A Multicenter, Multi-Outbreak, Randomized, Controlled Safety and Efficacy Study of Investigational Therapeutics for the Treatment of Patients with Ebola Virus Disease

Short Title: 2018 Ebola MCM RCT Protocol

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KEY ROLES

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
BDBV	species *Bundibugyo Ebolavirus*
CBC	complete blood count
CFR	Code of Federal Regulations
CNS	central nervous system
CRF	case report form
DAIDS	Division of AIDS
DCR	Division of Clinical Research
DRC	Democratic Republic of Congo
EBOV	species *Zaire Ebolavirus*
EHF	Ebola hemorrhagic fever
ETU	Ebola treatment unit
EVD	Ebola virus disease
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GP	Glycoprotein
HCW	health care worker
ICH	*International Council for Harmonisation*
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IND	Investigational New Drug Application
INRB	Institut National de Recherche Biomédicale
IRB/EC	Institutional Review Board/Ethics Committee
IV	Intravenous
kg	Kilogram
MAb	monoclonal antibody
MEURI	Monitored Emergency Use of Unregistered and Investigational Interventions
MoH	Ministry of Health
mg	Milligram
mL	Milliliter
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NHP	non-human primate
oSOC	optimized standard of care
PK	Pharmacokinetic
REGN-EB3	Regeneron's triple monoclonal cocktail REGN3470-3471-3479
RESTV	species *Reston Ebolavirus*
RCT	randomized controlled trial
RNA	ribonucleic acid
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event

Abbreviation	Term
SOC	standard of care
SUDV	species *Sudan Ebolavirus*
SUSAR	serious and unexpected suspected adverse reaction
TAFV	species *Taï Forest Ebolavirus*
UP	unanticipated problem
UPnonAE	unanticipated problem that is not an adverse event
WBC	white blood cell
WHO	World Health Organization

PROTOCOL SUMMARY

Full Title:	A Multicenter, Multi-Outbreak, Randomized, Controlled Safety and Efficacy Study of Investigational Therapeutics for the Treatment of Patients with Ebola Virus Disease
Short Title:	2018 Ebola MCM RCT Protocol
Clinical Phase:	2/3
IND Sponsor:	OCRPRO
Conducted by:	Multicenter Trial Consortium
Principal Investigators:	By participating countries
Sample Size:	N=725 for the Randomized Controlled Trial. Extension Phase will add up to 1500 patients.
Accrual Ceiling:	750, in order to enroll 725 to study treatment for the Randomized Controlled Trial. Extension Phase will accrue up to an additional 1500 patients.
Study Population:	Patients with known acute Ebola virus infection having symptoms of any duration
Accrual Period:	November 2018 – November 2023
Study Design:	Randomized controlled clinical trial. While awaiting data analysis an Extension Phase will offer study treatment for new patients.
Study Duration:	Start Date: November 2018 End Date: November 2023 (i.e., nominally up to 5 years, but could be shortened or lengthened depending upon the pace of subsequent outbreaks in order to reach desired sample size)
Primary Objective:	• To compare the mortality at 28 days in patients with Ebola virus disease who receive different investigational therapeutics relative to the control arm.
Secondary Objectives:	• To assess whether the mortality rates in the monoclonal arms support analysis of an antibody-class effect versus a direct-acting antiviral product. • If pooling the monoclonal arms is justified based upon the analysis of heterogeneity outlined above, then compare the safety, tolerability, and efficacy of antibody-based products as a class with a direct-acting antiviral product in the treatment of Ebola.

- To evaluate the safety and tolerability of investigational therapeutics.
- To compare the change in viral load between study arms.
- To compare mortality rates among patients whose baseline predictors of disease place them in high-risk versus low-risk categories for disease severity.
- To compare mortality rates of investigational arms up to 58 days after randomization.
- When possible, to evaluate the presence of Ebola viral RNA in the semen of male survivors at ETU discharge or Day 28 (whichever comes first) and Day 58.
- To assess the relationship between change in viral load over time with survival.
- To compare time to successful discharge from the ETU between participants receiving investigational therapeutics.
- To compare time to death of participants receiving investigational therapeutics
- To collect data on the oSOC available in each participating ETU and, when possible, on the oSOC provided to each participant.

Exploratory Objectives:

- To assess comparative ease of both preparation and administration of study agents.
- Pharmacokinetic assessments of investigational agents, when possible.
- Assessment of viral resistance over time, when possible.

Primary Endpoint:

- 28-day mortality.

Inclusion Criteria:

- Males or females of any age with documented positive RT-PCR in blood for acute Ebola virus infection within 3 days prior to enrollment and who have symptoms of any duration (see special provision for neonates).
- Willingness of study participant to accept randomization to any assigned treatment arm.
- All males and females of childbearing potential must be willing to use effective methods of contraception, from time of enrollment until Day 58 of study.
- Must agree not to enroll in another study of an investigational agent prior to completion of Day 28 of study.
- Ability to provide informed consent personally, or by a legally acceptable representative if the patient is unable to do so.

Exclusion Criteria:	• Patients who, in the judgment of the investigator, will be unlikely or unable to comply with the requirements of this protocol through Day 28. • Prior treatment with any investigational antiviral drug therapy against Ebola virus infection within 5 half-lives or 30 days, whichever is longer, prior to enrollment. (Patients who have received an experimental (or, in future, potentially a licensed) immunization against Ebola virus remain eligible).
Study Design	• A randomized controlled trial with interim monitoring to introduce new arms and allow early stopping for futility, efficacy, or safety. Comparisons of safety and efficacy will be based on data from concurrently randomized participants. • It is assumed that this study will continue across more than one outbreak and in several countries. To allow for country specific preferences about what constitutes an ethical and scientifically-acceptable control arm, there are two design options at present and as described below. In the event that both options enroll participants, analyses will be stratified by option for the common arms. o Option 1: Drug A as the control arm (4 arms, Drug A+oSOC vs Drug B+oSOC vs Drug C+oSOC vs Drug D+oSOC) o Option 2: oSOC as the control arm (5 arms, oSOC vs Drug A+oSOC vs Drug B+oSOC vs Drug C+oSOC vs Drug D+oSOC) This study will initially enroll participants in the Democratic Republic of Congo (DRC), which has chosen Option 1; therefore, the initial plan will randomize (1:1:1:1) enrolled participants to ZMapp™, remdesivir, MAb114, or REGN-EB3 each given with a backbone of oSOC. It is noted that a decision to explore Option 2 in a future outbreak would require a major revision to the current study design and analysis plan that are not described within the current protocol. It is also noted that accrual of data in DRC as well as the availability of other investigational therapeutics may change the number and nature of arms. • Randomization will be stratified by: RT-PCR cycle threshold (≤22.0 vs >22.0), ETU site, and outbreak.

- An independent data and safety monitoring board (DSMB) will actively monitor interim data to make recommendations about early study closure or changes to study arms. At the end of the outbreak, or if a predefined sample size is reached earlier, analyses will be presented to the DSMB. The DSMB will then recommend whether the results should be released or kept blinded until a stopping boundary is crossed or the study has fully enrolled.

- Outbreaks with filovirus species other than *Zaire ebolavirus* will require reconsideration of design and study arms with agents that have known activity for that species. The monoclonal therapies currently targeted for study are specifically designed for *Zaire ebolavirus* variants.

Study agents:

Four arms for the DRC outbreak (all arms also receive oSOC):

- ZMapp™, three doses of 50 mg/kg of body weight administered intravenously every third day beginning on Day 1.
- Remdesivir, administered intravenously with a loading dose on Day 1 (200 mg for adults and pediatric patients with body weight ≥ 40 kg and for pediatric patients weighing < 40 kg one loading dose of remdesivir 5 mg/kg) followed by 9 to 13 days of once-daily maintenance dosing starting on Day 2 and extending through Day 10 to 14 (100 mg for adults and pediatric patients with body weight ≥ 40 kg and for pediatric patients weighing < 40 kg remdesivir 2.5 mg/kg). The recommended remdesivir dosing duration is a total of 10 days, but dosing may be continued at the daily maintenance dosing levels described above for an additional 4 days if Ebola viral load remains detectable in blood at Day 10 of treatment.
- MAb114, at 50 mg/kg of body weight administered intravenously on Day 1 as a single infusion.
- REGN-EB3 at 150 mg/kg of body weight administered intravenously on Day 1 as a single infusion.

Study Synopsis:

- Informed consent for research participation upon admission into the treatment center.
- Baseline determination of clinical status according to a standardized case report form (CRF).
- Baseline collection of blood for quantitative Ebola viral load by RT-PCR to be processed by an appropriate laboratory facility.
- Centralized randomization assignment made.
- Provision of assigned study intervention, ideally immediately following randomization whenever possible, according to

assigned treatment arm and the individual pharmacologic or logistical requirements of the treatment intervention.

- 24- to 48-hour pharmacokinetic measurements of assigned intervention where appropriate and logistically feasible.
- Daily assessments of clinical status (including oSOC provided within the capabilities of the site facility) according to standardized CRFs and the study flow sheet.
- Serial collection of blood for quantitative viral load determination by RT-PCR for processing in an appropriate laboratory facility, as possible.
- Longer-term follow-up up to Day 58, when feasible, for any late onset clinical history, seminal viral persistence, or symptoms possibly consistent with delayed virologic relapse or drug toxicity.

PRÉCIS

Species *Zaire ebolaviruses* (EBOV) are members of the Filoviridae and are known primarily as the underlying cause of severe viral hemorrhagic fevers with disturbingly high case fatality rates. Between 1994 and the present, there have been many filovirus outbreaks affecting mostly central Africa, with 2 large outbreaks in 1995 in Kikwit, Democratic Republic of Congo (DRC), and in Gulu, Uganda in 2000-2001. The 2013-2016 West African outbreak significantly exceeded all previous outbreaks in geographic range, number of patients affected, and in disruption of typical activities of civil society. In 2018 there have been two additional outbreaks of EBOV infection, both in the Democratic Republic of the Congo and constituting the 9th and 10th recorded outbreaks of this infection in that country. The 10th outbreak is currently ongoing in the DRC as of December 2018 and has raised great concern because of the potential to expand greatly in scope and to spread to surrounding regions.

It has been suggested that one of the most important elements necessary to improve survival from Ebola virus infection is the provision of supportive care inclusive of hemodynamic support in the form of aggressive fluid replacement, ability to diagnose and correct severe metabolic derangements, early treatment of sepsis, and other standards of modern medical care. A small number of investigational therapeutics have been developed as putative antiviral strategies for treating this infection. Unfortunately, phase 1/2 data supporting the safety and efficacy of these agents are often limited, and thus there remains some degree of equipoise as to which of these interventions should be prioritized in the treatment of severe infection. The triple monoclonal antibody product ZMapp was studied through a randomized controlled trial (RCT) in the 2014-2016 West African outbreak and remains perhaps the best characterized of the available investigational products, but the end of that outbreak forced the RCT to close prior to crossing pre-specified evidentiary boundaries.

A WHO Research and Development Ebola Therapeutics Committee has agreed that, given the lethality of Ebola virus and the combination of human and non-human primate (NHP) efficacy data for ZMapp, either ZMapp+oSOC or oSOC alone could potentially be positioned as the control arm in comparative trials depending upon the preferences of the host countries. The DRC has chosen to use ZMapp + oSOC in the current protocol. However, both the nature and number of control and investigational arms may change over the course of the trial. Such changes would require protocol amendments.

This multicenter, multi-outbreak, randomized controlled trial will study the comparative safety and efficacy of additional investigational therapeutics compared to ZMapp in patients with known EBOV disease (Zaire) receiving oSOC. The primary endpoint of this comparison will be mortality by Day 28, with a number of secondary and exploratory endpoints also planned that should generate important knowledge about the safety, ease of administration, and antiviral activity of all of these investigational interventions.

1 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Background

1.1.1 Filoviruses

Ebolavirus is a large, negative-strand ribonucleic acid (RNA) virus composed of 7 genes encoding viral proteins, including a single glycoprotein (GP) (1-3). Ebolavirus is one of three genera in the Filoviridae family, which along with Marburgvirus, is known to induce viral hemorrhagic fever. Five distinct species, of which 4 have been implicated as etiologic agents of human Ebolavirus disease (EVD), formerly known as Ebola hemorrhagic fever (EHF), exist: Bundibugyo virus (BDBV), Reston virus (RESTV), Sudan virus (SUDV), Taï Forest virus (TAFV), and Zaire virus (EBOV) (4). The BDBV, EBOV, and SUDV species have been associated with large EVD outbreaks in Africa, with reported case fatality rates of up to 90% (5). Between 1994 and the present, there have been many filovirus outbreaks (Table 1) affecting mostly central Africa, with 2 large outbreaks in 1995 in Kikwit, DRC, and in Gulu, Uganda in 2000-2001. The 2013-2016 West African outbreak (approximately 28,000 cases and over 11,000 deaths) significantly exceeded all previous outbreaks in geographic range, number of patients affected, and in disruption of typical activities of civil society. EVD cases in persons who traveled from endemic areas were also reported in Italy, Spain, United States (US), and United Kingdom (UK) (6). While the World Health Organization (WHO) declared an end to the EVD public health emergency in March 2016, the risk that small outbreaks will continue to occur remains omnipresent (6). Given the frequency of international travel, EVD also remains a global threat to public health.

1.1.2 Transmission and Disease

Transmission of Ebolavirus to humans is not yet fully understood, but is likely due to incidental exposure to infected animals (7-9); through direct contact with blood, secretions, organs, or other bodily fluids of infected people (alive or dead); and through indirect contact with environments contaminated by such fluids (5). It is thought that people are infectious for as long as their blood and secretions contain the virus. Men who have recovered from the disease can potentially still transmit the virus through semen for an extended period of time after recovery from illness (5, 10, 11).

EVD has an incubation period of 2 to 21 days (7 days on average, depending on the species) followed by a rapid onset of non-specific symptoms such as fever, extreme fatigue, gastrointestinal complaints, abdominal pain, anorexia, headache, myalgias, and/or arthralgias. These initial symptoms, which last for about 2 to 7 days, are followed by more severe symptoms related to disease progression (e.g., hemorrhagic rash, epistaxis, hematuria, hemoptysis, hematemesis, melena, conjunctival hemorrhage, tachypnea, confusion, somnolence, and, in some cases, both internal and external bleeding) and are accompanied with low white blood cell (WBC) and platelet counts and elevated liver enzymes (5). These symptoms generally last for about 7 to 14 days. Death can occur at a variable time after the onset of symptoms, manifested by vomiting and diarrhea resulting in dehydration, shock, and then multi-organ failure (7, 12).

Immunoglobulin M (IgM) antibodies to the virus appear 2 to 9 days after infection followed by immunoglobulin G (IgG) antibodies at approximately 17 to 25 days after infection; the latter

coinciding with the recovery phase (13). In survivors of EVD, both humoral and cellular immunity are detected; however, their relative contribution to protection is unknown (13, 14).

1.1.3 Latest Outbreaks

On May 3, 2018, the Provincial Health Division of Equateur Province in the DRC alerted its Ministry of Health and Population (MoHP) of cases and community deaths clinically compatible with viral hemorrhagic fever (VHF) in the western region of that country. On May 8, 2018, an EVD outbreak (the 9th recorded outbreak in the DRC) was declared by the DRC MoHP. The epidemic spread geographically, including confirmation of cases reported in Mbandaka, the capital of Equateur province and a large urban area and center of trade. Overall, a total of 55 cases of EBOV disease were reported in the region, including 38 confirmed, 15 probable, and 2 suspected. The last confirmed case occurred on June 6, 2018, and 24 patients were reported to have been cured of their infections over the course of the epidemic. Through a series of coordinated public health interventions overseen by the MoHP (including the use of contact tracing, isolation, and safe burial practices), education, and possibly the use of Merck's experimental rVSV-Ebola vaccine according to a ring vaccination strategy, the outbreak was declared officially ended as of July 24, 2018.

Unfortunately, shortly after the outbreak in the western region of the DRC was declared over, on August 1, 2018, the Ministry of Health declared an outbreak of EVD following the confirmation of four cases of Ebola in the Mabalako health zone of the territory of Beni, North Kivu province, Eastern DRC. This is the first-time an Ebola outbreak was reported in this part of the country and constitutes the 10th known outbreak in DRC. As of August 3, 2018, a total of 49 cases had been reported across 7 health zones in two provinces, i.e., five health zones (Beni, Butembo, Oicha, Musienene and Mabalako) in North Kivu province and two health zones (Mandima and Mambasa) in Ituri province. As of 28 July 2019 – almost one year after the initial reports of the outbreak - a total of 2671 EVD cases, including 2577 confirmed and 94 probable cases, have been reported. A total of 1790 deaths have been reported (overall case fatality ratio 67%), including 1696 deaths among confirmed cases.

Adding to the difficulty of controlling the outbreak is the fact that the affected territories have been beset by ongoing armed conflicts and, as a result, formidable security challenges exist in protecting deployed staff, providing investigational vaccine to at-risk populations, and ensuring safe delivery of medical treatment to those infected.

Table 1: Ebola Virus Outbreaks

Viral species	Year	Outbreak location	# of human cases (% fatality)
Zaire Ebolavirus	1976	Yambuku, Zaire (DRC)	318 (88%)
	1977	Tandala, Zaire (DRC)	1 (100%)
	1994	Ogooue-Ivindo province, Gabon	52 (60%)
	1995	Kikwit, DRC	315 (79%)
	1996	Mayibout 2, Gabon	37 (57%)
	1996	Booué, Gabon and Johannesburg, South Africa	62 (74%)
	2001-02	Mbomo-Kéllé, Republic of Congo	59 (73%)

	2001-02	La Zadie, Ivindo, and Mpassa districts, Gabon	65 (81%)
	2002-03	Cuvette region, Republic of Congo	143 (89%)
	2003	Mbomo and Mbandza, Republic of Congo	35 (83%)
	2005	Etoumbi and Mbomo, Republic of Congo	12 (75%)
	2007	Mweka, Kasai Occidental province, DRC	264 (71%)
	2008-09	Mweka, Kasai Occidental province, DRC	32 (47%)
	2013-16	West Africa (primarily Liberia, Sierra Leone, and Guinea)	>28,000 (c. 40%)
	2014	Boende, Western DRC	69 (71%)
	2017	Likati, Bas Uélé province, Northern DRC	8 (50%)
	2018	Bikoro, Western DRC	54 (61%)
	2018	Beni-Mangina, Eastern DRC	Ongoing as of 9/2018
Sudan Ebolavirus	1976	Nzara, Maridi, Tembura, and Juba, Sudan	284 (53%)
	1979	Nzara, Yambio, Sudan	34 (65%)
	2000-01	Gulu, Masindi, Uganda	425 (53%)
	2004	Yambio, Sudan	17 (41%)
	2011	Luwero District, Uganda	1 (100%)
Taï Forest Ebolavirus	1994	Taï Forest, Ivory Coast	1 (0%)
	1995	Liberia or Ivory Coast	1 (0%)
Reston Ebolavirus	1989	Philippines and VA and PA, USA	3 asymptomatic (0%)
	1990	Reston, VA, USA	4 asymptomatic (0%)
	1992	Siena, Italy	0
	1996	Philippines and Alice, TX, USA	0
	2008	Philippines	6 asymptomatic (0%)
Bundibugyo Ebolavirus	2007-08	Bundibugyo District, Uganda	131 (32%)
	2012	Isiro, Haut-Uélé province, DRC	36 (36%)

Adapted from: Ebola: Years of Ebola Virus Disease Outbreaks, 40 Years of Ebola Virus Disease around the World. Centers for Disease Control and Prevention website. https://www.cdc.gov/vhf/ebola/history/chronology.html. Updated August 31, 2018. Accessed September 10, 2018.

