Trial for NEw and Repurposed Filovirus treatmentS

CORE Trial Protocol

Version 5.0
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R&DBlueprint
Powering research to prevent epidemics

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Abbreviations

AE	Adverse event
AESI	Adverse Event of Special Interest
eCRF	Electronic case record form
FVD	Filovirus Disease
GCP	Good clinical practice
ICH	International Conference on Harmonisation
IRR	Infusion Related Reaction
LLOQ	Lower limit of quantitation
MOH	Ministry of Health
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious Adverse Event
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
SSAR	Suspected Serious Adverse Reaction
WHO	World Health Organization

Table 1: Filovirus nomenclature and abbreviations used[1]

Disease	First subcategory	Second subcategory	Caused by
Filovirus disease	Ebola disease (ED)	Ebola virus disease (EVD)	Ebola Zaire virus (EBOV)
		Sudan virus disease (SVD)	Sudan virus (SUDV)
		Bundibugyo virus disease (BVD)	Bundibugyo virus (BDBV)
		Other specified Ebola disease	e.g. Tai Forest virus
		Ebola disease, virus unspecified	
	Marburg disease (MD)	Marburg virus disease	Marburg virus (MARV) or Ravn virus (RAVV)
		Other specified Marburg disease	
		Marburg disease, virus unspecified	

Signatures

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PREFACE: THE SOLIDARITY CORE TRIAL PROTOCOLS

Critical design features

Filoviridae is a family of single-stranded RNA viruses (classified in these protocols according to table 1), some of which cause severe diseases in humans. The most well-known filovirus diseases, Ebola disease and Marburg disease, have a high mortality rate. Outbreaks are devastating to affected communities and have severe social and economic consequences for countries. Despite this, testing promising candidate vaccines and treatments has been difficult because the timing and exact location of outbreaks is unpredictable. Clinical trials are the most robust way of assessing whether promising vaccines and drugs are safe and effective. They are designed to produce findings that are accurate and reliable, and they are conducted under regulations to ensure their quality and safety.

The SOLIDARITY vaccine and therapeutics CORE trials protocols outline WHO sponsored and endorsed trials to evaluate the most promising vaccines and treatments for these diseases across the countries most likely to experience an outbreak. These two trials will accelerate and harmonise the research response to filovirus outbreaks – so that we maximise our opportunity to save lives and protect communities.

They share the following **critical design features** designed to overcome previous barriers to *filovirus* research:

(a) **Expert-driven**: The WHO R+D platform convenes independent multidisciplinary Technical Advisory Committees that consider a broad range of evidence (e.g. results from studies in animals, case reports in humans) to shortlist and select the most promising therapeutic and vaccine candidates for including in the trial. There is representation from at-risk countries, triallists, regulatory authorities, and non-governmental response organisations in these committees. The trials are designed by world-leading experts in clinical trials and led by national investigators in affected countries.

(b) **Pre-positioned**: Designing and operationalizing a filovirus trial once an outbreak begins is too late. The trial might only begin when cases are dwindling or the outbreak is over – missing the opportunity to advance science. These trials will be pre-positioned, with regulatory approval and governance and operations all in place so that the trials can start earlier during an outbreak and have a better chance of enrolling enough participants to produce robust findings.

(c) **Harmonised**: Which country will experience the next filovirus outbreak is unknown – but there is a region at highest risk. These trials will operate across this region and make use of regional initiatives (such as AVAREF) to be more efficient. The trials will both benefit from and contribute to regional capacity sharing initiatives. New countries can join the trial at any time and their specific regulatory or other requirements are managed through a country specific annex.

(d) **Conserved across viruses**: Similarities in the viruses mean that key elements of the trial protocol (such as enrolment criteria, data collection schedules) apply for all filoviruses. In addition, certain vaccines or treatment candidates (e.g. broad-spectrum antivirals) might work for more than one virus subtype. Therefore, the CORE protocols are applicable irrespective of the *filovirus* causing an outbreak, with further virus specific details in annexes where required. These specific annexes undergo ethics and regulatory approval before the trial is implemented for a specific virus.

(e) **Conserved across outbreaks**: When a separate trial is launched for each outbreak the data collected may not be comparable to other trials and the number of participants may be too small to reach a reliable conclusion. In the SOLIDARITY trials, patients can be enrolled across multiple outbreaks and data from one outbreak can be combined with data from other outbreaks.

(f) **Uses adaptive platform design**: A platform trial is a clinical trial that can simultaneously study multiple interventions, and add, test, and remove new interventions as the trial progresses. Throughout the trial, if it becomes certain that a candidate drug or vaccine is futile or causes harm, it can be promptly discontinued from the trial. A new candidate can then replace it. Moreover, platform trials offer the flexibility to update the control, or 'usual care' group as the study progresses. This is useful if the platform trial shows a treatment it is testing to be superior to 'usual care'. In such cases, the newfound effective treatment can be integrated into the 'usual care' regime, benefitting patients immediately and creating a continuous cycle of improvement in patient care. Before any candidate is added or removed from the trial, an updated protocol with this change must be approved by ethics and regulatory authorities in the research countries.

(g) **Streamlined**: These protocols are designed to answer critical questions in real settings, rather than specialised research environments. The focus is on ensuring patient safety and the quality of the data. Streamlining data collection minimises the infection risks and administrative burden of healthcare teams responding to an emergency.

(h) **Incorporates 'quality by design'**: This approach used to ensure the trial is consistently performing at a high standard. Every aspect of the trial design and operations is considered and optimised from the beginning to prevent important mistakes and minimise waste.

(i) **Transparent**: Trial documents will be made freely available on the WHO R+D blueprint website. Trial findings will be made freely accessible.

(j) **Respectful of patients and communities**: These trials are designed with and for affected communities with their active participation and leadership.

(k) **Regulatory compliant**: The trials will be carried out in accordance with the Principles of the International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the Principles for Good Randomised Trials developed by the Good Clinical Trials Collaborative. The protocol, informed consent forms, recruitment materials, and all participant materials will be submitted to the WHO Ethical Review Committee and, in each country where the protocol will be implemented, the relevant human research ethics and regulatory agencies. Approval of both the protocol and the consent form is obtained

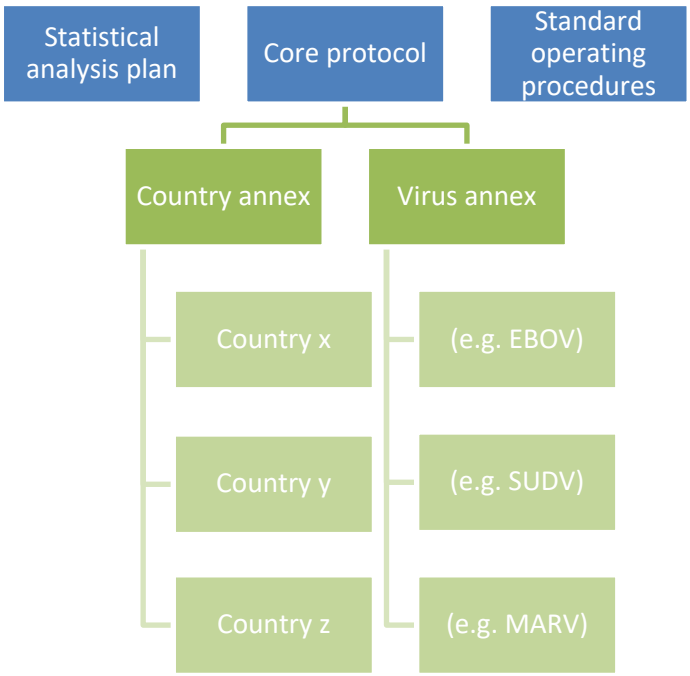
before any participant is enrolled. Any amendment to the protocol (such as inclusion of a new candidate vaccine or therapy as part of the platform design) is reviewed and requires approval by WHO and country Ethics and Regulatory Review Committees.

Outline of the protocol

This is one of two *filovirus* protocols – there is one protocol for vaccines, and one protocol for treatments. This CORE protocol details the key requirements of the trial irrespective of the location or cause of an outbreak but is supplemented by annexes that describe more detailed information for an outbreak in a particular regulatory jurisdiction (Country annexes), or for a particular virus (Virus annexes), see figure 1. The country annexes name national investigators and partner institutions. They specifically detail adaptations to comply with local regulatory requirements. These are usually governance requirements, ethics considerations (such as proxy or minor consent processes) and changes to reporting timelines. The virus appendices provide details of the treatments to be evaluated for a particular filovirus, and any data collection modifications.

The protocols sit alongside a detailed statistical analysis plan that will provide a pre-specified plan for assessing candidate therapeutic safety and efficacy. Standard operating procedures provide detail on how to interpret and implement the protocol.

Figure 1: Protocol Structure



Plain language summary (English)

Some filoviruses are dangerous to humans and can make people very sick or cause them to die. Two diseases caused by them – Ebola and Marburg – have caused outbreaks in countries in Africa. When these outbreaks happen they can cause lots of damage in communities, and cause problems for the country like children being out of school and businesses closing.

It is hard to know exactly when and where outbreaks will happen next. This makes it hard to develop vaccines or treatments to fight them. The best way to find out if a vaccine or drug really works and if it is safe is to run a clinical trial. People agree to take part and some of them are given the vaccine or treatment. Which they receive is decided at random (like tossing a coin) to ensure that the results are reliable. All participants are followed up to check for side effects and to find out what happens to them.

The World Health Organization is organizing clinical trials like these for filoviruses. They are called the SOLIDARITY trials and they are focused on finding the best vaccines and treatments for filoviruses. They aim to speed up and simplify research to save more lives.

The trials have key features:

1. Expert driven: Experts choose the treatments and vaccines to include based on what is known from research up until now.
2. Pre-positioned: Trials are ready to start before an outbreak so they can enroll people quickly.
3. Harmonized: The trial leaders work together across the region to share resources and learn from each other.
4. Conserved across viruses: The trial plan (protocol) works for different viruses.
5. Conserved across outbreaks: What is learned in the trial during one outbreak helps in future outbreaks.
6. Adaptive platform design: The trial can test more than one vaccine or treatment at once and can change as needed.
7. Streamlined: The trial focuses on getting true results without causing extra problems for participants or healthcare workers
8. Transparent: The trial plan and results are made freely available.
9. Respectful or patients and communities: Communities help design and run the trial so that the results are helpful for them
10. Regulatory compliant: The trials follow the rules of the WHO and countries for research.

Plain language summary (French)

Certains filovirus sont dangereux pour les humains et peuvent les rendre très malades ou les tuer. Deux maladies causées par les filovirus – Ebola et Marburg – ont provoqué des épidémies dans des pays d'Afrique. Lorsque ces épidémies se produisent, elles peuvent causer d'importants dommages dans les communautés et provoquer des difficultés pour le pays, tel que la fermeture des écoles et des entreprises.

Il est difficile de prévoir exactement quand et où les prochaines épidémies se produiront. Il est donc difficile de développer des vaccins ou des traitements pour les combattre. La meilleure façon de savoir si un vaccin ou un médicament est efficace et sûr est de mener un essai clinique. Des personnes acceptent de participer à l'essai et certaines d'entre elles reçoivent le vaccin ou le traitement. Puis elles font l'objet d'un suivi pour vérifier s'il y a des effets secondaires et savoir ce qui leur arrive.

