Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: The PREVAIL II Writing Group. A randomized, controlled trial of ZMapp for Ebola virus infection. N Engl J Med 2016;375:1448-56. DOI: 10.1056/NEJMoa1604330

This supplement contains the following items:
1. Original protocol (version 1.0), summary of approved amendments, and the final protocol (version 6.0).
2. Original statistical analysis plan (DSMB Charter) and the final statistical analysis plan. There were no formal amendments made to the original SAP. Rather, the Final SAP arose from a running series of discussions with FDA that culminated in the final plan that was DSMB-approved prior to unblinding of study data.

A Multicenter Randomized Safety and Efficacy Study of Putative Investigational Therapeutics in the Treatment of Patients with Known Ebola Infection

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CBC	Complete Blood Count
CFR	Code of Federal Regulations (US)
CI	Confidence Interval
CRF	Case Report Form
CSO	Clinical Safety Office
DCR	Division of Clinical Research
DRC	Democratic Republic of Congo
DSMB	Data and Safety Monitoring Board
EBOV	Ebola virus
ECG	electrocardiogram
EVD	Ebola hemorrhagic fever
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
HCW	health care workers
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
MCMs	medical countermeasures
NHP	nonhuman primate
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OCRPRO	Office of Clinical Research Policy and Regulatory Operations
OHRP	Office for Human Research Protections
oSOC	optimized standard of care
OTC	over-the-counter
PI	Principal Investigator
PK	Pharmacokinetics
POC	point-of-care
SAE	Serious Adverse Event/Serious Adverse Experience
SERF	Safety Expedited Report Form
SMM	Sponsor Medical Monitor
SOC	standard-of-care
SRCP	Safety Review and Communications Plan
SUSAR	Serious Unexpected Suspected Adverse Reactions
UP	Unanticipated Problem
UPnonAE	Unanticipated Problem that is not an Adverse Event
WBC	White Blood Cell Count

ZEBOV	Zaire ebolavirus

PROTOCOL SUMMARY

Full Title:	A Multicenter Randomized Safety and Efficacy Study of Putative Investigational Therapeutics in the Treatment of Patients with Known Ebola Infection
Short Title:	MCM RCT in EBOV
Clinical Phase:	1/2
IND Sponsor:	Office of Clinical Research Policy and Regulatory Operations (OCRPRO)
Conducted by:	Multicenter Trial
Principal Investigator:	Richard T. Davey, Jr., MD
Sample Size:	Up to 100 per arm
Accrual Ceiling:	1000
Study Population:	Patients with known Ebola infection
Accrual Period:	January 2015 – December 2016
Study Design:	Randomized clinical trial
Study Duration:	Start Date: January 2015 End Date: December 2016
Study Agents:	ZMapp^{tm}, convalescent plasma, favipiravir, TKM-Ebola, others
Primary Objective:	• To establish the safety and efficacy of investigational therapeutics in patients with Ebola virus infection
Secondary Objectives:	• Uniform observational database on clinical and virologic parameters associated with severe Ebola virus infection • To evaluate the comparative effects of investigational therapeutics on clinical parameters of Ebola infection • Comparative effects of different investigational agents on immediate plasma viral load kinetics • 24-48 hour pharmacokinetics of investigational therapeutics when possible and appropriate • Comparative frequency of adverse events (AEs) and serious adverse events (SAEs) • Duration of hospital stay • Time to viral load clearance
Primary Endpoint:	• Mortality at Day 28
Inclusion Criteria	• Males or females with documented positive PCR for Ebola virus infection within 10 days of enrollment • Willingness of study participant to accept randomization to any assigned treatment arm • Access to optimized standard-of-care (oSOC)

- All males and females of childbearing potential, must be willing to use effective methods of contraception, from time of enrollment through at least 90 days after viral clearance
- Must agree not to enroll in another study of an investigational agent prior to completion of last required protocol visit
- Patient or Surrogate must provide written informed consent

Exclusion Criteria:

- Any serious medical condition that, in the opinion of the site investigator, would place the patient at an unreasonably increased risk through participation in this study, including any past or concurrent conditions that would preclude randomization to one or more of the assigned treatment arms.
- Prior treatment with any investigational antiviral drug therapy against Ebola infection or investigational anti-Ebola vaccine within 5 half-lives or 30 days, whichever is longer, prior to enrollment.
- Patients who, in the judgment of the investigator, will be unlikely to comply with the requirements of this protocol

Study Design Principles:

A randomized, controlled adaptive trial, with frequent interim monitoring to facilitate the following: dropping of poorly performing arms, introduction of new candidate therapies and modification of current optimized standard-of-care (oSOC). Comparisons of safety and efficacy will be based on data from concurrently randomized participants. In its simplest iteration, the study can be viewed as a series of 2-arm comparisons whereby the superior treatment, if identified, from each pairwise comparison becomes the basis of the new supportive care backbone (hence the term "optimized SOC", or oSOC, to describe this potentially evolving backbone) common to each future arm of the study and against which additional investigational interventions may then be added to the protocol, tested and compared:
Arm A: optimized SOC alone
Arm B: Investigational treatment X + optimized SOC

- In the <u>initial</u> iteration and at protocol team discretion, the optimized SOC employed in Arm A is expected to consist of aggressive fluid replacement, hemodynamic support,

electrolyte monitoring and replacement, and other measures of advanced medical support, to be compared to Arm B in which both investigational therapeutic agent X plus that same optimized SOC are featured.

- If this pairwise comparison shows the superiority of Arm B over Arm A, then investigational treatment X featured in Arm B will be incorporated into the new oSOC common to each future arm of the study (assuming adequate drug supply exists to permit this).
- Conversely, if a given pairwise comparison of Arm A versus Arm B fails to yield a clear statistical winner in terms of the primary endpoint, then subsequent pairwise comparisons will not incorporate the "failed" intervention featured in current Arm B into the new oSOC backbone.

Study Synopsis:

- Informed consent for research participation upon admission into the treatment center
- Baseline determination of clinical status according to standardized CRF
- Baseline collection of plasma for viral load by PCR to be processed by an appropriate laboratory facility
- Centralized randomization assignment made
- Provision of Arm A or Arm B intervention according to assigned treatment arm and the individual pharmacologic or logistical requirements of the treatment intervention
- 24-48 hour pharmacokinetic measurements of assigned intervention where appropriate and possible
- Daily assessments of clinical status according to standardized CRF and flowsheet
- Serial collection of plasma for viral load determination by PCR for processing in an appropriate laboratory facility
- Primary and secondary endpoint determinations

PRÉCIS

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 EBOV 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. However, the 2014 West African outbreak significantly exceeds all previous outbreaks in geographic range, number of patients affected, and in disruption of typical activities of civil society.

There is strong consensus that the most important element necessary to improve survival from Ebola infection is the provision of full hemodynamic support in the form of aggressive fluid replacement, ability to diagnose and correct severe metabolic derangements, and other standards of modern medical care available in resource-rich environments. However, against this background, a small series of investigational agents or interventions have also been proposed as putative antiviral strategies of potential utility in treating this infection. Unfortunately, phase 1/2 data supporting the safety and efficacy of these agents is generally lacking, and thus there should be equipoise as to which, if any, of these interventions should be utilized in the treatment of severe infection.

In this multicenter randomized trial, we propose a flexible trial design with frequent interim monitoring to facilitate early elimination of poorly performing treatments as well as the introduction of new candidate therapies. The trial allows for a series of pairwise comparisons of novel interventions against a background of optimized medical care, with the goal of determining whether one or more of these interventions can improve the mortality over that achievable through optimized standard-of-care (oSOC) alone. The primary endpoint of this trial will be comparative mortality at Day 28, with a number of secondary endpoints that hopefully will generate generalizable knowledge about the relative safety and antiviral activity of these adjunctive interventions.

1 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Background

1.1.1 Filoviruses

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 EBOV outbreaks (Table 1) affecting mostly central Africa, with 2 large outbreaks in 1995 in Kikwit, DRC, and in Gulu, Uganda in 2000-2001. The ongoing West African outbreak significantly exceeds all previous outbreaks in geographic range, number of patients affected, and in disruption of typical activities of civil society.

Table 1: Ebolavirus Outbreaks

Viral species	Year	Outbreak location	# of human cases (% fatality)
	1976	Yambuku, Zaire (DRC)	318 (88%)
Zaire ebolavirus	1977	Tandala, Zaire (DRC)	1 (100%)
	1994	Ogooue-Invindo province, Gabon	51 (60%)
	1995	Kikwit, Democratic Republic of Congo	315 (79%)
	1996	Mayibout, Gabon	37 (57%)
	1996	Booue, Gabon and Johannesburg, South Africa	61 (74%)
	2001-02	Ogooue-Invindo province, Republic of Congo (RC)	124 (79%)
	2002-03	Cuvette region, RC and Ogooue-Invindo province, Gabon	143 (90%)
	2003	Mboma and Mbandza, Republic of Congo	35 (83%)
	2005	Etoumbi and Mbomo, Republic of Congo	12 (75%)
	2007	Kasai Occidental province, Democratic Republic of Congo	25 (not determined)
	2008/2009	Democratic Republic of the Congo	32 (47%)
Sudan ebolavirus	1976	Nzara, Maridi, Tembura, Juba, Sudan	284 (53%)
	1979	Nzara, Yambio, Sudan	34 (65%)
	2000-01	Gulu, Masindi, Uganda	425 (53%)
	2004	Yambio, Sudan	17 (41%)
	2011	Uganda (Luwero District)	1 (100%)
Taï	1994	Tai forest, Ivory Coast	1 (0%)
ebolavirus	1995	Liberia, Liberia	1 (0%)
Reston ebolavirus	1989	Reston, VA, USA	4 (0%)
	1992	Siena, Italy	0
	1996	Alice, TX, USA	0
	2008	Philippines	0

Bundibugyo ebolavirus	2007/2008	Uganda	131 (37%)

1.1.2 Therapy

To date the standard treatment of Ebola hemorrhagic fever (EVD) during the present 2014 outbreak has been strictly supportive, involving largely oral fluid and electrolyte replenishment and pain reduction. 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 have neither been available nor tested in most patients. However, in the few centers where such measures were able to be employed, a substantial reduction in mortality has been reported. Thus, substantial planning efforts are currently geared towards identification, standardization, and deployment of the most successful standard-of-care (SOC) measures that potentially could be introduced into these previously resource-poor areas where the majority of patients have been treated. In addition to ongoing epidemiologic measures to limit the spread to uninfected populations, there is widespread consensus that improved SOC measures could represent the single most effective means of reducing the substantial mortality rates associated with the disease in the affected regions.

In contrast, in the United States and other developed nations to which a small number of infected health care workers (HCW) have been medically evacuated, aggressive intravenous 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 optimized standard of care (oSOC) there 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 October 8, 2014, investigational treatment data were available on a total of 13 HCWs or other individuals with documented Ebola infection who had been medically evacuated to special isolation units in the US or Europe. The reported distribution to date of MCMs in these individuals was as follows:

- 2 have received no MCMs to date
- 6 have received 1 MCM to date
- 4 have received 2 MCMs to date
- 1 has received 3 MCMs to date

The reported list of MCMs employed in the experimental treatment of these individuals includes convalescent plasma (4 patients), zMapp triple monoclonal antibody cocktail (4 patients), Tekmira siRNA product (3 patients), favipiravir (4 patients), brincidofovir (2 patients), and zMaB monoclonal antibody cocktail (1 patient). In addition, to date 5 medically evacuated HCWs with serious needlestick exposures to Ebola virus, while in country, but no documented infection, have also received 1 putative MCM each: Tekmira siRNA in one case and the investigational VSVΔG-ZEBOV vaccine in the other four. It should be emphasized that in 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 humans 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 in rodent models, but either failed testing or were not thoroughly tested in the nonhuman primate (NHP) model, which is 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 current outbreak and, in fact, was also used in a limited number of patients during the Kikwit 1995 ZEBOV outbreak. However, its earlier success remains a matter of dispute (1). Experimentally, passive immunization with horse serum resulted in protection of Hamadryl baboons (2), whereas it only delayed death in Cynomolgus macaques (3, 4). Certain monoclonal antibody treatments have also been successful in rodent models (5-7) but have failed in preliminary nonhuman primate studies (8), indicating possible evasion of antibody neutralization as an escape mechanism of the virus. Other, more recent monoclonal antibody cocktails may avoid this limitation. However, it remains fair to say, at least at this time, that the therapeutic role of convalescent plasma or monoclonal preparations as treatment adjuncts remain as unsubstantiated in this disease as do direct antiviral agents.

1.2 Rationale for Study

The current state of medical science with respect to the treatment of filovirus infections such as Ebola does not adequately address the role of therapeutic adjuncts beyond supportive care in the successful management of these infections. In many cases, our understanding of the role that these adjunctive therapies may play is greatly hampered by lack of an adequate phase 1 safety and toxicity database of the lead drug candidates, or by lack of data concerning even how the candidates in more advanced development may perform in this particular patient population. The tragic dimensions of the ongoing Ebola epidemic in West Africa afford little time to explore these issues according to a more conventional time frame of traditional drug development, and argue strongly for an accelerated exploration of the safety, toxicity, and potential preliminary efficacy of lead agents in a controlled research setting.

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:

- Even in highly-resourced medical environments such as those available in the US, Europe, or other developed regions, the past record of being able to generate important and generalizable knowledge concerning the role of experimental therapies for infectious diseases of public health importance when those agents have been made available under single-use emergency IND, Emergency Use Authorization (EUA), or similar mechanisms has been disappointing at best. A consolidated multicenter approach to study lead candidates according to a single research protocol offers a potential opportunity to improve upon this record.

- Even if concentrated efforts to generate important comparative efficacy assessments between individual treatment interventions falls short, 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 receiving oSOC.

- Optimized SOC must be the mainstay of therapy and remain the backbone to which experimental treatment modalities must be introduced and compared.

- Depending upon site and resources, invariably differences in oSOC may occur that may obscure the potential additional contribution of experimental therapeutics. Therefore, every effort must be made to standardize the oSOC that exists as the backbone to this experimental treatment protocol. In situations where this may not be fully possible, i.e. in comparing in-country oSOC versus oSOC available in intensive care settings within developed nations, this difference must be taken into account when comparing outcome in different patient cohorts.

- Questions of equity concerning the ethics of allowing potentially beneficial experimental treatments to be studied in places where fully optimized supportive care may be possible, and not in places where optimized care has not been introduced to date, are certainly reasonable, heartfelt, and compelling but, if taken to their logical extreme when involving drugs in extremely limited supply and of unknown safety, could prevent their scientific study altogether and result in no generalizable knowledge being generated about the value of these agents in any setting, an outcome that would disadvantage society as a whole.