1.1.4 **Therapy**

Prior to the West African outbreak in 2013-2016, the standard treatment of EVD had been largely supportive, involving oral or intravenous fluid and electrolyte replenishment and pain reduction where possible. Due to the remote location of the outbreaks and the limited medical and logistical resources available in most of the affected regions, more aggressive treatment options usually had neither been available nor tested in most patients. However, some experimental interventions were explored in prior outbreaks. For example, during the Kikwit outbreak in 1995, 8 patients with EVD were treated with convalescent plasma harvested from EVD survivors; of those 8, 7 patients recovered from their acute illness (15). Overall, in certain centers where advanced treatment measures were able to be employed, a substantial reduction in mortality has sometimes been reported (16).

Wherever possible, the standard treatment for EVD continues to focus on management of symptoms that includes supportive oral or IV fluids, electrolyte replacement, maintaining oxygen status and blood pressure, and pain reduction. Efforts continue to identify, standardize, and deploy the most successful standard-of-care (SOC) measures that potentially could be introduced into previously resource-poor areas. As one example, WHO published *Clinical Management of patients with Viral Haemorrhagic Fever; A pocket guide for front-line health workers (February 2016)*, which provides guidance for standard treatment of viral hemorrhagic diseases (16).

Evidence-based guidelines provide support for improved or "optimized" SOC measures (oSOC) to reduce the high mortality rates associated with the disease in the affected regions.

In contrast, in the US and other developed nations to which a small number of infected HCWs had been medically evacuated during past outbreaks, aggressive IV fluid resuscitation, hemodynamic monitoring and support, point-of-care (POC) diagnostic modalities, and other aspects of critical care medicine have already been employed in the attempt to save these critically ill individuals. Against this background of oSOC has been the introduction of several different investigational therapeutics as adjunctive therapy, ranging from the administration of convalescent plasma from recovered patients to the use of direct antiviral agents provided under emergency IND as medical countermeasures (MCMs). As of 2015, investigational treatment data were available on a total of 27 HCWs or other individuals with documented Ebola infection who had been referred to special isolation units in the US or Europe after becoming infected while providing care in West Africa (17). The reported investigational agents used in these individuals were as follows:

- ZMapp or MIL77
- ZMab
- TKM-Ebola
- Favipiravir
- Brincidofovir
- FX06
- Convalescent plasma
- Convalescent whole blood
- Amiodarone
- Melanocortine

Conclusions about possible benefits or toxicities from these treatments were limited because they were not administered in the context of a study. Furthermore, in many cases these patients received multiple different MCMs either together or over a short period of time, making differentiation of either a beneficial treatment effect or toxicity attributable to any single one of these agents almost impossible to discern. In addition, 6 medically evacuated HCWs were brought back to the United States following a serious percutaneous exposure to Ebola virus while in West Africa, but without documented infection at the time of transfer, and each received 1 putative MCM each: Tekmira siRNA in one case and the investigational VSVΔG-ZEBOV vaccine in the remaining five (18). It should be emphasized that in almost all of these cases adequate phase 1 data to support the safety of the product in humans and/or data to support the safety and efficacy of the product in those with documented Ebola infection were either incomplete or lacking altogether. Also, while the use of these particular agents was facilitated in most cases by supportive preclinical data, it should be noted that several experimental treatment strategies were previously shown to be successful in *in vitro* or rodent models, but either failed testing or were not thoroughly tested in the NHP model, which is still considered the most accurate in modeling human disease.

In regard to immune-based approaches to therapy, convalescent serum harvested from recovered patients has been one of the most widely used MCMs to date in the West African outbreak and, as noted above, was also used in a limited number of patients during the Kikwit 1995 ZEBOV

outbreak. However, its earlier success remains a matter of dispute. Experimentally, passive immunization with horse serum resulted in protection of Hamadryl baboons (19), whereas it only delayed death in Cynomolgus macaques (20, 21). Certain monoclonal antibody treatments have also been successful in rodent models (22, 23) but have failed in preliminary NHP studies (24), indicating possible evasion of antibody neutralization as an escape mechanism of the virus. It is hoped that more recent monoclonal antibody products or cocktails may avoid this limitation. However, it remains fair to say, at least at this time, that a proven therapeutic role of convalescent plasma or monoclonal preparations as treatment adjuncts remains as yet unsubstantiated in this disease, as does the efficacy of direct antiviral agents that also appear promising in NHP studies.

1.1.5 RCT of ZMapp (PREVAIL II)

As an example of this uncertainty, beginning in March 2015 in West Africa, the Ministries of Health in Liberia, Guinea, and Sierra Leone collaborated with one another, the NIAID, and INSERM on a randomized, controlled trial of the triple monoclonal antibody product ZMapp (Mapp Biopharmaceuticals) plus SOC versus SOC alone in patients with EVD diagnosed by RT-PCR assay (25). In this study, named PREVAIL II, eligible patients of any age were randomly assigned in a 1:1 ratio to receive either the current oSOC or the current oSOC plus three IV infusions of ZMapp (50 mg per kilogram of body weight, administered every third day). Patients were stratified according to their baseline RT-PCR cycle-threshold (CT) values for the virus (≤22 vs. >22) and by country of enrollment. Oral favipiravir was part of the current SOC in Guinea. The primary endpoint was mortality at 28 days. Due to curtailing of the outbreak in that region, a total of only 72 patients could be enrolled at sites in Liberia, Sierra Leone, Guinea, and the US out of a desired accrual of 100 patients per arm. Of the 71 patients who could be evaluated, 21 died, representing an overall case fatality rate of 30%. Death occurred in 13 of 35 patients (37%) who received the current oSOC alone and in 8 of 36 patients (22%) who received the current SOC plus ZMapp. The observed posterior probability that ZMapp plus the current SOC was superior to the current oSOC alone was 91.2%, falling short of the prespecified threshold of 97.5%. Frequentist analyses yielded similar results (absolute difference in mortality with ZMapp, −15 percentage points; 95% confidence interval, −36 to 7). It was noted that baseline viral load was strongly predictive of both mortality and duration of hospitalization in all age groups. The authors concluded that although the estimated effect of ZMapp appeared to be beneficial, the result did not meet the prespecified statistical threshold for efficacy.

1.2 Rationale for Study

The current state of medical science with respect to the treatment of filovirus infections such as Ebola virus disease does not adequately address the role of therapeutic adjuncts beyond supportive care in the successful management of these infections. In some cases, our understanding of the role that these adjunctive therapies may play is greatly hampered by either incompleteness or lack of an adequate phase 1 safety and toxicity database of the lead drug candidates, or by lack of data concerning how the candidates in more advanced development may perform in this patient population. The tragic dimensions of the recent Ebola virus epidemic in West Africa afforded little time to explore these issues according to a more conventional time frame of traditional drug development, and argued strongly for an accelerated exploration of safety, toxicity, and potential efficacy of lead agents in a controlled research setting. Unfortunately, the recent advent of two more outbreaks in the DRC in 2018 has added further

impetus to identify safe and effective drug treatments as quickly as possible so that case fatality rates associated with EVD can be reduced.

Intrinsic to this rationale for expedited drug discovery in the current Ebola crisis are the following principles, which are by no means intended to be all-inclusive:

- A multicenter, multinational randomized controlled study of lead therapeutic candidates is the best strategy for acquiring rigorous data about the safety and efficacy of investigational Ebola virus therapeutics. Single-use emergency IND, Emergency Use Authorization (EUA), Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI), or similar mechanisms will not lead to generalizable evidence.

- Randomization is essential to establishing efficacy results. EVD mortality rates vary considerably according to multiple factors, only some of which are known (e.g., CT, age, ETUs). Randomization is needed to balance these risk factors across treatment arms, and thereby reduce potential confounding of treatment outcomes with other factors not directly related to treatments received.

- Collecting clinical and virologic data on enrolled patients according to standardized timelines and with a standardized collection instrument should provide valuable information about the clinical course, morbidities, and outcomes in these patients.

- oSOC treatment options of fluid resuscitation, electrolyte monitoring and replacement, and other conventional approaches are a mainstay of therapy and must be the backbone to which experimental treatment modalities are added and compared.

- Differences in oSOC may occur due to varying site resources and can obscure the potential additional contribution of experimental therapeutics. Therefore, every effort must be made to standardize the oSOC, both within and across treatment centers.

- The number of EVD cases available for enrollment in this trial during the present outbreak is unpredictable and potentially limited. Therefore, requirements for traditional levels of evidence must be reconsidered. Standards within other areas of rare diseases may provide guidance in this regard (26-28).

- Limited, intermittent, or even absent drug supply may exist for some lead candidates proposed for study. Hence, a flexible, adaptive treatment design may be required.

- At present, knowledge of the potential toxicity of lead candidates in this patient population may be limited. However, this toxicity risk is considered acceptable in the face of high individual mortality and community risk for continued Ebola virus transmission.

- The use of a flexible platform design is recommended for the following reasons:

    - Efficiency: This design can accommodate the study of more than 1 investigational therapy using a shared control group.

- Availability of study products: Some investigational products may be in limited, intermittent supply. The study design enables continuation of the study even if one product is not available.

- A single trial allows a data and safety monitoring board (DSMB) to provide close oversight of safety and early efficacy signals.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To compare the mortality at 28 days in patients with Ebola virus disease who receive different investigational therapeutics relative to the control arm.

2.2 Secondary Objectives

- To assess whether the mortality rates in the monoclonal arms support analysis of an antibody-class effect versus a direct-acting antiviral product.
- If pooling the monoclonal arms is justified based upon the analysis of heterogeneity outlined above, then compare the safety, tolerability, and efficacy of antibody-based products as a class with a direct-acting antiviral product in the treatment of Ebola.
- To evaluate the safety and tolerability of investigational therapeutics.
- To compare the change in viral load between study arms.
- To compare mortality rates among patients whose baseline predictors of disease place them in high-risk versus low-risk categories for disease severity.
- To compare mortality rates of investigational arms up to 58 days after randomization.
- When possible, to evaluate the presence of Ebola viral RNA in the semen of male survivors at ETU discharge or Day 28 (whichever comes first) and Day 58.
- To assess the relationship between change in viral load over time with survival.
- To compare time to successful discharge from the ETU between participants receiving investigational therapeutics.
- To compare time to death of participants receiving investigational therapeutics
- To collect data on the oSOC available in each participating ETU and, when possible, on the oSOC provided to each participant.

2.3 Exploratory Objectives

- To assess comparative ease both of preparation and administration of the individual study agents.
- Pharmacokinetic assessments of investigational agents, when possible.
- Assessment of viral resistance over time, when possible.

3 STUDY DESIGN

3.1 General

Study size: Up to 725 randomized subjects.

Study duration: Nominally up to 5 years, but could be shortened or lengthened depending upon the pace of subsequent outbreaks and other contextual factors (i.e., intended to potentially span across several outbreaks in order to reach desired sample size).

Study duration of individual subjects: Initially for 30 days following the primary endpoint (mortality at Day 28), or for a total of 58 days.

[Under the auspices of a separate protocol yet to be developed, interested subjects may also be offered the opportunity, where and whenever feasible, to participate in longer-term follow-up (e.g., up to 1 year or more past Day 58 depending upon need) of their illness in order to determine whether they are at risk for late onset of any history or symptoms consistent with delayed virologic relapse potentially arising from immunologically-privileged sites (e.g., the central nervous system (CNS) or the male testes).]

Sex distribution: Males and females.

Age range: Unrestricted.

Design: A multi-center, multi-outbreak, randomized, open-label, controlled clinical trial of experimental Ebola virus disease therapies, each administered with a backbone of oSOC. Figure 1 provides a schema of the study. Interim monitoring is included to introduce new arms or allow early stopping for futility, efficacy, or safety. Guidelines for early stopping will be described in Table 5 in Section 6.5. This is a superiority design using a 28-day mortality endpoint. For the EBOV outbreak in the DRC, eligible patients will be randomized 1:1:1:1 to receive either ZMapp™ as the control arm, remdesivir, REGN-EB3, or MAb114. The rationale for the selection of these specific drugs as the lead candidates is described in Section 3.4 below. This design assumes sufficient quantities of each drug will be available to initiate the trial. It also assumes that a sufficient quantity of ZMapp exists to complete the study as planned since ZMapp serves as the comparator or control arm. Should a treatment shortage occur in one of the investigational drug arms being compared to ZMapp, enrollment will continue to the remaining arms. Should a treatment shortage occur in any arm, enrollment will continue to the remaining arms. Comparisons will be limited to data from concurrently enrolled patients. Randomization will be stratified by PCR cycle threshold ≤22.0 vs >22.0, ETU, and outbreak. The selection of a threshold value of 22.0 was based on prior analysis of the distribution of CT values from a large cohort of Ebola virus-infected individuals during the West African crisis (25).

The study will continue across outbreaks, unless a recommendation to modify or close the study is made by the DSMB. It may be amended per DSMB request to drop or replace poorly performing arms including a modification of the control arm. At the end of the outbreak and at predefined enrollment numbers, analyses will be presented to the DSMB to evaluate safety and efficacy of each arm. The DSMB will recommend to the Steering Committee if results should be released or kept blinded until a stopping boundary is crossed or the study has fully enrolled.

It is understood that outbreaks with filovirus species other than the Zaire Ebola virus will require reconsideration of study drugs that have known activity for the circulating species. The monoclonal therapies currently targeted for study are specifically designed for the *Zaire ebolavirus* species. Therefore, future outbreaks not due to *Zaire ebolavirus* or its susceptible variants will require a new study design. If that were to occur, this would result in a separate new

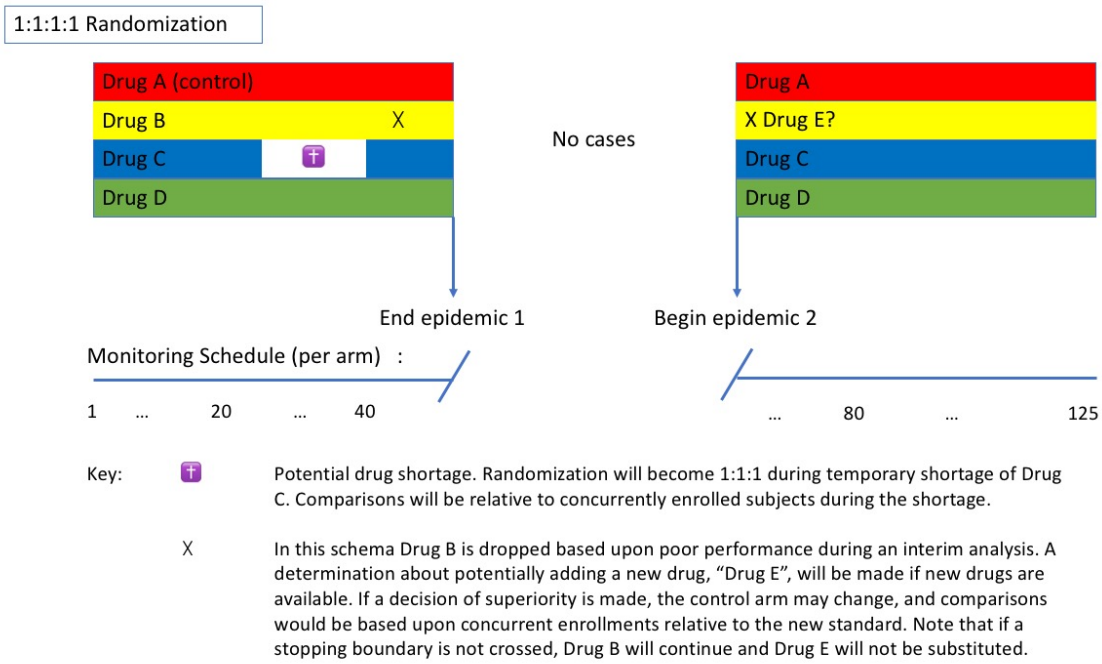
protocol with a new analysis plan and governance structure since the designs will not share the same drugs nor have a common control arm.

Study Arms: Four arms (all given with oSOC):

- ZMapp, three doses of 50 mg/kg of body weight administered intravenously every third day beginning on Day 1.
- Remdesivir, administered intravenously with a loading dose of 200 mg on Day 1 followed by 9 to 13 days (depending on Ebola viral load) of the 100-mg daily maintenance dose (see pediatric weight-based dosing adjustments).
- MAb114, at 50 mg/kg of body weight administered intravenously on Day 1 as a single infusion.
- REGN-EB3 at 150 mg/kg of body weight administered intravenously on Day 1 as a single infusion.

Extensive discussions with primary stakeholders in ETU management have clearly revealed that there is not necessarily consensus on what standards of care should be considered the minimal standards that all patients should receive, much less how the term "oSOC" treatment should be defined for the purposes of this study as a whole. Accordingly, attempts to legislate across all ETUs what a uniform definition of oSOC must include in order for a given site to qualify for study participation carries the risk of unfairly disenfranchising some sites, and therefore some patients, and therefore should be discouraged. As a general rule, however, an attempt to implement oSOC at study sites should include, but not necessarily be limited to, the provision of appropriate fluid resuscitation, hemodynamic and respiratory support, metabolic corrections, and treatment of concurrent infections (e.g. malaria), seizures, and other acute co-morbidities. In the field setting where ETU resources may be severely constrained, for example, a minimum oSOC should usually include regular physician assessments including collection of vital signs, provision of rehydration (by either oral or IV fluids as feasible), serial measurement and correction of electrolytes, provision of empiric antibiotics when appropriate, and empiric treatment for malaria until confirmatory testing is available. However, it is acknowledged that the physician team in charge of a given ETU has the ultimate latitude to adjust these provisions based upon both ongoing resource considerations and their clinical judgment as to the suitability of a given provision for a specific patient. A deviation from the general oSOC measures described above in this circumstance will not constitute a protocol violation nor make the site ineligible for ongoing participation in the trial.

Figure 1. Study Schema for Option 1.



Note: as stated above, this design assumes that a sufficient quantity of ZMapp will be provided to complete the study since that drug serves as the control arm. If there is insufficient supply of ZMapp for any reason, randomization to other arms will continue. Any instances of lack of supply for any reason will be reported and accounted for in the analyses.

3.1.1 Extension Phase

Refer to section 14.0 for PALM Extension Phase Plan.

3.2 Study Endpoints

Study endpoints will be evaluated by comparing randomized groups.

3.2.1 Primary Endpoint

- 28-day mortality.