L'Organisation Mondiale de la Santé (OMS) organise des essais cliniques comme ceux-ci pour les filovirus. Ce sont les essais SOLIDARITY qui ont pour objectif le développement de meilleurs vaccins et traitements contre les filovirus. Ils visent à accélérer et simplifier la recherche pour sauver plus de vies.

Ces essais cliniques ont les caractéristiques clés suivantes:

1. Menés par des experts : les experts choisissent les traitements et les vaccins à inclure en fonction de ce qui est connu de la recherche à l'instant présent.
2. Positionnés à l'avance : les essais sont prêts à démarrer avant l'apparition d'une épidémie afin de pouvoir recruter rapidement des personnes.
3. Harmonisés : les responsables des essais cliniques travaillent ensemble dans toute la région pour partager des ressources et des connaissances.
4. Maintenus entre virus : le plan d'essai (le protocole) peut s'appliquer pour des différents virus.
5. Maintenus entre épidémies : les leçons tirées d'un essai pendant une épidémie s'appliquent aux épidémies futures.
6. Conçus comme des interfaces adaptives : l'essai peut tester plusieurs vaccins ou traitements à la fois et peut être modifié selon les besoins.
7. Rationalisés : l'essai se concentre sur l'obtention de résultats robustes sans causer de problèmes supplémentaires aux participants et aux travailleurs de santé.
8. Transparents : le plan d'essai et les résultats sont librement mis à disposition.
9. Respectueux des patients et des communautés : les communautés contribuent à la conception et la mise en place de l'essai afin que les résultats leur soient utiles.
10. Conformes à la règlementation : les essais respectent les règles de l'OMS et des pays participants en matière de recherche.

1. THERAPEUTICS TRIAL SYNOPSIS

Type of study	Phase III adaptive platform randomised clinical trial of therapeutics
Clinical trial registration number	(pending)
Sponsor	World Health Organization
Central Coordinating Office (CCO)	University of Oxford, United Kingdom

Background: Despite over known 40 outbreaks of *Filoviridae,* only one clinical trial has led to approved treatments. These treatments are specific to *EBOV* and will not benefit patients infected with other virus subtypes. This protocol uses key critical design features (see preface) to pre-position a high-quality trial with a maximal chance of enrolling enough patients to produce clear findings.

Aim: The primary aim is to identify the effect of included therapies on all-cause mortality at 28 days after randomisation in patients admitted to a healthcare facility with filovirus disease.

Design: This is a multi-country, multi-outbreak randomised adaptive platform trial of potential treatments for filovirus disease (FVD). This includes Ebola disease, Marburg disease, and unspecified and emergent filovirus diseases[1]. The treatment comparisons included are determined by expert consultations convened by WHO[2]. If clear evidence of efficacy, futility, or a safety signal are not achieved for any of the comparisons during a given outbreak, the data remain blinded and protocol permits the continuation of relevant arms of the trial in future filovirus outbreaks until a clear result is achieved, as outlined in critical design considerations (e) and (f) in the preface[2].

Eligibility: Patients receiving inpatient care for laboratory-confirmed acute filovirus disease.

Randomisation: This is a randomised trial where there is 1:1 allocation between 'supportive care plus a candidate therapeutic' and a 'supportive care with no additional treatment' group. A fully factorial design is used (see section 2.3) and so more than one independent randomisation can be undertaken simultaneously for a participant.

Up to three comparisons will be active depending on the virus subtype.

- Monoclonal antibodies:
    - Randomised 1: 1 between supportive care with targeted monoclonal antibody/cocktail* vs supportive care without additional treatment
- Small-molecule virus-directed therapy:
    - Randomised 1: 1 between supportive care with small-molecule antiviral* vs supportive care without additional treatment

- Host-directed therapy:
    - Randomised 1: 1 between supportive care with host-directed therapy* vs. supportive care without additional treatment (this arm is initially only open for patients with *EBOV* infection.

**defined in Virus-specific annexes.*

Standard of care: All participants will receive usual standard of care according to WHO guidelines[3], and approved treatments when they exist.

Data to be recorded: At randomisation, information will be collected on participant age, sex, relevant co-morbidities, pregnancy status, filovirus RT-PCR time of collection and result, symptom onset date, date of admission, disease severity, contraindications to the study treatments, filovirus vaccination status, and the name of the facility enrolling the patient. Information collected on a single follow-up form will be death (with date and probable cause), hospitalisation status (with date of discharge, if appropriate), filovirus RT-PCR Ct values, treatments provided, and renal and liver function test results. In addition to study outcomes (e.g. mortality), Adverse Events will be recorded if they fall into one of the following groups:

a. Adverse Events of Special Interest (AESIs; e.g. infusion-related reactions).
b. Serious Adverse Events that are not considered to be due to the underlying *Filovirus* infection or pre-existing co-morbidity.
c. Serious (per standard regulatory definition) that are considered with reasonable probability to be related to one of the study medications (i.e. Suspected Serious Adverse Reactions, which includes Suspected Unexpected Serious Reactions [SUSARs]).

Pregnancy and foetal outcomes will also be recorded.

Study outcomes: The primary outcome will be 28-day mortality and the secondary outcome will be time to viral clearance (*Filovirus* RNA <LLOQ). Sub-group analyses will be conducted for groups defined by baseline features (defined in the statistical analysis plan).

Numbers to be randomised: The larger the number randomised the more accurate and informative the results will be and, over time, the more potential treatments can be assessed. In general, each comparison should be sufficiently large to provide good power (e.g. 90% power at 2P=0.01) to detect a proportional reduction in mortality of at least one third. The sample size required will be dependent on the mortality seen in patients enrolled in the trial (which will be dependent on the specific disease, and which may be lower in trial participants than the wider population hospitalised with Ebola or Marburg Disease, and which may evolve over time as treatment and supportive management evolves). The Trial Steering Committee (TSC), blind to information about the effects of ongoing treatment comparisons,

will monitor blinded event rates and adjust the required sample size for each comparison as data from the trial accrue.

Governance: The study is co-sponsored by WHO and the Ministry of Health in each participating country. It is overseen by a Trial Steering Committee (TSC) convened by the World Health Organization and a Data Monitoring Committee. The trial will be carried out in accordance with regulatory and ethics requirements as detailed in critical design feature (k) outlined in the preface.

1 BACKGROUND AND RATIONALE

1.1 Setting

Filoviridae have caused significant outbreaks in recent years, including Ebola Virus Disease in west Africa (2013-2016), Sudan Virus Disease in Uganda (2022) and Marburg Virus Disease in Equatorial Guinea and Tanzania (2023). These diseases have a high case fatality, with similarities in pathogenesis and somewhat overlapping clinical syndromes.

Ebola Disease is a complex multi-system illness that begins following an incubation period of 2-21 days. Illness usually begins with non-specific symptoms including fever, fatigue, and gastrointestinal distress. As the disease progresses, it is complicated by worsening gastrointestinal losses, shock, multi-organ failure, and sometimes haemorrhage. The pathogenesis of Ebola Disease is reviewed comprehensively elsewhere [4–6]. The virus disseminates broadly in body tissues and increasing viral load is a predictor of severe disease and death[7]. Severe disease is associated with coagulopathy[8], disruption of endothelial function[5] and a strong inflammatory response[9–12]. Estimates of the case-fatality rate are variable depending on the outbreak, but for *SUDV* infection range between 36-65%[13], and is usually between 50-70% for *EBOV* outbreaks.

Marburg Disease is less well characterised than Ebola Disease because there have been fewer cases and no large outbreaks in almost two decades. Following an incubation of 3-21 days[14], a non-specific febrile illness develops abruptly, followed by symptoms which may include conjunctival injection, rash, and abnormal bleeding. Gastrointestinal symptoms are described[15], but might be less prominent than for Ebola Disease. In comparison, bleeding manifestations might be more frequent[16]. Complications include renal and liver failure and pancreatitis[15,17,18]. Patients die following the onset of shock and multi-organ failure. Coagulopathy, endothelial leak, and an excessive inflammatory response occur and contribute to tissue damage[14,19]. As with other *Filoviridiae*, infection occurs following mucosal or broken-skin contact and the virus first infects macrophages and dendritic cells before infecting the organs[19]. There is significant variation in case fatality rates reported for Marburg (ranging from 23-88%), with the two largest outbreaks to date with mortality above 80%[20].

1.2 Treatment Options

The association between high levels of viraemia and Filovirus Disease severity suggests that therapies that target viral replication may benefit patients, and the association with pro-inflammatory mediators and death suggests a possible role for host-directed immunomodulatory treatment.

This protocol allows reliable assessment of the effects of multiple different treatments on major outcomes in Filovirus Disease.

The treatment comparisons to be assessed in the protocol are:

- Monoclonal antibody/ies [specific to each virus].

- Small-molecule antiviral [all patients] .
- Host-directed therapy: [initially only patients with *EBOV* infection].

Further details about these treatments and the reasons for including them are provided in *virus specific annexes*.

All patients will also receive standard of care consistent with WHO guidelines[3], and national guidelines where these exist. This includes (but is not limited to) rehydration, analgesia and other symptom relief, nutrition, and psychosocial care. If the standard of care evolves during the study (because new treatments are found to be effective), these will be incorporated into the protocol for all relevant patients. If participants receive an experimental or licensed vaccine, this would not interfere with their potential enrolment in this trial.

Where approved treatments exist, patients can receive these without interference with their potential enrolment in this trial. For *EBOV* infections, the monoclonal antibody products REGN-EB3 and mAb114 are strongly recommended by WHO[21] and approved by the US-FDA[22,23], based on the results of a previous clinical trial[24], but there are no approved or recommended host-directed therapies. There are currently no approved anti-viral or host-directed treatments for *SUDV* or *MARV* or other *Filoviridae.*

1.2.1 Modifications to the number of treatment comparisons:

In this adaptive platform trial, the TSC may elect to add new treatment comparison as evidence emerges that other candidate therapeutics or supportive care strategies should be evaluated (as outlined in critical design feature (f)). Conversely, the TSC may decide to stop some comparisons if there is no longer important uncertainty about the effects of a treatment. Any such changes would require approval by all relevant ethical and regulatory bodies prior to implementation, unless considered an urgent safety measure (e.g. if a treatment is found to be harmful).

In some patients, not all trial comparisons will be appropriate (e.g. due to contraindications or other co-morbidities); in some treatment centres, not all treatments will be available (e.g. due to cold storage requirements or delays to drug production); and at some times, not all treatment comparisons will be active (e.g. due to lack of relevant approvals and contractual agreements). In any of these situations, randomisation will only be between available and suitable treatments.

2 DESIGN

2.1 Study aims

This is an open-label, adaptive, randomised platform clinical trial to evaluate the impact of potential treatments on mortality in patients with filovirus disease.

2.2 Eligibility

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

(i) Admitted to a hospital or treatment unit for treatment of filovirus disease.
(ii) Positive *Filovirus* RT-PCR (or neonate aged seven days or younger born to a woman with acute laboratory confirmed Filovirus Disease).
(iii) No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if enrolled in the trial (e.g. known allergy to a study drug).
(iv) Not known to have been enrolled in this protocol previously.