- A unique and presently unavoidable factor in establishing pairwise comparisons identified for this trial is the limited, intermittent, or absent drug supply that may exist for several of the lead candidates proposed for study. The current flexible treatment design is an attempt to overcome this unpredictable element.

- As present knowledge of the potential toxicity of lead candidates in this patient population is as limited as knowledge of their potential therapeutic value, investigators should and must be able to maintain equipoise as to the introduction and role of individual agents in treating patients severely ill with Ebola infection.

- A key ethical feature and justification for this approach, based upon the current and foreseeable circumstances, is that there is a significant degree of 'acceptability of [trial drug] risk,' in the face of unprecedented individual and community risk for morbidity and mortality.

- The use of a common protocol is recommended for the following reasons:

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

    - As mentioned above, this design can accommodate staggered and intermittent availability of limited supplies of the anti-Ebola investigational drugs

- This design can also provide a more equitable means of allocating scarce product through randomization (much like a lottery) while also allowing critically important data to be gathered on the safety and efficacy of these investigational products that will benefit patients (i.e., knowledge of whether an investigational product is actually helping, hurting, or of no consequence).

- Having a randomized concurrent control group is essential to maximize the likelihood that the conclusions drawn from the trial are correct.

- A single trial design allows for having a data safety monitoring board (DSMB) and stopping rules in place. The stopping rules should be reasonable, and if one of the products is found to be effective at an interim time point but there is not a sufficient supply of the product that has been found to be effective, it may still be ethical to continue the common protocol. When sufficient supplies of the product become available, that product might be incorporated into the revised oSOC, as discussed earlier. If there are insufficient supplies of a product, even if efficacy has been shown, one may be able to argue that providing the scarce supplies of drug through a clinical trial is more equitable than other potential approaches in addition to allowing continued comparative data generation to improve the understanding of its appropriate use.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To establish the safety and efficacy of investigational therapeutics in patients with Ebola virus infection.

2.2 Secondary Objectives

- To create a uniform observational database on clinical and virologic parameters associated with severe Ebola virus infection
- To evaluate the comparative effects of investigational therapeutics on clinical parameters of Ebola infection
- To study the comparative effects of different investigational agents on immediate plasma viral load kinetics
- To obtain 24-48 hour pharmacokinetics of investigational therapeutics when possible and appropriate*
- To determine the comparative frequency of adverse events (AEs) and serious adverse events (SAEs)
- To compare the duration of hospital stay
- To compare the time to viral load clearance

* 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 of infectious samples falling under Select Agent regulations, could limit these explorations outside the context of a high containment laboratory such as a BSL-4 facility.

3 STUDY DESIGN

3.1 General

Study size: up to 1000 patients
Study duration: 24 months
Study duration of individual subjects: 30 days following the primary endpoint (mortality at day 28), or for a total of 58 days.
Sex distribution: males and females
Age range: unrestricted

A randomized, controlled clinical trial of experimental Ebola virus disease therapies compared to current oSOC. Treatment efficacy evaluations are based on outcome comparisons between treatment arms from concurrently enrolled subjects. The study can be conceptualized as a series of 2-arm comparisons between different therapeutic interventions: oSOC versus an experimental therapy plus oSOC. It is intended that the oSOC will be updated to incorporate an experimental therapy when the latter's efficacy has been demonstrated. While the updated oSOC should be the comparator for unproven therapies, this may not always be practical (e.g., when supply of the new drug is limited). Whether the updated oSOC is always added as optimized background therapy to existing unproven/experimental therapies will depend on practical considerations, including drug availability and the appropriateness of combining specific therapies. However, the intent is that the study will continue enrolling and employ the next selection of available medical countermeasure in the comparison if there is a temporary shortage of the present countermeasure being studied.

Stage 1: the initial phase (see figure 1)
Randomization to the following:

Arm A: $oSOC_1$** alone
or
Arm B: Investigational treatment X + $oSOC_1$**

*The subscript "1" indicates the first or current "optimized standard-of-care." In the initial iteration and at protocol design team discretion, Arm A will be an oSOC alone arm to be compared to Arm B in which both an investigational therapeutic agent (i.e. Drug "X") plus oSOC are combined.

** In developed countries, oSOC is defined as the application of aggressive fluid resuscitation, hemodynamic and respiratory support, metabolic corrections, diagnostic evaluation, and other modalities of advanced critical care that are generally available in most academic centers capable of caring for critically ill patients. In areas where such advanced methods may not be fully available (i.e., in advanced medical care units to be

built and supported in the affected countries of West Africa by the USG and other government entities), this definition should apply to the optimal standards of care possible in those settings.

If and when a statistical difference is shown between the 2 arms supporting superiority of one intervention over the other, the superior ("winning") intervention is then used as the basis of a modified oSOC in which incorporation of that intervention as an addition to the prior oSOC becomes the new basis of comparison. This is assuming that sufficient drug supply exists to permit the incorporation of that superior therapy into a new oSOC backbone and fuel additional comparisons. If that is not the case, then subsequent comparisons will have to revert back to the previous oSOC until such time as additional quantities of the superior therapy can be made available. If, however, incorporation into a new oSOC is possible, then that modified arm can then compared to new Arm C (i.e., consisting of a new therapeutic intervention not previously tested) so that the pairwise comparisons can continue until the list of favored treatment explorations is exhausted and/or until an optimal regimen appears clear. This can be summarized as follows:

Stages 2-K: the post-initial phase with up to K additional therapies.

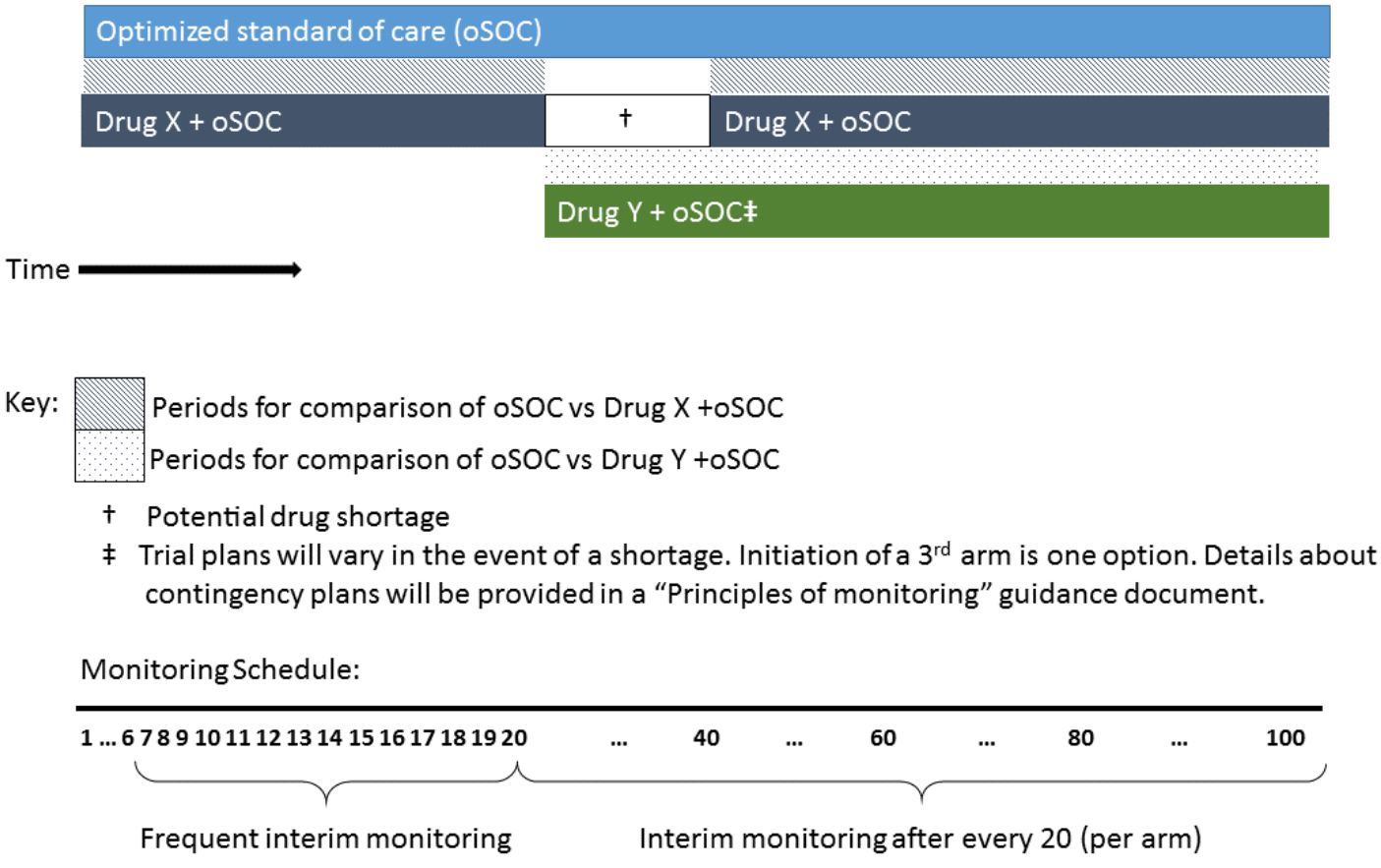
Randomization to the following:
Control arm: Updated current oSOC ($oSOC_{k;\ where}$ k=2,…, K to indicate the possible updated oSOCs)

Experimental arm: Investigational therapy + best oSOC, where the best oSOC may be the most current oSOC or the previous oSOC, depending on drug availability, appropriateness of combination therapy, etc. as determined by the study team in concordance with the DSMB.

Advisory stopping boundaries for efficacy (and futility) will be provided to the DSMB to guide decisions about when an experimental arm is deemed superior (or not worthy of further investigation). A description of these boundaries is provided in the statistics section (Section 7). Specifics about these boundaries will be provided in a DSMB statistical analysis plan.

While for illustrative purposes, the strategy is described with sequential pairwise comparisons, in practice, it can be adapted for more than 2 pairwise comparisons. The study might be modified accordingly, if there is compelling scientific interest to study more than 2 different interventions simultaneously ("Drug Y" example in Figure 1). Success at being able to demonstrate statistical difference between comparator arms will of course depend upon being able to enroll sufficient numbers into each arm to power these comparisons.

Figure 1: Example of Possible Clinical Trial Design Schematic for the Common Protocol – First Phase



3.2 Overview of Study Drugs

At the present time (fall 2014) preclinical studies, and/or past use of interventions with anecdotal evidence, have identified at least 7 candidate therapeutic interventions that might be considered as prime candidates for further study in patients with known Ebola infection. With time it is possible that additional antiviral or immune-enhancing agents with preclinical supporting data may be identified and added to this list. Conversely, emerging toxicity data, failure to replicate previous supportive findings in additional preclinical animal model testing, or similarly negative factors could also lead to narrowing of this list over time. Further, if inclusion were to be expanded to patients with high-risk exposures but no documented infection, the list of putative MCMs could be broadened even further and would likely include putative vaccine candidates. However, confining this proposed RCT to just enrollees with documented infection, the likely lead candidates for consideration of study would include:

- Convalescent or post-immunization plasma harvested from recent Ebola infection survivors:
  - In time it is possible that this category could potentially be expanded to include plasma donors who have participated in phase 1 anti-Ebola vaccine testing and whose plasma shows high neutralizing activity against the virus in animal or *in vitro* assays.
- zMapp triple monoclonal antibody cocktail from Mapp Biopharmaceutical:
  - A combination of 3 different humanized monoclonal antibodies against the glycoprotein of Ebola
- Tekmira siRNA (or "TKM-Ebola") from Tekmira Pharmaceuticals Corp:
  - A combination of small interfering RNAs targeting 2 of the 7 proteins in Ebola: Zaire Ebola L polymerase and Zaire Ebola polymerase complex protein (VP35), formulated with Tekmira's lipid nanoparticle technology.
- Favipiravir from Toyama Chemical Co., LTD:
  - A selective inhibitor of RNA-dependent RNA polymerase with activity against a wide variety of viruses.
- Brincidofovir (CMX001) from Chimerix:
  - An oral nucleotide analog with reportedly a more favorable toxicity profile than cidofovir and activity against DNA viruses that also has been shown in vitro to have activity against Ebola virus.
- BCX4433 from BioCryst
  - viral RNA-dependent RNA polymerase (RdRp) inhibitor
- AVI-7537 from Sarepta
  - phosphorodiamidate morpholino oligomer

3.3 Considerations in Choice of Study Drugs

Several factors influencing choice and sequence of study drugs/interventions to be compared in this protocol must be considered:

- Willingness of both the pharmaceutical sponsors and the FDA to allow each of these drugs to be studied according to this proposed trial design
- Sufficient and dedicated supply of individual agents to allow them to be available for study over the projected timeline of the trial
- Ongoing equipoise of the investigators that
  - No available individual agent has yet been demonstrated to be superior to oSOC
  - No available individual agent has yet been demonstrated to be superior to other agents
- No compelling safety/toxicity concern has emerged with respect to individual agents to favor their removal from consideration as study interventions
- The status of eIND access to these interventions during the projected timeline of this trial that may preclude, or circumvent, interest in enrollment of patients into this RCT.

With these considerations in mind, the starting choice of interventions to be entered into and compared in this trial will be determined by a consensus of the site investigators performing this study at their individual treatment centers. The most recent deliberations of this group are reflected in Appendix A of this protocol.

3.4 Definitions for the Purpose of this Study

Enrolled

For the purpose of collecting data and samples, and reporting AEs, a subject will be considered enrolled beginning from when the informed consent form is signed until the subject is considered either “discontinued”, or “completed”.

Discontinued

Subjects are considered discontinued when they meet 1 or more of the following criteria:

- Subject withdraws consent after being dosed and prior to the completion of Day 28 (see section 4.5)
- Subject is withdrawn after enrollment by investigator (see Section 4.6) including lost to follow-up

Completed

Subjects are considered completed when they 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 scheduled for that time

4 STUDY POPULATION

4.1 Research Subject Recruitment

Enrollees will be sought from amongst those HCWs and other individuals who are medically evacuated to the United States or other participating countries for additional medical care not available at the site of Ebola infection, whose infection was diagnosed in the United States or other participating countries following their return, or who may have acquired the infection as cases of secondary transmission. This trial will also be expanded to include medical treatment units in West Africa capable of providing an enhanced level of supportive care at the time that those facilities declare themselves capable of supporting clinical research endeavors of this type and complexity. At the very least this designation of being able to provide enhanced supportive care should include the provision of aggressive fluid resuscitation (preferably intravenously, but potentially orally through nasogastric tubes), hemodynamic monitoring, and point-of-care monitoring of fluid and electrolyte disturbances coupled with the ability to correct such abnormalities as they are detected.