3.2.2 Secondary Endpoints

- Incidence of serious adverse events (SAEs; see safety section for limitations on collection).
- Incidence of infusion-related adverse events (AEs).
- Frequency and characterization of clinically significant AEs related to study agent administration.
- Incidence of other AEs as revealed by laboratory monitoring (see safety section for limitations on collection).
- Mortality at Day 14 and Day 58.
- Viremia at Days 1, 2, 3, 4, 5, 6, 8, 10, 14, and 28.

- Ebola viral RNA in semen at ETU discharge or Day 28 (whichever comes first) and Day 58.
- Time to discharge from ETU.
- Time to death over 58 days.
- Time to first negative Ebola virus RT-PCR in blood.
- Time to two consecutive negative Ebola virus RT-PCRs in blood.
- oSOC provided to study participants at a site and, when possible, at an individual level
- Delayed onset (after 28 days) of any clinical symptoms possibly consistent with virologic relapse or drug toxicity within 58 days after enrollment.

3.2.3 Exploratory Endpoints

- Comparative ease both of preparation and administration of the individual study agents including supply and storage constraints.
- Pharmacokinetic assessments of investigational agents when possible.*
- Assessment of viral resistance over time, when possible.

* In general, pharmacokinetic measurements often involve processing (e.g., centrifugation) and testing of blood specimens with techniques or equipment not routinely available or safely performed in most point-of-care laboratory set-ups. These considerations, coupled with limitations on storage, transport, and analytical processing of infectious samples falling under Select Agent regulations, could limit these explorations outside the context of a high-containment laboratory such as a domestic BSL-4 laboratory or similar in-country facility.

3.3 Overview of Study Drugs

Because each of the investigational study agents is provided under IND and each sponsor may have proprietary information concerning the products that is not in the public domain, the detailed descriptions of study agents are provided separately as Appendices to the protocol. For now, these agents include: Appendix A (ZMapp™), Appendix B (remdesivir), Appendix C (MAb114), and Appendix D (REGN-EB3). Each of these appendices contains preclinical, NHP, and human data in support of the choice of these products, information about how they should be administered, and their known side effect profiles.

3.4 Considerations in Choice of Study Drugs

Several factors influencing the choice of study drugs/interventions to be compared in this protocol were considered:

- Willingness of both the pharmaceutical sponsors and the regulatory authorities to allow each of these drugs to be studied according to this proposed trial design.
- Dedicated supply of agents to be made available for the study over the projected timeline of the trial.
- Agreement on ongoing equipoise between study arms:
    - No available individual therapeutics candidate has yet been proven unequivocally to be superior to oSOC.
    - No therapeutics candidate has yet been demonstrated to be superior to another,
    - No compelling safety/toxicity concern has emerged with respect to individual therapeutics candidates to favor their removal from consideration as study interventions.
- Given the consensus view on the value of this RCT and that MEURI access to interventions during the trial could preclude, or circumvent, interest in enrollment of

patients into this RCT, the MEURI process will stop in participating sites where the trial is in progress, except for patients who cannot due to exceptional circumstances be enrolled in the study. Post-exposure prophylaxis activities will not be affected by the initiation of this RCT.

As summarized above, ZMapp, remdesivir, REGN-EB3 and MAb114 are the experimental therapeutics chosen for the implementation of the protocol during the second 2018 outbreak in the DRC. The decision to include these products in the study was based on several factors: 1) a desire to link to the data from the prior RCT of ZMapp during the 2014-16 outbreak to the current study; 2) the desire to study a direct acting agent with a different mechanism of action from monoclonal antibodies both to determine comparative efficacy as well as an important prelude to potential future combination drug trials; 3) the positive in vitro, NHP data, and early phase I safety data for MAb114 coupled with the strong desire of the host country to evaluate an agent for which they played a seminal role in development.

Initially the host country expressed a desire to restrict the study to no more than three arms (and limit the sample size to a total of 336 subjects) due to the complexity and feasibility of administering and accruing a study of this size. Accordingly, the initial version of the protocol that was designed, approved, and deployed was a three-arm design involving 1:1:1 randomization of patients to ZMapp, Mab114, or remdesivir. However, on October 11, 2018, in Geneva the WHO convened an Ad-Hoc Consultation on Clinical Trials for Ebola Therapeutics that involved subject matter experts on Ebola therapeutics and whose purpose was to review all available therapeutic options and ensure that all stakeholders were comfortable that the study design was optimal. On November 9, 2018, the summary document from that consultation was finalized. Among other recommendations was the primary recommendation to add a fourth investigational treatment arm (i.e. REGN-EB3) to the current RCT. The specific rationale given for doing so was summarized as follows:

"*There was discussion of the trade-offs for including a fourth arm in the current RCT. Adding a fourth arm would spread enrolment across four arms and would increase the time required to accrue a sufficient number of patients in the trial. The trial could address the conceptual question of monoclonal antibody-based therapy vs. small molecule drug treatment without adding a fourth arm. It was also mentioned that each of the investigational products is different, have different dosing regimens and for the purposes of product licensure would be based on the available data for each of the products; a point in support of adding a fourth arm. The RCT will likely run over multiple outbreaks, so including each of the four investigational products (Mab 114, Regeneron, Remdesivir and ZMapp) provides a chance for data to be gathered on each using the current trial (as opposed to a future trial that might start at some point after the current trial has been completed). Also mentioned were the relative differences in the resources required to administer each of the products in the field with some products having single dose regimens. As noted above, taking these trade-offs into consideration, overall the group's recommendation was to include the Regeneron product as a fourth arm in the current RCT."*

Based upon this recommendation, in late November, 2018, a revised Protocol Development Team was assembled and supported amending the initial three-arm design of the RCT to become a four-arm design involving the addition of REGN-EB3. Randomization will occur on a 1:1:1:1 basis to the four study arms in this amended design, and the study sample size will be increased to 500 patients (in protocol version 3.0).

Every attempt will be made to pre-position the investigational therapeutics under active study at the participating sites' local or regional pharmacies in advance of anticipated enrollments. Randomization of an individual patient to a given study drug will only occur when there is sufficient quantity of each drug to complete a full treatment course for that individual.

3.5 Definitions for the Purpose of this Study

Enrolled

For the purpose of collecting data and samples, and recording and grading of baseline SAEs/AEs, a subject will be considered enrolled beginning from when the informed consent form is signed and randomization to an assigned treatment has occurred, even if the subject expires before receipt of study drug, until the subject is considered either "discontinued" or "completed".

Discontinued

Subjects are considered discontinued when they meet the following criterion:

- Subject withdraws consent after being dosed and prior to the completion of Day 28 (see also Section 4.5).

Completed

Subjects are considered completed for the main study endpoint when they have died or are followed through Study Day 58 (i.e., 30 days past the primary endpoint measured at Day 28) and complete the final study follow-up visit or telephone contact scheduled for that time. If patients cannot be located or contacted (i.e., lost to follow-up) between the time of ETU discharge and study Day 58, their completion date will be considered the last known date of contact with them by study personnel. While no plans currently exist to do so, it is possible that a long-term follow-up protocol may be developed to enable that protocol's study personnel to collect additional information about the longer-term effects of EVD, the potential long-term effects of study drug administration, signs or symptoms possibly consistent with virologic relapse, and other relevant points of their clinical history for up to a year following ETU discharge. Patients will still be considered as having completed the current protocol if: 1) they decline this extended follow-up, or 2) they choose to discontinue extended follow-up prior to reaching 1-year past discharge.

4 STUDY POPULATION

4.1 Research Subject Recruitment

Persons with confirmed EBOV infection at participating health centers may participate in the trial as long as the site is willing to provide some measures of oSOC as described in Section 3.1 above. Although ultimately subject to discretion by the treating physician team at a given site, in most cases this care would include the ability to provide regular physician assessments, collection and recording of vital signs, and provision of "systematic care" including oral (by mouth or by nasogastric tube) and/or IV fluids as needed, measurement and correction of electrolytes, use of empiric antibiotics when appropriate, and treatment for malaria until confirmatory testing is available.

4.1.1 Participation of Site Employees

Site employees who meet eligibility criteria may participate in this study, with the following conditions:

- Neither participation nor refusal to participate in this protocol will have any effect on the subject's subsequent employment or work situation nor in their accessibility to post-exposure prophylaxis.

4.2 Inclusion Criteria

- Males or females of any age with documented positive RT-PCR for acute Ebola virus infection within 3 days prior to enrollment and who have symptoms of any duration (see special provision for neonates below).
- Willingness of study participant to accept randomization to any assigned treatment arm.
- All males and females of childbearing potential must be willing to use effective methods of contraception, from time of enrollment until Day 58 of study.
- Must agree not to enroll in another study of an investigational agent prior to completion of Day 28 of study.
- Ability to provide informed consent personally, or by a legally acceptable representative if the patient is unable to do so.

4.3 Exclusion Criteria

- Patients who, in the judgment of the investigator, will be unlikely or unable to comply with the requirements of this protocol through Day 28.
- Prior treatment with any investigational antiviral drug therapy against Ebola virus infection within 5 half-lives or 30 days, whichever is longer, prior to enrollment. (Patients who have received an experimental (or, in future, potentially a licensed) immunization against Ebola virus remain eligible.)

4.4 Vulnerable Populations

4.4.1 Pregnant Women

A full understanding of the potential risks from the study medications to human fetuses is lacking at this time. However, given the mortality associated with Ebola virus infection and the likelihood that there is a greater risk to the fetus from severe EVD than from the study medications themselves, pregnant women will be permitted entry into the study. However, there may still be certain antiviral medications (e.g., favipiravir) with known teratogenic potential that pregnant women should generally not receive, and these considerations must be reviewed on a case-by-case basis with study investigators.

The risks from the study medications to nursing infants are also unknown at this time. As women infected with Ebola will be quarantined in the ETU, breastfeeding will not be allowed.

For women who are pregnant, every attempt will be made to track the pregnancy outcome through delivery in order to determine the outcome of the study intervention on the fetus. In many cases this may not be possible due to the challenges associated with tracking patients' long term under difficult field conditions although every effort will be made to do so.

4.4.2 Inclusion of Children and Neonates

Similarly, the study medications have only been tested in limited fashion, or not at all, in children. Again, however, children of any age,will be eligible for enrollment given the likelihood that untreated Ebola infection may pose greater risk than exposure to the study medications. A neonate (defined as ≤ 7 days old) born to a mother who is RT-PCR positive for acute Ebola virus represents a special case. These neonates are presumed to be RT-PCR positive for acute Ebola virus at delivery, with untreated infection posing a greater risk than exposure to study medication. As such, neonates born to an infected mother who has not yet cleared the Ebola virus are eligible for enrollment even prior to RT-PCR confirmation (i.e. obtaining whose results could pose unnecessary delay). Neonates born to a mother who has cleared Ebola virus following a course of her assigned investigational medication may be enrolled prior to RT-PCR confirmation according to the discretion of the investigator regarding the likelihood that the neonate is infected (e.g., based on the interval between when the mother clears the virus and the baby is born). Regardless of when a neonate is enrolled, baseline blood for RT-PCR will be collected before study drug initiation.

4.4.3 Adults Who Are Unable to Provide Initial or Ongoing Consent

Adults who are unable to consent are eligible for enrollment in this protocol because of the high fatality rate with Ebola virus disease and the lack of other proven treatment options and the potential benefit provided by this study. Similarly, enrolled participants who lose the ability to provide ongoing consent during study participation may continue in the study. Capacity to provide initial and/or ongoing consent will be evaluated by the principal or associate investigator(s). Adults whose ability to consent is uncertain will be evaluated for the ability to consent according to local procedures. We will obtain assent for persons who are judged to have mental capacity above that of a 7-year-old. We will obtain permission for decisionally impaired adults via their appointed surrogate decision maker or another legally acceptable representative (such as a legal guardian). Local procedures will be followed for appointing a surrogate decision maker for adult participants who (a) are decisionally impaired, and (b) do not have a legal guardian. The risks of participation for adults unable to consent should be identical to those described for less vulnerable patients. The benefits for adults unable to consent are also the same because they will undergo the same procedures as participants who are able to provide consent.

4.5 Subject Withdrawal

Subjects can terminate full or partial study participation at any time without prejudice. If a subject terminates participation before completing the study, the reason for this decision will be recorded in the study record. Persons voluntarily withdrawing may elect to allow continued collection of outcome information. Subjects will continue clinical care per the local/site standard.

Best efforts will be made to follow withdrawn subjects who have received study interventions for safety.

4.6 Discontinuation of Subject by Investigator

The investigator has the right to withdraw subjects from the study. Subjects may discontinue study treatment if, in his/her best judgment, the investigator believes that continuation in the study would be detrimental to the subject and therefore that discontinuation of the study drug would be in the participant's best interests. In general, subjects withdrawn for AEs will still be

followed for safety follow-up, if possible, as well as for ascertainment of the Day 28 mortality endpoint.

The reason for discontinuation should be recorded in the study record. If an SAE is unresolved at the time of discontinuation, efforts should be made to follow up until the event resolves or stabilizes. Subjects will continue clinical care per the local/site standard.

4.7 Discontinuation of Study

The National Institute of Allergy and Infectious Diseases (NIAID), the Democratic Republic of Congo Ministry of Health, future countries who may join the study and their Ministries of Health, each institution's Institutional Review Board (IRB), the Protocol Steering Committee, or the U.S. Food and Drug Administration (FDA) may request to terminate this study at any time upon notification of the other stakeholders. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of an SAE in this or other studies indicates a potential health hazard to subjects.
- Subject enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete to the degree that objective evidence essential for determining the primary endpoint cannot be ascertained.
- Investigators do not adhere to the protocol or applicable regulatory guidelines in conducting the study.

5 STUDY PROCEDURES

5.1 Personnel for Study Procedures

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

The study will be conducted in accordance with the protocol, GCP, and all applicable US, INRB, and other host country regulations.

5.2 Site-Specific Considerations

Similar to prior outbreaks, the reality of the present outbreak of Ebola infection in the DRC is that patient care has been, and may likely continue to be, provided in a wide variety of different clinical settings, some of which may be fortunate to be comparatively resource-rich and others of which may face significant resource challenges. As long as sites will make every effort to fulfill the minimal standards of oSOC as outlined in Section 3.1 and obtain the necessary information to inform the primary endpoint, allowances should be made for differing site capabilities as a factor in study team expectations that sites collect and record both the full panel and complete frequency of data collection elements and safety assessments as outlined in the following sections.

The protocol has defined minimal standards for assessment of efficacy and safety as well as defined the optimal scheduled assessments to obtain, if able, for the purpose of full longitudinal data collection. **However, the inability of a site to collect the full optimal frequency of assessments as outlined below due to unavoidable resource limitations, and despite best efforts, will not constitute a protocol deviation.**

5.3 Schedule of Evaluations (see also Table 2 below)

The day when the subject is enrolled and randomized to their assigned treatment arm is denoted as Study Day 1. The first day after randomization is Study Day 2. Subsequent days will be numbered chronologically through Day 58 of study. For each investigational agent being evaluated a unique schedule of assessments will be developed. The schedule of assessments will be harmonized across comparisons to provide the longitudinal data collection. Patients who agree to extended follow-up through Day 58 to help characterize potential late-onset symptoms, evidence of possible virologic relapse, or other clinical changes will either be seen in person or contacted via phone as permitted. If necessary, and with the patient's verbal consent at the time they agree to this extended follow-up at time of ETU discharge, available medical staff and/or records at nearby treatment facilities may be consulted to determine whether the patient has recently been seen for any illnesses potentially consistent with any of these late-onset events. Performance of this extended follow-up will always remain subject to the patients' wishes as well as the logistics and feasibility of being able to contact individual participants following discharge.

Table 2. Schedule of Evaluations (subject to individual site capabilities)

Evaluation / Procedure	***Screen***	***Baseline***	***Follow Up[f]***									
Day +/- Window	**−1 to 1[a]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9+** while hospitalized	**28±7**	**58±7**
ELIGIBILITY/RANDOMIZATION												
Informed consent	X											
Demographics and medical history[b]	X											
Ebola RT-PCR from blood with CT	-3 to 1											
Randomize subject		X										
STUDY DRUG ADMINISTRATION [f]												
ZMapp™ (if randomized to receive ZMapp™)		X (Day 1 if possible)			+ 3 days from 1st dose			+ 3 days from 2nd dose				
remdesivir (if randomized to receive remdesivir)		Loading dose on Day 1 followed by 9 to 13 days of once-daily maintenance dosing.[e]										
MAb114 (if randomized to receive MAb114)		*Single infusion of 50mg/kg on Day 1*										
REGN-EB3 (if randomized to receive REGN-EB3)		*Single infusion of 150mg/kg on Day 1*										
MINIMUM STUDY PROCEDURES[c] ***(only obtained while in treatment unit)***												
Vital signs and weight (actual or estimated)	X	X	X	X	X	X	X	X	X	X	X	X
Record of oSOC		X	X	X	X	X	X	X	X	X		
Assessment of current symptoms/conditions, including AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X
Ebola RT-PCR from blood with CT[d]	X		X		X	X		X Then every 2-3 days until negative x 2				
Creatinine, Potassium, Sodium	X		X		X	X		X	X	X		
AST/ALT	X		X		X	X		X	X	X		
Malaria status	X											
OPTIMAL (Optional) STUDY PROCEDURES ***(In addition to the above. May include any or all of the below)***												
CBC with differential		X	X	X	X	X	X	X	X	Daily	X	X
Ebola RT-PCR from blood with CT		X	X	X	X	X	X	X	X	until 2 negatives	X	X
Metabolic Panel		X	X	X	X	X	X	X	X	Daily	X	X
Hepatic Panel		X	X	X	X	X	X	X	X	Daily	X	X
Lactate		X	X	X	X	X	X	X	X	Daily	X	X
Albumin		X	X	X	X	X	X	X	X	Daily	X	X
ionized Calcium		X	X	X	X	X	X	X	X	Daily	X	X
PT / aPTT / INR		X	X	X	X	X	X	X	X	Daily	X	X
D-Dimer (and/or fibrinogen if available)		X	X	X	X	X	X	X	X	Daily	X	X
Urinalysis, dipstick		X	X	X	X	X	X	X	X	Daily	X	X
Serum or urine pregnancy test		X										X

Stored plasma, serum specimens		X	X	X	X	X	X	X	X	X	X	X
Semen for Ebola viral RNA testing											X	X
Pharmacokinetic sample (when possible)		X	X	X	X	X	X	X	X	X		
CK-MB	X											

a. All efforts should be made to screen, randomize, and initiate treatment as soon as a diagnosis has been made.
b. It is the intent that a standardized CRF capturing expected disease symptoms will be completed at baseline and on each day that will guide the physician at bedside to conduct a consistent focused physical exam and history throughout the patient's ETU stay.
c. We will follow the minimal/optional laboratory assessments noted but will not interrupt study drug administration or make dose adjustments based on the results given the significant mortality associated with untreated (and likely partially treated) Ebola and the possible contribution of Ebola infection itself to these abnormalities. Also, the frequency and volume of blood draws is always subject to the clinical judgment of the site investigator as to safety and logistical considerations, and hence an inability to obtain the minimal laboratory assessments on a given day due to clinical or other extenuating circumstances will not constitute a protocol deviation.
d. Ebola RT-PCR from blood with quantitative CT should be performed on Study Days 1, 2, 3, 4, 5, 6, 8, 10, 14, and 28. As above, inability to obtain this testing on a given day due to clinical or other extenuating circumstances will not constitute a protocol deviation.
e. The recommended remdesivir dosing duration is a total of 10 days, but once-daily maintenance dosing may be continued for an additional 4 days if Ebola viral load remains detectable in blood at Day 10 of treatment.
f. Following the completion of formal accrual into the RCT, an Extension Phase of the protocol will begin during which randomization to the treatment arms will continue but the data collected will not count towards the primary endpoint. For a listing of the abbreviated data to be collected during the Extension Phase, see Section 14.0 of the protocol. Only MAb114 and REGN-EB3 will be used in the Extension Phase.