In addition, if the attending clinician believes that a patient should definitely not receive one of the active drug treatments (see virus specific annexes for contraindications) or that the patient should definitely be receiving one of the active treatments (e.g. corticosteroids for a licensed indication) or they have already received a treatment in that class during their course of illness, then they will not be eligible for randomisation in that comparison. Co-enrolment in other studies and trials is not an exclusion criterion (unless there is a risk to the validity of either trial, or if co-enrolment increases risk to participants).

2.2.1 Pregnancy and breastfeeding

Pregnant women will be eligible for enrolment in the trial, with a clear process to determine whether each comparison should be open to pregnant women. There is a high maternal mortality in pregnant women with Ebola Disease[25], and foetal survival is rare. There are only three known cases of Marburg Disease in pregnant women. All women died, and the only neonate delivered died shortly after birth[26]. For each candidate treatment considered for inclusion in the protocol, expert obstetric and teratology advice (that summarises evidence to date and considers potential risks and benefits) will be provided to the Trial Steering Committee (and regulatory authorities) to guide the decision regarding inclusion.

WHO recommends breastfeeding should be stopped in a lactating woman with Ebola Disease[18]. There may be rare circumstances (e.g. a concordantly infected child younger than six months old without a safe feeding substitute[27]) where a woman with a *Filovirus* infection continues to breastfeed. These decisions will be made independent of the trial. In the circumstance that a woman continues breastfeeding she would remain eligible for enrolment with any dose modifications specified in virus specific annexes.

2.2.2 Children

Mortality is higher in children compared to adults with Ebola Disease, but the association between age and death is not certain for Marburg Disease. Children of all ages are eligible for enrolment. Modifications for children are described in virus specific annexes.

2.2.3 Vaccination

Patients will be eligible for enrolment irrespective of whether they have been vaccinated for a *Filovirus*, including the use of experimental vaccines, and vaccines used as post-exposure prophylaxis. Vaccination status, including date and name of vaccine, will be recorded for all patients.

2.3 Randomisation design

A fully factorial design is used. This is a design where multiple comparisons (randomisations) may be carried out simultaneously for a given patient (see table 2)

Table 2: example randomisation schedule for a patient if two arms are active.

Randomisation	Allocation
Randomisation 1 (treatment 1)	50% chance of being allocated treatment 1, 50% chance of being allocated 'supportive care with no additional treatment'
Randomisation 2 (treatment 2)	50% chance of being allocated treatment 2, 50% chance of being allocated 'supportive care with no additional treatment'

For each randomisation, patients who are allocated to the treatment group (half) are compared with the no additional care group (half) – this is the main effect. Each randomisation occurs independently. This means for each randomisation, the size of each treatment group is half the total size of the study. This makes the trial design efficient because it is the size of the treatment groups that determines the statistical power of the trial to detect a given treatment effect. Moreover, factorial trials provide the optimum ability to test if the effect of any one treatment differs materially depending on whether another treatment is also given (ie, treatment interactions, such as synergy).

This trial design was selected for this trial because of the following advantages

a. It is efficient – multiple treatments are tested in a single study.
b. Sample size reduction – compared to conducting separate trials for each candidate treatment, the sample size required is smaller.

c. It minimises the proportion of patients who do not receive access to one or more candidate treatments.Interaction effects – synergy or antagonism between candidate treatments can be explored efficiently.

d. Reflects real life practice – patients would likely receive more than one effective treatment for Filovirus disease if these are available.

When randomising, there is the possibility of chance imbalances in key baseline prognostic factors. These could impact the study results. To reduce this risk, randomisation will, wherever possible, be performed with minimisation. Minimisation works by assigning the next participant to the treatment group that reduces the imbalance in pre-defined key baseline prognostic factors. Minimisation factors will be age strata (children, younger adults, older adults) and viral load. A 10% stochastic element will be included in the minimisation (so every 10th patient has treatment allocated by simple randomisation). If minimisation is not possible (for example because of lack of internet), simple randomisation will be performed.) Minimisation is pre-programmed into the secure IT platform used for randomisation for this trial, and is not decided by trial or site staff.

sIf one of the treatments is not available at the site or not suitable for the individual patient they will not be eligible for randomisation in that comparison but remain eligible for randomisation in the other comparisons. For example, if monoclonal antibody(s) are not available at the site, then a patient may be randomised in the antiviral therapy (antiviral vs. no additional treatment) and host-directed therapy (host-directed therapy vs. no additional treatment) comparisons only.

2.4 Interventions

Randomisation will be between treatment comparisons outlined in table 3.

Table 3. Randomisation comparisons.

Comparison	**Filovirus x (e.g. SUDV)**	**Filovirus y (e.g. EBOV)**	**Filovirus z (e.g. MARV)**
Randomisation 1 (monoclonal antibody/ies)*	Virus specific monoclonal antibody vs no additional treatment (1:1)	Virus specific monoclonal antibody vs no additional treatment* (1:1)	Virus specific monoclonal antibody vs no additional treatment (1:1)
Randomisation 2 (antiviral)	Small-molecule antiviral vs no additional treatment (1:1)		
Randomisation 3** (host-directed)	Host directed therapy vs no additional treatment (1:1)		

*Where a licensed monoclonal product exists e.g. MAb114 or REGEN-EB3 for EBOV, patients should receive the licensed monoclonal product as part of supportive care and would therefore not be randomised into the monoclonal comparison.
**Initially, this arm is open only for patients with *EBOV* infection.

Details on the specific treatments included for each virus are described in virus specific annexes.

2.5 Study outcomes

2.5.1 Primary outcome

- All-cause mortality at 28 days following randomisation

2.5.2 Secondary outcome

- Time (days) to *Filovirus* RNA <LLOQ (lower limit of quantitation) within 28 days [Viral clearance, using results from study or routine clinical samples, is defined as the first negative *Filovirus* RT-PCR test without a subsequent positive test result or subsequent in-study death. In the unlikely scenario that a patient is discharged home without two successive negative RT-PCR tests, the date of the first negative test or, if there is no negative test result, the date of medical discharge will be used.]

2.5.3 Other outcomes

- Viral load (measured by cycle threshold) on blood samples taken at Day 3, 5, 7 10, 13 and 16.
- Progression of organ dysfunction, measured on blood samples taken at Day 3, 5, 7, 10, 13 and 16.

2.5.4 Safety outcomes

In addition to study outcomes (e.g. mortality), Adverse Events will be recorded if they fall into one of the following groups:

a. Adverse Events of Special Interest (AESIs; e.g. infusion-related reactions).
b. Serious Adverse Events that are not considered to be due to the underlying *Filovirus* infection.
c. Serious (per standard regulatory definition) that are considered with reasonable probability to be related to one of the study medications (i.e. Suspected Serious Adverse Reactions, which includes Suspected Unexpected Serious Reactions [SUSARs]).

Pregnancy and foetal outcomes will also be recorded.

Study outcomes will be assessed based on data recorded up to the time of death, hospital discharge or 28 days after randomisation (whichever occurs first). Pregnant women will be followed up to completion of pregnancy.

3 STATISTICAL ANALYSIS

All analyses for reports, presentations and publications will be prepared by the Statistical Analysis Team. The purpose of this section is to describe the main statistical approaches to be used in the trial. Additional technical details (e.g. cut points for subgroup analyses) will be defined by the Trial Steering Committee and Statistical Analysis Team and made publicly available prior to any unblinding of effects of study treatments (including any subsequent revisions) .

3.1 Main analysis approach

Each treatment comparison will include all participants randomised to that comparison, irrespective of whether they received some, none, or all of their allocated treatment (i.e. these comparisons will be based on “intention-to-treat” analyses).

The primary analyses will involve pairwise comparisons between the active ‘experimental’ and ‘reference’ arms as follows:

- Effect of monoclonal antibody: monoclonal vs. no additional treatment.
- Effect of antiviral: antiviral vs. no additional treatment.
- Effect of host-directed therapy: host-directed therapy vs no additional treatment.

Logistic regression adjusted for baseline levels of key prognostic factors (including the minimisation factors) will be used to estimate the conditional odds of 28-day mortality for each treatment group relative to its control (ie, the 28-day conditional odds ratio) and its 95% confidence interval. A two-tailed P-value <0.05 will be considered as statistically significant. Logistic regression (based on vital status at Day 28, regardless of the time to death within this 28-day range) will be used in preference to Cox regression because the latter might give undue weight to the exact times of death of the very poor-prognosis patients (thereby giving inadequate weight to the death or survival of the better-prognosis patients). However, for illustrative purposes, Kaplan-Meier plots showing the pattern of survival over the first 28 days will also be created, both overall and within prognostic categories. For the primary objective of assessing the effects of each study treatment on 28-day mortality, discharge alive before day 28 will be assumed as survival to day 28 (unless there are additional data confirming otherwise).

For the secondary objective of assessing the effects of each treatment on time to *Filovirus* RNA <LLOQ within 28 days, differences in days to *Filovirus* RNA <LLOQ will be tested using the Wilcoxon rank-sum test, imputing deaths prior to day 28 as the worst ranks, with earlier deaths having a worse rank than later deaths. The study will collect viremia data at baseline and approximately days 3, 5, 7, 10, 13, and 16. Patients who are discharged from inpatient care but without an available *Filovirus* RT-PCR test result will be assumed to have *Filovirus* RNA <LLOQ on their day of discharge (unless in a particular case there is good evidence to the contrary).

For each treatment, the main comparisons will ignore any other treatments that the patient may have been randomised to in a factorial manner. However, subgroup analyses of each treatment effect will include analyses by such factorial treatments.

3.1.1 Management of control groups

Since not all treatments may be available or suitable for all patients, those in the 'no additional treatment' arm will only be included in a given comparison if, at the point of their randomisation, they *could* alternatively have been randomised to the active treatment of interest (i.e. the active treatment was available at the time and it was not indicated or contra-indicated). The same applies to any further treatment comparisons that may be added at a later stage; they will be compared only to those patients recruited concurrently.

3.1.2 Adjustment for baseline characteristics

The main logistic regression analyses described above will adjust for important prognostic markers recorded at baseline (eg, age, RT-PCR Ct value, virus type, and time since symptom onset). This provides a safeguard against the impact that any chance imbalances in their frequencies between randomised groups may have on the randomised comparisons. In addition, even if there were no such imbalances, adjustment for baseline characteristics somewhat increases statistical power by ensuring that, effectively, better-prognosis patients are compared only with each other and that worse-prognosis patients are compared only with each other. Exact details of the prognostic factors adjusted for in the logistic regression analyses will be provided in the SAP prior to any unblinded analyses being done.

3.1.3 Pre-specified subgroup analyses

Pre-specified subgroup analyses of the effects on the primary and secondary outcome will be conducted for each part of the main randomisation. Tests for heterogeneity (or tests for trend between 3 or more ordered groups) will be conducted to assess whether there is any good evidence that the effects in particular subgroups differ materially from the overall effect seen in all patients combined. The results of subgroup analyses will be interpreted with appropriate caution. In particular, due allowance for the number of such analyses will be made in the interpretation of the results noting that even if a treatment truly works similarly well in all patients, by chance it is highly likely that it will seem not to in some subgroups (and may even appear to be harmful). The following subgroups will be considered:

- Marburg or Ebola disease (and by virus strain e.g. MARV, RAVV, *EBOV, BDV SUDV*).
- Age (children, younger adults, older adults).
- *Filovirus* nucleoprotein cycle-threshold (Ct) value using quantitative RT-PCR from latest test conducted prior to randomisation (high, low).
- Number of days since symptom onset (divided at the approximate median).
- *Filovirus* vaccination status (yes, no, unknown).
- Randomised allocation in other completed factorial comparisons.

