World Health Organization

Sudan Ebolavirus – Experts deliberations

Candidate treatments prioritization and trial design discussions

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Background

Given that there is no known effective treatment for Sudan ebolavirus (SUDV) and considering the current SUDV outbreak in Uganda, several meetings were held throughout October and November 2022 to plan and implement a clinical trial protocol for candidate therapeutics against Sudan ebolavirus disease.

These expert consultations included clinicians and researchers from the Ugandan Ministry of Health, organizations supporting Ebola treatment centers (ETCs), filovirus experts, experts in the field of randomized controlled trials (RCTs) for evaluation of investigational therapeutics (clinical experts, trialists, and statisticians) and regulatory experts.

The objectives of the consultations were:

1. To review and critically appraise the existing evidence regarding different investigational therapeutic agents and reach a consensus on prioritization of therapeutics for a clinical trial.
2. To discuss the design options and reach consensus on the design and implementation of a clinical trial.
3. To discuss a proposed protocol based on the prioritized trial design options.

The expert consultation participants also considered designs with the ability to cumulatively collect evidence across multiple outbreaks if needed.

Prioritization of candidate treatments to be included in a trial in Uganda

Developers were invited to present information on their candidate therapeutics to the expert consultation working group. The table below describes the summary of evidence shared by developers for seven experimental therapeutics and consensus of the working group.

Prioritization was based on the following criteria:

- Non-human primate (NHP) challenge studies against Sudan ebolavirus
- Safety data in humans
- Pharmacokinetic (PK) data in humans
- Clinical efficacy in humans against Sudan ebolavirus
- Other considerations including feasibility of administration, number of required doses, etc.
- Availability of GMP batches allowing for rapid inclusion in an RCT was an important feasibility factor

As of 31 October 2022, both MBP134 and Remdesivir have been approved by the Ugandan National Regulatory Authority for compassionate use.

Table 1. Summary of Investigational Therapeutics and Recommendations

Product (Developer)	Type	Summary of Evidence	Availability	Recommendations
MBP134 (MBP047 and MBP087 mAbs) (**Mappbio**)	Monoclonal antibody cocktail (MAbs)	**NHP Challenge:** This product has reported efficacy in non-human primate (NHP) challenge studies against Sudan ebolavirus. **Safety in Humans:** Safety data from first in human study is available. **PK in Humans:** Data not yet available. **Clinical Efficacy in Humans:** No clinical efficacy data is currently available against Sudan ebolavirus in humans.	30 doses are available immediately and an additional 100 doses will be available in early December.	MBP134 is recommended for inclusion in the RCT for evaluation as both a monotherapy and combination therapy.
Remdesivir (**Gilead**)	Antiviral (AV)	**NHP Challenge:** This product has reported efficacy against Sudan Ebolavirus in NHP models[1]. However, in the PALM study[2] against Zaire ebolavirus, Remdesivir was not significantly different than ZMapp in treatment effect, while MAb114 and REGN-EB3 significantly decreased mortality compared to ZMapp. NHP data evaluating the combination of Remdesivir and MBP431[2]	The product is commercially available in large amounts.	Remdesivir is recommended for inclusion in the RCT for evaluation as both monotherapy and combination therapy. Use of remdesivir as monotherapy is less of a priority compared to MAbs but should still be considered.

[1] https://insight.jci.org/articles/view/159090

[2] https://www.nejm.org/doi/10.1056/NEJMoa1910993?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

Product (Developer)	Type	Summary of Evidence	Availability	Recommendations
		demonstrated increased efficacy compared to the Remdesivir alone or MBP431 alone in stringent testing conditions against Sudan ebolavirus. **Safety in Humans:** Available for other indications. **PK in Humans:** Available for other indications. **Clinical Efficacy in Humans:** No clinical efficacy data is currently available against Sudan ebolavirus in humans. **Other Considerations:** The need of repeated IV infusions may make this antiviral less appealing from a clinical practice perspective, but this is not considered a factor for exclusion from the trial.		
Inmazeb (**Regeneron**)	Monoclonal antibody cocktail	This product is a cocktail of three monoclonal antibodies and is currently licensed for treatment of Zaire ebolavirus. Only one of the monoclonal antibodies (maftivimab) can potentially neutralize Sudan ebolavirus. **NHP Challenge:** Preliminary NHP results showed no or limited efficacy for both the cocktail and monoclonal antibody. **Safety in Humans:** Available for other indications[3]. **PK in Humans:** Available for the cocktail but not the active MAb alone. **Clinical Efficacy in Humans:** No clinical efficacy data is currently available against Sudan ebolavirus in humans.	660 treatment courses of 150mg/kg currently available	Inmazeb and Maftivimab are not recommended to be included in the first RCT given limited currently available data.
Maftivimab - REGN3479 (**Regeneron**)	Monoclonal antibody		250 treatment courses of 150 mg/kg will be available by mid-December	
CM-JLD1, A cocktail of 2 mAbs CM-SV1 and CM-X52 (**Celdara Medical**)	Monoclonal Antibody Cocktail	**NHP Challenge:** This product has reported efficacy in two NHP studies. **Safety in Humans:** No data available in humans. **PK in Humans:** No data available in humans. **Clinical Efficacy in Humans:** No clinical efficacy data is currently available against Sudan ebolavirus in humans. **Other Considerations**: It would be important to evaluate if one dose is efficacious, instead of the currently proposed two doses.	It is anticipated that it will take up to 6 months to have GMP batches that could be tested in clinical trials.	It is premature to consider this product for inclusion in the first RCT.