4.1.1 Participation of Site Employees

Site employees who meet inclusion 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.
- To protect the privacy and confidentiality of employee's participation the employee participant must not work directly for the Principal Investigator (PI) or any of the associate investigators on this protocol.

4.2 Inclusion Criteria

- Males or females with documented positive PCR for Ebola virus infection within 10 days of enrollment
- Willingness of study participant to accept randomization to any assigned treatment arm
- Access to oSOC
- All males and females of childbearing potential, must be willing to use highly effective [e.g. absolute abstinence from potentially reproductive sexual activity, hormonal, surgical or multiple barrier/combined] methods of contraception, from time of enrollment through at least 90 days after viral clearance
- Must agree not to enroll in another study of an investigational agent prior to completion of last required protocol visit
- Ability to provide informed consent personally, or by a legally-authorized [per applicable local laws and regulations] representative [LAR] if the patient is unable to do so.

4.3 Exclusion Criteria

- Any medical condition that, in the opinion of the site investigator, would place the patient at an unreasonably increased risk through participation in this study, including any past or concurrent conditions that would preclude randomization to one or more of

the assigned treatment arms (e.g., severe nausea and vomiting precluding use of oral therapies).

- Prior treatment with any investigational antiviral drug therapy against Ebola infection or investigational anti-Ebola vaccine within 5 half-lives or 30 days, whichever is longer, prior to enrollment.
- Patients who, in the judgment of the investigator, will be unlikely to comply with the requirements of this protocol

4.4 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 infection than from the study medications themselves, pregnant women will be permitted entry into the study. However, there may still be certain study medications (e.g., favipiravir) with known teratogenic potential to which pregnant women should not be assigned, and these considerations must be reviewed on a case-by-case basis with study investigators. If favipiravir happens to be the drug currently under study, pregnant women should not be enrolled in the trial during the period this particular drug is being tested. The risks from the study medications to nursing infants are also unknown at this time. Therefore, female subjects will be required to avoid breastfeeding during the study to minimize any potential risk.
Whenever possible, every attempt will be made to track the pregnancy until delivery in order to determine the outcome of the study intervention on the fetus.

4.4.1 Inclusion of Children

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 study participation.

4.5 Subject Withdrawal

Subjects can terminate 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. Subjects who withdraw prior to receipt of their assigned experimental treatment intervention will be replaced and will not be counted against the cap/arm.

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 be withdrawn from the study for any of the following reasons:

- The investigator believes that continuation in the study would be detrimental to the subject. In general, subjects withdrawn for AEs will still be followed for safety follow-up if possible.
- If in the investigator's best judgment discontinuation is in the subject's best interest.

The reason for withdrawal from the study is to be recorded in the study record. If a non-serious AE is unresolved at the time of discontinuation, efforts should be made to follow up until the event resolves or stabilizes, the subject is lost to follow-up, or there is some other resolution of the event. The investigator is to make every attempt to follow all SAEs to resolution.

4.7 Discontinuation of Study

The National Institute of Allergy and Infectious Diseases (NIAID), each institution's Institutional Review Board (IRB), or the Food and Drug Administration (FDA) may terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of an AE in this or other studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Data recording is inaccurate or incomplete
- Investigators do not adhere to the protocol or applicable regulatory guidelines in conducting the study

5 TREATMENT

5.1 Randomization and Blinding

This study follows an open-label randomization design. A randomization scheme will be generated by the Data Management Center prior to the initiation of the study.

5.2 Study Drugs

Every attempt will be made to pre-position the study drugs under active study at the participating sites' pharmacies in advance of enrollments. Randomization of individual patients to a given study drug will only occur when there is sufficient quantity of that drug to complete a full treatment course for those individuals.

6 STUDY PROCEDURES

6.1 Personnel for Study Procedures

The physical examination (excluding vital signs) will be performed by a physician, nurse practitioner, or physician's assistant, as allowable by state or local regulations. All other assessments may be performed by other members of the investigative team (as noted on the Delegation of Responsibilities form).

6.2 Schedule of Assessments

The day when the subject is enrolled and randomized to their assigned treatment arm is denoted as Study Day 0. The first day after enrollment/randomization is Study Day 1 and will

generally be the day in which an investigational treatment intervention will be initiated (if part of the assigned treatment arm). Subsequent days will be numbered chronologically through Day 58 of study.

Table 2: Schedule of Assessment

Day	0	1	2	3	4	5	6	7	10	14	21	28	58
ELIGIBILITY	X												
informed consent	X												
medical history & physical	X	X	X	X	X	X	X	X	X	X	X	X	X
enrollment	X												
RANDOMIZATION TO TREATMENT ARM	X												
baseline laboratory studies*	X**	X**											
pregnancy testing (if applicable)	X												
INITIATE ASSIGNED INTERVENTION		X											
baseline PCR	X**	X**											
MONITORING													
Serial PCR			X	X	X	X	X	X	X	X	X	X	X***
Serial laboratory safety studies*			X	X		x	X	X	X	X	X***	XX***	X***
PK if feasible (baseline & serial samples)****		X	X										
STANDARDIZED CRF													
baseline	X												
daily or specific day		X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X***
SPECIMEN STORAGE*****	X	X	X	X				X	X	X	X	X	X***

* whenever possible, full panel of POC studies to include CBC with diff, PT/PTT/INR, D---Dimer, acute/hepatic/mineral chemistry panels, and U/A

** indicates test can be done either on Day 0 or pre---drug on Day 1

*** as clinically warranted

**** where technically feasible according to appropriate safety precautions and Select Agent regulations

***** serum, plasma, and PBMCs, where possible to do so under Select Agent storage regulations

6.2.1 Screening and Informed Consent

The investigator or a qualified and previously designated member of the study team will review informed consent with the subject.

6.2.2 Demographics

The following information should be recorded:

- Age
- Sex
- Ethnicity
- Race

6.2.3 Medical History

The following information should be recorded:

- Medical history including any chronic medical conditions
- Current use of prescription and over-the-counter (OTC) medications within the last 14 days
- History of allergies
- Current participation in any recent research protocols
- Reproductive history to include contraceptive experience, current practice, and willingness to adhere to protocol requirements

6.2.4 Clinical Data

- Vital signs

6.2.5 Physical Exam

A focused physical exam to ensure there are not medical conditions that would increase a subject's risk for participation in this study

6.2.6 Laboratory Testing

When possible, the following tests will be performed and recorded as baseline determinations:

- CBC with differential
- Acute/hepatic/mineral chemistry panels as available via POC testing
- PT/aPTT/INR
- D-Dimer
- Urinalysis (evaluating RBC, protein, and glucose only) if available as POC test

Serum or urine pregnancy test (females of childbearing potential only) if available as POC test

6.2.7 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 (or told directly if found ineligible during screening evaluation), and the reason for ineligibility will be discussed.

If desired by the subject, and if applicable for the reason for ineligibility, the results will be shared with their outside health care provider.

6.3 Day 0

6.3.1 Informed Consent

For subjects evaluated for enrollment, the investigator/qualified designee will review the study specific informed consent with the subject. Subjects interested in participating will complete the study specific informed consent on or before Day 0.

6.3.1.1 Baseline Evaluation

Prior to study drug administration, a baseline evaluation will be performed as follows consisting of an interval history and exam plus clinical safety laboratory testing if more than 24 hours has elapsed since prior measurements.

6.3.1.2 Interval History and Exam

An interval medical history will be performed. This will include:

- Any new medical conditions
- Any baseline symptoms
- Current prescription and OTC medications
- Allergies
- A brief physical exam to ensure there are not medical conditions that would increase a subject's risk for study participation

6.3.1.3 Clinical Safety Laboratory Testing

The following clinical laboratory tests will be performed and documented either on study Day 0 or on study Day 1 prior to administration of any investigational treatments:

- CBC with differential (evaluating only the WBC, hemoglobin, hematocrit, and platelets)
- Acute/hepatic/mineral chemistry panels as available via POC testing
- PT/aPTT/INR
- D-Dimer
- PCR
- Urinalysis (evaluating RBC, protein, and glucose only) if POC testing available
- Serum or urine pregnancy test (females of childbearing potential only) if appropriate and POC testing available

As these are performed for baseline assessment only the pregnancy test needs to be resulted prior to proceeding with initiation of an investigational treatment assignment.

6.4 Study Day 1

It is possible that Study Day 0 may be consumed by longitudinal determination of patient's overall clinical status, implementation of oSOC provisions, assessment for study eligibility, and study randomization. Therefore, it is likely that actual implementation of an investigational study intervention (if part of the assigned treatment arm) will be deferred until study Day 1.

6.4.1 Baseline CRF completion

This will include:

- Any past medical conditions or symptoms
- Comprehensive assessment of current clinical status and oSOC interventions
- Vital signs and physical examination
- Baseline safety laboratory measurements
- medications

6.4.2 Reference Laboratory Testing

The following reference laboratory tests will be collected and stored:

- Blood for Ebola PCR
  - Consideration of other bodily fluid sampling as clinically appropriate

6.4.3 Pharmacokinetic Sampling

- 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:
  - 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

6.5 Study Days 2+

For those medical interventions where the drug is to be administered on a serial basis according to known PK, the sponsor's recommended dose and schedule of administration will be followed and recorded on interval CRFs.

6.5.1 Interval History and Exam

Interval medical history and physical exam will be performed daily. This will include:

- Any new medical conditions or symptoms
- Current medications
- Vital signs
- Physical exam
- Adverse events
- Discharge date and clinical status, as appropriate

6.5.2 Clinical Safety Laboratory Testing

The following clinical laboratory tests will be performed and documented according to the study flowsheet:

- CBC with differential (evaluating only the WBC, hemoglobin, hematocrit, and platelets)
- Acute/hepatic/mineral chemistry panels as available via POC testing
- Urinalysis (evaluating RBC, protein, and glucose only) if POC testing available
- PT/aPTT/INR

- D-Dimer
- PCR

6.5.3 Reference Laboratory Testing

The following reference laboratory tests will be collected and stored:

- Blood for Ebola PCR as per study flowsheet
  - Consideration of other bodily fluid sampling as clinically appropriate
  - Date of first PCR negative result

6.5.4 Vital Signs, Including SaO_2

Vital signs assessments should include BP, HR, temperature, respiration rate, and pulse oximetry whenever possible.

7 STATISTICAL METHODS

7.1 Background

A statistically valid plan for conducting a randomized trial of limited and unproven treatment options for Ebola virus disease is not straightforward. Such a trial is unlike most others in several respects: 1) the mortality rate of the "control" arm, i.e., best supportive care arm, is not well known, nor are the factors associated with improved outcome, 2) the oSOC may change as a result of accumulating results from the trial, 3) although the target number of patients is 100/arm, the actual number may be much smaller because the supply of one or more treatments may be severely limited and intermittent, superiority of one arm over another might be established with lesser numbers, and/or the epidemic itself may resolve . However, rather than precluding a randomized controlled trial (RCT), these circumstances favor it, for an RCT is the most efficient and accurate means of evaluating the benefits of alternative therapies. Nonetheless, an unusual amount of flexibility in trial design is needed to seamlessly accommodate changing circumstances. Flexibility is critical for many reasons. For example, if evidence supports updating the existing oSOC (and dissemination of the new standard is feasible), this change should be implemented seamlessly. If however, the new standard requires a drug with a supply that is nearly depleted (and will remain so for some time), immediate changes to the oSOC may not be possible. Continuation of randomization to the treatment (with the nearly depleted supply) versus the initial standard may be the preferred strategy to allocate the limited supply. Plans for every potential scenario are not possible to specify *a priori*, which leaves such decision making to the domain of the study team in consultation with the DSMB. The present study design attempts to maximize the informational content of the limited data generated, given the above considerations.

7.2 Design

The trial will commence with randomization to oSOC (i.e., best supportive care) versus an experimental arm receiving oSOC plus treatment. **Randomization will use permuted blocks with variable but small block sizes, and will be stratified by duration of clinical symptoms (0-5 days versus >5 days) and site of treatment (western Africa versus the United States/Europe).** The trial endpoint is mortality by 28 days. The high mortality rate of Ebola virus disease and the

uncertainty associated with the oSOC efficacy, mandate aggressive interim monitoring, which is described in the next section. If more than 2 treatment strategies are evaluated, the design will follow the same stopping rules outlined below, but randomization will proceed with equal probability to each of the arms. Strict control of the type I error rate would require adjustment of boundaries for comparison of multiple arms. We recommend against such adjustments, given the exigent circumstances surrounding the Ebola epidemic. Intention-to-treat analyses will be employed. Each patient will undergo only a single randomization in the study.

7.3 Interim Monitoring

Methods of monitoring clinical trials generally require knowledge of the total amount of information at trial's end. Boundaries are then constructed to guide decisions to control the probability of falsely declaring a treatment benefit at one or more interim analyses, including the final analysis. Such boundaries correspond to scenarios in which the level of evidence in support of treatment efficacy (or the lack thereof) exceeds some pre-determined threshold. Early boundaries are usually very difficult to cross, while boundaries at the end of the trial are similar to what they would be in the absence of monitoring. Our setting requires a somewhat different paradigm because although the target sample size is 100/arm, circumstances beyond our control may lead to a smaller number of patients. Moreover, we would like the flexibility of modifying the oSOC arm quite early if results show the superiority of an experimental agent plus oSOC, for example. We recommend monitoring beginning with 6 participants in an experimental arm and 6 in the best supportive care arm, and continuing after every additional patient per arm, if necessary, up to 20. After that, monitoring would be after every 20 patients per arm until the target number of 100/arm is reached or the trial ends for other reasons. Any decision to curtail for other reasons will be made by a group blinded to trial results. The boundary we recommend is motivated from a Bayesian perspective. Bayesians formulate their prior opinion about the size of the treatment effect through a `prior' distribution, which is updated to a `posterior' distribution after observing data. We give details of the specification of the prior distribution and the construction of the boundary later. What are most important are the boundary itself and its statistical properties such as type I error rate (the probability of crossing the boundary inappropriately, i.e., when the 2 arms are equally effective) and power (the probability of crossing the boundary appropriately, i.e., when one arm is superior to the other).