5.4 Screening and Informed Consent

The investigator or a qualified and previously designated member of the study team will review informed consent with the subject. If a subject is incapable of reading the informed consent, the study will be explained in the local language preferred by the subject. Each consent will be witnessed, and the witness will also sign the informed consent. Each consent will include the date signed. A separate participant consent is required for a neonate born to a female study participant in order to enroll the neonate. The informed consent process will occur on or before Day 1.

5.4.1 Demographics

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

- Age
- Sex
- Ethnicity
- Race
- Country of birth
- Contact information for patient and patient's family

5.4.2 Medical History

The following information should be recorded:

- Focused medical history regarding EVD, including all prior RT-PCR results if known
- Current symptoms
- Current participation in any recent research protocols

5.4.3 Clinical Data

- Vital signs (temperature, heart rate, respiratory rate, blood pressure) with oxygen saturation as possible
- Weight (actual or estimated)

5.4.4 Determination of Eligibility

Once the screening evaluation is complete, eligibility will be determined based on the inclusion and exclusion criteria. Subjects that are found to be ineligible will be informed during the screening evaluation, and the reason for ineligibility will be discussed.

5.5 Day 1

5.5.1 Baseline Evaluation

Within 24 hours prior to randomization, a baseline clinical evaluation will be performed with documentation of current targeted symptoms (below) and significant comorbid/pre-existing clinical conditions including vital signs.

The list of targeted symptoms and signs to assess includes: fever, cough, mental state change, hearing loss, vision loss, headache, vomiting, diarrhea, abdominal pain, shortness of breath, hiccups, rash, edema, conjunctival injection, convulsions, and hemorrhage.

5.5.2 Baseline Laboratory Testing

When possible, the following tests will be performed and recorded as baseline determinations. Baseline laboratory testing shall be performed within 24 hours of study entry (randomization).

5.5.2.1 Minimum Baseline Requirements:

- Creatinine
- Potassium
- Sodium
- AST/ALT
- Malaria test
- Ebola virus RT-PCR with CT from blood sample
    - Although any positive Ebola virus RT-PCR from blood collected up to 3 days prior to informed consent provides eligibility, a baseline specimen should be collected on Day 1 if the prior specimen was collected >24 hours, as the viral load may have substantially changed. Baseline blood for RT-PCR will be collected for all neonates before study drug initiation, but results are not needed for eligibility as described in Section 4.4.2.
    - If a patient is a recent Merck rVSV-ZEBOV vaccine recipient (within 5 days prior to RT-PCR testing) then it is possible that a positive RT-PCR test for GP only could be due to GP expression from the VSV viremia that results from vaccination rather than to true Ebola infection. In such cases a secondary confirmatory test using a different Ebola gene target (e.g., NP gene) will be needed in order to document acute Ebola infection.

5.5.2.2 Optimal Baseline Laboratories

- CBC with differential
- Acute/hepatic/mineral chemistry panels as available via POC testing, defined as:
    - Metabolic Panel = Na, K, Cl, HCO3, blood urea nitrogen, creatinine, glucose, Ca, Mg
    - Hepatic Panel = AST/SGOT, ALT/SGPT, Alkaline phosphatase, t-Bilirubin
    - Lactate
    - Albumin
    - ionized Calcium
- Ebola RT-PCR with CT and/or quantitative copies/mL from blood
- PT/aPTT/INR
- D-Dimer (and/or fibrinogen if available)
- Urinalysis, dipstick
- Serum or urine pregnancy test (females of childbearing potential only) if available as POC
- Specimen storage if possible
- CK-MB

5.5.3 Randomization

A randomization scheme will be generated by the Data Management Center prior to the initiation of the study. Randomization occurs on Day 1 with the site communicating with the regional operations center for the randomization. Randomization will only occur when a given individual has met all of the eligibility criteria as outlined above, including determination of their baseline PCR results necessary for stratification (see exception for neonates above).

5.6 Study Drug Administration and Pharmacokinetic Sampling

It is possible that Study Day 1 may be consumed by longitudinal determination of a patient's overall clinical status, implementation of oSOC provisions, assessment for study eligibility, study randomization, and other exigencies. Therefore, while not preferable, it is possible that actual administration of the investigational study intervention (as part of the assigned treatment arm) might need to be deferred until Study Day 2. Refer to the Pharmacy SOP for specific administration details of each product.

5.6.1 Pharmacokinetic Sampling

Although not feasible in most settings, for those interventions where additional PK sampling may be of value and where sample processing can be performed safely and serial samples stored appropriately according to Select Agent regulations, as locally possible:

- Collection of baseline drug level prior to assigned treatment intervention
- Initiation of serial PK blood draws whose frequency and duration (24-48 hours) will be guided by anticipated PK profile based upon preclinical data.

5.7 Follow-Up Study Days

The plan for study drug administration, clinical assessments, and lab monitoring are outlined in the Schedule of Evaluations. Details on assessments are as follows:

5.7.1 Follow-up Daily Assessment and oSOC

This will include documentation of:

- Current symptoms or conditions, including identification of any new or worsening (S)AEs compared to baseline or last prior status, focusing on:
    - targeted symptoms (above list)
    - organ dysfunction, failure, or possible drug toxicity
    - known or suspected study agent toxicities
- Vital signs
- oSOC received
- Study agent administration, as applicable
- Laboratory (as performed)
- Urinalysis (as performed, optional)
- Imaging and fluid resuscitation (as performed, optional)
- Discharge/Outcome information, as appropriate

5.7.2 Clinical Safety Laboratory Testing

5.7.2.1 Minimum Requirements

The required minimum safety laboratory testing is as follows. For the frequency of this required testing, refer to the Schedule of Evaluations in Section 5.3. While every effort should be made to obtain these laboratories per the above schedule, note that the frequency and volume of blood draws is always subject to the clinical judgment of the site investigator as to safety and logistical considerations. Hence any inability to obtain the minimal laboratory assessments on a given day due to clinical or other extenuating circumstances will not constitute a protocol deviation.

- Creatinine
- Potassium
- Sodium
- AST/ALT
- Ebola virus RT-PCR with CT from blood
- Malaria test

5.7.2.2 Optimal Daily Laboratory Monitoring

Refer to Schedule of Evaluations (Table 2) in Section 5.3. Testing should be performed during hospitalization and thereafter additionally as clinically indicated:

- CBC with differential
- Chemistry panels as available via POC testing
- Ebola virus RT-PCR with CT from blood
    - After two negative Ebola virus RT-PCRs in blood, at least 24 hours apart, testing may be discontinued if consonant with local ETU testing policy.
    - Consideration of other bodily fluid sampling as clinically appropriate
    - Date of first RT-PCR negative result in blood
- PT/aPTT/INR
- D-Dimer (and/or fibrinogen if available)
- Urinalysis, dipstick
- Specimen Storage
- CK-MB

5.8 Special Follow-up Assessments

5.8.1 Day of Discharge

Additional information will be obtained on the day of discharge regarding the criteria for discharge and negative Ebola virus RT-PCR testing prior to discharge.

5.8.2 Day 28

As the primary endpoint is 28-day mortality, the Day 28 assessment provides the essential data needed for determining this endpoint. Accordingly, all efforts should be made to ensure the timely collection of data for this timepoint.

5.8.3 Day 58

Effort should be made to conduct a study visit or telephone contact at Day 58 whenever possible. Minimum and optional procedures for this visit are outlined in Table 2.

5.8.4 Pregnancy

As noted previously, whenever possible efforts will be made to follow any pregnant women enrolled into this study through delivery or end of pregnancy, for the express purpose of evaluating any reproductive impacts of study participation.

5.8.5 Extended Follow-Up

Under the auspices of a separate protocol yet to be developed and approved, survivors of EVD enrolled in this study may be contacted later either in person or by telephone to answer questions according to a special case report form dedicated to eliciting a history of signs or symptoms potentially consistent with late onset of a virologic relapse, possibly with a particular focus on ocular or neurologic symptoms (i.e., that may represent re-emergence of virus from a CNS source).

6 STATISTICAL CONSIDERATIONS

6.1 Design overview

This is a randomized platform trial of candidate Ebola therapies, as described above. Brief background about the two options is described here. Figure 1 provides a study schema of the design.

As discussed above, results about ZMapp from PREVAIL II were promising, but not definitive at the traditional levels of evidence. Mortality rates were 37% and 22% (2-tailed p=0.18) for the oSOC and ZMapp arms respectively (25). NHP models showed a survival benefit (29). These results, in combination with concerns about the high mortality rate from EVD, have led many to conclude that ZMapp must be provided as a control treatment, at least until additional data is accrued. This was the reasoning for the DRC decision to select Option 1 for the current outbreak in the DRC. However, to anticipate the possibility that other options might be preferred in different countries or outbreaks, Option 2 is also included. Details about Option 2 will require further development, discussion, an approved protocol amendment, and possibly a different protocol and trial governance structure prior to implementation. See Section 1.2 for more details about the design rationale for DRC.

6.2 Less strict error rate control

Most clinical trials that intend to provide definitive evidence opt for strict control of the two-tailed type 1 error rate at level 0.05, with adjustments for multiple comparisons of arms. This necessitates larger sample sizes to ensure high power. The current circumstances of high mortality, intermittent outbreaks, and the need to find effective treatments as quickly as possible argue for less austere statistical penalties. As a result, the current trial will use Boschloo's exact two-tailed tests at alpha=0.05 for each pairwise comparison. There will be no multiple comparison adjustment for the fact that multiple experimental arms are compared with the control. Similar reasoning has been used in other trials. For example, PREVAIL II allowed a type 1 error rate somewhat higher than the usual one-tailed level of 0.025, and trials involving

rare cancers have allowed even higher one-tailed type 1 error rates such as 0.10 (26, 27). The need for multiple comparison adjustment has always been somewhat controversial. The products in this trial are made by different manufacturers, so one could view the comparisons almost like separate trials. The argument that no multiple comparison adjustment would be made in separate trials becomes even more compelling considering the special circumstances described above for this Ebola setting.

6.3 Study hypotheses and statistical analysis

Primary hypothesis

The primary hypothesis is that the 28-day mortality rate of the investigational arms will be lower than that of the control arm. Boschloo's test will be used to evaluate the primary hypothesis. For comparison of a given arm to control, two-tailed tests will be used. Note that an exact procedure was chosen in anticipation of early looks with limited numbers. Boschloo's test was chosen over Fisher's exact test due to less conservative small-sample performance.

Secondary hypotheses

Heterogeneity of mortality probabilities among antibody arms will be assessed using a global chi-squared test and separate pairwise chi-squared tests. The antibody arms will be deemed combinable if the two-tailed p-values from the global and pairwise tests all exceed 0.10.

If the antibody arms are deemed combinable using the criteria described above, mortality in the combined antibody arm will be compared to that of the DAA arm using Boschloo's test, as described in the primary analysis.

Safety will be evaluated by comparing the proportion of patients with at least one serious adverse event (SAE) for each arm relative to the control arm, using Boschloo's test. Proportions of specific SAEs, to include infusion-related events, will be reported.

Viremia hypothesis: Differences in median days to viral clearance will be tested using a rank-based test, imputing deaths prior to day 28 as the worst ranks, with earlier deaths having a worse rank than later deaths.

Propensity score analyses: Because some patients may be too sick to be saved by any treatment, principal stratification will be used to evaluate whether treatment effect differs by baseline risk of mortality. This risk (or propensity) of death will be evaluated using baseline predictors (e.g., CT, symptoms, age). Treatment effects will be evaluated stratifying participants according to low- and high-risk. Full details will be provided in the statistical analysis plan.

Differences in mortality by day 14 and day 58 between relevant comparator arms will be tested with Boschloo's test in the manner described for the primary hypothesis.

Time-to-death: A log-rank test comparing time-to-death up to day 28 (and up to day 58) will be performed.

Time-to-discharge: Differences in median days to becoming eligible for discharge will be tested using a rank-based test, imputing deaths prior to day 28 as the worst rank, with earlier deaths having a worse rank than later deaths. Note that discharge decisions may not always be based on objective clinical data. For example, during PREVAIL II, some patients were not discharged if a caseload was low and a relative was still under current treatment at the ETU. For these reasons, time to meeting criteria for discharge will be analyzed rather than time to actual discharge.

Proportions of patients with delayed onset of clinical symptoms possibly consistent with virologic relapse or drug toxicity within 58 days of enrollment will be summarized with descriptive statistics and 95% confidence intervals.

Ease of preparation and administration of investigational products will be summarized according to mean preparation and infusion times for each arm, with 95% confidence intervals.

6.4 Power and sample size

The sample size will be 725 participants in total, with approximately 170 enrolled in the REGN-EB3 arm and 185 enrolled in each of the ZMapp, MAb114 and remdesivir arms. This target is updated in this protocol (version 4.0) to increase power for smaller effect sizes as outlined in Table 4.

Comparisons will be made between each experimental arm and the ZMapp+oSOC control,using a two-sided type I error rate of 0.05. The initial mortality rate of 30% was based, in part, on a meta-analysis of eight clinical studies conducted during the 2014-2016 West African Ebola outbreak. This analysis indicated that the mortality rates within PREVAIL II were lower than other studies across both treatment and control arms. Hence, we expect the mortality rate with ZMapp may be higher than the point estimate from PREVAIL II, which was 22%. Table 3 gives sample sizes for 80%, 85%, and 90% power, and

Deleted

Table 4 gives power for sample sizes of 125, 170 vs 185 and 185 per arm for various mortality rates in 2 arms (ZMapp vs 1 experimental arm).

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Table 3. Sample sizes for 80%, 85%, and 90% power for two-sided 0.05 level Boschloo exact tests for 20%, 40%, and 50% reductions relative to that of the oSOC plus ZMapp control.

True mortality rates			Sample size **per arm:** 80% Power	Sample size **per arm:** 85% Power	Sample size **per arm:** 90% Power
Control arm	New experimental arm	Relative reduction			
0.5	0.4	20%	392	449	520
0.5	0.3	40%	95	109	127
0.5	0.25	50%	60	66	78
0.4	0.32	20%	570	651	758
0.4	0.24	40%	135	154	181
0.4	0.2	50%	84	94	112
0.3	0.24	20%	870	995	1160
0.3	0.18	40%	203	230	269
0.3	0.15	50%	122	139	165
0.2	0.16	20%	1465	1676	1954
0.2	0.12	40%	341	382	445
0.2	0.1	50%	205	232	271

Table 4. Power for sample sizes of 125 per arm, 170 REGN vs 185 ZMapp, and 185 per arm (for comparisons of ZMapp with either mAb114 or Remdesivir) for two-sided 0.05 level Boschloo exact tests for 20%, 40%, and 50% reductions relative to that of the oSOC plus ZMapp control.

True mortality rates					
Control arm	New experimental arm	Relative reduction	125 per arm	170 REGN-EB3 185 ZMapp	185 per arm (for comparisons of ZMapp with either mAb114 or Remdesivir)
0.5	0.4	20%	35%	46%	48%
0.5	0.3	40%	90%	97%	98%
0.5	0.25	50%	98%	>99%	>99%
0.4	0.32	20%	26%	34%	35%
0.4	0.24	40%	78%	90%	91%
0.4	0.2	50%	94%	99%	99%
0.3	0.24	20%	18%	23%	24%
0.3	0.18	40%	60%	75%	76%
0.3	0.15	50%	81%	92%	93%
0.2	0.16	20%	12%	16%	16%
0.2	0.12	40%	39%	52%	54%
0.2	0.1	50%	58%	74%	76%

6.5 Interim monitoring

Interim efficacy monitoring: Interim monitoring will use symmetric upper and lower boundaries for comparisons of a given arm to the control. The O'Brien-Fleming alpha-spending procedure will truncate boundaries at a one-sided type I error rate of 0.001. Four interim looks (including the final analysis) are planned, roughly corresponding to endpoint data from 33, 65, 100 and full enrollment (170 REGN-EB3 and 185 in each of the other 3 arms). The upper boundaries for the z-scores at these looks are 3.09, 3.09, 3.09, and 1.98. The timing of analyses might change depending on the size of the outbreak. A separate DSMB guidance document will be developed to address such issues as adding new therapeutics, changing the control group, dropping therapeutics due to futility, and sample size adjustments.

Table 5 shows the numbers of deaths by day 28 in each arm to cross a boundary at the first interim analysis with 20 patients per arm. For example, if 8 out of 20 die within 28 days in one arm, and no-one dies by day 28 in the other arm, the boundary is crossed. The boundary is also crossed if there are 12 deaths by day 28 in one arm and 2 deaths or fewer in the other arm.

Table 5. Numbers of deaths by day 28 in each arm to cross the boundary at the first interim analysis with 20 patients per arm.

Number of deaths out of 20 in one arm	Number of deaths out of 20 in the other arm
8	0
9	0
10	1 or fewer
11	1 or fewer
12	2 or fewer
13	3 or fewer
14	4 or fewer
15	4 or fewer
16	6 or fewer
17	7 or fewer
18	8 or fewer
19	10 or fewer
20	12 or fewer

Conditional power: Conditional power will be calculated under various assumptions about the treatment effect for future data. A rough guideline for futility is a conditional power of under 20%, computed under the original assumption of a 50% relative reduction in mortality. Details about these calculations and the resulting boundaries will be provided in a statistical analysis plan and a DSMB guidance document. These calculations and boundaries are advisory, and the DSMB will consider them along with the totality of evidence when making recommendations.

Final Analysis Plan: A data analysis plan developed and approved by all partners for evaluating the study endpoints will be formulated and presented to the DSMB for review and approval prior to locking of the study database and unblinding of the investigators before the first interim analysis.

7 RISKS AND BENEFITS

7.1 Potential Risks

7.1.1 Unknown Risks

In addition to the underlying EVD itself, the primary risks to participants are due to study interventions whose human safety profile is very early and evolving in most cases. Animal and/or early/first in human clinical trials are ongoing, and changes to the risk/benefit profile for study interventions are anticipated during the course of this study. Known toxicity profiles of the included agents are summarized in the appendices. Safety profiles, risks, and other information relevant to participants decision to continue or to enroll in the study will be updated and provided under guidance of human subject protection oversight bodies and per regulatory bodies, requirements and guidance. The study may itself generate information that is relevant to human subjects, which will be provided under appropriate guidance standards and entities. Relevant

current risks, to the degree they are known or reasonably suspected, have been outlined in the informed consent/assent documents.