Further exploratory subgroup analyses will include:

- Severity of disease at time of randomisation on the basis of one or more of:
  (a) Extent of physiological disturbance at the time of enrolment (e.g. qSOFA score[17] in adults (0-1, 2 or more); or PEWS score[28] in children (0-2, 3 or more).
  (b) Evidence of organ dysfunction at the time of enrolment (e.g. creatinine > 150 umol/L; aspartate transaminase or alanine transaminase > 5 times the upper limit of normal).

3.1.4 Allowance for multiple comparisons

The mortality results for 1:1 comparisons in the factorial design are uncorrelated with any other results and will therefore be reported without formal adjustment for multiple testing. Throughout, due allowance for the number of analyses (including of secondary and other outcomes and of effects in subgroups) will be made in interpreting the results.

3.2 Sample size estimation

The larger the number randomised, the more accurate and informative the results will be and, over time, the more potential treatments can be assessed. However, it is not possible to make precise sample size estimates in the context of an outbreak where there are many unknowns. The numbers required will be influenced by many factors, including the case fatality and speed of presentation and diagnosis at a clinical facility, changes in usual standard of care, and how much the proportional reduction in mortality differs between better-prognosis and worse-prognosis patients.

Ideally, each comparison should be sufficiently large to provide good power (e.g. 90% power to achieve 2P=0.01) to detect a proportional reduction in mortality of at least one third. This may require randomisation of several hundred patients in each comparison. For example, if mortality in the reference arm was 50%[12,18,19], randomisation of around 520 participants in a single comparison would give more than 90% power at 2P=0.01 to detect a proportional reduction in mortality of one-third and more than 80% power at 2P=0.05 to detect a smaller (but still useful) reduction in mortality of one-quarter. (Note that with 50% mortality in the reference arm, the above mortality *risk* reductions of one-third or one quarter would represent mortality *odds* reductions of, respectively, one-half or two-fifths.)

However, it is possible that any single outbreak might end before the trial has recruited such numbers during that outbreak, or in some instances, that availability of some of the study interventions will limit enrolment. Even these more limited numbers, perhaps from a single outbreak, might still deliver clear results and change clinical practice. Suppose, for example, that 120 patients were randomised between a monoclonal antibody plus supportive care vs. supportive care alone. The primary analysis of the effects of adding the antibody to supportive care would then be based on only 60 vs 60 patients, far fewer than ideally needed. Nevertheless, suppose that the antibody reduced 28-day mortality from 30% to 10% in the better-prognosis half of all patients and from 90% to 70% in the worse-prognosis half (approximately as was seen for patients with high and low RT-PCR Ct values with two

successful antibodies to *EBOV* in the PALM trial in eastern DRC). Combining the results from 2x2 analyses within each of these two prognostic strata would then yield clear evidence of benefit at 2P<0.01. This does not mean that 120 patients is the ideal trial size, but it does indicate that useful information *could* emerge from even quite a small trial and may be achievable in a single outbreak. If this trial, or some parts of it, extends over multiple outbreaks in various locations, it could eventually include substantial numbers and address additional questions[2].

3.2.1 Review and potential to modify sample size

Throughout the trial, the TSC, blind to information about the effects of ongoing treatment comparisons, will monitor event rates (both overall and by groups with different prognoses) to determine whether, in its view, sufficient participants have been randomised in each comparison. For instance, if the blinded mortality rate turns out to be much lower than anticipated in section 4.2, then the TSC may decide to increase the number of patients in order to achieve the desired power to detect a mortality risk reduction of one third. At the end of an outbreak, for each comparison the TSC may elect to: (a) close it and report the unblinded results; or (b) pause it (remaining blind to the results) with a view to re-opening it in the case of a new outbreak[2]. In this context, it is recognised that some potential treatments may only be relevant for MARV, SUDV or EBOV infections (e.g. a particular monoclonal antibody) whilst others may be relevant for a broad range of patients with Filovirus Disease regardless of the particular virus (e.g. host-directed immunomodulatory treatments).

4 DATA MONITORING COMMITTEE (DMC)

During the study, interim analyses of all study data will be supplied in strict confidence to the independent DMC. The DMC will request such analyses at a frequency relevant to the emerging data from this and other studies. Planned interim analyses will occur after every 100 patient enrolments. Further details of the roles and responsibilities of the DMC will be described in a Data Monitoring Committee Charter.

The DMC will independently evaluate these analyses and any other information considered relevant. The DMC will determine if, in their view, the randomised comparisons in the study have provided evidence on mortality that is strong enough (with a range of uncertainty around the results that is narrow enough) to affect national and global treatment strategies.

In such a circumstance, the DMC will inform the TSC who will be responsible for considering any amendments to the protocol and trial comparisons and for plans to make the results available to the public. Unless this happens, the TSC, Principal Investigator(s), study staff, investigators, study participants, funders and other partners including WHO and relevant Ministries of Health and pharmaceutical partners supplying study treatments will remain blind to the interim results until 28 days after the last patient has been randomised for a particular intervention arm (at which point unblinded analyses may be conducted for that comparison).

4.1 Early stopping for benefit

The DMC will advise the TSC if, in its view, the randomised comparisons in the study provide "proof beyond reasonable doubt" that one of the study treatments reduces the primary outcome of mortality. In making this determination, the DMC would be expected to consider both the results for the overall population and for important subgroups of patients (see section 3.1.3) Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but in general a benefit of at least 3 standard errors in an interim analysis on the primary outcome would be needed to justify halting the study prematurely for efficacy[29]. If, in the view of the DMC, the evidence is not sufficiently convincing to affect national and global treatment strategies, then it would not be expected to recommend stopping the trial for efficacy. This approach has the practical advantage that the number of interim analyses has a negligible impact on the final significance level at which the primary outcome is tested.

4.2 Blinding

This is an open-label study. However, while the study is in progress, access to tabular results by allocated treatment allocation will not be available to the research team, patients, Ministries of Health, pharmaceutical partners supplying study treatments, or members of the Steering Committee (unless the DMC advises otherwise).

5 STUDY PROCEDURES

5.1 Practical considerations

Detailed information on how to implement trial procedures will be provided in standard operating procedures. Country-specific modifications to this core protocol (e.g. due to differences in age of consent, or proxy consent regulations) are contained in the relevant annexes. Trial operations will be streamlined (see critical design feature (g)) and embedded in routine clinical workflow where possible to maintain high levels of familiarity, reduce error, and minimise duplication of effort (see critical design feature (h)).

5.2 Identification

Potential participants will be identified from the point that they are admitted to a Filovirus Treatment Unit. Patients are eligible for enrolment at any point during their acute illness.

5.3 Consent

Informed consent must be obtained for each patient before enrolment into the study. To maximise the opportunity for potential participants to make their own decisions about participation prior to potential clinical deterioration, patients with suspected Filovirus Disease can be approached for consent, although they will not be enrolled in the study until laboratory confirmation of disease.

For children, consent will be sought from their parents or legal guardian. The age where a child is able to consent for themselves will adhere to legislation in the country of trial operation (provided in country-specific annexes). Where possible, children who are 10 years old or more will also be asked for assent.

If an adult patient cannot provide consent, reasonable attempts will be made to reach the next of kin to provide consent by proxy. Proxy consent must be witnessed but may be obtained over the telephone if a parent/guardian or legally acceptable representative cannot be physically present (e.g. due to treatment unit visiting rules or parental quarantine, isolation, or illness).

Due to the severity of Filovirus Disease, patients who lack capacity to consent due to severe disease, and for whom a relative to act as the legally designated representative is not available, randomisation and consequent treatment will proceed with consent provided by a clinician (independent of the clinician seeking to enrol the patient and not connected with the conduct of the trial) who will act as the legally designated representative (if allowed by local regulations). If a participant subsequently regains capacity prior to discharge, they should be provided with information about the trial, their rights, and how to exercise them. Provision of such information should be documented in the medical record.

Consent will include provision for secondary use of data which includes use by the pharmaceutical partners that supply study treatments, regulators, public health and academic organisations.

5.4 Baseline information

The following information will be recorded where possible. For laboratory tests, the most recent value obtained for routine clinical practice is used, if available.

- Clinical facility (e.g. name of treatment unit) enrolling patient.
- Patient details (e.g. name, date of birth, sex).
- Active major comorbidities (e.g. malaria, HIV, tuberculosis, diabetes, malnutrition, previous *Filovirus* infection).
- Date of Filovirus Disease symptom onset.
- Date of admission to treatment facility.
- Latest *Filovirus* test result (date, strain, Ct value).
- Vital signs (heart rate, blood pressure, respiratory rate, O2 saturations).
- Focused symptom assessment (bleeding, confusion).
- Biochemistry results (creatinine, ALT and/or AST).
- Malaria test result.
- Pregnancy test result (in women with childbearing potential) with estimated gestational age or trimester.
- Contraindication to each of the study drugs.
- Use of relevant concomitant medication (e.g. antivirals, corticosteroids, antimalarials).

Vaccination (including date) for *Filovirus.*

5.5 Randomised allocation of treatment

All participants will receive usual standard of care guided WHO recommendations[12] and can receive licensed therapies (where they exist). Randomisation will be undertaken using a web-based service.

5.5.1 Treatments

Treatment and dosing information is provided in relevant annexes. Up to three arms will be active for a given virus.

5.6 Administration of allocated treatment

Treatments are provided open-label. Drugs will be prescribed by a clinician delegated by the principal investigator to do so, and administered by appropriately trained clinical staff. Treatments should be administered as soon as possible following randomisation (although it is recognised that logistic issues may mean that initiation of some treatments may be delayed). The patient's own doctors are free to reduce the infusion rate of the treatment or stop study treatments if they feel it is in the best interests of the patient without the need for the patient to withdraw from the study. Medications can be given to treat potential adverse events (such as antihistamines, and corticosteroids (irrespective of allocation in trial)). Virus-specific annexes will provide details regarding management of resumption of infusion for specific treatments where required.

5.7 Schedule of assessments

Staff safety takes precedence over study assessments. Where assessments are undertaken for clinical need (e.g. RT-PCR), these are not duplicated as a study-specific procedure.

Schedule of assessments

	B	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D13	D16	D+	Death or discharge	D28	D60	Pregnancy outcome
	Baseline assessments																	
Consent	X																	
Name and demographics	X																	
Clinical facility	X																	
Clinical severity assessment	X																	
Vital signs	X																	
Malaria test result	O[§]																	
Pregnancy test result [a]	X[§]														X[b]			X
	Study assessments																	
Survival															X	X	X	
RT-PCR Ct result	X[§*]	O	O	X	O	X	O	X	O	O	X	X	X	O	X	X		
Biochemistry (Cr, ALT and/or AST)	X			X		X		X			X	X	X					
Key medications	X														X	X		
Maternal and foetal outcomes	X														X			X
Safety assessments		R	R	R	R	R	R	R	R	R	R	R	R	R	R	R		R
Study treatment		R	R	R	R	R	R	R	R	R	R	R	R	R				
	[§] Most recent result prior to enrolment. X: Study assessment (clinically collected samples will not be duplicated). O: Result recorded when collected for clinical reasons but not collected as a study assessment. R: Result collected when applicable. (a) in women of child-bearing age, (b) in women of child-bearing age discharged alive.																	