Table 3 illustrates the design's flexibility by showing the boundaries assuming that factors beyond our control result in only 20 participants per arm by trial's end instead of the planned 100 per arm (stopping boundaries for 100 subjects per arm are included in Appendix B). For example, with 6 people evaluated in each arm, we declare superiority of one arm over the other only if all 6 die in one arm and none die in the other. On the other hand, with 10 people per arm, we cross the boundary if the numbers of deaths out of 10 in the 2 arms are as follows:

1. 7 or more and 0,
2. 8 or more and 1
3. 9 or more and 2

4. 10 and 3

Notice that the boundaries at the end of the trial are more lenient than interim boundaries: interim boundaries use a probability level of 99.9%, whereas the final boundary uses a level of 97.5%. This reinforces the need for a blinded group to make stopping recommendations for reasons other than safety or efficacy; otherwise, inflation of the type I error rate could result from lowering the boundary for the final analysis. Boundaries for a sample size of 100 per group will be generated following this same procedure and will be distributed to the DSMB.

Type I Error Rate

Table 4 shows the probability of crossing the boundary and declaring a treatment difference if we begin monitoring after 6 patients per arm and continue monitoring after each additional patient in both arms up to 20/arm, then every 20 per arm up to 100/arm. This probability of crossing the boundary depends on the true mortality probabilities in each arm, but the maximum value when the event probabilities in the 2 arms are equal is approximately 6% for a trial with 100 participants per arm. Even though the Bayesian methodology does not explicitly aim to control the type I error rate, that rate is controlled at close to the conventional level of 0.05. The first 5 rows of numbers in Table 4 also show type I error rate if circumstances beyond our control result in a final sample size of 20, 40, 60, or 80 per arm.

Power and Sample Size

The last 6 rows of numbers in Table 4 show scenarios with event probabilities differing in the 2 arms. With 100 per group, power is 88% to detect a difference if the true mortality probabilities in the 2 arms are 0.20 and 0.40, a 50% relative reduction. The selected sample size of 100/arm also gives reasonably high power (83%) to detect a difference if the true mortality probabilities are 0.30 and 0.50, a 40% relative reduction.

Table 5 shows the average sample size, taking into account the possibility of stopping early, for the scenarios with a treatment effect. If the true mortality rates in arms A and B are 0.3 and 0.5, respectively, and a sample size of 100 is targeted, then the study will stop for efficacy, on average, with only 76 patients (per arm).

Table 3: Flexibility of Trial Design

The top row gives the number of patients per arm, and the boundaries in parentheses are the numbers of deaths in the 2 arms, with + indicating that number or greater (e.g., in the “8” column, 7+ means 7 or 8).

6	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
(6,0)	(6+,0)	(7+,0)	(7+,0)	(7+,0)	(7+,0)	(7+,0)	(7+,0)	(8+,0)	(8+,0)	(8+,0)	(8+,0)	(8+,0)	(8+,0)	(4+,0)
	(7,1)	(8,1)	(8+,1)	(8+,1)	(9+,1)	(9+,1)	(9+,1)	(9+,1)	(10+,1)	(10+,1)	(10+,1)	(10+,1)	(10+,1)	(6+,1)
			(9,2)	(9+,2)	(10+,2)	(10+,2)	(10+,2)	(11+,2)	(11+,2)	(11+,2)	(11+,2)	(11+,2)	(12+,2)	(8+,2)
				(10,3)	(11+,3)	(11+,3)	(11+,3)	(12+,3)	(12+,3)	(12+,3)	(13+,3)	(13+,3)	(13+,3)	(9+,3)
					(11,4)	(12,4)	(12+,4)	(13+,4)	(13+,4)	(13+,4)	(14+,4)	(14+,4)	(14+,4)	(11+,4)
						(12,5)	(13,5)	(13+,5)	(14+,5)	(14+,5)	(15+,5)	(15+,5)	(15+,5)	(12+,5)
							(13,6)	(14,6)	(15,6)	(15+,6)	(15+,6)	(16+,6)	(16+,6)	(13+,6)
									(15,7)	(16,7)	(16+,7)	(16+,7)	(17+,7)	(14+,7)
										(16,8)	(17,8)	(17+,8)	(18+,8)	(15+,8)
											(17,9)	(18,9)	(18+,9)	(16+,9)
												(18,10)	(19,10)	(17+,10)
													(19,11)	(17+,11)
														(18+,12)
														(19+,13)
														(19+,14)
														(20,15)
														(20,16)

Table 4: Probability of Crossing the Boundary for Different Mortality, Probabilities, and Sample Sizes in the 2 Arms

		Simulated Type I Error Rate*				
Mortality probability treatment A (P_A)	Mortality probability treatment B (P_B)	20 per group	40 per group	60 per group	80 per group	100 per group
0.1	0.1	0.038	0.039	0.042	0.050	0.048
0.2	0.2	0.049	0.052	0.049	0.049	0.053
0.3	0.3	0.046	0.051	0.052	0.054	0.055
0.4	0.4	0.042	0.057	0.056	0.054	0.057
0.5	0.5	0.041	0.061	0.061	0.055	0.063
		Simulated Power				
Mortality probability treatment A (P_A)	Mortality probability treatment B (P_B)	20 per group	40 per group	60 per group	80 per group	100 per group
0.1	0.3	0.36	0.63	0.80	0.90	0.96
0.1	0.4	0.61	0.90	0.98	1.00	1.00
0.1	0.5	0.82	0.99	1.00	1.00	1.00
0.2	0.4	0.27	0.50	0.67	0.80	0.88
0.2	0.5	0.50	0.82	0.94	0.98	1.00
0.3	0.5	0.23	0.46	0.62	0.74	0.83

*These type I error rates refer to comparisons of two arms and do not reflect the study-wise type I error rate.

Table 5: Average Final Sample Size per Arm using Stopping Criteria Defined Above

Mortality probability treatment A (P_A)	Mortality probability treatment B (P_B)	Targeted sample size (per arm)			
		40	60	80	100
		Average final sample size (per arm)			
0.1	0.3	39	54	67	75
0.1	0.4	35	44	48	49
0.1	0.5	29	32	32	32
0.2	0.4	38	56	70	82
0.2	0.5	35	47	53	56
0.3	0.5	38	56	71	84

The frequency of monitoring can be altered. For example, if patient heterogeneity is large, one may not conduct the first interim analysis until more patient outcome data has accrued (e.g., 10 per arm). Regardless of the monitoring frequency, the data and safety monitoring board's recommendation to stop or continue an ongoing trial will be based on consideration of multiple factors. The Bayesian perspective allows calculation of `credibility' intervals (analogous to confidence intervals) for the difference in mortality probabilities between arms whether or not advisory boundaries are crossed.

Comparison to Other Boundaries

Even though the boundaries were motivated from a Bayesian perspective, they are actually quite similar to Haybittle-Peto boundaries using either Fisher's exact test or Barnard's test. Suppose circumstances beyond our control limit the total sample size to 20 participants per arm. A comparison of the 3 boundaries is shown, in Figures 2 and 3 for interim analyses after 10 and 15 participants, and in Figure 4 at the final analysis after 20 participants per arm. The proposed boundary is quite similar to, but slightly less conservative than, Barnard's test. Fisher's exact test is slightly more conservative.

Figure 2: Interim Analysis after 10/Arm

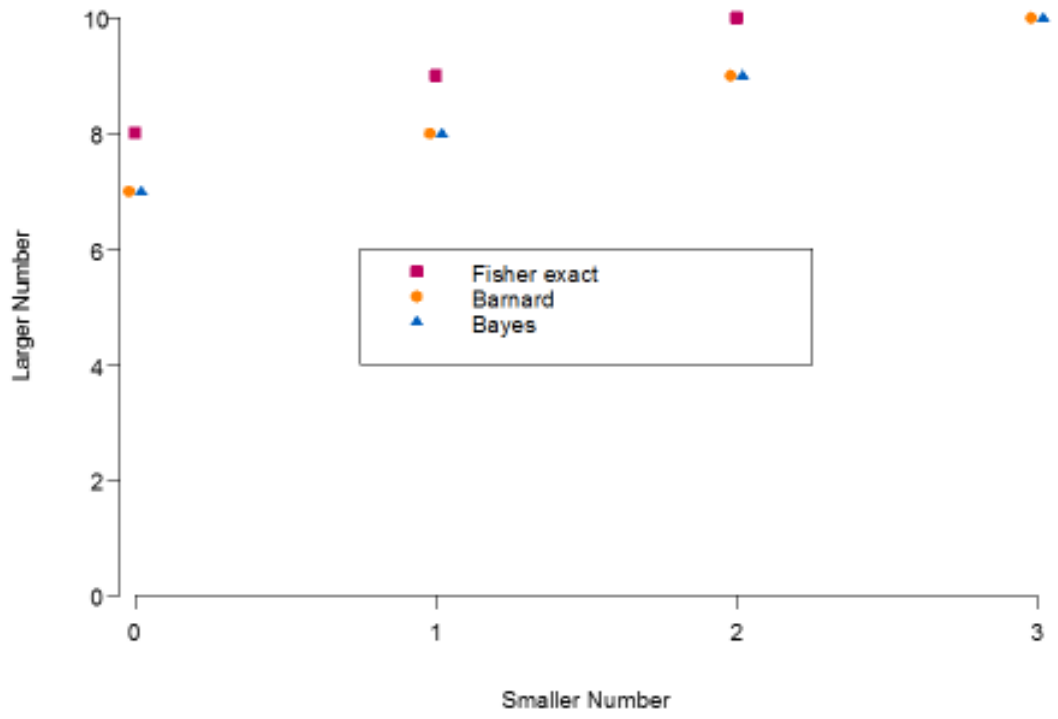


Figure 3: Interim Analysis after 15/Arm

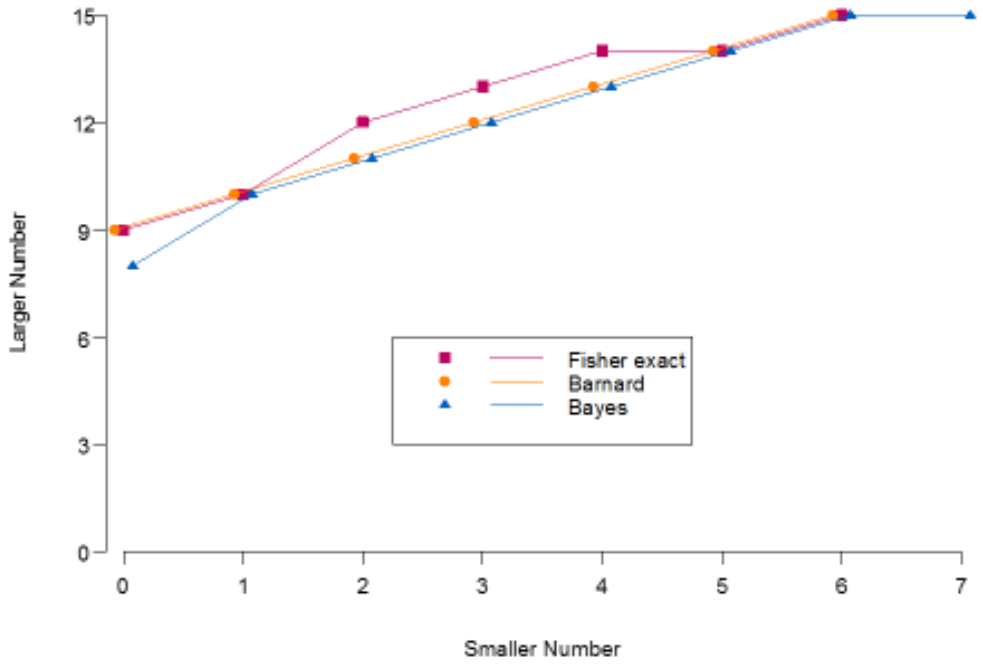
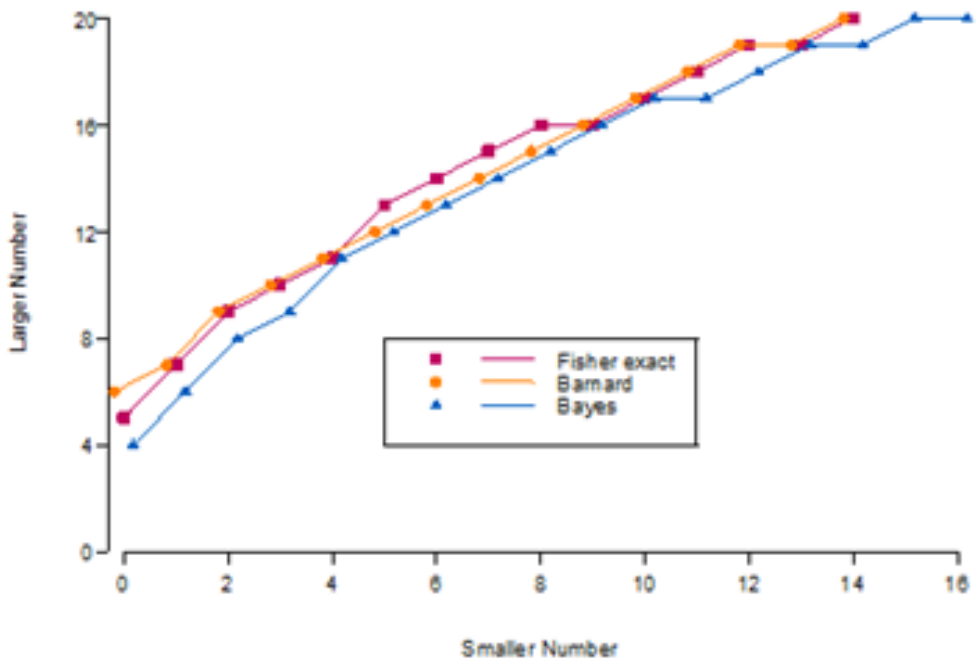


Figure 4: Interim Analysis after 20/Arm



Advisory Futility Boundaries

Advisory boundaries for futility will be computed using the conditional probability of reaching a statistically significant result at the end of the trial with 100 per arm, given the results observed at an interim analysis (called conditional power). Serious consideration for stopping a treatment for futility will be given if the conditional power is less than 20% even assuming the relative treatment benefit for remaining patients is 50%.