7.1.2 Risks of Phlebotomy

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

7.1.3 Risks to the Study Personnel and the Environment

The principal risk for study personnel is exposure in the clinical setting to infectious pathogens from study subjects through various contact mechanisms (e.g., needlestick or mucous membrane exposure to blood borne pathogens or infected bodily fluids). Adherence to mandatory hygiene practices and infection control practices, including consistent and appropriate use of PPE, for working with patients infected with Ebola is of absolutely paramount importance throughout the conduct of this trial. Any perceived break in those practices must be reported immediately to the appropriate supervisory authorities in each institution per established algorithms.

7.2 Potential Benefits

There is no definite expectation of benefit to participants or to society at large. However, the agents planned for investigation in this study are all thought to have some potential to offer benefits to individual subjects, based upon previous pre-clinical and, in some cases, clinical investigation. Hence, while the potential benefits, if any, of a given medical intervention are presently unknown, it is possible that one or more interventions may subsequently be shown to offer evidence of a greater reduction in morbidity and mortality than that usually provided by oSOC alone. This may be manifested by a reduction in the length or the severity of disease, which may be life-saving in some cases given the nature of Ebola infection. If this is so, it is quite possible that this evidence will be suggestive, but not definitive, at this early stage of testing. However, even if no experimental treatment intervention is shown conclusively to provide this benefit, the knowledge gained from their study will provide important information that should help better inform what role such interventions should or should not play as adjunctive treatments in managing this disease. Thus, it is possible that both positive and negative results will help inform rapidly evolving treatment paradigms, and thus may offer a societal benefit.

7.3 Alternatives

The alternative to participating in this protocol is not to participate and to receive access either to supportive care measures alone or to experimental therapies available through MEURI or other similar mechanism in a non-participating ETU.

8 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS, AND DATA

8.1 Intended Use of the Samples/Specimens/Data

Samples and data collected under this protocol may be used to determine the interventional agent safety and efficacy, anti-viral effects, development of anti-drug antibodies, effects on immune

response, pharmacokinetics, and related characterizations. Viral specific items of interest include: diagnostics and viral pathogenesis.

8.2 Storage of Samples/Specimens/Data

It is understood that blood, other bodily fluids, and tissue samples from this protocol will potentially be of great value in advancing our knowledge both of EVD pathogenesis and the treatment effects of investigational countermeasures. The first priority for samples collected in this study is to complete analyses outlined in this protocol. Accordingly, when possible, serial samples from the enrolled patients that may help address these important questions in Ebola research will be collected and stored. As part of this, reliable long-term storage in facilities capable of storing such samples safely and under appropriate storage conditions (e.g. having secure access, monitored freezer units, connection to a reliable electrical grid, etc.) will be arranged. Samples obtained in this study must adhere to national regulations for long term storage. Any export of samples outside of DRC will necessitate approval from the Ministry of Health of DRC.

For any potential U.S. sites for sample storage, CDC regulations govern the storage of blood obtained from patients infected with Select Agents in other than BSL-4 containment facilities, which specifically require documentation of destruction of potentially infectious samples after more than 7 days' time according to established CDC guidelines. Whenever possible, sites which have access to a secure BSL-4 laboratory repository should attempt to transfer samples to that repository for longer-term storage according to approved shipping regulations applicable to select agents.

In the future, other non-protocol investigators (both locally in the affected countries, at NIH, and at other research centers) may wish to study these samples and/or data. In that case, IRB/ERB approval must be sought prior to any sharing of samples and/or data. Any clinical information shared about the sample with or without patient identifiers would similarly require prior IRB/ERB approval.

The research use of stored, unlinked or unidentified samples from any US site may be exempt from the need for prospective IRB review and approval. Exemption requests will be submitted in writing to the NIH Office of Human Subjects Research, which is authorized to determine whether a research activity is exempt.

8.3 Reporting Loss or Destruction of Samples/Specimens/Data

Any loss or unanticipated destruction of locally maintained samples (for example, due to freezer malfunction) or data (for example, misplacing a printout of data with identifiers) that meets the definition of a protocol deviation, unanticipated problem, and/or compromises the scientific integrity of the data collected for the study, will be reported to the institution's IRB or recognized ERB and to the protocol team.

9 REMUNERATION PLAN

In general, subjects will not be compensated for the time and inconvenience of active study participation, including for any outpatient assessments that may occur within the first month following hospital discharge. However, individual participating institutions may choose to offer

partial compensation for time and transportation costs associated with extended follow-up assessments.

10 ASSESSMENT OF SAFETY

Regulatory requirements, including FDA regulations and ICH Guideline for Good Clinical Practice, set forth safety monitoring and reporting responsibilities of Sponsors and Investigators to ensure the safety and protection of human subjects participating in clinical trials.

10.1 Definitions

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

Adverse Reaction: An AE that is caused by an investigational agent (drug or biologic).

Suspected Adverse Reaction (SAR): An AE for which there is a reasonable possibility that the investigational agent caused the AE. "Reasonable possibility" means that there is evidence to suggest a causal relationship between the drug and the AE. An SAR implies a lesser degree of certainty about causality than AR, which implies a high degree of certainty.

Serious Adverse Event (SAE): An SAE is an AE that results in one or more of the following outcomes:

- death
- a life-threatening event (places the participant at immediate risk of death from the event as it occurred)
- an inpatient hospitalization or prolongation of an existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect or fetal loss/miscarriage
- a medically important event*

*Medical and scientific judgment should be exercised in deciding events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

Unexpected Adverse Event: An AE is unexpected if it is not listed in the investigator's brochure or package insert (for marketed products) or is not listed at the frequency, specificity or severity that has been observed. It is the responsibility of the IND sponsor to make this determination.

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

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

1. unexpected in terms of nature, severity, or frequency in relation to
   a. the research risks that are described in the IRB-approved research protocol and informed consent document, Investigator's Brochure, or other study documents; and
   b. the characteristics of the participant population being studied; and
2. possibly, probably, or definitely related to participation in the research; and
3. places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. (Per the IND sponsor, an AE with a serious outcome will be considered increased risk.)

Unanticipated Problem that is not an Adverse Event (UPnonAE): A UP that does not fit the definition of an AE, but which may, in the opinion of the investigator, involve risk to the participant or others, or significantly impact the integrity of research data. For example, we will report occurrences of breaches of confidentiality, overdose, accidental destruction of study records, or unaccounted-for study drug.

Protocol Deviation: A protocol deviation is defined as any change, divergence, or departure from the IRB approved study procedures in a research protocol. Protocol deviations are designated as serious or non-serious and further characterized as

1. Those that occur because a member of the research team deviates from the protocol.
2. Those that are identified before they occur, but cannot be prevented.
3. Those that are discovered after they occur

Serious Protocol Deviation: A deviation that meets the definition of an SAE or compromises the safety, welfare or rights of subjects or others.

Non-compliance: The failure to comply with applicable NIH HRPP policies, IRB or ERB requirements, or national and international regulatory requirements for the protection of human subjects. Non-compliance is further characterized as

1. Serious: Non-compliance that
   a. Increases risks, or causes harm, to participants
   b. Decreases potential benefits to participants
   c. Compromises the integrity of the NIH-HRPP
   d. Invalidates the study data
2. Continuing: Non-compliance that is recurring
3. Minor: Non-compliance that, is neither serious nor continuing.

10.2 Assessment of Safety

The primary purpose of safety data collection in a putative therapeutic study is to permit monitoring for the safety of those enrolled, and to gather data on study interventions to inform use and to protect other current and potential future users of the study-agents.

The study population will generally be in hospital or will present due to symptoms of one of the most fulminant and deadly infections known. Signs and symptoms of Adverse Events are likely to progress through grade levels, and may achieve seriousness criteria in minutes to hours in many cases. This may occur prior to any study specific/investigational treatment. The highly infectious nature of the disease and characteristics of treatment facilities and the need to protect

health care providers will each add layers of unavoidable challenge to the assessment and care process and to study activities.

The above factors will limit, within reason, and for good cause, the nature and timing of data collected and reported for safety.

Every attempt will be made to document the nature [name/type] and the severity [grade per DAIDS toxicity table version 2.1, July 2017] of conditions present at baseline, particularly as pertains to the status of Ebola infection and vital organ function, so that meaningful data can be collected on the safety and efficacy impact of study interventions. It is acknowledged at the outset that this effort will likely be incomplete, and there may be unavoidable inconsistencies over time and from place to place, due to harsh conditions at treatment/study sites. Nonetheless the study team is committed to working with the sponsor safety office and with all stakeholders to obtain the most complete and accurate dataset possible.

Safety event assessment, recording, reporting, and cumulative evaluation will be aimed at achieving optimal safety for those enrolled in the study, and in pursuit of study objectives. Every attempt will be made to promptly identify relevant toxicity patterns that may require changes to the design or the conduct of the study, and to inform the use of these study interventions elsewhere.

The Data Coordinating Center will grade the severity of laboratory values and other events according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.1, July 2017 (https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf). The "Common Terminology Criteria for Adverse Events (CTCAE)" version 5.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm) will be used to grade drug infusion reactions.

10.3 Investigator Assessment of Serious Adverse Events

The Investigator will evaluate all SAEs with respect to **Seriousness** and **Causality** (relationship to study agent and relationship to research) as defined below.

10.3.1 Causality

Causality assessment is based on available information at the time of the assessment of the event. The investigator may revise the causality assessment as additional information becomes available. The likelihood that the SAE is related to the study agent will be assessed by the investigator according to the following simplified categorization. Due to the severity of Ebola illness and limitations of an ETU, further detailed breakdown will not occur:

Reasonable Possibility

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

No Reasonable Possibility

- does not have a reasonable temporal relationship

  OR
- reasonable evidence for a more likely alternative etiology

10.4 Timing and Scope of (S)AE Collection, and of Assessments and of Reporting Responsibilities to the Sponsor

SAE/AE data collection/recording, assessment/grading, reporting, and cumulative evaluation will be conducted/limited as follows:

- At BASELINE, and as close to dosing as is feasible, there will be collection, recording, and grading of targeted symptoms and of significant baseline conditions prior to study agent administration.
- BEGINNING AT INITIAL STUDY DOSING, AND DAILY, THROUGHOUT INPATIENT STAY there will be collection and recording (based upon both open-ended questioning and targeted solicitation) of targeted symptoms (see list), and of significant baseline conditions. During this period, ONLY the following SAEs are graded and are required to be individually reported to the Clinical Safety Office:
    - New/worsening events considered unlikely or 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.

  NOTE: ALL SAEs that are reportable **per the above two bulleted criteria** are to be reported to the Clinical Safety Office as follows, by the agreed upon reporting mechanism:
    - Deaths and Immediately Life Threatening SAEs:
        - By close of the next business day after the day of site awareness.
    - All other SAEs:
        - By close of the third next business day after the day of site awareness.
- All other S/AEs (those not subject to the above criteria) that are recorded for the study will be included in a MONTHLY cumulative 'line listing' and summary report across all subjects, in a format to be agreed upon by the study team and the Clinical Safety Office, to enable regulatorily compliant safety monitoring of the overall study.
- The study Principal Investigator, subject to review and confirmation by the Sponsor Medical Monitor, will recommend an initial determination of expectedness for all SAEs.

10.4.1 Unanticipated Problems

An Unanticipated Problem is any event, incident, experience, or outcome that is

1. unexpected in terms of nature, severity, or frequency in relation to
    a. the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents;
    b. the characteristics of the subject population being studied (persons with life threatening Ebola infection); and
2. possibly, probably, or definitely related to participation in the research; and
3. places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unanticipated Problems must be reported to the Data Coordinating Center and local IRB/ERB as per local institutional requirements. Unanticipated problems may include problems with protocol implementation, participant safety, and/or concerns regarding informed consent. Initial reports must be communicated no later than 7 calendar days of site awareness of the event.

Report all Unanticipated Problems that are also SAEs on the SAE CRF.

10.4.2 **Pregnancy**

Pregnancy itself is not an AE. However, complications of pregnancies are AEs and may be SAEs. Any complications that are SAEs will be reported on the SAE CRF within the above timelines.

If obtainable, pregnancy outcome data (e.g., delivery outcome, spontaneous or elective termination of the pregnancy) will be recorded on a protocol-specified form. Pregnant participants should be advised to notify their obstetrical care provider of study agent exposure, if applicable. In the event that the obstetrical care provider requires additional information on the pregnant participant, they will be referred to the study team for consultation.

10.5 Reporting Procedures to the IRB

As a general statement, SAEs, serious and non-serious UPs, and deaths will be reported per the institutional requirements of each participating entity. Unanticipated problems, non-compliance, and other reportable events will be reported to the NIAID IRB according to Policy 801.

10.5.1 **Annual Reporting to the IRB**

- A high level summary of the following events will be reported to the NIAID IRB per NIH Policy 801at the time of continuing review:
    a. Major and minor deviations
    b. Noncompliance reported to the IRB that is not related to a protocol deviation
    c. Adverse events and serious adverse events (that do not meet the definition of a UP). Address if the expected frequency and severity of the events occurred as expected, or occurred in a manner that affected the safety assessment (i.e., rose to the level of a UP).
    d. UPs reported to the IRB
- The following items will be reported to all other applicable IRB/ERBs in summary at the time of continuing review:
    a. Serious and non-serious UPs.
    b. SAEs that are possibly, probably, or definitely related to the research.
    c. SAEs that are not related to the research.
    d. All collected AEs, except expected AEs granted a waiver of reporting (e.g. the large number of AEs expected to be due to the underlying disease and judged not attributable to study drug).
    e. Serious and non-serious protocol deviations. Anticipated deviations in the conduct of the protocol will not be reported to the IRB unless they occur at a rate greater than anticipated by the study team.
    f. Serious, continuing, and minor non-compliance.

g. Any trends or events which in the opinion of the investigator should be reported.

10.6 Follow-Up of Serious Adverse Events

Whenever possible, SAEs that have not resolved by the end of the initial follow-up period will be followed until final outcome is known. Pregnancy will be followed up as well as to outcome if feasible and if consent has been provided for such. If it is not possible to obtain a final outcome for an SAE (e.g., the subject is lost to follow-up), the reason a final outcome could not be obtained will be recorded by the investigator on the AE CRF (if the CRF is still open) and the SERF.

10.7 Sponsor's Reporting Responsibilities

Serious and unexpected suspected adverse reactions (SUSARs) as defined in ICH E6 5.17 and as determined by the IND Sponsor will be reported to FDA, all participating country regulatory authorities, and all participating Investigators as IND Safety Reports.

The IND Sponsor will also submit an IND Annual Report of the progress of the investigation to the FDA and all participating country regulatory authorities as defined in 21 CFR 312.

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

10.8 Safety Oversight

10.8.1 Investigator Safety Monitoring

The Investigator or designee may interrupt the administration of study drug to an individual subject if indicated for unanticipated problems or SAEs. In addition, the Investigators are responsible for:

- Protecting the safety and welfare of subjects
- Evaluating subject safety
- Notifying the sponsor of SAEs and immediately-reportable events
- Informing the IRB/IEC of SAEs, as per institutional requirements

10.8.2 Sponsor Medical Monitor (SMM)

A Medical Monitor, representing the IND Sponsor, may be appointed for oversight of safety in this clinical study.

10.8.3 Safety Review and Communications Plan

A safety review and communications plan (SRCP) has been developed for the protocol. The SRCP is an internal communications document between the Principal Investigator and the Clinical Safety Office, which delineates the safety oversight responsibilities of the Principal Investigator, the Clinical Safety Office, and other stakeholders. The SRCP also includes the overall plan for conducting periodic safety surveillance assessments.

10.8.4 Data and Safety Monitoring Board (DSMB)

An independent DSMB with international representation of the host countries participating in the trial will review the study no less frequently than twice a year. The DSMB may convene additional reviews as necessary, dependent on the rate of subject accrual. The DSMB will review

the study data to evaluate the safety, efficacy, study progress, and conduct of the study. All SAEs, all unanticipated problems, and all IND Safety Reports will be reported by the Data Coordinating Center to the DSMB at the same time they are submitted to the IRB or IND Sponsor. The Principal Investigator will submit the DSMB's written summary open reports with the DSMB's recommendations to the IRB. A specific DSMB charter will be put in place establishing the roles and responsibilities of members after review and approval by the Study Steering Committee.

- The DSMB will monitor safety, efficacy, and quality of trial conduct measures closely throughout the trial and may pause enrollment in the event of unanticipated study-related deaths or SAEs that are considered study-related.
- The DSMB will also review the completeness of follow-up and other aspects of study conduct.
- After each meeting they will recommend that the study be continued as planned, modified, or terminated.

11 CLINICAL MONITORING STRUCTURE

11.1 Site Monitoring Plan

As per ICH-GCP 5.18 and FDA 21 CFR 312.50, clinical protocols are required to be adequately monitored by the study sponsor. This study monitoring will be conducted according to the "NIAID Intramural Clinical Monitoring Guidelines." If feasible, monitors under contract to the NIAID/Office of Clinical Research Policy and Regulatory Operations (OCRPRO) or their designee may visit the clinical research site to monitor aspects of the study in accordance with the appropriate regulations and the approved protocol. The objectives of a monitoring visit would be: 1) to verify the existence of signed informed consent documents and documentation of the Informed Consent Form process for each monitored subject; 2) to verify the prompt and accurate recording of all monitored data points, and prompt reporting of all SAEs; 3) to compare data abstracts with individual subjects' records and source documents (subjects' charts, laboratory analyses and test results, medical progress notes, nurses' notes, and any other relevant original subject information); and 4) to help ensure investigators are in compliance with the protocol. The monitors also may inspect the clinical site regulatory files to ensure that regulatory requirements (Office for Human Research Protections [OHRP]), FDA, and applicable guidelines (ICH-GCP) are being followed. During the monitoring visits, the investigator (and/or designee) and other study personnel should be available to discuss the study progress and monitoring visit.

12 ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 Informed Consent Process

Informed consent is a process where information is presented to enable persons to voluntarily decide whether or not to participate as a research subject. It is an on-going conversation (in a language understood by the subject) between the human research subject and the researchers about the essential information about the study, which begins before consent is given and continues until the end of the subject's involvement in the research. Discussions of essential information about the research will include the study's purpose, duration, experimental procedures, alternatives, risks, and benefits, and subjects will have the opportunity to ask questions and have them answered.

Participants over 18 years of age will sign the informed consent document (in a language understood by the subject) prior to any procedures being done specifically for the study. The signature of a legally acceptable representative of the potential subject will be obtained for adults who are impaired and unable to provide informed consent. In the case of adults whose ability to consent is uncertain, capacity to consent will be evaluated by the principal or associate investigator(s). Parental/guardian permission and minor assent for children through 17 years of age will be obtained according to local standards and country-specific requirements.

The participants may withdraw consent at any time throughout the course of the trial. If possible from an infection control standpoint, a copy of the informed consent document will be given to the participants for their records. The researcher will document the signing of the consent form in the subject's medical record. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Due to the biohazard of Ebola virus contaminated documents, special safety provisions must be made for how source documents are collected and stored. For example, it may be necessary for a photograph or scanned image of the informed consent signature page to be stored as an "electronic source document" rather than retaining a paper version. CRFs may also be used as source documents under these conditions.