[3]https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(18)30397-9/fulltext

Product (Developer)	Type	Summary of Evidence	Availability	Recommendations
		Clinical Efficacy in Humans: No clinical efficacy data is currently available against Sudan ebolavirus in humans.		
Molnupiravir (**Merck**)	Antiviral	**NHP Challenge:** No data available. **Safety in Humans:** Data available for other indications[4],[5]. **PK in Humans:** Data available for other indications. **Clinical Efficacy in Humans:** No clinical efficacy data is currently available against Sudan ebolavirus in humans. **Other Considerations:** Animal studies for Zaire ebolavirus reported efficacy when used as a prophylaxis or early treatment.	The product is commercially available.	NHP data are needed to determine if this product should be prioritized for evaluation in an RCT for either treatment or post-exposure prophylaxis.
FX-06 (**F4 Pharma**)	Antiviral	This product targets endothelial integrity. **NHP Challenge:** One NHP treated for Ebola. **Safety in Humans:** Data available for other indications. **PK in Humans:** Data not yet available. **Clinical Efficacy in Humans:** A case study for compassionate use against Zaire ebolavirus[6] showed the patient fully recovered. No clinical efficacy data is currently available against Sudan ebolavirus in humans.	100g available now, 80g of polypeptide and 1,000g pre-drug available in 3-4 months. 3,000 ready to use vials but would need to be redirected from other research.	NHP data are needed to the determine if this product should be prioritized for evaluation in an RCT.
Other candidate treatment types considered		**Corticosteroids, such a dexamethasone.** It was generally agreed that since disease caused by filovirus infection, including from Sudan ebolavirus, presents several features of increased inflammation, especially once disease progresses, testing of dexamethasone should be incorporated as secondary randomization in the same trial.		Low dose corticosteroids (e.g. dexamethasone) was recommended for inclusion in the RCT for evaluation.
		Other polyclonal and monoclonal products		Other products are still in early development and therefore available data is insufficient to support a recommendation for inclusion into the RCT. It will be important to

[4] https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4237902

[5] https://www.nejm.org/doi/full/10.1056/NEJMoa2116044

[6] https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)62384-9/fulltext

Product (Developer)	Type	Summary of Evidence	Availability	Recommendations
				continuously monitor their progress.
		Convalescent plasma		Convalescent plasma should be included in the list of potential treatment options, provided the product can be sufficiently titrated with high level of neutralizing antibodies.
		Other immunomodulatory agents, e.g. tocilizumab, or other similar candidate treatments		It was concluded that it is currently not a priority for inclusion into the RCT.

Prioritization of Treatment Study Designs

There was consensus on the need for randomization to evaluate the safety and efficacy of these investigation therapeutics with minimal bias.

Experience from previous trials such as PALM and PREVAIL was considered. Table 2 summarizes the different study designs discussed during the meetings among a group of trialists and Ugandan researchers.

As of October 31, 2022, some treatments are provided in Uganda under MEURI protocol or compassionate use. Experts agreed that study designs 1-3 were credible and would provide evidence of efficacy, while design 4 should be excluded.

Ugandan clinicians and other experts determined that study design 3 was the most feasible given the local context, while still maintaining the benefits of randomization. The proposed study design includes secondary randomization to dexamethasone for all participants.

Table 2. Summary of Proposed Trial Design Options

Option	Trial Design Option	Strengths	Limitations
1	Standard of care (SOC) + Monoclonal versus SOC + Antiviral versus SOC + Monoclonal + Antiviral versus SOC alone (Full Factorial) design Secondary randomization corticosteroids	Including a SOC arm will permit the most valid and interpretable estimation of potential treatments effect. This design is efficient and could provide the results relatively quickly.	As the candidate therapeutics are already in use, the SOC arm was considered less acceptable for a disease with very high baseline mortality.
2	SOC + Monoclonal versus SOC + Monoclonal + Antiviral versus SOC alone Secondary randomization corticosteroids	Including a SOC arm will permit the most valid and interpretable estimation of potential treatments effect. This design will provide understanding on the impact of the monoclonal and the synergistic impact of the combination therapy.	As the candidate therapeutics are already in use, the SOC arm was considered less acceptable for a disease with very high baseline mortality. The design does not provide direct information on the effect of the antiviral alone.
3	SOC + Monoclonal versus SOC + Antiviral versus SOC + Monoclonal + Antiviral Secondary randomization corticosteroids	If an SOC alone arm cannot be implemented, this design can provide evidence on any differential effect of monoclonal antibodies vs antiviral, and on any efficacy of the two combined.	If the synergistic effect of a monoclonal plus an antiviral is low, the sample size could increase.
4	SOC + Monoclonal versus SOC + Monoclonal + Antiviral Secondary randomization corticosteroids	Reduction in the number of treatment arms and a potential reduction in sample size.	All agreed this option should be excluded as it would provide limited direct information about both the monoclonal and antiviral in comparison to testing each in isolation and in combination.