Technical Details of Boundary Construction

Thoughtful specification of the prior distribution is crucial in Bayesian analysis. We want conclusions to depend primarily on data from the trial, not on prior opinion. This argues for a skeptical prior distribution that does not already assume that a treatment works. Let *p* denote the probability of survival in a given arm. Our prior distribution on *p* can be formulated by imagining having data on 2 people treated with a given agent, and observing that exactly 1 of the 2 survived. The probabilistic equivalent is to assume a beta prior distribution on *p* with parameters 1 and 1, equivalent to a uniform distribution on the interval (0,1). This is consistent with an overall survival probability of 0.50 for the current Ebola outbreak, but with wide variability reflecting substantial uncertainty about *p*. Moreover, a uniform distribution for p ensures very little influence of our prior opinion on conclusions. The observed data very quickly dominate in decision-making. For instance, if 20 people are given the treatment and 12 of them survive, the posterior distribution for the survival probability is beta with parameters 13 and 9. In other words, combining our prior opinion with the observed data equates to observing 13+9=22 people, 13 of whom survived. Our prior opinion constitutes only 2 of the 22

people, and therefore has very little effect on the conclusions. Also, we use the same prior distribution in different arms. That way, our prior opinion does not favor any treatment over oSOC. If p_A and p_B denote the survival probabilities in arms A and B, respectively, we use independent beta posterior distributions in the 2 arms to calculate the probability that $p_A<p_B$, namely that the survival probability in arm B exceeds that in arm A. At any interim analysis preceding the final analysis, we declare arm B superior if this probability exceeds 99.9%. At the final analysis, we declare superiority of arm B if this probability exceeds 97.5%.

7.4 Analyses

Differences in mortality probabilities between an experimental arm and the best supportive care arm will be estimated using 95% Bayesian credibility intervals akin to confidence intervals. The treatment effect will be expressed in both an absolute and relative terms, and will be estimated in the overall group and in the pre-defined strata: **duration of clinical symptoms (0-5 days versus >5 days) at baseline and where the patient was treated (western Africa versus the United States/Europe).** The posterior probability that the relative treatment benefit differs by strata will be calculated; if this probability exceeds 97.5% that will be taken as evidence of a differential treatment effect by strata.

As noted earlier, Bayesian analysis with the non-informative prior distribution specified above is very similar to classical statistical analysis using Barnard's test. To highlight this point, we will also present classical confidence intervals for the absolute and relative treatment benefit based on Barnard's test.

Some patients may receive MCMs other than the randomized treatment. This will be documented in the record, but it is extremely problematic statistically to try to account for the effect of supplementary treatment that may be administered in response to a patient's failing health. A sensitivity analysis will be conducted by treating such patients as if they would have died by 28 days in the absence of the additional MCMs.

Similar sensitivity analyses will be conducted for patients missing the primary endpoint of 28 day mortality.

8 RISKS AND BENEFITS

8.1 Potential Risks

8.1.1 Unknown Risks

The primary risks to participants are due to study interventions whose human safety profile is either absent or, in most cases, early and accumulating, due to ongoing animal and/or early/first in human trials. Generally these are either still in early phase 1 testing, have not yet entered phase 1 testing, or, for those interventions in more advanced development, have not yet been tested in a human population infected with Ebola virus. Thus, unlike conventional phase 2 trials in which a safety database has already been generated to guide the dosing and schedule of study drug administration, it is presently unknown what toxicities these agents

could cause when used in this critically ill patient population or, for that matter, in any humans at all.

It is anticipated that additional animal safety and toxicity studies will be in-progress at the time of trial initiation for some agents. Results will be made available to the study investigation team and pertinent regulatory bodies for review promptly, as they are available. In addition, in some cases phase 1 testing of lead candidates in normal human volunteers may commence during the same interval of time that this trial is conducted. Should it be concluded from any of these studies that there are additional significant risks to study subjects, participants will be informed and additional administration of study product may be suspended until review by the FDA as well as by each institution's IRB.

8.1.2 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.

8.1.3 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.

8.2 Potential Benefits

There is no definite expectation of benefit to participants or to society at large. However, the agents likely to be investigated 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 conceivable that one or more interventions may subsequently be shown to offer evidence of a greater reduction in morbidity and mortality than that 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 very early stage of testing. However, even if no experimental treatment intervention is shown 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.

8.3 Alternatives

The alternative to participating in this protocol is not to participate and to receive access either to supportive care measures or to experimental therapies through other approved regulatory means.

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

9.1 Intended Use of the Samples/Specimens/Data

Samples and data collected under this protocol will be used to determine the safety, immunogenicity, and antiviral effects of the treatment interventions.

9.2 Storage of Samples/Specimens/Data

Samples obtained in this study must adhere to CDC regulations governing 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 investigators (both at NIH and outside) may wish to study these samples and/or data. In that case, IRB approval must be sought prior to any sharing of samples. Any clinical information shared about the sample with or without patient identifiers would similarly require prior IRB approval.

The research use of stored, unlinked or unidentified samples 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.

9.3 Storage of Genetic Samples

No samples are being stored for genetic testing on the subjects.

9.4 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) will be reported to the institution's IRB and to the protocol team.

10 REMUNERATION PLAN

Subjects will not be compensated for the time and inconvenience of study participation, including for any outpatient assessments that may occur following hospital discharge.

11 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.

11.1 Documenting, Recording, and Reporting Adverse Events

At each contact with the subject, information regarding adverse events will be elicited by appropriate questioning and examinations and will be:

- immediately documented in the subject's medical record/source document,
- recorded on the Adverse Event Case Report Form (AE CRF) or electronic database, and
- reported as outlined below (e.g., IND Sponsor, IRB, FDA)

11.2 Definitions

Adverse Event (AE)

An adverse event 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 (AR)

An adverse event that is caused by an investigational agent (drug or biologic).

Suspected Adverse Reaction (SAR)

An adverse event for which there is a reasonable possibility that the investigational agent caused the adverse event. 'Reasonable possibility' means that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which implies a high degree of certainty.

Serious Adverse Event (SAE)

A Serious Adverse Event is an AE that results in one or more of the following outcomes:

- death
- a life threatening (i.e., an immediate threat to life) event
- 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
- a medically important event*

* Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but they 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 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 a Suspected Adverse Reaction that is both Serious and Unexpected.

Unanticipated Problem (UP)
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; and
    b. the characteristics of the subject population being studied; 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. (Per the IND Sponsor, an AE with a serious outcome will be considered increased risk.)

Unanticipated Problem that is not an Adverse Event (UPnonAE)
Unanticipated problem that is not an Adverse Event (UPnonAE): An unanticipated problem that does not fit the definition of an adverse event, but which may, in the opinion of the investigator, involve risk to the subject, affect others in the research study, or significantly impact the integrity of research data. Such events would be considered a non-serious UP. For example, we will report occurrences of breaches of confidentiality, accidental destruction of study records, or unaccounted-for study drug

Protocol Deviation: 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 a Serious Adverse Event or compromises the safety, welfare or rights of subjects or others.

Non-compliance: The failure to comply with applicable NIH HRPP policies, IRB requirements, or 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.

11.3 Investigator Assessment of Adverse Events

If a diagnosis is clinically evident (or subsequently determined), the diagnosis rather than the individual signs and symptoms or lab abnormalities, will be recorded as the AE.

The Investigator will evaluate all AEs with respect to **Seriousness** (criteria listed above), **Severity** (intensity or grade), and **Causality** (relationship to study agent and relationship to research) according to the following guidelines.

11.3.1 Severity

The Investigator will grade the severity of each AE according to the Division of Aids Table for Grading the Severity of Adult and Pediatric Adverse Events Version 1.0, December, 2004, (Clarification August 20) which can be found at:
http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/daidsaegradingtable.pdf

11.3.2 Causality

The likelihood that the event is related to the study agent will be assessed considering the factors listed under the following categories:

Definitely Related

- reasonable temporal relationship
- follows a known response pattern
- clear evidence to suggest a causal relationship
- there is no alternative etiology

Probably Related

- reasonable temporal relationship
- follows a suspected response pattern (based on similar agents)
- no evidence of a more likely alternative etiology

Possibly Related

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

Unlikely Related

- does not have a reasonable temporal relationship

OR

- good evidence for a more likely alternative etiology

Not Related

- does not have a temporal relationship

OR

- definitely due to an alternative etiology

Note: Other factors (e.g., dechallenge, rechallenge) should also be considered for each causality category when appropriate. Causality assessment is based on available information at the time of the assessment of the AE. The investigator may revise the causality assessment as additional information becomes available.

11.4 Investigator Reporting Responsibilities to the Sponsor

11.4.1 Adverse Events

Line listings, frequency tables, and other summary AE data will be submitted to the IND Sponsor when needed for periodic safety assessments, review of IND annual reports, review of IND safety reports, and preparation of final study reports.

11.4.2 Serious Adverse Events

All SAEs (regardless of relationship and whether or not they are also UPs) must be reported on the Safety Expedited Report Form (SERF) and sent to the Sponsor Clinical Safety Office (CSO) by fax or e-mail attachment. Deaths and immediately life threatening SAEs must be reported to the CSO within 1 business day after the site becomes aware of the event. All other SAEs must be reported within 3 business days of site awareness.

SPONSOR CLINICAL SAFETY OFFICE CONTACT INFORMATION:

OCRPRO Clinical Safety Office
5705 Industry Lane
Frederick, MD 21704

Phone 301-846-5301
Fax 301-846-6224
E-mail: rchspsafety@mail.nih.gov

11.4.3 Unanticipated Problems

Unanticipated Problems that are also adverse events must be reported to the CSO and sent by fax or e-mail attachment no later than 7 calendar days of site awareness of the event. UPs that are not AEs are not reported to the Sponsor CSO.

Report all UPs that are also adverse events to the CSO on the NIH Problem Report Form.

11.4.4 Pregnancy

Pregnancy itself is not an AE. However, complications of pregnancies are AEs and may be SAEs. Pertinent obstetrical information for all pregnancies will be reported to the CSO via fax or email within 3 business days from site awareness of the pregnancy.

Pregnancy outcome data (e.g., delivery outcome, spontaneous or elective termination of the pregnancy) will be reported to the CSO within 3 business days of the site's awareness on a protocol-specified form.

In the event of a pregnancy:

- Withdraw from the study but continue in follow up for safety
- Report to safety oversight committee and IRB
- Advise research subject to notify the obstetrician of study agent exposure

11.5 Reporting Procedures to the IRB

11.5.1 Expedited Reporting to the IRB

Serious and non-serious Unanticipated Problems, deaths, serious deviations, and serious or continuing non-compliance will be reported within 7 calendar days of investigator awareness. Serious Adverse Events that are possibly, probably, or definitely related to the research will be reported to the institution's IRB within 7 calendar days of investigator's awareness, regardless of expectedness.

11.5.2 Waiver of Reporting Anticipated Protocol Deviations, Expected UPnonAEs and Deaths to the IRB

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. Expected adverse events will not be reported to the IRB unless they occur at a rate greater than that known to occur in the general population. If the rate of these events exceeds the rate expected by the study team, the events will be classified and reported as though they are unanticipated problems. Deaths will be immediately reported as expedited SAEs.

11.5.3 Annual Reporting to the IRB

The following items will be reported to the IRB in summary at the time of Continuing Review:

- Serious and non-serious unanticipated problems
- Expected serious adverse events that are possibly, probably, or definitely related to the research

- Serious adverse events that are not related to the research
- All adverse events, except expected AEs and deaths granted a waiver of reporting.
- Serious and Non-Serious Protocol deviations
- Serious, continuing, and minor non-compliance
- Any trends or events which in the opinion of the investigator should be reported

11.6 Follow-Up of Adverse Events and Serious Adverse Events

AEs that occur following enrollment of the subject (by signing the informed consent) are followed until the final outcome is known or until the end of the study follow-up period, Day 28.

SAEs that have not resolved by the end of the follow-up period are followed until final outcome is known. 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.

SAEs that occur after the study follow-up period, Day 28, that are reported to and are assessed by the Investigator to be possibly, probably, or definitely related must be reported to the CSO, as described above.

11.7 Sponsor's Reporting Responsibilities

Serious and unexpected suspected adverse reactions (SUSARs) as defined in 21 CFR 312.32 and determined by the IND Sponsor will be reported to FDA 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 as defined in 21 CFR 312.33.

11.8 Treatment Interruption or Discontinuation

A subject's study treatment may be discontinued at any time at the subject's request or at the discretion of the Investigator or Sponsor. The following may be justifiable reasons for the Investigator to discontinue a subject from treatment:

- The subject was erroneously included in the study (i.e., was found to not have met the eligibility criteria)
- The subject experiences an AE that precludes further study participation
- The subject is unable to comply with the requirements of the protocol
- The subject participates in another investigational study without the prior written authorization of the Sponsor

11.9 Halting Decision

Halting the study requires immediate discontinuation of study agent administered for all subjects and suspension of enrollment until a decision is made whether or not to continue

study agent administration. The Sponsor/Medical Monitor will be notified by the PI (or designee) within 24 hours if any subject develops any of the following:

- An SAE, a Grade 4 AE or a Grade 4 laboratory event, for which no clear alternative explanation, other than study drug, exists.
- Two or more of the same grade 3 AE that is related (possibly, probably, or definitely) to the study drug and which persists for >48 hours.

Upon notification, the Sponsor/Medical Monitor must evaluate the clinical relevance of the reported AEs against the background of an underlying disease with a high case fatality rate and make a determination of whether or not to halt the study based upon this consideration from a safety perspective. The DSMB should be notified immediately of the Sponsor/Medical Monitor's decision in this regard. If the decision is made to halt the study, the Site Investigator must inform the PI and the local IRB that a decision to put the study on hold has been made according to their requirements. The IND Sponsor will notify all sites that the study has been halted.

The Sponsor/Medical Monitor can request additional information that might be needed (such as listing of graded adverse events) to evaluate the data. The Sponsor/Medical Monitor will ultimately make the decision to resume the study, ask for formal Data and Safety Monitoring Board (DSMB) review, or stop the study.

If the trial is stopped due to unacceptably high AE or stopping criteria, the IRB will be notified.

11.9.1 Resumption of a Halted Study

The IND Sponsor, in collaboration with the PI and the DSMB will determine if it is safe to resume the study. The IND Sponsor will notify the Site Investigators of this decision. The conditions for resumption of the study will be defined in this notification. The Site Investigators will notify their local IRB(s) of the decision to resume the study.