5.8 Monitoring of patients

Detailed guidance on procedures for monitoring patients during and after infusions will be provided in trial standard operating procedures. In particular, patients should be monitored during infusions sufficient for early recognition and treatment of anaphylaxis or other infusion-related reactions, with emergency drugs (e.g. adrenaline, antihistamine) readily available.

5.9 Collecting follow-up information

The following information will be ascertained at the time of death or discharge or at 28 days after randomisation (whichever is sooner) for the primary analysis, and up to 60 days wherever possible:

- Vital status (alive / dead, with date and cause of death, if appropriate).
- Hospitalisation status (inpatient / discharged, with date of discharge, if appropriate).
- Results of *Filovirus* RT-PCR tests performed as part of routine clinical practice (date of tests, positive / negative and Ct value), including tests for viral recrudescence.
- Use of supportive treatment if available (e.g. blood products, non-invasive or invasive mechanical ventilation, renal replacement therapy).
- Use of any treatments included in this protocol (including drugs in the same class) or other purported treatments for Filovirus Disease.
- Participation in other randomised trials of interventions (vaccines or treatments) for Filovirus Disease.
- Result of repeat pregnancy test in women of child-bearing age.

Follow-up information is to be collected on all study participants who have not withdrawn consent to follow up, irrespective of whether or not they complete the scheduled course of allocated study treatment. If the trial team become aware of any deaths from direct or indirect late effects of *Filovirus* infection after Day 28 these should be recorded.

5.9.1 Duration of follow-up

All randomised participants are to be followed up until death, discharge from hospital or 28 days after randomisation (whichever is sooner). Attempts may be made to contact patients post-discharge at day 28 and at day 60 but failure to do so will not be considered a protocol deviation.

5.9.1.1 Follow up of pregnant participants

Additional data will be collected for women who are pregnant at the time of enrolment into the trial. Reasonable efforts will be made to follow-up pregnant women until the conclusion of their pregnancy to identify pregnancy outcomes, congenital anomalies and neonatal complications. This will be undertaken through structured telephone interviews with the mothers or their healthcare providers. Any maternal, neonatal or infant outcomes that constitute a potential SSAR will be reported to the Country Principal Investigator and managed in accordance with protocol. Offspring of pregnant participants and neonates

should be referred to national programmes for longitudinal follow up where these programmes exist.

5.10 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. 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). For participants who lack capacity, if their legal representative withdraws consent for treatment or methods of follow-up then these activities would cease. Withdrawal of consent will not affect supportive care provided at the clinical site, or participation or benefit from other programmes or research.

6 DATA AND SAFETY MONITORING

In addition to study outcomes (e.g. mortality), Adverse Events will be recorded if they fall into one of the following groups:

1. Adverse Events of Special Interest (AESIs; e.g. infusion-related reactions).
2. Serious Adverse Events that are not considered to be due to the underlying *Filovirus* infection.
3. Serious (per standard regulatory definition) that are considered with reasonable probability to be related to one of the study medications (i.e. Suspected Serious Adverse Reactions, which includes Suspected Unexpected Serious Reactions [SUSARs]).

Pregnancy and foetal outcomes will also be recorded wherever possible to the end of the pregnancy.

Other adverse events will not be collected because of the severity of the underlying disease (including a high risk of mortality) and to avoid an excessive burden on staff working in a high-risk clinical environment. In this context, the occurrence of non-serious adverse events (which are not AESIs) is of limited importance to regulatory and clinical decisions. All Adverse Events that meet one of the criteria above should be reported on the case report form.

6.1 Adverse Events of Special Interest

AESIs will be reported on the case report form whether serious or not. They will include Infusion-Related Reactions (IRRs). An IRR is defined as an adverse reaction to an infusion of a study drug that occurs during or within one hour after completion of an infusion. These will be classified according to severity:

- Mild: no specific treatment required.
- Moderate: treatment with antihistamines or steroids required.
- Severe: treatment with adrenaline required, including anaphylaxis.

Further AESIs will be specified as necessary in the disease-specific annexes.

6.2 Serious Adverse Events that are not considered to be due to the underlying *Filovirus* infection

In critically ill patients, a very large proportion of patients will suffer an SAE that is unrelated to the drug being evaluated[30]. Recording SAEs that are a part of the natural history of the disease or are captured through primary or secondary endpoints does not add to reliable evaluation of the safety and efficacy of a drug. In fact, recording such data is more likely to reduce the likelihood of a reliable assessment since it will distract from the accurate and complete collection of more important data. In this trial the SAE of death is recorded through the primary endpoint. New or worsening events that meet the definition of an SAE and are

considered by the site investigator to be unlikely to be related to underlying filovirus disease will not(?) be reported on the case report form.

6.3 Suspected Serious Adverse Reactions

The focus is on those events that, based on a single case, are highly likely to be related to the study medication. Examples include anaphylaxis, cytokine release syndrome, Stevens Johnson Syndrome, or bone marrow failure, where there is no other plausible explanation.

Any Serious Adverse Event* that is believed with a reasonable probability to be due to one of the study treatments will be considered a Suspected Serious Adverse Reaction (SSAR). In making this assessment, there should be consideration of the probability of an alternative cause (for example, Filovirus Disease itself), the timing of the event with respect to study treatment, the response to withdrawal of the study treatment, and (where appropriate) the response to subsequent re-challenge.

All SSARs will be reported on the case report form as soon as possible and in addition notified to the CCO by the site investigator (or delegated staff) on the same day by telephone so that the details required for potential expedited reporting can be collected and confirmed.

6.3.1 Central assessment and onward reporting of SUSARs

The CCO with the national Principal Investigator are responsible for expedited review of reports of SSARs received. An assessment will be made of whether the event is “expected” or not (assessed against the relevant Summary of Product Characteristics or Investigator Brochure). 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 and to relevant regulatory authorities, ethics committees, and investigators in an expedited manner in accordance with local regulatory requirements. In addition the DMC will receive all SSARs (whether expected or not) at the time of their regular meetings.

6.4 Pregnancy and foetal outcome

Pregnant women who are enrolled in the trial will be followed until conclusion of the pregnancy. Pregnancy outcomes will be recorded in the case report form system.

* Serious Adverse Events are defined as those adverse events that result in death; are life-threatening; require in-patient hospitalisation or prolongation of existing hospitalisation; result in persistent or significant disability or incapacity; result in congenital anomaly or birth defect; or are important medical events in the opinion of the responsible investigator (that is, not life-threatening or resulting in hospitalisation, but may jeopardise the participant or require intervention to prevent one or other of the outcomes listed above).

7 QUALITY MANAGEMENT

7.1 Quality By Design Principles

This study is designed and is to be conducted in accordance with the Principles for Good Randomised Trials developed by the Good Clinical Trials Collaborative[31], the ICH Principles of Good Clinical Practice, and the recommendations and guidelines issued by relevant 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 Filovirus Disease) 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 minimise the burden on busy clinicians working in an overstretched clinical service during a major outbreak.
- To ensure that suitable patients have access to the trial medication without impacting or delaying other aspects of their emergency or supportive care, or the care of other patients in the clinical environment.
- 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 minimise additional risk to health and safety of study staff.

In assessing any risks to patient safety and well-being, a key principle is that of proportionality. Risks associated with participation in the trial must be considered in the context of usual care. At present, there are no proven treatments for *SUDV or MARV* and mortality for patients with *Filovirus* infections is high.

7.2 Training and monitoring

In accordance with the Quality by Design principles (see section 7.1), 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.

Any serious breach of the Principles of ICH-GCP in the conduct of the clinical trial will be handled in accordance with regulatory requirements. Prior to initiation of the study at each Local Clinical Centre (usually a *Filovirus* Treatment Facility or hospital) (LCC), the national Principal Investigator will confirm that the LCC has adequate facilities and resources to carry out the study. LCC site investigators and study staff will be provided with training materials.

A site initiation monitoring visit will be planned for each site, with the format dependent on operational considerations. The CCO or national Principal Investigator may arrange monitoring visits to LCCs as considered appropriate based on speed of recruitment, perceived training needs and the results of central monitoring of study data. The purpose of such visits will be to ensure that the study is being conducted in accordance with the protocol, to help LCC staff to resolve any local problems, and to provide extra training

focussed on specific needs. There will be routine frequent communication between sites and the CCO.

7.3 Source documents and archiving

Source documents for the study constitute the case report forms and records held in the study main database. When documentation is paper-based, source data collected at the patient bedside (e.g. consent forms) will not be removed due to infection control requirements, and will be destroyed. Copies of these documents will be made using digital photography prior to destruction, and these copies will be retained and used for source data verification. The ability to store documents at local sites will be limited by infection control requirements and operational challenges (e.g. temporary opening during a local outbreak). Study documents will be retained for the duration directed by national legislation from the completion of the study by the principal investigator in secure physical or electronic storage. The sponsor, regulatory agencies and any organisation that donates study treatment will have the right to conduct confidential audits of relevant records in the CCO and LCCs. However, such audit activities should be mindful of (a) the workload facing participating clinical sites, (b) the infection control requirements during a *Filovirus* outbreak, and (c) the temporary nature of many clinical facilities and trial sites.

7.4 Data management

Treatment centre staff will use the study IT applications for study management and to record participant data (including case report forms) in accordance with the protocol. Data will be held in central databases located on secure cloud servers. Randomisation will always be done electronically (the outcome may be transmitted between site and trial managers by phone [e.g when internet connection is intermittent] or electronically). Although data entry should be mindful of the desire to maintain integrity and audit trails, in the circumstances of a *Filovirus* outbreak the priority is on the timely entry of data that is sufficient to support reliable analysis and interpretation about treatment effects. CCO staff will 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 as an electronic signature in accordance with regulatory requirements. Staff will have access restricted to the functionality and data that are appropriate for their role in the study.

7.5 Laboratory assays

Samples will not be duplicated if they are collected on the same day for clinical reasons. Paediatric samples will be reduced in volume according to standard procedures. Standard care samples will be prioritised over research samples if volume reduction is required. Ability to take samples is dependent on staff availability, the availability of suitable laboratory

facilities and caseload. Research samples may therefore be reduced or missed if needed to maintain care standards and staff safety, and to reflect the assays that can be performed by the laboratory attached to a treatment facility. Therefore missing values would not be considered a protocol violation.

***Filovirus* testing:** *Filovirus* RT-PCR are performed per local clinical laboratory protocols as part of standard care. The virus species tested will be dependent on the species responsible for outbreak at the time of testing. The results of these tests (quantitative result and assay used) will be recorded at baseline and according to the data collection schedule shown in section 5.7. Samples obtained for PCR are typically ≤4 ml whole blood in an EDTA tube. Finger or heal-pricks of blood on a dry swab are sometimes obtained when venepuncture is not possible.

Malaria testing: Malaria diagnostic tests are performed on the triage blood sample as part of standard care. The result will be recorded at baseline.

