Platform Adaptive Randomised Trial for NEw and Repurposed Filovirus treatmentS

PARTNERS TRIAL overview

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

Design: Multi-country, multi-outbreak open-label, randomised adaptive platform trial of potential treatments for filovirus disease (FVD).

Open-label,

randomised controlled (1:1)

Factorial design

adaptive platform trial

for patients with laboratory-confirmed acute Filovirus Disease

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BDBV comparisons

Comparison arm	
Monoclonal antibody	1:1 MBP134 vs supportive care alone
Small molecule antiviral (remdesivir)	1:1 remdesivir vs supportive care alone

Allocations (all on a baseline of oSoC)
25% Monoclonal and remdesivir
25% Monoclonal alone
25% Remdesivir alone
25% No additional therapy

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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 allergy to a study drug)

(iv) Not known to have been enrolled in this protocol previously

(v) Not known to have received antiviral (e.g remdesivir or monoclonal antibody) treatment for Filovirus Disease during this infection (e.g. through Monitored Emergency Use of Unregistered and Investigational Interventions)

All ages, includes pregnant women, includes breastfeeding women.

Includes people who are already in other trials (e.g. vaccination)

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Primary outcome

All-cause mortality at 28 days following randomisation

Discharge alive before the relevant time period (28 days after randomisation) will be assumed as absence of the event (unless there are additional data confirming otherwise)

Other outcomes

Secondary outcome

Time (days following randomization) to viral clearance

Other outcomes

Viral load (measured by cycle threshold) on samples taken at Day 3, 5, 7 and 10.

Progression of organ dysfunction.

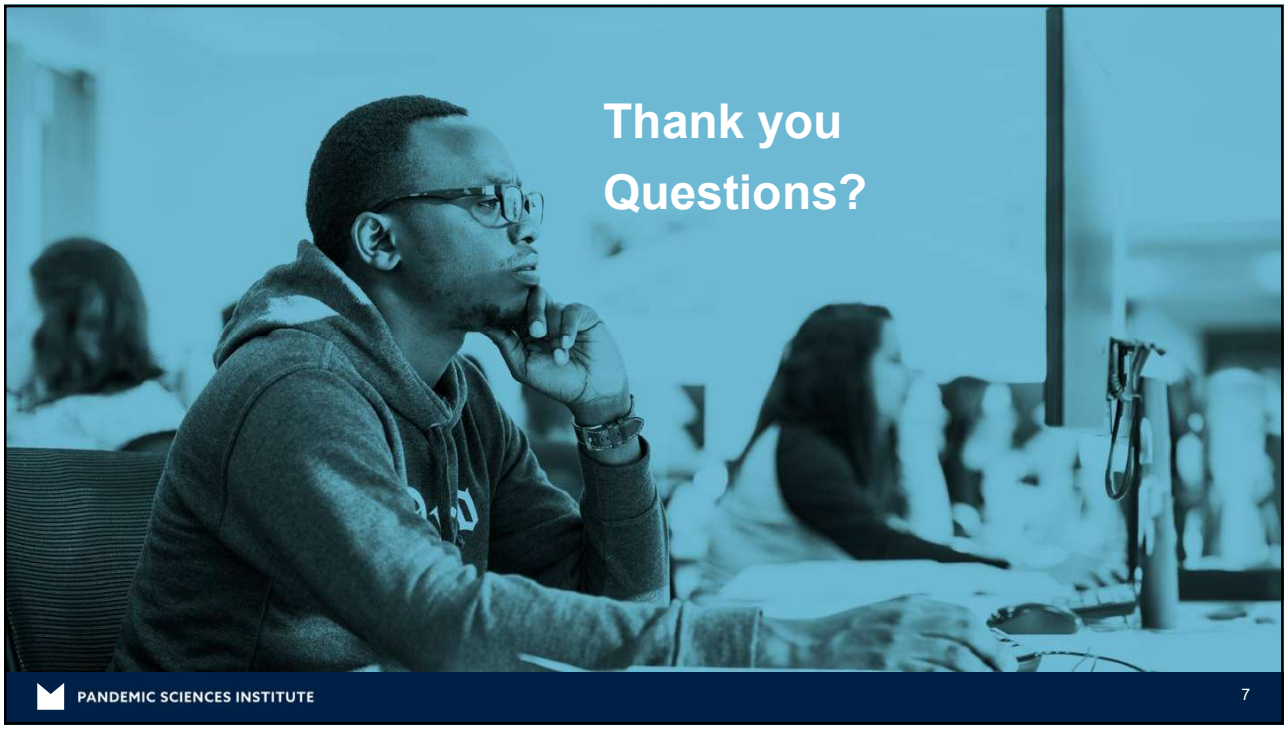
Safety assessments

•Adverse events of special interest (e.g infusion reaction)