11.10 Safety Oversight

11.10.1 Investigator Safety Monitoring

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

- Protecting the safety and welfare of subjects
- Evaluating subject safety, including physician assessment of AEs for seriousness, severity, and causality
- Notifying the sponsor of SAEs and immediately-reportable events
- Providing detailed written reports, including confirmatory tests promptly following immediate initial reports
- Informing the IRB/IEC of SAEs
- Notifying the DSMB of SAEs

11.10.2 Safety Review and Communications Plan (SRCP)

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

11.10.3 Sponsor Medical Monitor (SMM)

A Medical Monitor, representing the IND Sponsor, has been appointed for oversight of safety in this clinical study. The SMM will be responsible for performing safety assessments as outlined in a Safety Review and Communications Plan (SRCP).

11.10.4 Data and Safety Monitoring Board (DSMB)

The NIAID Intramural DSMB or a similarly constituted committee will review the study prior to initiation and no less frequently than twice a year thereafter. The Board may convene additional reviews as necessary. The Board will review the study data to evaluate the safety, efficacy, study progress, and conduct of the study. All serious adverse events, all unanticipated problems, and all IND Safety Reports will be reported by the PI to the DSMB at the same time they are submitted to the IRB or IND Sponsor. The PI will notify the Board at the time pausing or halting criteria are met and obtain a recommendation concerning continuation, modification, or termination of the study. The PI will submit the written DSMB summary reports with recommendations to the IRB.

12 CLINICAL MONITORING STRUCTURE

12.1 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." Monitors under contract to the NIAID/Office of Clinical Research Policy and Regulatory Operations (OCRPRO) will 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 will be: 1) to verify the existence of signed informed consent documents and documentation of the Informed Consent Form (ICF) 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, physicians' 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 will 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 will be available to discuss the study progress and monitoring visit.

A specific protocol monitoring plan will be discussed with the PI and study staff prior to enrollment. The plan will outline the frequency of monitoring visits based on such factors as study enrollment, data collection status, and regulatory obligations.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 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 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.

The participants will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. 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.

13.2 Subject Confidentiality

All records will be kept confidential to the extent provided by federal, state and local law. 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, or the sponsor's designee.

14 DATA MANAGEMENT AND MONITORING

14.1 Data Management Responsibilities

The 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 collected in the electronic data system, and must 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.

14.2 Data Capture Methods: RedCap or similar system to be identified

Study data will be collected at the study site(s) as CRFs and maintained, preferably in an electronic data system. Manual CRFs will be used to collect data for sites without access to

electronic data systems. This data will be completed on an ongoing basis during the study. Data entered into such systems shall be performed by authorized individuals. Corrections to electronic data systems will be tracked electronically (password protected or through an audit trail) with time, date, individual making the correction, and what was changed.

14.3 Types of Data

Source documents include, but are not 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.

14.4 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. Data from the institutional Data System will be collected directly from subjects during study visits and telephone calls, or will be abstracted from subjects' medical records. The subject's medical record must record his/her participation in the clinical trial and, study treatment/vaccination (with doses and frequency) or other medical interventions or treatments administered, as well as any adverse reactions experienced during the trial.

14.5 Record Retention

The investigator is responsible for retaining all essential documents listed in the ICH Good Clinical Practice Guideline. All essential documentation for all study subjects are to be maintained by the investigators in a secure storage facility for a minimum of 3 years per NIAID policies. 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 law.

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STATISTICAL APPENDIX

Power Tables

More extensive power tables: Table 6 shows the approximate power for a range of sample sizes and mortality probabilities in the 2 arms, while Table 7 shows the sample sizes required for approximately 80% and 90% power.

Table 6: Approximate Power under Different per Arm Sample Sizes (n) when the Larger and Smaller Mortality Probabilities are p_A and p_B, Respectively

Powers of 80% or higher are boldfaced.

P_A	P_B	n=20	n=30	n=40	n=50	n=60	n=70	n=80	n=90	n=100
0.2	0.1	0.14	0.16	0.24	0.27	0.32	0.38	0.42	0.47	0.51
0.3	0.1	0.35	0.49	0.63	0.72	0.79	**0.86**	**0.90**	**0.93**	**0.95**
	0.2	0.10	0.14	0.18	0.21	0.24	0.27	0.30	0.34	0.37
0.4	0.1	0.61	0.79	**0.90**	**0.95**	**0.98**	**0.99**	**1**	**1**	**1**
	0.2	0.27	0.39	0.50	0.60	0.67	0.74	**0.80**	**0.84**	**0.88**
	0.3	0.08	0.12	0.15	0.18	0.20	0.23	0.26	0.29	0.31
0.5	0.1	**0.82**	**0.95**	**0.99**	**1**	**1**	**1**	**1**	**1**	**1**
	0.2	0.49	0.69	**0.82**	**0.89**	**0.94**	**0.97**	**0.98**	**0.99**	**1**
	0.3	0.22	0.35	0.46	0.55	0.62	0.67	0.73	0.79	**0.83**
	0.4	0.08	0.12	0.16	0.18	0.20	0.22	0.24	0.26	0.31
0.6	0.1	**0.94**	**0.99**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
	0.2	0.73	**0.90**	**0.97**	**0.99**	**1**	**1**	**1**	**1**	**1**
	0.3	0.45	0.66	**0.80**	**0.88**	**0.92**	**0.95**	**0.97**	**0.98**	**0.99**
	0.4	0.21	0.35	0.46	0.54	0.61	0.67	0.72	0.75	**0.83**
	0.5	0.08	0.12	0.16	0.18	0.20	0.22	0.24	0.26	0.31
0.7	0.1	**0.99**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
	0.2	**0.90**	**0.99**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
	0.3	0.71	**0.90**	**0.96**	**0.99**	**1**	**1**	**1**	**1**	**1**
	0.4	0.45	0.66	**0.80**	**0.88**	**0.92**	**0.95**	**0.97**	**0.98**	**0.99**
	0.5	0.22	0.35	0.46	0.55	0.62	0.67	0.73	0.79	**0.83**
	0.6	0.08	0.12	0.15	0.18	0.20	0.23	0.26	0.29	0.31

Table 7: Sample Sizes required for 80% and 90% Power for Different Values of the Larger and Smaller Mortality Probabilities, p_A and p_B.

p_A	p_B	n_{80}	n_{90}
0.2	0.1	198	264
0.3	0.1	61	81
	0.2	293	392
0.4	0.1	31	40
	0.2	81	109
	0.3	357	476
0.5	0.1	19	26
	0.2	39	52
	0.3	95	126
	0.4	392	520
0.6	0.1	13	17
	0.2	23	30
	0.3	41	57
	0.4	97	128
	0.5	392	520
0.7	0.1	10	12
	0.2	15	20
	0.3	22	31
	0.4	41	57
	0.5	95	126
	0.6	357	477

SAMPLE INFORMED CONSENT FORM TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

INTRODUCTION

We invite you to take part in a research study at the [Institution Name].
First, we want you to know that:
Taking part in this research is entirely voluntary.
You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled.
You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.
Second, some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your doctors or research team before you agree to the study.
Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone on staff here, or with family, friends, or your personal physician or other health professional with whom you are able to communicate.

PURPOSE OF THIS STUDY

You have Ebola infection and have been referred to this medical facility for advanced level care. Advanced level care in this case refers to the use of modern medical methods that may be available in this treatment unit for restoring fluid losses, diagnosing and correcting metabolic imbalances, and treating other abnormalities in patients that are caused by the virus. Most physicians with experience in treating Ebola patients believe that by promptly and effectively reversing these fluid losses and providing other types of modern supportive care that the mortality caused by the infection can be greatly reduced. In this research protocol we are seeking to learn whether the addition of one or more experimental antiviral drugs or treatments in addition to this background of advanced level care can reduce the mortality from Ebola infection even further. If so, it is possible that the knowledge we gain from this study will help us improve the treatment of Ebola patients both here and elsewhere.

Unfortunately, essentially all of the experimental drugs or treatments for Ebola infection that are currently available for testing are in very early stages of drug development and have not received prior in-depth study to determine their safety, toxicity in the human body, or even their effectiveness in suppressing the Ebola virus. Even those that have been tested in humans previously have been used mostly in patients with other types of infectious diseases but generally not as often in those with Ebola infection. Therefore, much of what we know about these treatments is quite limited and is based upon their study either in the test tube or in animal models of Ebola virus that may or may not truly mimic the course of human infection with Ebola. Because so little is known about these treatments to date, there is always the possibility that they may actually cause harm to humans and no benefit, especially when administered to ill patients. However, despite this concern, the scope of the current Ebola crisis in West Africa has forced us to accelerate the usual timeline by which we would normally study their safety and

potential toxicity in humans prior even to fully testing whether they actually have any benefit in suppressing or reversing the often fatal course of Ebola virus infection.

STUDY DESIGN

You are eligible to be in this study because you have recently been diagnosed as having Ebola infection, usually by a laboratory test called the Polymerase Chain Reaction, or "PCR", and have been hospitalized in an isolation unit for treatment of this infection. The PCR test shows that you have genetic material, such as RNA, from the virus circulating in your bloodstream that is indicative of active infection. Participants in this protocol can be from the general public as well as health care workers who were infected by the virus during the course of caring for Ebola patients.

All eligible persons will undergo a medical evaluation to determine:

- _When and where the infection likely occurred
- _How you were likely infected (e.g., by skin contact, accidental needle stick, etc.)
- _Your past and current medical condition and any medical care delivered thus far
- _Any aspects of your past medical history that might be relevant to the standard medical care you are being given, or to the use of any proposed experimental treatment(s) that might be offered you.

This evaluation will generally be done by the physician or medical team in charge of your overall care while in the hospital. After the initial evaluation, we will decide whether it is safe to enroll you on this study for possible experimental treatment in addition to the advanced level care you will automatically receive. However, the decision whether to actually accept enrollment on this experimental protocol is entirely your own, and if you decline enrollment you will still receive the same advanced level care that the hospital can provide. To enroll on this study you must be willing to sign an informed consent document that explains your rights and responsibilities as a potential research participant.

Enrollment in this protocol is voluntary. If you decide to enroll on this study, you will be randomly assigned (that is, like the flip of a coin) to 1 of at least 2 different treatment groups, each of which will provide a different study intervention. It is very important to understand that, at this time, there is no scientific basis for either you or your physicians to choose one particular type of drug over another, nor is there even any reason at present to believe that adding an experimental drug to the backbone of advanced level care you will automatically receive will produce a better outcome than just that backbone alone. Indeed, the addition of that experimental drug could potentially harm, not improve, the course of your clinical recovery from Ebola. Hence, one of the treatment arms to which you may be randomly assigned may employ just that backbone itself, and it will then be compared experimentally to an arm that consists of that backbone plus an experimental antiviral drug. The choice, of which experimental antiviral drugs or treatments to study in this protocol and the order in which they are to be studied, was made by a panel of physicians with expertise in the care and management of patients with Ebola infection.

By the type of comparison planned in this study, we hope to learn whether adding a given experimental drug does or does not improve upon the recovery rate that is possible when advanced level care measures are used alone. If it does, and especially if it does not cause any

severe side effects when given in this manner, it is possible that that experimental drug may then be recommended to become part of the standard care that Ebola patients receive in the future. Conversely, if it does not, or if it causes severe side effects that complicate a patient's care, then it may be less likely that a given antiviral drug will be recommended in the future for this particular purpose.

Overall, the study teams hope to compare a small number of experimental antiviral drugs or treatments in the manner described above. At present, that none of these experimental drugs is currently approved by the United States Food and Drug Administration (FDA) for the treatment of Ebola. It is possible that some of these may be helpful to a patient's recovery, some may potentially be harmful, and some may have no effect at all. By the end of the study we hope to learn whether adding one or more of the "helpful" drugs to the backbone of advanced level care will be an important improvement in our successful care of patients with Ebola infection.

WHAT YOU SHOULD EXPECT

If a mutual decision is made by you, your doctor, and the study team, you will be offered enrollment in the protocol. A member of the study team will speak in person with you. If you agree, you will be asked to sign this informed consent document.

After enrollment, your protocol team will learn to which study treatment arm you have been assigned by chance. Baseline blood studies (e.g., a complete blood count, chemistry measurements, coagulation measurements, etc.) may be drawn to document your medical condition at the time of enrollment, and another PCR test may also be collected in order to learn what level of Ebola virus is circulating in your blood at the time of study entry. In some cases these will already be part of your standard medical care and may not increase the amount of blood drawn from you for this purpose. If your assigned arm involves the addition of an experimental antiviral drug or treatment, it is likely that this medication will already be available at your hospital to begin its administration within 24 hours of your enrollment. Depending upon the nature of the particular drug or treatment, this medication may be given to you by oral (by mouth) or intravenous (given by vein) means. Because different drugs remain in the bloodstream for different lengths of time, it is possible that a single dose of a particular drug or treatment may not be sufficient and that dosing may need to be repeated on subsequent days in order to keep the bloodstream levels of that medication in the desired range.

Over the course of your hospitalization, frequent blood tests will be drawn in order to determine your overall medical condition, to determine if your assigned treatment is causing any side effects that may be reflected in the bloodstream (e.g., liver or kidney abnormalities, bone marrow effects, etc.), and also to monitor the level of Ebola virus circulating in your body. We may also collect samples of other body fluids (e.g., saliva, urine, stool, vaginal fluid, etc.) to learn if Ebola virus may be present in those fluids or secretions as well. If it is both safe and possible to process blood specimens for this purpose within your hospital's laboratory, the level of study medication in your bloodstream may be monitored by drawing a series of timed blood tests over the first 24 to 48 hours after that medication is given to you.

The information we learn about your individual clinical course, the possible effect of your assigned treatment arm on the level of Ebola virus in your bloodstream, and the potential side

effects of any experimental treatment you receive will, by itself, not be sufficient for us to conclude anything meaningful about how your assigned treatment did or did not affect your clinical recovery from Ebola infection. However, by combining your information with that of other enrolled patients receiving the same treatment, and comparing that information with similar data from patients assigned to a different treatment arm, we hope to be able to learn whether one treatment was better than the other in terms of possibly speeding the time to recovery, causing fewer side effects, and similar such conclusions. Alternatively, we may learn that no experimental treatment appears to improve greatly upon what is currently possible through providing advanced level care in a hospital setting where such care is available. In any case, for this study to be successful we will need a sufficient number of patients enrolled in each of the treatment arms in order to make these comparisons statistically meaningful, and at this time we cannot predict how many individuals will be available to join this study. Thus, there is always a risk that it will not be possible to draw firm conclusions from this study as currently planned. However, the study team feels strongly that this risk is greatly outweighed by the potential to add to our knowledge of how to care optimally for patients with Ebola infection.