Deliberations on the proposed clinical trial protocol

On November 4, 2022 a draft protocol developed with support from the University of Oxford was discussed[7]. This protocol summarized a three-arm, open-label, randomized trial to simultaneously evaluate virus-directed therapies (Remdesivir vs MBP134 vs Both) and host-directed therapies (low-dose corticosteroids vs no additional treatment) as a second randomization, for treatment of Sudan ebolavirus disease using an adaptive trial design. A number of design attributes were discussed. In brief, the deliberations included the following topics:

Outcomes: There was consensus that the primary outcome should be 28-day mortality, with discussion on the secondary outcomes such as time-to-viral-clearance, and other outcomes including viral load (for example on days 3, 5, 7, and 10, incorporating viral load data that is available post-randomization). Safety will also be assessed.

Eligibility: Experts agreed that individuals should be RT-PCR positive to be included in the trial; efforts to increase turnaround of laboratory results so to not delay entry into the study are warranted. Pregnant and breastfeeding women and children are included given their high-risk. Neonates within 7 days of age, born to SUDV positive mothers, should also be considered for inclusion given the exceptionally high rate of neonatal positivity and high mortality.

Randomisation: Experts discussed if secondary randomization for low-dose corticosteroids should be among all patients, generally agreeing that the question was appropriate based on current knowledge of Ebola disease pathophysiology.

Sample Size and Statistical Analysis: Experts agreed on the required sample size and outlined statistical analysis given limited information known about case fatality rates for each therapeutic. The planned comparisons could answer questions on efficacy and could fulfil the needs of regulatory bodies if results are interpretable. Nonetheless, there was consensus that a RCT remains the best option to generate informative results despite the absence of a SOC arm.

Flexibility: The group agreed that the protocol must be flexible and adaptive in order to accommodate multiple outbreaks, including the potential for Zaire ebolavirus outbreaks.

Agreed Next Steps

- WHO will continue to convene meetings with the expert group for remaining questions on the protocol and as new therapeutics become available.
- WHO will meet with Ugandan researchers to review the protocol and outstanding questions.
- WHO will hold separate meetings to discuss the needed for post-exposure prophylaxis options.

[7] TO BE ADDED WHEN PUBLICALLY AVAILABLE

Appendix I: List of Participants

Invited Experts	Institution
Andrew Owen	Liverpool University, UK
Anton Camacho	Epicentre, France
Armand Sprecher	MSF, Belgium
Bruce Kirenga	Univ Makerere, Uganda
Charles Olaro	Ministry of Health, Uganda
Derek Eisnor	BARDA, US Government
Aanyu Hellen	Chair clinical care sub-pillar, Uganda
Paska Apiyo	Uganda
Kyobe	MOH Uganda
Elizabeth Higgs	NIAID, US
Emmie de Wit	NIAID, US
Gail Potter	NIAID, US
Gavin Screaton	Oxford Medical Sciences, UK
Ira Longini	University of Florida, US
John Dye	USAMRIID, US
Julia Tree	UKHSA, UK
Karen Martins	BARDA, US
Lori Dodd	NIH, US
Marco Cavaleri (Chair)	EMA, EU
Martin Landray	University of Oxford, UK
Matthew Coldiron	Epicentre, France
Mohammed Lamorde	Makerere University College of Health Sciences, Uganda
Peter Horby	University of Oxford, UK
Richard Peto	Consultant, UK
Rick Davey	NIAID, US
Rob Fowler	University of Toronto, Canada
Saschveen Singh	MSF, France
Stephan Gunter	University of Hamburg, Germany
Tom Fleming	University of Washington, US
Tom Geisbert	UTMB, US
William Fisher	UNC, US

Invited Developer	Developer Organization
Petra Wuelfroth	F4 Pharma
Jake Reder	Celdara Medical
Tomas Cihlar	Gilead
Danielle Porter	Gilead
Rachel Bright	Gilead
Rob Hyland	Gilead
Anu Osinusi	Gilead
Larry Zeitlin	Mappbio
Chia-wei Tasi	Mappbio
Mapp - Tara Nyhuis	Mappbio
Carisa Stadlman De Anda	Merck
Sanjeev Ahuja	Partner Therapeutics

John McManus	Partner Therapeutics
Christos Kyratsous	Regeneron
Paula Dakin	Regeneron
Alina Baum	Regeneron
Isabel Lauren	True North BioPharm

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