12.2 Subject Confidentiality

All records will be kept confidential to the extent provided by federal, state and local laws in the jurisdictions in which the study is conducted. The study monitors and other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records. Records will be kept locked and all computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the NIAID, the OHRP, the INRB, or the sponsor's designee.

13 DATA MANAGEMENT AND MONITORING

13.1 Data Management Responsibilities

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

13.2 Data Capture Methods

Study data collected at the bedside at study sites will later be recorded as paper or electronic CRFs with subsequent transmission to the Data Coordinating Center. Data Coordinating Center personnel shall enter data into an electronic database. Corrections to electronic data systems will be tracked electronically (password protected and through an audit trail) with time, date, individual making the correction, and what was changed.

13.3 Types of Data

While greatly constrained within the physical setting of an ETU, source documents conceivably could include, but not be limited to, the subject's medical records, laboratory reports, ECG tracings, x-rays, radiologist's reports, subject's diaries, biopsy reports, ultrasound photographs, progress notes, pharmacy records, and any other similar reports or records of procedures performed during the subject's participation in the study.

13.4 Source Documents and Access to Source Data/Documents

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

Due to the biohazard of Ebola virus contamination, any original written source documents created at the bedside (i.e. in the 'hot zone') must be treated as potentially infectious unless an effective means of decontamination can be instituted. Where possible, photographs, digital scans, or other electronic data capture methods may be obtained instead.

13.5 Record Retention

The protocol team is responsible for retaining all essential documents listed in the ICH Good Clinical Practice Guideline. All essential documentation for all study subjects is to be maintained by the investigators in a secure storage facility for a minimum of 3 years per NIAID policies or per in-country local or federal regulatory requirements (whichever is longer). The FDA requires study records to be retained for up to 2 years after marketing approval or disapproval (21 CFR 312.62), or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational agent for a specific indication. These records are also to be maintained in compliance with IRB/EC, state, and federal medical records retention requirements, whichever is longest. All stored records are to be kept confidential to the extent required by federal, state, and local laws in the jurisdiction in which they are stored.

13.6 Data Sharing Plan

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

13.7 Trial Organization

To be outlined according to the governance model in development.

14 PALM Extension Phase

On August 9, 2019, the DSMB recommended stopping the PALM RCT and made a recommendation for the extension phase to commence with randomization to REGN-EB3 or MAb114. These recommendations were based an interim analysis of 499 participants enrolled into the RCT, which revealed that REGN-EB3 crossed an early monitoring boundary for efficacy over ZMapp. The DSMB also noted that mAb114 was close to crossing an early monitoring boundary for efficacy relative to ZMapp. Furthermore, the mortality rates for MAb114 and REGN-EB3 were not statistically significantly different, justifying the continued randomization to these two therapies. The final PALM RCT cohort will include 681 participants, the number enrolled up until the DSMB recommendation,

While these results were strong enough to recommend immediate changes to the PALM RCT, the final analysis must wait until the primary outcome data have been collected on the remaining participants and the database has been locked, which could take 6-8 weeks. During this period, the PALM Extension Phase will continue to randomize participants in order to generate additional safety and efficacy data related to these two therapies that may further inform the appropriate use of these investigational products. No formal hypothesis tests are planned. Confidence intervals on the 28-day mortality differences between the two arms will be computed.

The PALM study team will continue to consent and randomize new cases of EVD to the remaining investigational treatments during the PALM Extension Phase of the trial. This phase will continue until the following conditions have BOTH been met:

- study outcomes have been released and
- a new revised treatment plan for future management of EVD, if needed, has been designed, approved, and implemented by the medical and regulatory authorities based upon those outcomes. It is expected that this revised plan will be formulated and communicated very quickly once the RCT outcomes are known.

Depending upon those outcomes, for example,

- a revised prioritization of the existing study drugs may be needed
- combination therapies may be considered
- other treatment strategies may be adopted

During this Extension Phase, the existing stratification and randomization algorithm to determine treatment assignments (i.e. using hard-copy envelopes distributed to sites) of the present RCT will continue to be followed; HOWEVER two possible exceptions may apply:

- not all drugs may be available at all times, in sufficient quantity, to support this, or
- the DSMB, which will continue to monitor the PALM Extension, may recommend that one of the two arms be stopped.

There is a strong rationale for continuing to enroll and randomize new EVD patients during this Extension Phase:

- The support that the RCT has been providing to the overall outbreak response, and to the ETUs in particular, has been viewed as critical to their ongoing operations and should be continued if possible.
- It will be less disruptive for sites to continue the current enrollment process in which they have already been trained rather than switch back to a compassionate release (MEURI) drug allocation process.
- Continued oversight of the trial by the current DSMB during the Extension Phase will provide an additional layer of safety to the provision of investigational agents to this vulnerable patient population.
- Equipoise on the part of site investigators for the two study drugs will continue based on similar results during the interim analysis.
- The Extension Phase will tend to make optimal use of the existing RCT infrastructure (data collection, data management, pharmacy support, etc.) already in place at the ETUs
- Continuing the RCT enrollment process will facilitate more rapid transition to a new RCT if a decision to launch a new investigational study (e.g. a combination drug study) is undertaken based upon the RCT results.
- The additional data collected about the study drugs during the Extension Phase will continue to contribute significant additional information to the overall efficacy and safety profiles of these agents that are still in early development, even if the data cannot be combined statistically with those data generated under the formal RCT for the primary endpoint.

Inasmuch as the data collected under the Extension Phase cannot contribute directly to the primary endpoint of the RCT, a streamlined set of data elements will be collected during this phase that represents a pared-down version of those elements collected during the formal RCT. This reduced dataset will minimize the burden to the sites to continue to enroll and randomize patients during this period, and will also require only a minimum of additional staff training at the site level. While every effort will be made to determine the study outcomes as quickly as possible, the exact duration of the Extension Phase will depend upon the timing of such factors as when data on the Day 28 visits are collected, when the study team can be unblinded to perform primary outcome analyses, when the study results are ready for dissemination, and when a follow-up plan for overall future management of EVD is developed, approved, and implemented within the DRC (and potentially other affected countries). It is anticipated that the results of the RCT may greatly influence that follow-up plan, although the scope of that influence cannot be predicted at this time while the study results remain blinded.

Similarly, the number of additional patients to be enrolled during the Extension Phase cannot be predicted with accuracy both because of the uncertain number of patients who may present to the four participating ETUs during this period as well as the unknown (but presumably brief) interval of time it may take to formulate and enact a new “open access” treatment plan once the RCT results are known and decisions have been made about the most appropriate treatments to be offered to future patients. For example, over the course of a 12-week period and at the current rate of new cases being identified, it is possible that between 100 and 200 new patients could present themselves to an ETU for admission and possible enrollment during this extension period. With this uncertainty in mind, there will be a generous ceiling of an additional 1500 patients imposed upon the enrollment during this phase as long as:

- adequate investigational drug supply, as defined in this protocol, exists to support provision of treatment under this mechanism, and
- ETU resources remain adequate to conduct the Extension Phase, and
- no recommendation to otherwise amend or halt the extension is made by the DSMB, the IRBs, or other regulatory bodies.

As outlined above, a reduced data collection plan will be implemented during the Extension Phase. The case report forms that will still be completed (as applicable) and collected are:

- Screening
- Eligibility
- Randomization Request
- Randomization Assignment
- Study Drug Infusion (modified)
- Discharge (with Ebola RT-PCR)
- A Revised Day 28/End of Study Composite Form
- Death
- SAEs
- Pregnancy

Accordingly, the following CRFs will **not** be collected:

- Vital signs
- Daily follow-up (daily chemistries may still be performed but those results will be recorded in source documents only)
- Day 58
- Optional Procedures
- Semen Collection

Other than the exceptions noted above, study conduct will proceed as described in prior sections of this protocol (e.g. safety oversight and reporting).

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Appendix A. ZMapp Drug Information

See attached.

Appendix B. Remdesivir Drug Information

See attached.

Appendix C. MAb114 Drug Information

See attached.

Appendix D. REGN-EB3 Drug Information

See attached.

Appendix E. Oversight and/or Governance Committees:

As a multi-center, multilateral protocol whose full accrual may require extension of the trial over several EVD outbreaks that may arise in different countries over time, the complete listing of names of participating sites, investigators, and other members of the various governance committees may evolve over time. For this reason it is expected that this current list may change over time as new investigators and regional representatives are added or replaced as subsequent outbreaks occur that affect other regions. **Accordingly, any changes in the current listings below will not constitute a protocol deviation**.

Original Protocol Team:
Listed below are the names and brief contact information of the extended protocol team who were involved in the initial design and implementation of the original 3-arm trial launched on November 20, 2018, during the current (10^{th}) outbreak in DRC. This list includes members of the DRC INRB and other investigators, various government and non-government representatives from the U.S. Department of Health and Human Services, various academic partners and subject matter experts, commercial drug manufacturers, the World Health Organization, Médecins Sans Frontières, and other NGO groups such as Alima and IMC involved in conducting the trial at clinical sites.

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This original team was then transitioned in late November, 2018 (see Section 3.4 of the protocol) to the following members of the Protocol Development Team who were involved in the redesign and implementation of the 4-arm protocol design that then became active in December, 2018:

Protocol Development Team (PDT) RCT Ebola Therapeutics

The scope of the PDT was to finalize the protocol and supporting documents and include amendments as pertinent.1 Membership is specific for each country and/or outbreak. This is a WHO-led (or a WHO-delegated entity) expert group, which includes international experts with expertise in Ebola clinical management; Ebola therapeutics; Ebola diagnostics/lab; RCTs; Statistics; Ethics; Regulatory; and Drug Development.

The following experts were nominated by their institutions and agreed to serve as members of the Protocol Development Team:

- Dr Richard Kojan - Alliance for International Medical Action (ALIMA)
- Prof Jean-Jacques Muyembe - Institut National de la Recherche Biomédicale (INRB)
- Prof Sabue Mulangu - Institut National de la Recherche Biomédicale (INRB)
- Dr Nzolo Didier- Institut National de la Recherche Biomédicale (INRB)
- Dr Adam Levine – International Medical Corps (IMC)
- Dr Els Torreele - Médecins sans Frontières (MSF)*
- Dr Rebecca Grais - Médecins sans Frontières (MSF)
- Dr Pontiano Kalebuu - MRC/UVRI Uganda Research Unit
- Dr Lori Dodd - National Institutes of Health (NIH)
- Dr Richard Davey - National Institutes of Health (NIH)
- Prof Ira Longini – Representative from the R&D Blueprint RCT expert group
- Prof Peter Horby - Representative from the R&D Blueprint RCT expert group
- Prof Richard Peto - Representative from the R&D Blueprint RCT expert group
- Dr Janet Diaz – World Health Organization (WHO)
- Dr Ana Maria Henao-Restrepo - World Health Organization (WHO)
- Dr Marie-Pierre Preziosi - World Health Organization (WHO)
- Dr Pierre Gsell - World Health Organization (WHO)
- Ms Virginia Benassi - World Health Organization (WHO)

The DRC RCT Protocol DSMB:

The current DSMB membership overseeing the current version of the protocol consists of the following:

DRC RCT Protocol DSMB Roster

Name	**Affiliation**
Lisa A. Cooper, MD, MPH, FACP Chair	Johns Hopkins University Baltimore, MD
Salim Abdulla, PhD, MSc	Ifakara Health Institute Ifakara, Tanzania
Dave DeMets, PhD	University of Wisconsin Madison, Wisconsin
Albert Faye, PhD	Robert Debré University Children's Hospital Paris, France
Scott M. Hammer, MD	Columbia University Medical Center NY, NY
Amadou Traore, MD, MSc	Agence Nationale de Sécurité Sanitaire Conakry, Guinea
Ann Sarah Walker, PhD, MSc	NIHR Oxford Biomedical Research Centre Oxford, England
Anita Katherine McElroy, MD, PhD	University of Pittsburgh Pittsburgh, Pennsylvania
Michael Jacobs, PhD	Royal Free London NHS Foundation Trust London, England
Thomas Fleming, PhD	University of Washington Seattle, Washington
Jean-Marie Denis Malvy, MD, PhD	Centre Hospitalier Universitaire Bordeaux Bordeaux, France
Aissatou Toure, PharmD, MSc	Institut Pasteur Dakar Dakar, Senegal
Hippolyte Situakibanza, MD	University of Kinshasa Kinshasa, Democratic Republic of the Congo

Steering Committee:

The members of the trial Steering Committee are as follows: TBD

Medical Monitors:

Sponsor Medical Monitor:	Marc J. Teitelbaum, MD, MS Clinical Monitoring Research Program Directorate Frederick National Laboratory for Cancer Research Leidos Biomedical Research, Inc. Support to: Regulatory Compliance & Human Subjects Protection Program / NIAID / NIH 5705 Industry Lane Frederick, Maryland 21704 Phone 301-228-4707 Fax 301-846-6224 Marc.Teitelbaum@nih.gov
INRB Medical Monitor:	Prof Tona Lutete Gaston, PhD. Head, Unit of Clinical Pharmacology and Pharmacovigilance University of Kinshasa Kinshasa, Democratic Republic of the Congo tonalutete@gmail.com

Appendix F: Sample Informed Consent and Assent for the RCT

RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY AUTHORIZATION FORM

NIAID Protocol #:	19-I-0003
Protocol Title:	A Multicenter, Multi-Outbreak, Randomized, Controlled Safety and Efficacy Study of Investigational Therapeutics for the Treatment of Patients with Ebola Virus Disease
Sponsors:	United States National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) Democratic Republic of the Congo (DRC) National Institute for Biomedical Research
Principal Investigators:	Jean-Jacques Muyembe-Tamfum, MD, PhD (DRC) Richard T. Davey, Jr., MD (US)
Site:	Democratic Republic of the Congo (DRC), Central Africa

1. What you should know about this study:

- You are being asked to join a research study because you have Ebola. This consent form explains the research study and your part in the study.
- Read this consent form carefully or have someone you trust read it to you. Take as much time as you need to understand the study.
- Ask the study team to explain any words or information that you do not understand.
- You are a volunteer and you do not have to join this study. You should talk to your doctor about what your options are if you do not want to be in this study.
- If you join the study, you can change your mind later. You can decide not to take part or you can quit at any time. There will be no penalty or loss of benefits if you decide not to join or to quit the study. Your care within your community will not be affected.
- During the study, we will tell you if we learn any new information that might affect whether you wish to continue to be in the study.
- If you are signing for a person who cannot consent for themselves, such as a child or a person who is too sick to read and understand this, the word "you" in this consent form refers to that person. If you are signing for a baby born within the past 7 days to a mother who has Ebola, we will assume that the baby also has Ebola. In this case, we may not wait for the baby's Ebola blood test result to confirm an Ebola infection before starting them on this study.

2. What is this study about?

We are looking for new treatments for Ebola virus disease. Ebola virus can make people very sick and some people can die from it. There are no approved medicines for Ebola. There are some possible Ebola medicines that are called experimental medicines because we are not sure if they work to treat Ebola. We need to test the experimental medicines to see if they help people recover from Ebola virus disease. To do this, we need the help of people who have Ebola and are in a treatment center where we can test these experimental drugs and compare them to each other in a controlled way. The experimental drugs that we are testing in this study (the "study drugs") are described below.

3. How many people will be in this study?

We expect about 725 people to join the study in several Ebola treatment centers.

4. What will happen if you join this study?

Before you can join the study, we will ask you some questions, review your health history, assess your symptoms, and collect some of your blood to test for Ebola.

If you are eligible and choose to join, you will be in the study for about 2 months. At the beginning, you will stay at the Ebola treatment center for treatment of your Ebola. How long you stay in the treatment center will depend on how sick you are. While you are in the treatment center, you will continue to get supportive care. This includes getting fluids to replace those you lose due to your illness. Your blood pressure and other vital signs will be measured to see if you are getting better or worse. We will take blood to check your health status and give you medicine to treat your symptoms. These specific steps are not experimental. This is standard care for Ebola patients in the treatment center. Any procedures done as part of this standard care will be explained to you as will the risks.

We will use a needle to put a small plastic tube in your arm for several days. This is called an IV line. Fluids to help you, and also study drug, will be given through the IV.

We will check you a few times each day to see if you are getting better or worse. We will need to read your medical records. We may ask you to give us some of your urine in a cup, and we will take some blood. We will use the blood and urine to guide your care, and for research tests. This will help us see how your body responds to Ebola and to the study drug.

After you have recovered enough in the treatment center, you will be allowed to go home. We will contact you about 1 month and 2 months after you started the study. We will ask how you are feeling and if you have been sick. If possible, we will collect blood samples from all participants and semen samples from male participants for research and routine lab tests to check your health. After 2 months, you will be done with this study. For women who are or become pregnant during the study, we may ask you to let us know if there were any problems with your pregnancy or with your child.

We may contact you and ask if you want to help us by being in other research studies in the future to learn more about how best to care for people who have survived Ebola.

5. What are the study drugs and their side effects?

Each person in this study will get 1 of the 4 study drugs described below. All study participants will also get routine medical care for Ebola. If you join the study, the study drug you get will be randomly assigned (that is, like throwing dice). Right now, nobody is sure if any of the study drugs are better than the others. There may be some side effects with the study drugs.

The study team will tell you which study drug you will get, and will talk with you about it. You will only receive 1 of the study drugs while you are in this study. You will not be able to receive any other experimental drugs for 1 month.

Study Drugs

The 4 different study drugs we are using on this study are called

- ZMapp
- remdesivir
- MAb114
- REGN-EB3

Information about how these drugs are given and their risks is given below. These experimental drugs have not been studied in very many people, so there may be risks that we do not know about. It is possible for people to have allergic reactions to any drug, including hives, trouble breathing, or other allergic responses. This is very rare. Severe allergic reactions (called anaphylaxis) can cause heart attacks and, if untreated, even death. The study doctors will be prepared to promptly and appropriately treat any severe allergic reaction to any of the study drugs.

ZMapp: If you get ZMapp, we will give it to you 3 times, with about 3 days between each dose. Each dose is given through your IV line and will take about 4 hours to give. If you have side effects while we are giving the ZMapp, let us know. We can slow down how fast we give you the drug to help with the side effects. You will be monitored closely for side effects while you are getting the ZMapp, and we will have medicine and equipment available to treat side effects, including severe effects, if necessary. If you have severe side effects that do not get better, we will not give you any more doses.

ZMapp has been tested in other studies in people with Ebola. Some of the side effects seen in people who received ZMapp were flushing (skin redness), fast heart rate, chills, a rise or fall in blood pressure, itchiness, swelling, fever, chest pain, shortness of breath, nausea and vomiting, a drop in blood sugar, seizures, and skin rash. These side effects may be caused by ZMapp and may be serious. We do not know if the drug caused all of these side effects. Some of them may have been caused by the Ebola infection. Some people have lived and some people have died after receiving ZMapp.