Follow-up
Your participation in the protocol will continue for the duration of your hospitalization or, if you are discharged early, for a total of up to 58 days following enrollment. In addition, there may be interest in evaluating you for any long-term effects of the experimental treatment(s) you may have received. If so, you may be asked to return after hospital discharge for 1 or more outpatient visits on a voluntary basis. The potential need for these evaluations will be determined on a case-by-case basis by your treating physicians and the study team. Your participation in these evaluations is voluntary and may be discontinued at any time without affecting your potential eligibility for other care, including enrollment on other research protocols.

Risks of Protocol Participation
Your major risk of study participation generally includes the risks of any experimental drug or treatment to which you are assigned (see below). These will be discussed with you at the time of treatment. Also, any new significant findings that may emerge during the course of the study that may affect your willingness to participate will be provided to you.

Also, blood draws may cause pain and bruising and, rarely, infection at the place where the blood is taken. Sometimes drawing blood causes people to feel lightheaded or even faint.

Risks of Treatment Arm A

Treatment Arm A will consist of providing advanced level care for your infection. This will include fluid replacement for gastrointestinal or other body losses of fluids caused by Ebola, monitoring of your blood pressure and other vital signs to measure your body's response to the infection, frequent monitoring of electrolytes (e.g. sodium, potassium, and other minerals within your bloodstream whose proper levels are essential to health) to indicate when deficiencies in these electrolytes might be present and must be replaced, the use of oral or intravenous licensed medications [e.g. loperamide (or Lomotil^{tm}) to treat diarrhea, or ondansetron (or Zofran^{tm}) to treat nausea] to treat some of the known side effects of Ebola, and other standard measures of good medical care to help you fight Ebola and aid your recovery. In some hospitals even more

advanced levels of care, such as providing mechanical ventilation to combat respiratory failure, or hemodialysis to combat kidney failure, might also be available and may also be used to help improve your chances of recovery. While none of these therapies is considered experimental, and while their value in treating Ebola has been shown by experience, like any medical procedure each does carry its own separate risk of potentially causing harm in a given individual. Your doctor will explain to you how each therapy will be used and what the potential risks of each procedure might be in your case.

If you are assigned to Treatment Arm A it is important that you do not receive investigational medications for treating Ebola by other means outside of this clinical trial, as doing so will impair the ability to determine whether the treatments used in Arm A were responsible for your recovery from the infection. As mentioned previously, it is also possible that those experimental medications could cause harm to you rather than benefit.

Risks of Treatment Arm B

If you are randomly assigned to Treatment Arm B, you will receive the same level of advanced care described above for Treatment Arm A but will also receive an experimental medication in addition. The type of experimental medication you will receive will be described to you in a separate written document and will also be explained to you in person by your study team. The known facts about that medication, whether and how it has been used previously in humans, and the potential side effects will be included in the written description of the medication. You will be given ample opportunity to ask questions about the experimental medication prior to it being given to you. Depending upon which experimental medication is being studied, it may be given to you by mouth or intravenously through an IV line. It may also need to be given to you on a daily basis rather than as just a one-time dose. If given intravenously, it may take up to several hours to complete each infusion of medication through your IV line.

Potential Benefits

We do not know if you will receive any direct benefit for participating in this study. While it is possible that you may be assigned to receive an experimental treatment that is later shown to have antiviral activity against Ebola, this activity cannot be assumed to exist at this time. It is also possible that even if such activity exists, it may be compromised by side effects caused by the treatment that overall may outweigh the value of giving this particular therapy to patients in the future. However, what we learn from this study may allow us to better understand the disease process and potentially develop better ways of treating the infection.

Alternative to Participation

The alternative to enrollment in this protocol is to continue to receive advanced level care through your hospital as previously outlined. In some circumstances it may also be possible for your physicians to apply to the FDA and various drug manufacturers to receive access to experimental therapies through other regulatory mechanisms beyond the bounds of this research protocol.

Stored Samples and Future Research
It is likely that we will store blood and possibly tissue samples from you to permit the performance of additional testing in the future either for clinical or for research purposes related to Ebola infection. If for clinical purposes, these tests may also help guide your medical evaluation as new or improved tests become available. If for research purposes, these tests may help us to better understand Ebola and how it causes disease. However, there are federal regulations that govern the long-term storage of samples from patients infected with a known "Select Agent" pathogen such as Ebola virus. Such regulations may restrict the storage of such specimens after a certain number of days to only a small number of containment laboratories operating at what is termed Biosafety Level 4 containment. If access to such a facility for long-term storage of your samples is not possible, it may be necessary to destroy your samples according to approved disposal methods.

Future Studies
Other investigators may want to study your stored blood or tissue samples if it is safe to do so. One example might be scientists from the Centers for Disease Control and Prevention who guide clinicians in the care and management of patients with Ebola infection. If so, your study team may agree to send your samples to them, and may also share information such as your gender, age, health history, or ethnicity. In some cases, your hospital's Institutional Review Board (IRB) will need to review other new research that uses your samples. Investigators will use your samples only for research and will not sell them. Future research that uses your samples may lead to new products, but you will not receive payment for these products.

Confidentiality
The data collected from your participation in the protocol may be published, but your identity will remain strictly confidential.

Compensation
There will be no financial compensation offered for your participation in this protocol.

Conflicts of Interest
The policy of the NIH is to evaluate investigators for any conflicts of interest. Research participants may review the system for assessing conflicts of interest by checking the web 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.

A description of this clinical trial will be available on http://www.Clinicaltrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most the Web site will include a summary of the results. You can search this Web at any time

Consent Document. Please keep a copy of this document in case you want to read it again.
COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

_____

Signature of Adult Patient/Legal Representative Date
Print Name

_____

Signature of Investigator Date
Print Name

_____

Signature of Witness Date
Print Name

APPENDIX A

On November 11, 2014, a meeting was held that included investigators from the 3 high containment patient care units (Emory University Hospital, University of Nebraska Medical Center, and the NIH Clinical Center) in the United States who have cared for individuals medically evacuated from West Africa as well as representatives of various US government agencies (NIH, FDA, BARDA/ASPR, CDC, and various constituencies within the DoD) who have been involved in the US response to the 2014 Ebola crisis. This meeting was conducted in follow up to a prior meeting of these groups on October 27, 2014, in which the attendees endorsed the concept of performing a randomized clinical trial of adjunctive medical countermeasures of potential utility in treating patients with documented Ebola virus infection, whether seen here in the US, Europe, or in 1 of the affected countries in West Africa. Two major outcomes of that initial meeting had been:

1. The group concluded that it was both ethical and scientifically desirable to attempt to conduct an RCT in which one of the initial comparator arms would be optimized standard of care (oSOC) alone, acknowledging that the level of supportive care that defines oSOC would almost certainly vary between the different geographic regions who might participate in such a study. While available resources, personnel, and other constraints will likely not permit the level of oSOC achievable in West Africa to approach that currently available in the United States and other developed nations within a short time frame, the hope was that the provision of additional outside resources currently planned might improve the level of oSOC in some of the ETUs operating, or planned to open in, some regions of the affected West African countries and that these units might then be able to support the performance of clinical research in addition to their primary commitment to clinical care.
2. While the investigators had at least some familiarity with most of the MCMs proposed for study in the context of an RCT, overall they felt that there were significant gaps in the group's mutual understanding of the preclinical and early clinical trial results supporting the potential utility of individual agents. Accordingly, they felt it was critical that the group undertake a comprehensive review of the available *in vitro*, animal (NHP and other animal model data) and early clinical data that the manufacturers have compiled about these individual agents in terms of their activity against Ebola virus.

With this background, the investigator group reconvened on November 11, 2014, and invited company representatives of the lead candidates with putative antiviral or immune-enhancing activity against EBOV to present their products' supportive data, toxicity data, and early in-man experience. Over the course of that meeting 7 different products, including convalescent plasma, were individually reviewed and discussed with the sponsors, and then afterwards a closed session was held in which the investigators discussed which of the products they felt had the strongest preclinical and early clinical data to support prioritizing its study within the context of an RCT in EBOV patients. Important elements of this discussion included the following:

1. It was again reiterated that the only scientific approach with a reasonable likelihood of being able to determine conclusively the potential therapeutic benefit or harm of a given

experimental therapeutic adjunct is one in which that adjunct can be compared to a backbone of oSOC.

2. There were no decisions made at this time to exclude any of the reviewed products for further consideration of inclusion within an RCT.
3. Some of the products were less far advanced in terms of their preclinical development, and could potentially benefit from further animal and toxicity testing before being prioritized for immediate study within the proposed RCT.
4. Not all of the data from ongoing or recently completed preclinical testing was available for each agent, and in at least 1 case allusion was made to preliminary animal test results that reportedly did not support activity of the agent in that particular animal model. Hence, subsequent, more complete knowledge of those findings could likely influence the prioritization of individual agents within the study queue.
5. The molecular drift of the current circulating Guinea strain of EBOV from the previous Zaire strain may not necessarily be optimized as a target for all of the agents, and modifications of product towards this newest strain may be necessary in some cases.
6. The available or predicted drug supply of each of the agents varied from product to product, and the potential limited availability of certain agents would likely be an important factor in planning pairwise comparisons of product against oSOC at least in the near term.
7. The likelihood of quickly raising the oSOC available in West African ETUs to the level currently afforded in most US or European hospitals was deemed quite low. However, it was again emphasized that the most important outcome comparison to be made in an RCT was between the backbone oSOC available in the individual setting into which an experimental MCM was being introduced as an adjunct to that oSOC, not the comparison between different levels of oSOC available in different treatment settings.

With the considerations above in mind, the investigators concluded that they would be most supportive of initiating an MCM RCT beginning with ZMapp^{tm} triple monoclonal antibody cocktail as the lead candidate for study. This was concluded despite the absent supply of this agent currently as well as the likelihood that only fairly limited quantities of this product would be capable of being produced until early in 2015. ZMapp^{tm} is produced by Mapp Biopharmaceutical, Inc./LeafBio, Inc. and consists of a triple monoclonal antibody product that is manufactured in *Nicotiana benthamiana* (tobacco species) and that is directed against the surface glycoprotein (GP) of Ebola virus. There are compelling data from an infectious challenge model in NHPs (*Rhesus macaques*) showing that the drug cocktail may be capable of rescuing infected animals from death when the product is administered as late as 5 days after what would otherwise be a lethal challenge in that animal model. In addition, there is now anecdotal experience with use of 1-3 treatment doses of this monoclonal cocktail in 8 different patients with EBOV who received this drug under the auspices of eIND or compassionate use mechanisms thus far in 2014. Of those 8 patients, some of whom received additional MCMs, 6 survived to resolution of their illness, whereas 2 died.

As a fallback to consideration of use of ZMapp^{tm} as the lead study candidate, however, the investigators also recommended that convalescent plasma be prioritized as the second lead candidate for inclusion in the RCT. In addition to anecdotal experience overseas with the use of convalescent plasma in both prior and the current Ebola virus outbreaks, current experience

with using plasma in patients medically evacuated to the United States equals or exceeds that of other MCMs. Currently, 8 of 9 patients with EBOV treated in the US have survived, and of those 8 survivors, 6 have received either infusions of whole blood or convalescent plasma as part of their adjunctive therapy in addition to other MCMs. These infusions have occurred at different times in their clinical illnesses, and from different sources of donor plasma. However, 4 of the more recent 6 convalescent plasma recipients have received plasma infusions from the same donor patient. To date these infusions have generally been well tolerated according to the investigators involved with their administration.

Unfortunately, standardization of donor units according to anti-Ebola antibody titers, including neutralizing activity, has not occurred on a uniform basis and, in the case of the most frequent plasma donor, plasma as been obtained from different points in his convalescent period. A reliable, consistent, and well-characterized source of plasma to fuel an RCT would be a significant challenge to incorporation of this strategy into an RCT unless additional measures were undertaken to identify and collect a sufficient supply of this material in advance. In this regard, it was suggested that post-immunization plasma harvested from individuals who have received 1 of the current Ebola vaccines currently in phase 1 and early phase 2 testing might conceivably be an acceptable alternative to convalescent plasma given its expected abundance and relative ease of procurement from normal volunteer vaccine recipients. However, from the standpoint of a broadly protective response in individuals with established infection, it could also be argued that the more restricted, likely oligoclonal, antibody response generated by these GP-based vaccines may or may not be comparable to the broader polyclonal response induced by natural infection and presumably present in convalescent plasma. The current vaccine trials are actively evaluating the degree of both humoral and cell-mediated immunity induced by the 2 major vaccine constructs under study, and consideration should be given to evaluating plasma from vaccine recipients in a post-exposure prophylaxis model.

These 2 choices recommended for research prioritization in an RCT are obviously immune-based approaches, a strategy for which there is substantial precedent in other viral diseases. The investigator group briefly also touched upon the issue of which of the available directly-acting antiviral agents under consideration might be recommended as the third or fourth category of agents to be entered into such a study. As part of this consideration, the potential ease with which candidate agents could be introduced and studied within a research setting lacking reliable access to parenteral therapy should be a significant factor in this choice. However, no single agent was uniquely identified for prioritization from the discussion that ensued, and clearly more discussion of this topic within the group is warranted in the very near term.

APPENDIX B

Stopping Boundaries based upon 100 Subjects per Arm

Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm	
6		7		8		9		10		11		12		13		14		15	
Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm	
Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*
6	0	6	0	7	0	7	0	7	0	7	0	7	0	7	0	8	0	8	0
		7	1	8	1	8	1	8	1	8	0	8	0	8	0	9	1	9	0
						9	2	9	2	9	1	9	1	9	1	10	1	10	1
								10	3	10	2	10	2	10	2	11	2	11	2
										11	4	11	3	11	3	12	3	12	3
												12	5	12	4	13	5	13	4
														13	6	14	6	14	5
																		15	7

* Note that number of deaths given in arm B refers to the given number OR FEWER for the corresponding number of deaths in arm A.