Pregnancy testing: For women of childbearing age (15-49 years) a βHCG test is performed on the triage blood sample as standard of care. Urine testing is also acceptable. The result will be recorded at baseline. A further test will occur at discharge or day 28 (which ever comes earliest) as a study specific sample.

Biochemistry: Creatinine, AST, and ALT will be collected at baseline and according to the data collection schedule in section 5.7, per local clinical laboratory protocols.

8 COMMUNITY ENGAGEMENT

Patient and public involvement and engagement activities will be prioritised and included in all stages of the trial design. The trial will, where possible, integrate with existing community engagement activities being undertaken as part of an outbreak response.

A community advisory panel will be convened who may contribute to activities including writing and review of the study protocol, patient facing materials (such as consent forms), and media communications (such as press releases) to ensure they are inclusive and appropriate. Other specific activities may vary country by country depending on the priorities of affected communities.

9 ADMINISTRATIVE DETAILS

9.1 Sponsor and coordination

WHO is the sponsor of the trial. The trial will be coordinated by a Central Coordinating Office. The data will be collected, analysed, and published independently of the source of funding and any companies or organisations providing one or more of the study treatments.

9.2 Funding

WHO will be responsible for organising funding for the trial.

9.3 Indemnity

WHO will provide indemnity for all individuals and organisations involved in the design, conduct and analysis of the trial, including members of the Trial Steering Committee, Data Monitoring Committee, Statistical Analysis Team, Central Coordinating Office, and participating site investigators and other study staff.

9.4 Supply of study treatments

For licensed treatments (e.g. corticosteroids) all aspects of treatment supply, storage, and management will be in accordance with standard local policy and practice for prescription medications. Treatment issue to randomised participants will be by prescription. Such study treatments will not be labelled beyond that required for routine clinical use. They will be stored alongside other routine medications with no additional monitoring. No accountability records will be kept beyond those used for routine prescriptions.

For unlicensed treatments, manufacture, packaging and delivery will be the responsibility of the pharmaceutical donor. For these treatments, inventory, dispensing and accountability of study treatment will be controlled and any requirements for specific storage conditions will be followed. Treatment dispensed but not used will not be returned due to infection control procedures and will be destroyed. Further details will be provided in trial Standard Operating Procedures.

9.5 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.

9.6 Publications and reports

The Trial Steering Committee will be responsible for drafting the main reports from the study and for review of any other reports. In general, papers initiated by the TSC (including the primary manuscript) will be written in the name of the Trial Collaborative Group, with individual investigators (including those from each participating country and each participating site) named personally at the end of the report (or, to comply with journal requirements, in web-based material posted with the report). Pharmaceutical companies donating treatments will be provided with a draft of the main reports for review and comment, but the decision to publish and authorship will remain under the control of the TSC. Data and analyses that were produced for the main reports will be provided to companies donating treatments.

The TSC will also establish a process by which proposals for additional publications (including from independent external researchers) are considered by the TSC. The TSC will facilitate the use of the study data and approval will not be unreasonably withheld. However,

the Trial Steering Committee 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 TSC will have the right to review and comment on any draft manuscripts prior to publication

Efforts will be made to disseminate the findings with relevant clinicians and at-risk communities.

9.7 Substudies

Substudies (e.g. pharmacokinetics, viral sequestration and viral recrudescence) are encouraged to answer important unanswered questions about *Filoviridiae*. These are not contained in the CORE protocol because they may not be feasible at all sites, particularly during the early stages of an outbreak. Proposals for such substudies must be approved by the TSC and by the relevant ethics committee and competent authorities (where required) as a substantial amendment or separate study protocol 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 or the ability of the participating sites to provide care to all patients under their care).

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11 VERSION HISTORY

Version number	Date	Brief Description of Changes
1.0	16-Nov-2022	Initial draft
2.0	8-Dec-2022	Response to WHO REC and Joint Review convened by National Council for Science and Technology (Uganda)
3.0	15-Feb-2022	Inclusion of Marburg Virus Disease.
4.0		Removal of treatment specifics to appendices
5.0	29-July-2024	Updated following expert advice from regional experts attending WHO R+D meeting in Kampala.

Appendix 1: Organisational Structure and Responsibilities

Coordinating Investigator

The coordinating investigator has overall responsibility for:

(i) Producing and updating the trial protocol

(ii) Managing oversight of the Trial Master File

(iii) Ensuring compliance with reporting responsibilities to the Sponsor and regulatory authorities

(iv) Analysis of the study in collaboration with the Statistical Analysis Team.

Principal Investigator(s)

The Principal Investigator has overall responsibility within his/her country for:

(i) Contributing to the study design for that country in collaboration with the Trial Steering Committee.
(ii) Ensuring necessary national regulatory and ethics committee approvals.
(iii) Conduct of the study in collaboration with the Central Coordinating Office.
(iv) Monitoring and reporting safety information in line with the protocol and regulatory requirements and as agreed in terms of reference with the CCO.
(v) Dealing with technical, medical, and administrative queries from LCCs.

Steering Committee

The Trial Steering Committee is responsible for:

(i) Agreement of the Protocol and the Statistical 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 Trial 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 comparisons).

Statistical Analysis Team

(i) Advising the Trial Steering Committee on statistical issues related to the development and implementation of the protocol.
(ii) Development of the Statistical Analysis Plan.
(iii) Conduct of statistical analyses for publications and presentations in accordance with the Statistical Analysis Plan and Protocol.

Central Coordinating Office (CCO)

The CCO is responsible for the overall coordination of the Study, including:

(i) Study planning and organisation of Trial Steering Committee meetings.
(ii) Ensuring documents are prepared for necessary regulatory and ethics committee approvals.
(iii) Development of Standard Operating Procedures and computer systems.
(iv) Monitoring overall progress of the study.
(v) Provision of study materials to Principal Investigators.
(vi) Maintaining the Trial Master File.

Local Clinical Centres (LCC)

The LCC Lead Investigator and LCC clinic staff are responsible for:

(i) All trial activities at the LCC, including appropriate training and supervision for clinical staff.
(ii) Conducting trial procedures at the LCC in line with all relevant local policies and procedures.
(iii) Dealing with enquiries from participants and others.

Appendix 2: Organisational Details

TRIAL STEERING COMMITTEE

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

Co-chairs

Principal Investigators*

Members

Co-chairs

Principal Investigators*

Members

*other PIs will be added for each outbreak and each country that is involved in the trial.

DATA MONITORING COMMITTEE

(Interim analyses and response to specific concerns)

<TBC>

Chair

Members

Statistician (non-voting)

STATISTICAL ANALYSIS TEAM

(Statistical analyses for publication and dissemination)

<TBC>

PROTOCOL AUTHORS

This protocol was written in accordance with the treatment and design recommendations given by the WHO Expert deliberations for candidate treatments prioritisation and trial design for Filoviruses.

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National Investigators (Uganda): Paska Apiyo, Pauline Byakika

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Thu, 10 Oct 2024 15:59:27	**Ana Maria Henao-Restrepo** Signed the Document (IP: 178.192.176.137)


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UNITED STATES OF AMERICA

World Health Organization

SOLIDARITY PARTNERS

Platform Adaptive Randomised Trial for NEw and Repurposed Filovirus treatmentS

MARV annex

Version 5.0
October 4, 2024

R&DBlueprint
Powering research to prevent epidemics

Table of contents

Filovirus nomenclature used[1]

Disease	First subcategory	Second subcategory	Caused by
Filovirus disease	Ebola disease (ED)	Ebola virus disease (EVD)	Ebola Zaire virus (EBOV)
		Sudan virus disease (SVD)	Sudan virus (SUDV)
		Bundibugyo virus disease (BVD)	Bundibugyo virus (BDBV)
		Other specified Ebola disease	e.g. Tai Forest virus
		Ebola disease, virus unspecified	
	Marburg disease (MD)	Marburg virus disease	Marburg virus (MARV) or Ravn virus (RAVV)
		Other specified Marburg disease	
		Marburg disease, virus unspecified	

Signatures

Rwandan Chief Investigator	David Turatsinze	D Turatsinze 10/Oct/2024 16:11:52 David Turatsinze
International Chief Investigator	Peter Horby	P horby 10/Oct/2024 16:36:05 peter horby
Sponsors Representative	Ana Maria Henao-Restrepo	A M Henao-Restrepo 11/Oct/2024 17:12:41 Ana Maria Henao-Restrepo

1 BACKGROUND

SOLIDARITY PARTNERS is a platform trial of treatments for any *filoviridae* disease. The trial protocol describes the trial. While some treatments may work across a variety of filovirus diseases (e.g. remdesivir and host-directed therapies), others are specific to the particular virus causing the disease. The purpose of this annex is to supplement the trial protocol to describe in detail the treatment comparisons for patients with MARV infection (see figure 1).

Marburg Disease is less well characterised than Ebola Disease because there have been fewer cases and no large outbreaks in almost two decades. The most recent outbreak was in Equatorial Guinea in 2013. There is significant variation in case fatality rates reported for Marburg (ranging from 23-88%), with the two largest outbreaks to date with mortality above 80%[2].

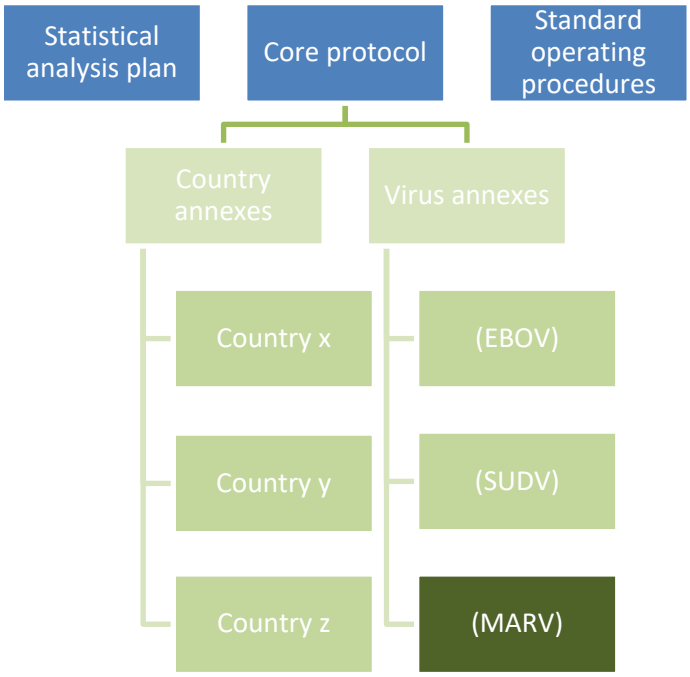

Figure 1. Protocol structure: The relationship of this appendix (dark green) to other important trial documents is shown.

2 SUMMARY OF VIRUS SPECIFIC ADDITIONS

Trial protocol section	Arm-specific additions
Trial design	No additions from master protocol
Randomisation domains	**Virus specific additions to the master protocol**
Eligibility criteria	No additions from master protocol
Treatment allocation	No additions from master protocol
Schedule of assessments	No additions from master protocol
Primary outcome	No additions from master protocol
Secondary outcomes	No additions from master protocol
Safety outcomes	No additions from master protocol
Safety reporting	No additions from master protocol

3 RANDOMISATION DOMAINS

Randomisation will be between the following treatment domains in a factorial manner.