Risks of antihistamine and acetaminophen: If you have some kinds of side effects from ZMapp, we may give you antihistamine or acetaminophen to help treat it. Sedation is the major expected side effect of antihistamine and may last up to several hours after the antihistamine is given. Other common side effects of antihistamine include tiredness, sleepiness, dizziness, disturbed coordination, drying and thickening of oral and other respiratory secretions, and stomach upset. An antihistamine may also cause blurred vision, double vision, tremor, loss of appetite, or nausea.

Significant side effects from a single dose of acetaminophen are uncommon but could include allergic-type reactions (for example, hives, rash, shortness of breath), minor stomach upset, and jaundice.

Remdesivir: If you get remdesivir, we will give it to you through your IV line 1 time every day for 10 to 14 days in a row. Each dose takes about 30 to 60 minutes to give. We will monitor you closely for side effects while you are getting the remdesivir and will have medicine and equipment available to treat side effects, including severe effects, if necessary. If you have severe side effects that do not get better, we will not give you any more doses.

Remdesivir has been given to a small number of people in other research studies, and some of these people had side effects. These included changes in laboratory tests that measure liver health. The liver changes lasted longer than a few days but came back to normal levels. Some people also had constipation, heartburn, itching, unusual feelings in the ear, dizziness, loss of appetite, nausea, vomiting, shaking of the leg and arm, headache, loose stool, or upset stomach. These side effects are temporary and should not last more than a few days. None of the side effects have been serious.

Before drugs are tested in people, they are tested in animals first. When remdesivir was tested in animals, some of the animals had kidney damage. The animals' kidneys went back to normal after the drug was stopped. Some of the animals also had redness around the spot of the drug infusion. We have not seen any kidney problems in the people who have taken this drug but since it is still being studied, it could still happen. We will be monitoring your blood during the study to check for kidney damage.

Remdesivir has an ingredient called SBECD. When SBECD was given to animals in research studies, it caused changes in the kidneys but did not affect how well the kidneys worked. SBECD has been approved for use in the United States and is used to give other approved medications.

You should not drink alcohol for 14 days after you start receiving remdesivir. You should also not take paracetamol (acetaminophen).

MAb114: If you get MAb114, we will give you only 1 dose of MAb114 through your IV line. It will take about 30 to 60 minutes. If you have side effects while we are giving the MAb114, let us know. We can slow down how fast we give you the drug to help with the side effects. You will be monitored closely for side effects while you are getting the

MAb114, and we will have medicine and equipment available to treat side effects, including severe effects, if necessary.

MAb114 has been given to some healthy volunteers and some people with Ebola, and some people had side effects that included general discomfort, muscle pain, headache, chills, nausea, and joint pain.

Since MAb114 has been given to very few people, we do not know all the side effects that could occur, but drugs that are made like MAb114 can cause side effects that can sometimes be serious. Most side effects occur within the first 24 hours. These may include fever, chills, shaking, nausea, vomiting, pain, headache, dizziness, trouble breathing, high or low blood pressure, itchiness, rash, hives, lip or face swelling, diarrhea, racing heart, or chest pain.

Some drugs like MAb114 have a risk of more serious reactions or side effects like serum sickness. Serum sickness is a type of allergic reaction that may happen several days to 3 weeks after this type of drug is given, but it has not been seen in anyone who has gotten MAb114. This reaction can include hives or rash, fever, enlarged lymph nodes, muscle pains, joint pains, chest discomfort, and shortness of breath.

Some drugs like MAb114 contain larger amounts of an ingredient called sucrose. This may cause temporary damage to the kidneys. MAb114 contains less sucrose than those other drugs, but we will still monitor your kidneys closely with blood tests during this study.

Some drugs like MAb114 attack human proteins and can increase the risk of serious infections. MAb114 is not expected to increase the risk of serious infections because it attacks the Ebola virus and not a human protein.

REGN-EB3: If you get REGN-EB3, we will give you only 1 dose through your IV line. It will take about 2 hours. If you have side effects while we are giving the REGN-EB3, let us know. We can slow down how fast we give you the drug to help with the side effects. You will be monitored closely for side effects while you are getting the REGN-EB3, and we will have medicine and equipment available to treat side effects, including severe effects, if necessary.

REGN-EB3 has been given to some healthy volunteers in a clinical study and some people with Ebola, and some people had side effects. The most common side effects were headache and muscle pain.

Since REGN-EB3 has been given to very few people, we do not know all the side effects that could occur, but drugs that are made like REGN-EB3 can cause side effects that can sometimes be serious. Most side effects occur within the first few hours of the infusion. These may include wheezing, trouble breathing, chills, shaking, dizziness, fainting, shortness of breath, cough, low blood pressure, rash, hives, or swelling around the mouth, throat, or eyes.

Some drugs like REGN-EB3 have a risk of more serious reactions or side effects including allergic reactions. For example, there is a type of delayed allergic reaction that may happen several days to 3 weeks after this type of drug is given, although it has not been seen in anyone who has gotten REGN-EB3. This reaction could include hives or rash, fever, enlarged lymph nodes, joint pains, chest discomfort, and shortness of breath.

Low levels of an antibiotic called doxycycline is used to make REGN-EB3. You should tell your study doctor or study staff if you have an allergy to doxycycline or any other medications.

6. What are the other risks or discomforts of the study?

The needle used to draw blood or place an IV line can hurt. You may get a black and blue mark where the needle went in. Sometimes drawing blood causes people to feel lightheaded or even to faint. There is a very small risk of getting an infection where the needle went into the vein.

We will be careful to keep your study information confidential, but there is a small risk that someone not involved in the study could get this information.

7. What do I need to know about pregnancy or breastfeeding during the study?

Women: We do not know the effects of the study drugs on a developing fetus. If you can become pregnant, we may do pregnancy testing while you are on this study. If you are pregnant or become pregnant around the time you receive the study drug, there may be risks to you, the embryo, or fetus. These risks are not yet known. If you are a woman who can get pregnant, you must agree to use an effective method of birth control from the beginning of the study through the last study visit. If you find out that you were pregnant during the study, you must tell your doctor immediately. If you are breastfeeding or plan to breastfeed an infant, it is recommended by the World Health Organization that you avoid breast feeding for a period of time until your breast milk is tested to show that Ebola virus is not present. We also do not know if the study drugs can pass through in breast milk, and the risks to a nursing infant are not yet known.

Men: The effects of the study drugs on sperm is not known. To protect against possible side effects, you should not get a sexual partner pregnant while taking part in this study. You must agree to use a condom from the beginning of the study through the last study visit. Research studies have found that Ebola virus can persist in the semen of Ebola survivors for extended periods after recovery from an Ebola infection, and might infect a sexual partner. Therefore, we recommend that you either don't have sex or that you use condoms during sexual intercourse for as long is currently recommended by the World Health Organization, or until your semen is tested to show that Ebola virus is not present. We would like to test your semen for virus in this study when you leave the ETU and again about 2 months after you start the study.

If you recover from Ebola, we will talk with you about precautions you should continue to take to prevent passing the virus to others through bodily fluids.

8. Are there benefits to being in the study?

We do not know if you will benefit from being in this study. It is possible that the study drug you receive will help treat your Ebola infection. But we do not yet know whether any of the treatments are effective. It is also possible that even if a drug is effective, it may cause serious side effects that make it more harmful than helpful.

What we learn from this study may allow us to better understand Ebola and develop better ways of treating patients with Ebola in the future.

9. What will happen to your samples and personal information?

We will store your samples and data (information) for a very long time to use for future research on Ebola. Your stored samples and data will be marked with a code and not with your name. Only researchers linked to this study can get the codes.

Your study information will be placed in a secure electronic system. It will not include your name. We must get approval from the DRC and US ethics boards that review this study before we share samples and data with other researchers. Other information, such as your sex, age, or health history might also be shared, but your name will not. This information cannot be traced back to you. You will not get any information about future research. Your sample will not be sold. You will not be paid for any products that result from this research.

The only risk of allowing us to store your sample would be an accidental release of your identity.

If you change your mind and decide you do not want us to store your sample or data, please let us know. We will do our best to follow your wishes but cannot promise that we will always be able to destroy your samples or data.

10. Will it cost you anything to be in this study?

It will not cost you anything to be in this study.

11. Will you be paid if you join this study?

No, you will not be paid.

12. Who is watching over this study?

A Data and Safety Monitoring Board (DSMB) will be looking at the study information very closely. The DSMB is made up of doctors and other people who are not directly involved in the study and who have a good understanding of Ebola and research studies. The DSMB may recommend changing the study drugs being used or stopping the study earlier than planned if they think it is not safe to continue or if they find out early that a drug is working better. The DRC and US ethics boards will also be watching over this study and have the authority to stop it at any time.

13. How will your privacy be protected?

We will keep your study information private. All files with information that could identify you will be kept in locked cabinets or secure computers. People responsible for making sure that the research is done properly may look at your study records. This might include people from the DRC and the US including the NIH and their designees. All of these people will also keep your identity private. Results from this study, but not your identity, may be shared with local medical providers or government health organizations to help them better understand Ebola virus infection.

14. What other things should you know about this research study?

a. ClinicalTrials.gov

A description of this study will be on the internet at http://www.ClinicalTrials.gov. This website will not include information about you. At most, the website will include a summary of the results. You can search this website at any time.

b. Conflict of Interest

The policy of the NIH is to evaluate investigators at least yearly for any conflicts of interest. Research participants may review the system for assessing conflicts of interest by checking the web site link: http://ethics.od.nih.gov/forms/Protocol-Review-Guide.pdf. Copies of the standards may also be requested by research patients. This study has investigators that are NIH employees and some that are not. All non-NIH investigators are required to follow the principles of the Protocol Review Guide but are not required to report their financial holdings to the NIH.

The US NIH and the research team for this study have developed one of the drugs being used in this study. This means it is possible that the results of this study could lead to payments to NIH and Institut National de Recherche Biomédicale (INRB) scientists and to the NIH. By law, US government scientists are required to receive such payments for their inventions. You will not receive any money from the development of the drugs being used in this study.

c. What is the Ethical Review Committee and how does it protect you?

Your government's ethics committee will review this study. It protects the rights and welfare of the people taking part in research studies. You can contact Patrick Kayembe Kalambayi, coordinator of the DRC ethics board (Tel: 0818111182) to answer questions you may have about being part of this study and your rights as someone who is in a study. The ethics committee at the US NIH has also reviewed and approved this research.

d. What do you do if you have questions about the study?

If you have questions about the study, you may contact the principal investigators. Dr. Jean-Jacques Muyembe-Tamfum (DRC) can be reached by phone +243 898949289, or by email jjmuyembet@gmail.com. Dr. Richard T. Davey, Jr. (US NIH) can be reached by email rdavey@niaid.nih.gov.

e. What should you do if you are injured or ill as a result of being in this study?
We do not expect any harm from participating in this study. However, unforeseeable risks may be present. The study doctors will give you short-term medical care if you are hurt by being in this study.

If you agree to be in this study, please sign or put your fingerprint below.

_____ Date: _____/_____/_____
Signature or fingerprint of participant or guardian dd mm yy

_____
Printed name of participant or guardian

_____ Date: _____/_____/_____
Signature of investigator/designee dd mm yy

_____
Printed name of investigator/designee

Complete if participant is illiterate:

Witness to Consent Interview

On the date given next to my signature, I witnessed the consent interview for the research study named above in this document. I attest that the information in this consent form was explained to the subject, and the subject indicated that his/her questions and concerns were adequately addressed.

_____ Date: _____/_____/_____
Signature of witness dd mm yy

_____
Printed name of witness

MINOR ASSENT TO PARTICIPATE IN STUDY

NIAID Protocol #:	19-I-0003
Protocol Title:	A Multicenter, Multi-Outbreak, Randomized, Controlled Safety and Efficacy Study of Investigational Therapeutics for the Treatment of Patients with Ebola Virus Disease
Sponsors:	United States National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) Democratic Republic of the Congo (DRC) National Institute for Biomedical Research
Principal Investigators:	Jean-Jacques Muyembe-Tamfum, MD, PhD (DRC) Richard T. Davey, Jr., MD (US)
Site:	Democratic Republic of the Congo (DRC), Central Africa

1 Introduction

You are being asked to be in this study because you have Ebola. Ebola can make people very sick. Some people can die from it. There are no approved medicines for treating Ebola, so we are trying to learn more about how best to treat it.

First, we want to explain the study to you. Then, you can decide if you want to be in it. You do not have to be in this study if you do not want to.

2 What is this study about?

This is a research study where we are testing possible medicines. We want to find out if any of these medicines could help treat Ebola. We call these medicines the "study drugs." We do not know if any of them will be helpful. They have been given to some people before, but not many. We need to test them in more people, including kids, so we can make sure they are safe and see if any of them can help treat Ebola.

3 Do I have to be in this study?

No. You can decide not to be in the study. You can talk to your family, friends, and doctor before you decide. Even if you want to be in the study now, you can change your mind later and stop being in the study at any time.

4 What will happen in this research study?

If it is okay with you and you agree to join this study, we will give you 1 of the study drugs. There are 4 study drugs that we are testing. You will only get 1 of them, but we do not know which one yet. You cannot pick which one you want but we will tell you when we find out.

During the study, you will stay in the Ebola treatment center for a while. You may stay up to a few weeks if you are very sick. You will continue to get regular care for Ebola. We will use a needle to put a small tube in your arm for several days. We will give you the study drug through the tube in your arm. We will also collect some blood and we may ask you to give us some urine in a cup for tests.

After some time in the treatment center, when the doctor thinks it is safe for you, you can go home. We will contact you 2 more times to ask how you are feeling. If possible, we will give you a check up and take some more blood for tests. Then you will be done with the study. Your total time in the study will be about 2 months.

5 Will any part of the study hurt?

Taking a study drug may make you feel sick, but you may also feel sick from the Ebola. The study drugs have not been given to a lot of people, so the study drug you get may cause changes that hurt or bother you that we do not know about. It may also not have been given to children before, so we may not know whether it may cause side effects in kids that were not seen in adults. In a very small number of people, the study drugs could cause something dangerous that people could die from. It is important that you always tell the study staff how you are feeling.

If you get the study drug called "ZMapp," you will get it 3 times. It might give you a fever or make you feel cold. It might make your skin red or itchy, give you a rash, or make your body swell. It might make you throw up or feel like you are about to throw up. You could feel like your heart is beating too fast or you are out of breath. You could feel a pain in your chest. You might get seizures.

If you get the drug called "remdesivir," you will get it 10 to 14 times. It might make you feel itchy, dizzy, or shaky. You might feel like your chest is warm or burning. It might make your head hurt. It might make your ears feel funny. It might make your stomach hurt, and it could make you have diarrhea, throw up, or feel like you might throw up. You could have trouble pooping for a while.

If you get the drug called "MAb114," you will get it 1 time. It might make you feel sick, cold, dizzy, or shaky, and it might give you a fever. It could make you have diarrhea, make you throw up or feel like you might throw up. It could make your head, muscles, or joints hurt. It could make you feel itchy, give you a rash or hives, or make your lips or face swell up. You could have trouble breathing. You could feel like your heart is beating too fast. It could give you a pain in your chest.

If you get the drug called "REGN-EB3," you will get it 1 time. It might make your head or muscles hurt. It could make you feel cold, shaky, or dizzy, or give you a fever, rash, or hives. It could make you cough or faint, make your joints hurt, or make your lips, face, or throat swell up. You could have trouble breathing. It could give you a pain in your chest.

You will just get 1 of these drugs. You might have some of these things happen, or you might not feel any of them. We will watch you carefully when you get the study drug. If the drug makes you feel bad, we can sometimes give you medicines to help you feel better.

It might hurt when we put a needle in your arm to draw blood or put in the plastic tube. Your arm may get swollen and sore where the needle goes in, and you might get a black and blue mark. These things should go away on their own. There is a very small chance that you could get an infection.

6 What do I need to know about pregnancy during the study?

If you are female: We do not know the effects of the study drugs in pregnancy or in a nursing baby. If you can become pregnant, we may do pregnancy testing while you are on this study. If you are pregnant or get pregnant around the time you get the study drug, we don't know if there may be effects on you or your baby. Therefore, you should avoid getting pregnant for 2 months after getting the study drug. You will need to use birth control if you are sexually active, unless you are not able to get pregnant. If you think that you have gotten pregnant during the study, tell the study team right away, and find medical care for your pregnancy.

If you are male: The effects of the study drugs on sperm are not known. Therefore, you should not get a sexual partner pregnant for at least 2 months after getting the study drug. You should use a condom every time you have sex for 2 months after getting the study drug.

7 Will the study help me?

We do not know if you will be helped by being in this study. We do not know if the study drug will make you feel better or get well sooner. It is possible that the study drug could make you worse.

8 Will the study help others?

We might find out things from this study that will help other people with Ebola someday.

9 Do I have other choices?

You do not have to be in this study. It is up to you. You can talk to your parents and your doctor about your options.

No one will be upset if you don't want to do this study. If you say okay now, but you want to stop later, that is okay too. If you decide to stop being in the study, all you have to do is tell your doctor or nurse that you don't want to do the study anymore. No one will be mad at you if you change your mind.

If you say no, you will still be given your regular care for Ebola. We will not give you the study drugs.

10 What if I have questions?

If you want to talk to anyone about this research study because you think you have been hurt by being part of the study, or you if have any other questions about the study, you should tell the study team: Phone number +243 826792353.

Also, you can contact Dr. Jean-Jacques Muyembe-Tamfum (Tel: +243 898949289) to answer questions you may have about being part of this study and your rights as someone who is in a study.

If you have any questions at any time about this research study, you may ask someone on the study team.

If you decide to be in the study, please write your name below.

I have had this study explained to me in a way that I understand, and I have had the chance to ask questions. I agree to take part in this study.

Signature or fingerprint of Minor Patient: _____ Date: _____

Print Name: _____

Signature of Investigator/Designee: _____ Date: _____

Print Name: _____

Appendix G: Sample Informed Consent and Assent for the Extension Phase

RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY AUTHORIZATION FORM

NIAID Protocol #: 19-I-0003

Protocol Title: A Multicenter, Multi-Outbreak, Randomized, Controlled Safety and Efficacy Study of Investigational Therapeutics for the Treatment of Patients with Ebola Virus Disease

Sponsors: United States National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)
Democratic Republic of the Congo (DRC) National Institute for Biomedical Research

Principal Investigators: Jean-Jacques Muyembe-Tamfum, MD, PhD (DRC)
Richard T. Davey, Jr., MD (US)

Site: Democratic Republic of the Congo (DRC), Central Africa

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1. What you should know about this study:

- You are being asked to join a research study because you have Ebola. This consent form explains the research study and your part in the study.
- Read this consent form carefully or have someone you trust read it to you. Take as much time as you need to understand the study.
- Ask the study team to explain any words or information that you do not understand.
- You are a volunteer and you do not have to join this study. You should talk to your doctor about what your options are if you do not want to be in this study.
- If you join the study, you can change your mind later. You can decide not to take part or you can quit at any time. There will be no penalty or loss of benefits if you decide not to join or to quit the study. Your care within your community will not be affected.
- During the study, we will tell you if we learn any new information that might affect whether you wish to continue to be in the study.
- If you are signing for a person who cannot consent for themselves, such as a child or a person who is too sick to read and understand this, the word "you" in this consent form refers to that person. If you are signing for a baby born within the past 7 days to a mother who has Ebola, we will assume that the baby also has Ebola. In this case, we may not wait for the baby's Ebola blood test result to confirm an Ebola infection before starting them on this study.