•SAE not due to filovirus infection

•SSARs/SUSARs

•Pregnancy and foetal outcomes



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Inclusion of Pregnant Women in the Study Trial

Pregnant women are more likely to die from Filovirus infections.

Very few fetuses survive birth to an Ebola infected pregnant woman (four case reports cumulatively from all outbreaks – three of these received experimental treatments). There are no known survivors for Marburg Disease.

When a new drug is added into the protocol, expert teratology advice will be provided to the trial steering committee to support or prevent enrolment of pregnant women in an arm.

Our current advice is to include pregnant women in the initial trial arms.

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Safety reporting

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 (e.g. infusion-related reactions)
b. Serious (per standard regulatory definition) and 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])
c. Serious but are not considered to be due to the underlying filovirus infection
d. Pregnancy or foetal outcome

We recognise the importance of assessing the safety of treatments but this must be proportionate to the risks that the disease itself poses to the patients. In the context of a disease with a 50% mortality rate, the occurrence of non-serious adverse events is of limited importance to regulatory and clinical decisions

Safety reporting

This approach is consistent with the PALM RCT, which did not collect all SAEs regardless of causality.

PALM Protocol states

- *"ONLY [their emphasis] the following SAEs are graded and are required to be individually reported to the Clinical Safety Office:*
  - *New/worsening events considered unlikely/definitely unrelated to underlying Ebola infection, and/or*
  - *New/worsening events considered possibly, probably, or definitely related to study interventions or to a non-Ebola condition, including any baseline comorbidity that has worsened.'*

This approach is also consistent with other trials for patients with severe acute infectious diseases e.g. REMAP- CAP https://www.remapcap.org/protocol-documents.

MBP 134

MBP134 is a cocktail of two mAbs.

In comparison to licensed mAb therapeutic options for Ebola Disease which are specific to EBOV, the components of this cocktail are broadly neutralising.

They target highly conserved epitopes on the ebolavirus glycoprotein (GP) and inhibit GP-mediated membrane fusion across all known species of Ebolavirus.

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MBP134 – NHPdata

Cell Host Microbe. 2019 Jan 9;25(1):49–58.e5. doi: 10.1016/j.chom.2018.12.005

- 6 animals infected with BDBV received a single 25 mg/kg IV dose on day 7 post-infection, when they were already viremic and clinically ill.
- Five of the six treated animals survived, while all controls died.
- The treatment also produced reversal of disease: by day 10, five of six treated animals had no detectable infectious virus in blood, and clinical scores returned to baseline by day 12 in survivors.
- The single non-survivor had severe liver injury before treatment, suggesting disease may have been too advanced to reverse.

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MBP134

Phase I safety data available.

Used under MEURI during SUDV Outbreak Uganda.

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Remdesivir

BDBV is susceptible to remdesivir in vitro

•potency is broadly comparable to EBOV and SUDV

- doi: 10.1038/s41598-023-29517-9
- doivhttps://doi.org/10.1128/jvi.00643-21

But direct efficacy evidence in BDBV animal models or humans remains limited compared with EBOV/SUDV

The safety profile of RDV very well understood, including in Ebola (PALM trial)

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Remdesivir and Mab combination therapy

- Rhesus macaques challenged with Sudan virus (SUDV) - https://pmc.ncbi.nlm.nih.gov/articles/PMC9220838/
- Treatment initiated at **day 6 post-infection** (advanced disease stage)
- **Remdesivir monotherapy:** 20% survival
- **MBP431 monotherapy:** 20% survival
- **Remdesivir + MBP431 combination therapy:** 80% survival

Study demonstrated improved efficacy of combination therapy compared with either agent alone in advanced SUDV infection