Table 1. Randomisation domains

Domain	**Randomisation**
Randomisation 1: Monoclonal antibody/ies	MBP091 (MARV specific monoclonal antibody) vs no additional treatment (1:1)
Randomisation 2: Antiviral	Remdesivir vs no additional treatment (1:1)
Randomisation 3: Host-directed	Not presently active

Note: If one of the treatments is not available at the site or not suitable for the individual, patient randomisation may be between fewer arms. For example, if the monoclonal antibody is not available at the site, then a patient may be randomised in the antiviral therapy (antiviral vs. no additional treatment) comparison only.

4 INCLUDED TREATMENTS

MBP091

For further information on MBP091, refer to the current investigator's brochure (IB) (v3.0, 12 March 2024), including information on the following:

- Nonclinical pharmacology
- Nonclinical pharmacokinetics (PK)
- Toxicology

MBP091 contains a single immunoglobulin G subclass 1 (IgG1) lambda monoclonal antibody (mAb) isolated from a MARV infected survivor four years after infection and convalescence. The mAb binds to the MARV glycoprotein (GP) thereby blocking binding to the host receptor NPC1 and neutralising the virus, which is considered to be the primary mechanism of action.

Results from nonclinical studies of MBP091 in animal models suggest therapeutic potential. To date, the efficacy of MBP091 (and its predecessor MR191-N) has been evaluated in 5 studies of rhesus macaques administered otherwise lethal challenges of MARV (see table 1 for summary). The efficacy of MBP091 in treating MVD in humans has not been evaluated; however, MR191-N has been administered to one otherwise healthy adult patient as a post-exposure prophylaxis therapeutic following a needlestick injury with a MARV-contaminated needle. No AEs or SAEs were reported. The safety of MBP091 was evaluated in a phase I study and it was well tolerated in healthy adult volunteers, and there were no reported SAEs or Grade 3 AEs.

Table 2: Summary of Rhesus Macaque Efficacy Studies of MR191-N and MBP091 (*Table 4 in MBP091 IB v3.0)*

Study	IM Challenge Agent (Target 1000 PFU)	Treatment Day(s) Post-Infection	IV Dose (mg/kg)	Treatment	n	Survival (%)	Control Survival
1	UTMB MARV ANGOLA	4/7	50	MR191-N	3	100	0/1
2	UTMB MARV ANGOLA	5/8	50	MR191-N	5	80	0/1
3	UTMB MARV ANGOLA	4/7	50	MR191-N	4	100	0/2
		4/7	50	MBP091	6	100	
4	FANG/WRCEVA MARV ANGOLA	5/8	50	MBP091	5	40	0/2
		5	100	MBP091	5	60	
5	TBRI MARV ANGOLA	4	100	MBP091	6	100	0/6
		5	100	MBP091	6		

FANG: Filovirus Animal Non-Clinical Group; IM: Intramuscular; PFU: Plaque-forming unit; WRCEVA: World Reference Center for Emerging Viruses and Arboviruses

Safety Profile

A detailed MBP091 safety profile and reference safety information (RSI) can be found in the current IB. Key highlights of this information are provided below. Assessment of adverse

reactions is based on data from a human safety and PK study in healthy adult volunteers (CLINPRT-4).

MBP091 was administered as a single IV infusion, approximately 2 hours in duration, in the absence of infusion reactions. All participants were monitored and assessed for safety and the incidence of AEs over the course of the entire study. Throughout the study, 28 treatment emerging adverse events (TEAEs) were reported in 12 (42.9%) participants. Twenty-three (23) TEAEs were reported in 9 (45.0%) participants who received MBP091 and 3 (37.5%) TEAEs were reported in participants who received placebo. Twenty-six (26) TEAEs were mild in severity and 2 TEAEs were moderate in severity (one of which occurred in a participant receiving placebo and was judged not related to study drug); none were severe. Of the 28 TEAEs, 1 was considered to be definitely related to MBP091 (mild drug eruption in a participant in cohort 1 receiving 5 mg/kg MBP091. Three TEAEs, considered to be probably related to MBP091, occurred in one participant in Cohort 2 receiving 15 mg/kg. These TEAEs were fatigue and infusion related reaction (both were mild and occurred during the infusion), and moderate headache (occurred during follow-up). Ten (10) TEAEs were considered to be possibly related to the study drug, and consisted of diarrhea, dysgeusia, papule, pruritus and infusion related reaction (consisting of 4 mild TEAEs in a participant in cohort 2).

Both AEs of infusion related reactions were mild and occurred in 1 participant in cohort 2. The infusion related reactions consisted of flushing of the neck and chest, palpitations, tingling and clamminess in both hands, and dry mouth during the infusion. This participant also reported mild fatigue during the infusion. The study PI considered flushing of the neck and chest and fatigue to be probably related to MBP091, and palpitations, tingling and clamminess in both hands, and dry mouth to be possibly related.

The most common TEAEs following treatment were administration site bruise, catheter site pain, vessel puncture site bruise, dysgeusia, and headache.

There were no SAEs or deaths reported in the study. There were no clinically significant abnormalities for clinical chemistry, hematology, urinalysis parameters, or 12-lead electrocardiogram parameters. Overall, a single dose of MBP091 was safe and well tolerated at 5, 15, 50, and 100 mg/kg by all participants in the study. No safety or tolerability concerns emerged from this study.

MR191-N (the predecessor to MBP091) has been administered to one otherwise healthy adult patient as post-exposure prophylaxis following a high-risk needle stick injury with a MARV-contaminated needle. No AEs or SAEs were reported.

MBP091, as with any other mAb treatment, has the potential to cause severe, including fatal, infusion reactions. Symptoms, signs, and sequelae observed with other IV administered mAb products have included, but are not limited to: fever, chills, nausea, urticaria, hypotension, hypertension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylaxis, anaphylactoid events, and death. None of these Aes have been observed within the limited clinical experience with MBP091. It is not known whether they will occur.

In the first in human study of MBP091, mild infusion related reactions were reported in one participant and consisted of flushing of the neck and chest, palpitations, tingling, and clamminess in both hands, fatigue, and dry mouth during the infusion.

Anaphylactic and other hypersensitivity reactions have been reported following the IV administration of proteins, including antibodies, to people. Medicinal products for the treatment of hypersensitivity reactions, *e.g.*, epinephrine (adrenaline) and antihistamines, should be available for immediate use in the event of such reactions during administration of this product.

Risks associated with MBP091 treatment administered at the same time as or following any other experimental therapeutic or prophylactic agent for MARV are unknown. The possibility of allergic/immune sensitization to MBP091 due to prior treatment with other monoclonal antibody products is a potential risk.

Formulation
Infusions must be administered using an infusion set with a 0.2 µm or 0.22 µm, low-protein binding, polyethersulfone (PES), in-line filter. MBP091 has been studied in infusion sets containing tris(2-ethylhexyl) trimellitate (TOTM) and IV bags containing di(2-ethylhexyl) phthalate (DEHP) plasticizers. Baxter 0.9% Sodium Chloride Injection or dextrose 5% in water (D5W) in VIAFLEX Plastic Container(s) and B. Braun Primary Administration Set Caresite® infusion sets with an in-line filter, or equivalent, must be used.

MBP091 Administration details are provided in the pharmacy manual and in the relevant SOLIDARITY Partners Standard Operating Procedure.

Storage
MBP091 DP diluted in diluent for IV infusion may be stored at room temperature for up to 8 hours. Attempts should be made to complete the IV infusion within 4 hours of preparation. Refer to the Pharmacy Manual for additional details.

Remdesivir

Remdesivir (RDV, GS-5734; VEKLURY®) is a nucleotide prodrug that is intracellularly metabolized into an analog of adenosine triphosphate that inhibits viral RNA polymerases and has broad spectrum activity against members of the filoviruses (e.g. MARV, EBOV, BDBN, SUDV). RDV is a widely approved antiviral therapy for the treatment of coronavirus disease 2019 (COVID-19) caused by the virus SARS-CoV-2. RDV has an established clinical safety profile and is generally safe and well tolerated.

For further information on RDV, refer to the current investigator's brochure (IB) for RDV for Coronavirus Disease, Ebola Virus Disease, Marburg Virus Disease, and Respiratory Syncytial Disease (edition 12, 12 August 2024) including information on the following:

- Nonclinical pharmacology
- Nonclinical pharmacokinetics (PK)
- Toxicology

RDV is a monophosphoramidate prodrug of an adenosine nucleoside analog that interferes with viral RNA-dependent RNA polymerase activity, inhibiting viral RNA synthesis through the mechanisms of delayed chain termination and template mediated inhibition[4,5]. RDV inhibits the EBOV replication in relevant human cell types including primary macrophages and endothelial cells with half-maximum effective concentration (EC50) between 0.06-0.14 µM in vitro 10.

In vitro antiviral testing has shown that RDV exhibits consistent broad spectrum antiviral activity against multiple EBOV-related filoviruses. In addition to inhibiting EBOV Kikwit, Makona, and Mayinga, RDV has shown potent in vitro antiviral activity against the Sudan, Bundibugyo, and MARV, with $_{EC50}$ values of 0.06 to 0.24 µM (Table 2)[6]

Table 3. In Vitro Antiviral Activity of RDV Against Filoviruses

Virus	RDV $_{EC50}$ (µM)
EBOV (Kikwit)	0.14
EBOV (Makona)	0.19
EBOV (Mayinga)	0.014
Bundibugyo	0.19
Sudan	0.24
MARV	0.06

EC_{50} = half-maximal effective concentration; EBOV = Ebola virus; MARV = Marburg virus; RDV = remdesivir

The in vivo efficacy of RDV has been assessed in multiple studies of lethal infection models of EBOV-infected rhesus monkeys and MARV-infected cynomolgus monkeys that mimic the course of Ebola virus disease (EVD) and Marburg disease (MD), respectively, in humans. Treatment of EBOV-infected animals with a 10-mg/kg loading dose on Day 3 or Day 4 post-infection, followed by 5 mg/kg maintenance doses by intravenous (IV) administration for a total of 12 days, resulted in 100% survival, a significant reduction of EBOV plasma viremia, and a marked reduction in clinical EVD signs (Study PC-399-2024.[4]). Treatment of MARV Angola/2005-infected cynomolgus monkeys with a 12-day regimen consisting of a single 10-mg/kg loading dose and 5 mg/kg maintenance doses initiated on Day 4 or Day 5 post-infection resulted in 83% survival and reduced MVD-associated manifestations, compared with no survival in control vehicle-treated animals (Study PC-399-2039).

A follow-up study evaluated the efficacy of once-daily IV injection of RDV, a single dose of the MARV mAb MR186-YTE, or both treatments in combination, in rhesus monkeys infected with MARV Angola/2005[13]. Monotherapies with RDV or MR186-YTE alone, initiated 5 days postinfection, resulted in rescue from lethal MVD in 4 of 5 and 4 of 4 animals, respectively. In addition, the combination of both therapeutics administered 6 days post infection rescued 4 of 5 animals from late-stage disease, when each monotherapy failed to rescue any animal.

Additional non-clinical experience with RDV in other infections can be found in the IB for RDV.