2. What is this study about?

We are looking for new treatments for Ebola virus disease. Ebola virus can make people very sick and some people can die from it. There are no approved medicines for Ebola.

There are some possible Ebola medicines that are called experimental medicines because we are not sure if they work to treat Ebola. We have recently been testing four experimental medicines to see if they help people recover from Ebola virus disease. To do this, we have needed the help of people who have Ebola and are in a treatment center where we can test these experimental medicines and compare them to each other in a scientific and precise way.

Four study drugs were given in the Randomized Control Trial portion of this study which is now closed to people with known Ebola virus disease. Some people have lived and some have died.

From an early review of the study results we now know that 2 of the 4 study drugs were better at treating Ebola than the others. We do not yet know if one of these 2 might be better than the other because we are still reviewing the data. We wish to continue to offer these experimental medicines to people who might benefit from them. As soon as we analyze the final results, we will take standard steps to make that information public.

The purpose of the current study is to offer you access to these experimental medicines.

3. How many people will be in this study?

We have set a limit of 1500 patients who can join the study while we are waiting for the final results of the comparison study to become available. We expect it may take a few weeks to a few months for those results to become available.

4. What will happen if you join this study?

Before you can join the study, we will ask you some questions, review your health history, assess your symptoms, and collect some of your blood to test for Ebola.

If you are eligible and choose to join, you will be in the study for about 1 month. At the beginning, you will stay at the Ebola treatment center for treatment of your Ebola. How long you stay in the treatment center will depend on how sick you are. While you are in the treatment center, you will continue to get supportive care. This includes getting fluids to replace those you lose due to your illness. Your blood pressure and other vital signs will be measured to see if you are getting better or worse. We will take blood to check your health status and give you medicine to treat your symptoms. These specific steps are not experimental. This is standard care for Ebola patients in the treatment center. Any procedures done as part of this standard care will be explained to you as will the risks.

We will use a needle to put a small plastic tube in your arm for several days. This is called an IV line. Fluids to help you, and also study drug, will be given through the IV.

We will check you a few times each day to see if you are getting better or worse. We will need to read your medical records. We may ask you to give us some of your urine in a cup, and we will take some blood. We will use the blood and urine to guide your care, and for research tests. This will help us see how your body responds to Ebola and to the study drug.

If you have recovered enough in the treatment center, you will be allowed to go home. We will contact you about 1 month after you started the study. We will ask how you are feeling and if you have been sick. If possible, we will collect blood samples from all participants and perform routine lab tests to check your health. After 1 month, you will be done with this study. For women who are or become pregnant during the study, longer follow-up may be needed during which we may ask you to let us know if there were any problems with your pregnancy or with your child.

We may contact you and ask if you want to help us by being in other research studies in the future to learn more about how best to care for people who have survived Ebola.

5. What are the study drugs and their side effects?

Each person in this study will get 1 of the 2 study drugs described below. However, it is possible that both drugs will not be available at all times. All study participants will also get routine medical care for Ebola. If you join the study, the study drug you get will be randomly assigned (that is, like throwing dice). If we run out of one of the study drugs, you will be randomly assigned to the study drug that is available. Right now, nobody is sure if one of the study drugs is better than the other. There may be some side effects with the study drugs.

The study team will tell you which study drug you will get, and will talk with you about it. You will only receive 1 of the study drugs while you are in this study. You will not be able to receive any other experimental medicines for 1 month.

Study Drugs

The 2 different study drugs we are using on this study are called

- mAb114
- REGN-EB3

Information about how these drugs are given and their risks is given below. As of now these experimental medicines have only been studied in a few hundred people each, so there may be risks that we do not know about. It is possible for people to have allergic reactions to any drug, including hives, trouble breathing, or other allergic responses. This is very rare. Severe allergic reactions (called anaphylaxis) can cause heart attacks and, possibly, death. The study doctors will be prepared to promptly treat any severe allergic reaction to any of the study drugs.

If you have side effects while we are giving the study drug, let us know. We can slow down how fast we give you the drug to help with the side effects.

mAb114: If you get mAb114, we will give you only 1 dose of MAb114 through your IV line. It will take about 30 to 60 minutes. You will be monitored closely for side effects while you are getting the mAb114, and we will have medicine and equipment available to treat side effects, including severe effects, if necessary.

mAb114 has been given to some healthy volunteers and some people with Ebola, and some people had side effects that included general discomfort, muscle pain, headache, chills, nausea, and joint pain.

Since mAb114 has been given to very few people, we do not know all the side effects that could occur, but drugs that are made like mAb114 can cause side effects that can sometimes be serious. Most side effects occur within the first 24 hours. These may include fever, chills, shaking, nausea, vomiting, pain, headache, dizziness, trouble breathing, high or low blood pressure, itchiness, rash, hives, lip or face swelling, diarrhea, racing heart, or chest pain.

Some drugs like mAb114 have a risk of more serious reactions or side effects like serum sickness. Serum sickness is a type of allergic reaction that may happen several days to 3 weeks after this type of drug is given, but it has not been seen in anyone who has gotten mAb114. This reaction can include hives or rash, fever, enlarged lymph nodes, muscle pains, joint pains, chest discomfort, and shortness of breath.

Some drugs like mAb114 contain larger amounts of an ingredient called sucrose. This may cause temporary damage to the kidneys. mAb114 contains less sucrose than those other drugs, but we will still monitor your kidneys closely with blood tests during this study.

Some drugs like mAb114 attack human proteins and can increase the risk of serious infections. mAb114 is not expected to increase the risk of serious infections because it attacks the Ebola virus and not a human protein.

REGN-EB3: If you get REGN-EB3, we will give you only 1 dose through your IV line. It will take about 2 hours. You will be monitored closely for side effects while you are getting the REGN-EB3, and we will have medicine and equipment available to treat side effects, including severe effects, if necessary.

REGN-EB3 has been given to some healthy volunteers in a clinical study and some people with Ebola, and some people had side effects. The most common side effects were headache and muscle pain.

Since REGN-EB3 has been given to very few people, we do not know all the side effects that could occur, but drugs that are made like REGN-EB3 can cause side effects that can sometimes be serious. Most side effects occur within the first few hours of the infusion. These may include wheezing, trouble breathing, chills, shaking, dizziness, fainting, shortness of breath, cough, low blood pressure, rash, hives, or swelling around the mouth, throat, or eyes.

Some drugs like REGN-EB3 have a risk of more serious reactions or side effects including allergic reactions. For example, there is a type of delayed allergic reaction that may happen several days to 3 weeks after this type of drug is given, although it has not

been seen in anyone who has gotten REGN-EB3. This reaction could include hives or rash, fever, enlarged lymph nodes, joint pains, chest discomfort, and shortness of breath.

Low levels of an antibiotic called doxycycline is used to make REGN-EB3. You should tell your study doctor or study staff if you have an allergy to doxycycline or any other medications.

6. What are the other risks or discomforts of the study?

The needle used to draw blood or place an IV line can hurt. You may get a black and blue mark where the needle went in. Sometimes drawing blood causes people to feel lightheaded or even to faint. There is a very small risk of getting an infection where the needle went into the vein.

We will be careful to keep your study information confidential, but there is a small risk that someone not involved in the study could get this information.

7. What do I need to know about pregnancy or breastfeeding during the study?

Women: We do not know the effects of the study drugs on a developing fetus. If you can become pregnant, we may do pregnancy testing while you are on this study. If you are pregnant or become pregnant around the time you receive the study drug, there may be risks to you, the embryo, or fetus. These risks are not yet known. If you are a woman who can get pregnant, you must agree to use an effective method of birth control from the beginning of the study through the last study visit. If you find out that you were pregnant during the study, you must tell your doctor immediately. If you are breastfeeding or plan to breastfeed an infant, it is recommended by the World Health Organization that you avoid breast feeding for a period of time until your breast milk is tested to show that Ebola virus is not present. We also do not know if the study drugs can pass through in breast milk, and the risks to a nursing infant are not yet known.

Men: The effects of the study drugs on sperm is not known. To protect against possible side effects, you should not get a sexual partner pregnant while taking part in this study. You must agree to use a condom from the beginning of the study through the last study visit. Research studies have found that Ebola virus can persist in the semen of Ebola survivors for extended periods after recovery from an Ebola infection, and might infect a sexual partner. Therefore, we recommend that you either don't have sex or that you use condoms during sexual intercourse for as long is currently recommended by the World Health Organization, or until your semen is tested to show that Ebola virus is not present. If you recover from Ebola, we will talk with you about precautions you should continue to take to prevent passing the virus to others through bodily fluids.

8. Are there benefits to being in the study?

We do not know if you will benefit from being in this study. It is possible that the study drug you receive will help treat your Ebola infection. But we do not yet know which study drug is more effective. It is also possible that even if a drug is effective, it may cause serious side effects that make it more harmful than helpful.

What we learn from this study may allow us to better understand Ebola and develop better ways of treating patients with Ebola in the future.

9. What will happen to your samples and personal information?

We will store your samples and data (information) for a very long time to use for future research on Ebola. Your stored samples and data will be marked with a code and not with your name. Only researchers linked to this study can get the codes.

Your study information will be placed in a secure electronic system. It will not include your name. We must get approval from the DRC and US ethics boards that review this study before we share samples and data with other researchers. Other information, such as your sex, age, or health history might also be shared, but your name will not. This information cannot be traced back to you. You will not get any information about future research. Your sample will not be sold. You will not be paid for any products that result from this research.

The only risk of allowing us to store your sample would be an accidental release of your identity.

If you change your mind and decide you do not want us to store your sample or data, please let us know. We will do our best to follow your wishes but cannot promise that we will always be able to destroy your samples or data.

10. Will it cost you anything to be in this study?

It will not cost you anything to be in this study.

11. Will you be paid if you join this study?

No, you will not be paid.

12. Who is watching over this study?

A Data and Safety Monitoring Board (DSMB) will be looking at the study information very closely. The DSMB is made up of doctors and other people who are not directly involved in the study and who have a good understanding of Ebola and research studies. The DSMB may recommend changing the study drugs being used or stopping the study earlier than planned if they think it is not safe to continue or if they find out early that a drug is working better. The DRC and US ethics boards will also be watching over this study and have the authority to stop it at any time.

13. How will your privacy be protected?

We will keep your study information private. All files with information that could identify you will be kept in locked cabinets or secure computers. People responsible for making sure that the research is done properly may look at your study records. This might include people from the DRC and the US including the NIH and their designees. All of these people will also keep your identity private. Results from this study, but not your

identity, may be shared with local medical providers or government health organizations to help them better understand Ebola virus infection.

14. What other things should you know about this research study?

a. ClinicalTrials.gov

A description of this study is on the internet at http://www.ClinicalTrials.gov. This website will not include information about you. At most, the website will include a summary of the results. You can search this website at any time.

b. Conflict of Interest

The policy of the NIH is to evaluate investigators at least yearly for any conflicts of interest. Research participants may review the system for assessing conflicts of interest by checking the web site link: http://ethics.od.nih.gov/forms/Protocol-Review-Guide.pdf. Copies of the standards may also be requested by research patients. This study has investigators that are NIH employees and some that are not. All non-NIH investigators are required to follow the principles of the Protocol Review Guide but are not required to report their financial holdings to the NIH.

The US NIH and the research team for this study have developed one of the drugs being used in this study. This means it is possible that the results of this study could lead to payments to NIH and Institut National de Recherche Biomédicale (INRB) scientists and to the NIH. By law, US government scientists are required to receive such payments for their inventions. You will not receive any money from the development of the drugs being used in this study.

c. What is the Ethical Review Committee and how does it protect you?

Your government's ethics committee will review this study. It protects the rights and welfare of the people taking part in research studies. You can contact Patrick Kayembe Kalambayi, coordinator of the DRC ethics board (Tel: 0818111182) to answer questions you may have about being part of this study and your rights as someone who is in a study. The ethics committee at the US NIH has also reviewed and approved this research.

d. What do you do if you have questions about the study?

If you have questions about the study, you may contact the principal investigators. Dr. Jean-Jacques Muyembe-Tamfum (DRC INRB) can be reached by phone +243 898949289, or by email jjmuyembet@gmail.com. Dr. Richard T. Davey, Jr. (US NIH) can be reached by email rdavey@niaid.nih.gov.

e. What should you do if you are injured or ill as a result of being in this study?

We do not expect any harm from participating in this study. However, unforeseeable risks may be present. The study doctors will give you short-term medical care if you are hurt by being in this study.

If you agree to be in this study, please sign or put your fingerprint below.

_____ Date: _____/_____/_____
Signature or fingerprint of participant or guardian dd mm yy

_____
Printed name of participant or guardian

_____ Date: _____/_____/_____
Signature of investigator/designee dd mm yy

_____
Printed name of investigator/designee

Complete if participant is illiterate:

Witness to Consent Interview

On the date given next to my signature, I witnessed the consent interview for the research study named above in this document. I attest that the information in this consent form was explained to the subject, and the subject indicated that his/her questions and concerns were adequately addressed.

_____ Date: _____/_____/_____
Signature of witness dd mm yy

_____
Printed name of witness

MINOR ASSENT TO PARTICIPATE IN STUDY

NIAID Protocol #:	19-I-0003
Protocol Title:	A Multicenter, Multi-Outbreak, Randomized, Controlled Safety and Efficacy Study of Investigational Therapeutics for the Treatment of Patients with Ebola Virus Disease
Sponsors:	United States National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) Democratic Republic of the Congo (DRC) National Institute for Biomedical Research
Principal Investigators:	Jean-Jacques Muyembe-Tamfum, MD, PhD (DRC) Richard T. Davey, Jr., MD (US)
Site:	Democratic Republic of the Congo (DRC), Central Africa

1 Introduction

You are being asked to be in this study because you have Ebola. Ebola can make people very sick. Some people can die from it. There are no approved medicines for treating Ebola, so we are trying to learn more about how best to treat it.

First, we want to explain the study to you. Then, you can decide if you want to be in it. You do not have to be in this study if you do not want to.

2 What is this study about?

We recently completed a research study where we tested 4 possible medicines to find out if any of these medicines could help treat Ebola. From an early review of the study results we now know that 2 of the 4 study drugs were better at treating Ebola than the others. We do not yet know if one of these 2 might be better than the other because we are still reviewing the data. While we are waiting to learn the results of the research study, we wish to make these medicines available to more people, including kids, who have Ebola.

3 Do I have to be in this study?

No. You can decide not to be in the study. You can talk to your family, friends, and doctor before you decide. Even if you want to be in the study now, you can change your mind later and stop being in the study at any time.

4 What will happen in this research study?

If it is okay with you and you agree to join this study, we will give you 1 of the study drugs. There are 2 study drugs that we are testing. You will only get 1 of them, but we do not know which one yet. You cannot pick which one you want but we will tell you when we find out which study drug you will receive.

During the study, you will stay in the Ebola treatment center for a while. You may stay up to a few weeks if you are very sick. You will continue to get regular care for Ebola. We will use a needle to put a small tube in your arm for several days. We will give you the study drug through the tube in your arm. We will also collect some blood and we may ask you to give us some urine in a cup for tests.

After some time in the treatment center, when the doctor thinks it is safe for you, you can go home. We will contact you at least one more time to ask how you are feeling. If possible, we will give you a check up and take some more blood for tests. Then you will be done with the study. Your total time in the study will be about 1 month.

5 Will any part of the study hurt?

Taking a study drug may make you feel sick, but you may also feel sick from the Ebola. The study drugs have not been given to a lot of people, so the study drug you get may cause changes that hurt or bother you that we do not know about. It may also not have been given to many children before, so we may not know whether it may cause side effects in kids that were not seen in adults. In a very small number of people, the study drugs could cause something dangerous that people could die from. It is important that you always tell the study staff how you are feeling.

If you get the drug called “mAb114,” you will get it 1 time. It might make you feel sick, cold, dizzy, or shaky, and it might give you a fever. It could make you have diarrhea, make you throw up or feel like you might throw up. It could make your head, muscles, or joints hurt. It could make you feel itchy, give you a rash or hives, or make your lips or face swell up. You could have trouble breathing. You could feel like your heart is beating too fast. It could give you a pain in your chest.

If you get the drug called “REGN-EB3,” you will get it 1 time. It might make your head or muscles hurt. It could make you feel cold, shaky, or dizzy, or give you a fever, rash, or hives. It could make you cough or faint, make your joints hurt, or make your lips, face, or throat swell up. You could have trouble breathing. It could give you a pain in your chest.

You will just get 1 of these drugs. You might have some of these things happen, or you might not feel any of them. We will watch you carefully when you get the study drug. If the drug makes you feel bad, we can sometimes give you medicines to help you feel better.

It might hurt when we put a needle in your arm to draw blood or put in the plastic tube to give you the study drug. Your arm may get swollen and sore where the needle goes

in, and you might get a black and blue mark. These things should go away on their own. There is a very small chance that you could get an infection.

6 What do I need to know about pregnancy during the study?

If you are female: We do not know the effects of the study drugs in pregnancy or in a nursing baby. If you can become pregnant, we may do pregnancy testing while you are on this study. If you are pregnant or get pregnant around the time you get the study drug, we don't know if there may be effects on you or your baby. Therefore, you should avoid getting pregnant for 2 months after getting the study drug. You will need to use birth control if you are sexually active, unless you are not able to get pregnant. If you think that you have gotten pregnant during the study, tell the study team right away, and find medical care for your pregnancy.

If you are male: The effects of the study drugs on sperm are not known. Therefore, you should not get a sexual partner pregnant for at least 2 months after getting the study drug. You should use a condom every time you have sex for 2 months after getting the study drug.

7 Will the study help me?

We do not know if you will be helped by being in this study. We do not know which study drug will make you feel better or get well sooner. It is possible that the study drug could make you worse.

8 Will the study help others?

We might find out things from this study that will help other people with Ebola someday.

9 Do I have other choices?

You do not have to be in this study. It is up to you. You can talk to your parents and your doctor about your options.

No one will be upset if you don't want to do this study. If you say okay now, but you want to stop later, that is okay too. If you decide to stop being in the study, all you have to do is tell your doctor or nurse that you don't want to do the study anymore. No one will be mad at you if you change your mind.

If you say no, you will still be given your regular care for Ebola. We will not give you the study drugs.

10 What if I have questions?

If you want to talk to anyone about this research study because you think you have been hurt by being part of the study, or if have any other questions about the study, you should tell the study team: Phone number +243 826792353.

Also, you can contact Dr. Jean-Jacques Muyembe-Tamfum (Tel: +243 898949289) to answer questions you may have about being part of this study and your rights as someone who is in a study.

If you have any questions at any time about this research study, you may ask someone on the study team.

If you decide to be in the study, please write your name below.

I have had this study explained to me in a way that I understand, and I have had the chance to ask questions. I agree to take part in this study.

Signature or fingerprint of Minor Patient: _____ Date: _____

Print Name: _____

Signature of Investigator/Designee: _____ Date: _____

Print Name: _____