With respect to human data, in the PALM randomised controlled trial, remdesivir was compared against the monoclonal antibody cocktail ZMapp in patients with *EBOV* infection. This study found no survival benefit in patients who received remdesivir[14]. There was no untreated control group in this comparison, and a clinically significant difference in case fatality rate between this and a previous outbreak where clinical trial control data existed means that comparison was not useful. This means there continues to be some level of uncertainty regarding the possible efficacy of remdesivir for *EBOV* infection. There are no data on the possible benefit of remdesivir when used in combination with either mAb114 or REGN-EB3 for *EBOV* infection.

RDV Safety Profile

A detailed RDV safety profile and reference safety information (RSI) can be found in the current IB for RDV[3]. Key highlights of the information are provided below. Assessment of adverse reactions is based on data from four Phase 1 studies, four large Phase 3 studies, from hospitalized patients with COVID-19 and from patients who received RDV in a compassionate use program.

Warnings and Precautions are described in the CCDS portion of the IB and summarized below. Please refer to the CCDS for full information.

Hypersensitivity Including Infusion-related and Anaphylactic Reactions: Hypersensitivity reactions, including infusion-related and anaphylactic reactions, have been observed during and following administration of RDV. Signs and symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. Monitor patients for hypersensitivity reactions during and following administration of RDV as clinically appropriate. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of RDV and initiate appropriate treatment.

Adverse Drug Reactions: Adverse drug reactions to RDV are summarized in Table 3.

Table 4. RDV: Adverse Drug Reactions by System Organ Class

System Organ Class	Adverse Drug Reaction
Gastrointestinal disorders	Nausea
Hepatobiliary disorders	Transaminases increased
Immune system disorders	Anaphylactic reaction Hypersensitivity
Injury, poisoning and procedural complications	Infusion-related reaction

Other Important Safety Information: Important safety issues for RDV that are under monitoring by Gilead are summarized below:

Prothrombin Time/INR

In a clinical study of participants with mild-to-moderate and severe disease COVID-19 (Study CO-US-540-5776 [ACTT-1]), the incidence of increased PT or INR (predominantly Grades 1 and 2) was higher in participants who received RDV compared with placebo, with

no difference observed in the incidence of bleeding events between the 2 groups. In Study GS-US-540-9012 (PINETREE), the incidence of increased PT or INR was similar in patients treated with VKY compared with placebo (Section 9.1 of the CCDS).

Pediatrics
The safety assessment of RDV in pediatric patients 28 days of age and older and weighing at least 3 kg with COVID-19 is based on data from a Phase 2/3, open-label clinical study (GS-US-540-5823) that enrolled 53 patients who were treated with RDV. The adverse reactions observed were consistent with those observed in clinical trials of RDV in adults.

Clinical safety in patients with Filovirus Disease

In the PALM trial, a total of 9 SAEs judged by the site investigator as not related to underlying EVD were reported for participants receiving RDV. Of these, an event of hypotension, which occurred during administration of the loading dose and led to fatal cardiac arrest, was considered related to RDV. The independent pharmacovigilance committee noted that the death could not be readily distinguished from underlying fulminant EVD.

PREVAIL IV was a double-blind, 1:1 randomized, 2-phase, placebo-controlled, Phase 2 trial of RDV designed to assess the antiviral activity, longer-term clearance of seminal EBOV RNA, and safety in Liberian and Guinean men with persistent EBOV RNA in semen. According to the preliminary report, there were no SAEs in the study. The study allowed for blinded dose reductions for transaminase elevations; there was 1 individual dose reduction in the RDV group and 5 in the placebo group.

During the 2018-2020 EBOV outbreak in DRC, the following investigational treatments were provided under Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI) protocols: ZMapp, REGN-EB3, mAb114, and RDV. Of the 756 patients who were assigned to receive treatment, 56.2% were female, 50.5% were aged at least 30 years, 63.1% had low viral load (CT-nucleoprotein > 22), 52.3% were treated within 5 days of symptoms, and 12.3% were vaccinated with recombinant vesicular stomatitis virus-Zaire Ebola virus (rVSV-ZEBOV) vaccine. The overall case fatality rate (95% CI) was 38.5% (35.1%-42.0%). The case fatality rate was 32.1% (26.7%-38.1%) for mAb114, 31.5% (25.8%-37.7%) for REGN-EB3, 51.1% (44.6%-57.6%) for RDV, and 47.1% (34.1% to 60.5%) for ZMapp. It was concluded that low viral loads, shorter time between onset of illness and initiation of treatment, and being vaccinated were associated with an increased probability of survival. These prognostic factors were relatively balanced across the 4 treatments offered.

An outbreak of EVD caused by Sudan Ebolavirus (SUDV) occurred in Uganda from 22 September 2022 to 11 January 2023. The Ugandan Ministry of Health provided single-patient expanded access to RDV and MBP-134 (a combination of 2 mAbs). Twenty-one patients were treated with RDV, 4 of whom also received MBP-134. Among those treated with RDV, 5 patients died, of whom 1 also received MBP-134.

Details of individual expanded access cases are provided in the IB.

Formulation
RDV will be supplied as a lyophilized formulation for injection.

Preservative-free lyophilized RDV will be provided in 100 mg single-dose vial contains a sterile that is to be reconstituted with 19 mL of Sterile Water for Injection and diluted into 0.9% sodium chloride prior to administration by intravenous infusion. Following reconstitution, each vial contains 100 mg/20 mL (5 mg/mL) of RDV concentrated solution. The lyophilized formulation also contains 3 g sulfobutylether-β-cyclodextrin sodium salt (SBECD), water for injection, USP, and may include hydrochloric acid and/or sodium hydroxide for pH adjustment.

RDV preparation prior to administration: RDV preparation will follow the instructions in the Investigator's Brochure.

Storage

Do not reuse or save unused RDV lyophilized powder or injection concentrated solution for future use. Store RDV for injection, 100 mg, vials below 30°C (below 86°F) until required for use. Do not use after expiration date.

After reconstitution, vials should be used immediately to prepare diluted solution. RDV diluted solution for infusion can be stored up to 24 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) prior to administration.

5 DRUG-SPECIFIC CONTRAINDICATIONS

Remdesivir

- Known allergy to remdesivir or excipient

MBP091

- Known allergy to MBP091 or excipient

6 DRUG SPECIFIC ADVERSE EVENTS OF SPECIAL INTEREST

Remdesivir

- Infusion related reactions

MBP091

- Infusion related reactions

7 ADULT DOSING

Remdesivir:

The recommended dosing duration is 10 days.

Duration of infusion
Remdesivir is to be administered via intravenous (IV)-infusion over 30 to 120 minutes.

Adult Patient Dose
The recommended dosage for adults and paediatric patients weighing at least 40 kg is a single loading dose of RDV 200 mg on Day 1 followed by once-daily maintenance doses of RDV 100 mg from Day 2 onwards for up to nine days (for a total treatment course of up to ten days).

MBP091:

Patients receive 1 dose.

Infusion Rate
In the absence of infusion reactions, the MBP091 infusions will be administered at a constant infusion rate. The infusion rate is not to exceed 800 mL/hr.

Duration of infusion
MBP091 is to be administered via intravenous (IV)-infusion over a minimum of 2hrs.

Adult Patient Dose
Dose preparation is according to table 5.

Table 5. MBP091: Dose preparation by body weight

Body Weight (kg)	Volume of 50 mg/mL MBP091 Concentrate (mL)	Diluent Volume[a] (mL)	Final Infusion Volume (mL)	Syringe or Infusion Bag Size (mL)
0.5	2.0 mL per kg of body weight	2.5	3.5	10 mL syringe compatible with IV infusion pump
1		5	7.0	10 mL syringe compatible with IV infusion pump
2 to 5		10	14 to 20	25 mL IV bag
6 to 15		40	52 to 70	100 mL IV bag
16 to 40		75	107 to 155	250 mL IV bag
41 to 90		100	182 to 280	500 mL IV bag
≥91		250	432 and above	500 mL - 1,000 mL IV bag (as needed)

[a] *For IV administration, the diluent volume column includes the volume of diluent needed in the infusion bag.*

[b] *Larger size bags than indicated can be used by removing a sufficient volume of the original contents.*

8 DOSING ADJUSTMENTS FOR PREGNANT AND BREASTFEEDING WOMEN

Remdesivir

There are no clear data on survival of fetuses or neonates born from filovirus infected women treated with remdesivir. Animal studies have failed to reveal evidence of embryofetal toxicity. In rats and rabbits, this drug showed no adverse effect on embryofetal development when administered to pregnant animals at systemic exposures (AUC) of the main circulating metabolite of this drug (GS-441524) that were up to 4 times the exposure in humans at the recommended human dose. However, there are no controlled data in human pregnancy and in filovirus infection. There are insufficient data available on the use of this drug in pregnant women to inform a drug-related risk. It should be used during pregnancy only when the benefit outweighs the risk. US FDA pregnancy category: Not assigned.

A Phase 4, prospective, open-label, non-randomized study to evaluate the PK and safety of RDV when administered to pregnant and non-pregnant women of childbearing potential for treatment of COVID-19 was conducted. The study showed that RDV, when administered to pregnant and non-pregnant women hospitalized with COVID-19, was generally well tolerated with no detected effect, via newborn physical exam, on infants born during the study. No participants in either arm died during the study. The majority of AEs experienced by pregnant women and non-pregnant women in this study are consistent with pregnancy and the presence of COVID-19 disease. Newborn physical exams demonstrated that the majority of infants born were born ≥ 37 weeks gestational age and the mean Apgar scores at 1 and 5 minutes were 8.1 and 8.6, respectively.

Based on limited data, it does not appear that mothers using this drug need to avoid breastfeeding; however, until more data are available, this drug should be used with careful infant monitoring during breastfeeding.

There are no dose adjustments.

MBP091

There are no human data of pregnant women treated with MBP091. There are no animal studies to determine embryofetal toxicity. A GLP tissue cross-reactivity study of

MBP091 was conducted *in vitro* with cryosections of selected fetal human tissues to determine the potential off target cross-reactivity of biotinylated MBP091 in these tissues. No specific binding was present with biotinylated MBP091 in the fetal human tissue panel examined. This was expected as MARV GP is not expressed in normal fetal human tissues.

9 DOSING ADJUSTMENTS FOR CHILDREN

Remdesivir

The recommended dosage of remdesivir in pediatric patients weighing between 1.5kg less and 40kg is provided below.

Table 6. RDV: Dose adjustments for pediatric patients

Pediatric Patient Population	Loading Dose	Maintenance Dose
At least 28 days old and 3 kg to less than 40 kg	5 mg/kg on Day 1	2.5 mg/kg once daily from Day 2
At least 28 days old and 1.5 kg to less than 3 kg	2.5 mg/kg on Day 1	1.25 mg/kg once daily from Day 2
Less than 28 days old and at least 1.5 kg		
Preterm infants less than 56 days old and at least 1.5 kg		

MBP091

No modifications

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11 VERSION HISTORY

Version number	Date	Brief Description of Changes
1.0	30-Aug-2023	Initial draft
Version break to align with main protocol.		
5.0 5.0	29-July-2024 04-Oct-2024	Updated following WHO meeting in Kampala Updated to reflect new IBs for MBP091 and remdesivir

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