Stopping Boundaries based upon 100 Subjects per Arm

Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm	
16		17		18		19		20		40		60		80		100	
Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm	
Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*
8	0	8	0	8	0	8	0	8	0	9	0	9	0	9	0	5	0
9	0	9	0	9	0	9	0	9	0	10	0	10	0	10	0	6	0
10	1	10	1	10	1	10	1	10	1	11	1	11	0	11	0	7	1
11	2	11	2	11	2	11	1	11	1	12	1	12	1	12	1	8	1
12	3	12	2	12	2	12	2	12	2	13	2	13	1	13	1	9	2
13	4	13	3	13	3	13	3	13	3	14	2	14	2	14	2	10	3
14	5	14	4	14	4	14	4	14	4	15	3	15	2	15	2	11	3
15	6	15	6	15	5	15	5	15	5	16	4	16	3	16	3	12	4
16	8	16	7	16	7	16	6	16	6	17	4	17	4	17	3	13	4
		17	9	17	8	17	7	17	7	18	5	18	4	18	4	14	5
				18	10	18	9	18	8	19	6	19	5	19	5	15	6
						19	11	19	10	20	6	20	6	20	5	16	7
								20	12	21	7	21	6	21	6	17	7
										22	8	22	7	22	6	18	8
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APPENDIX C:

ZMapp Triple Monoclonal Antibody Cocktail

Sponsor's Name:	LeafBio
Investigational Product Name:	ZMapp™
Investigational Product Description:	Three chimeric human/murine monoclonal antibodies (13C6-FR1, c2G4 and c4G7; IgG_1 , kappa isotype) against the Ebola (Zaire) surface glycoprotein.

LeafBio, Inc. (LeafBio) is developing ZMapp™ as a therapeutic for Ebola virus disease (EVD). ZMapp™ is a combination of three chimeric human/murine monoclonal antibodies (c2G4, c4G7, and c13C6-FR1; IgG_1, kappa isotype) against the Ebola virus (Zaire, EBOV) surface glycoprotein found on virions and infected cells. Two of these mAbs (c2G4, c4G7) bind only to the EBOV glycoprotein (Qiu *et al.*, 2011), while the third mAb (c13C6-FR1) binds to the glycoproteins of Sudan virus, Tai Forest virus, and Reston virus in addition to EBOV (Wilson *et al*., 2000).

Each of the three mouse/human chimeric mAbs (c2G4, c4G7, and c13C6-FR1) comprises one ZMapp™ Drug Substance. The monoclonal antibodies comprising ZMapp™ are produced using a transient expression system in genetically engineered tobacco (*Nicotiana benthamiana)* plants. The ZMapp™ Drug Substance mAbs have highly homogenous mammalian-type glycans, mitigating safety concerns about immune reactions to plant specific glycans.

Several non-clinical efficacy studies in guinea pigs and non-human primates (NHP) have shown that ZMapp™ provides protection in these organisms against lethal EBOV infection (Qui *et al*., 2014). In guinea pigs, four of six animals administered one dose (5 mg) of ZMapp™ at 3 days post-infection (dpi) with guinea pig-adapted EBOV survived, while none of the four control animals survived.

Efficacy in the NHP model of EBOV infection is thought to be the best predictor of potential efficacy in humans. Several studies evaluating the efficacy of the ZMapp™ in rhesus macaques administered lethal doses of EBOV have been conducted. The preliminary NHP study used a cocktail termed ZMappA, comprised of c13C6-FR1 and c2G4 (both produced in *Nicotiana benthamiana*) and murine 4G7 (produced in hybridoma). Six animals were treated with three doses of 50 mg/kg ZMappA on 3, 6 and 9 days post infection. All animals administered ZMappA survived, while the two control animals succumbed to infection. In a second NHP study, animals were treated with three doses of 50 mg/kg ZMapp™ initiated at 3, 4, or 5 days post infection (six animals

per group). The doses were administered three days apart. All six animals in each of the three ZMapp™ groups survived, while the three control animals succumbed to EBOV infection. In the third NHP study, the efficacies of two dose levels (25 mg/kg or 50 mg/kg ZMapp™) and frequencies (1, 2 or 3 doses of 50 mg/kg ZMapp™, separated by three days) were evaluated. In this study, ZMapp™ treatment was initiated 5 dpi for all groups. Three of the four animals administered 3 doses of 50 mg/kg ZMapp™ survived infection, and five of the six animals administered 2 doses of 50 mg/kg ZMapp™ survived infection (unpublished data). The data from the NHP studies were used to base the dose and regimen for ZMapp™ administration in humans.

Additional nonclinical studies are being conducted to support the use of ZMapp™ in patients with EVD. Specifically, a GLP rat toxicology study has been completed, and a final study report is expected in 2015. A preliminary non-GLP tissue cross reactivity study found no specific binding of the mAbs comprising ZMapp™ to human tissue, and a GLP tissue cross reactivity study is currently underway.

ZMapp™ has not been tested in clinical trials. There are limited data available for administration of ZMapp™ to human patients. ZMapp™ has been administered under expanded access emergency INDs in the US and compassionate use provisions in Spain, the UK, and Liberia. A total of twenty doses of ZMapp™ have been administered to nine patients. Doses levels have ranged from approximately 42.5-50 mg/kg, and patients have received between 1 and 3 doses.

A Phase 1a study evaluating the safety and pharmacokinetics of ZMapp™ following a single 50 mg/kg administration in healthy volunteers is planned, and a Phase 2 study evaluating the safety and efficacy of ZMapp™ in patients with EVD will be conducted concurrently. The dose (50 mg/kg) and dose regimen of 2-3 doses, administered once every three days) for ZMapp™ is based on the three non-human primate (NHP) studies of ZMapp™ discussed above.

1. Physical, Chemical, and Pharmaceutical Properties and Formulation

1.1 Product Description

ZMapp™ is composed of three mouse/human chimeric IgG_1, kappa mAbs, c13C6-FR1, c2G4 and c4G7; each of these were derived from three mouse mAbs directed against three epitopes in EBOV glycoprotein. The parental mouse mAbs were termed 2G4 and 4G7 (Qiu *et al*., 2011) and 13C6 (Wilson *et al*., 2000). The mouse mAbs were chimerized by fusing the mouse heavy and light chain variable regions with the human IgG_1 heavy chain and kappa light chain constant regions, respectively. These mouse/human chimeric mAbs are termed c2G4, c4G7, and c13C6. The chimeric c13C6 was further modified by the insertion of "humanizing" mutations in the mouse variable regions of both heavy and light chains. This partially humanized mouse/human chimeric mAb is termed c13C6-FR1.

Two of these mAbs, c2G4 and c4G7 bind only to the EBOV glycoprotein (Qiu *et al*., 2011), while the mouse progenitor of the third mAb, c13C6-FR1 binds to the glycoproteins of other members of the Ebola genus (Sudan virus, Tai Forest virus, and Reston virus) in addition to EBOV (Wilson *et al.*, 2000).

The mAbs in ZMapp™ are produced in a tobacco (*Nicotiana benthamiana)* based transient expression system (ICON Genetics, Halle, Germany; Giritch A *et al.*, 2006). The tobacco produced mAbs have highly homogenous mammalian-type N-glycans via the use of a transgenic strain of *N. benthamiana* in which plant specific glycosyltransferases (α1,3 fucosyltransferase and β1,2 xylosyltransferase) are inhibited by siRNA (Strasser R *et al.*, 2008)

1.2 Product Characterization

The Drug Substance mAbs included in ZMapp™ Drug Product are ≥ 90% monomeric, with ≤5% aggregates. Protein impurities, including product related mAb species (such as charge variants and oxidized species) and host cell proteins may be present in low quantities. Residual nicotine from the production platform may be present at levels of <1 mg/dose, and residual host cell DNA may be present at levels of less than 20 ng/dose.

1.3 Product Formulation

Each of the three mouse/human chimeric mAbs (c2G4, c4G7, and c13C6-FR1) comprises one ZMapp™ Drug Substance. The three individual mAb Drug Substances are combined in equal mass ratio in the ZMapp™ Drug Product to be administered intravenously after dilution in normal saline (4 mg/mL). The Drug Product is supplied in an aqueous formulation buffer including the following excipients: 20 mM histidine, 100 mM NaCl, 4% sucrose, and 0.001% Tween 80, pH 6.0.

1.4 Storage and Handling

The ZMapp™ Drug Product will be stored at -20°C. ZMapp™ should be stored frozen at -20°C until use, and must be diluted in normal saline (4 mg/mL) prior to administration.

Doses of ZMapp™ should be prepared in infusion bags containing normal saline. Preparation of multiple infusion bags at one time is recommended. Preparation of 100 mL, 250 mL or 500 mL infusion bags is acceptable. Vials should be thawed at room temperature out of direct sunlight. At least 1-4 hours should be allowed for vials to fully thaw. Vials should not be immersed in a water bath or other medium to accelerate thawing. Please see the ZMapp™ Pharmacy Guide (January 2015, version 1.0) for further instructions.

Partially used, thawed ZMapp™ vials may be stored at 4°C for up to 3 days. Diluted ZMapp™ in infusion bags may be stored at room temperature for up to 24 hours. Do not re-freeze vials. All thawed, partially used ZMapp™ material (if any) should be destroyed and records of this destruction should be provided to the study director.

2. Effects in Humans

No clinical studies of ZMapp™ have been completed. However, there are limited data available (presented in section 2.2 below) for administration of ZMapp™ to human patients under expanded access emergency INDs in the US and compassionate use provisions in the Republic of Liberia, Spain, and the United Kingdom.

2.1 Pharmacokinetics and Product Metabolism in Humans

No data are available on the pharmacokinetics PK or metabolism of ZMapp™ in humans. A Phase 1a study evaluation the safety and pharmacokinetics following a single ZMapp™ administration in three healthy volunteers is planned.

2.2 Safety and Efficacy

ZMapp™ has not been studied in clinical trials, therefore, no human efficacy data are available. A total of twenty doses of ZMapp™ have been administered to nine patients under expanded access provisions of the US FDA and similar "compassionate use" provisions in jurisdictions outside of the US. Doses ranged from approximately 42.5-50 mg/kg. Infusion rates ranged from 50 mg/hr to 800 mg/hr. Limited safety data are available from these cases.

Five patients received a full course of treatment (3 doses at approximately 50 mg/kg; two patients treated in Liberia and the US, and three patients treated in Liberia). In each patient, possible adverse effects were noted during administration of their first dose ("itchy palms" was reported in one patient; tachypnea and flushing in one patient; elevation in fever was reported in three patients; and seizure was reported in one patient). In each case the infusion rate was reduced, and the full dose was able to be administered. For the patient who experienced seizure, paracetamol and phenergan were administered mid-way through the infusion for fever management and patient comfort. Subsequent to administration of these drugs, the patient experienced a generalized seizure with convulsions. The infusion was interrupted upon onset of the seizure, which subsided in approximately 15 min. Two hours after seizure onset, the patient's temperature had returned to 98°F, and the infusion was resumed without recurrence of the event. Included in the differential diagnosis for this event would be the patient's pre-existing malaria infection, atypical infusion reaction, or other undiagnosed seizure disorder (with the administration of phenergan possibly contributing by lowering the seizure threshold). No infusion reactions or adverse events were noted during administration of the second doses for these patients. During the third infusion, one patient experienced an adverse event of chest pain, difficulty breathing, fever with rigors (102.8°F), tachycardia (max HR 144 bpm) and hypotension (min BP 85/50). The ZMapp™ infusion was halted and patient was administered promethazine and 2 L of saline. The differential diagnosis for this event would include possible cardiac event (arrhythmia or infarction) or an atypical infusion reaction exacerbated by hypovolemia. Approximately 90 minutes following initiation of saline infusion, the patient's condition stabilized and the adverse event resolved. No other adverse events were reported during administration of the third infusion to these patients

One patient received only two doses of ZMapp™, as the patient was found to have no detectable viral load following administration of the second dose. During the administration of this patient's first dose, the patient experienced tachycardia and rash. The infusion rate was temporarily reduced by 50% in response to this event. After the symptoms resolved, the infusion rate was re-escalated according to the treatment plan with no recurrence of the event. No adverse reactions were reported during administration of the second dose to this patient.

Three patients received only one dose of ZMapp™. The first patient succumbed due to systemic organ failure following the first dose. In the impression of the treating physician, this death was due to progression of the patient's Ebola virus infection. During administration of this patient's dose, fever, decreased blood pressure and difficulty breathing were reported, possibly also due to the patient's Ebola virus infection. The infusion rate was reduced, and the full dose was able to be administered. A second patient received one dose of ZMapp™. No adverse reactions were reported during administration of the single dose of ZMapp™ to this patient. A third patient received only one dose of ZMapp™, and succumbed due to multi-organ failure following the first dose. Mild tremor was noted during the ZMapp™ infusion, the infusion was slowed and the tremor was resolved. It was the opinion of the treating physician that this event was not related to ZMapp™ administration.

Clinical Experience with ZMapp In Ebola Infection:

Outcome of Patients Administered ZMapp™

Patient Number	Number of Doses Received	Outcome	Comment	Criteria for discharge and sequelae / Cause of death
1	3	Recovered	Patient received convalescent plasma	Asymptomatic and PCR-negative for two consecutive days. No significant sequelae.
2	3	Recovered		Asymptomatic and PCR-negative for two consecutive days. Sequelae restricted to a mild peripheral sensory neuropathy without motor involvement.
3	1	Died		Multiple organ failure with respiratory distress and severe

Patient Number	Number of Doses Received	Outcome	Comment	Criteria for discharge and sequelae / Cause of death
				shock attributed to progression of EVD
4	3	Recovered		PCR negative and asymptomatic for 24 hours. No significant sequelae.
5	3	Recovered		PCR negative and asymptomatic for 24 hours. No significant sequelae.
6	3	Died		Progressive neurological and cognitive impairments including disorientation, depression and rapid onset of stupor attributed to progression of EVD
7	2	Recovered		Asymptomatic and blood PCR-negative for six consecutive days. No significant sequelae.
8	1	Recovered	Patient received several other experimental treatments, including convalescent plasma, brincidofovir and TKM-Ebola.	Unknown
9	1	Died	Patient received convalescent plasma	Multiple organ failure

Summary of Data and Guidance for the Investigator

Non-clinical efficacy studies in guinea pigs and non-human primates (NHP) have shown that ZMapp™ provides protection in these organisms against lethal EBOV infection (Qui *et al*., 2014). The data from the NHP studies were used to base the dose and regimen for ZMapp™ administration in humans. Notably, studies evaluating the efficacy of ZMapp™ in rhesus macaques administered lethal doses of EBOV have shown that the majority of animals administered 2 or 3 doses of 50 mg/kg ZMapp™ (spaced 3 days apart) survive infection. When the survival data from animals administered 3 doses of 50 mg/kg ZMapp™ from NHP Studies 2 and 3 are considered together, a total of 9 of 10 animals survived when ZMapp™ treatment was initiated 5 days post-infection and 5 of 6 animals treated with 2 doses of 50 mg/kg ZMapp™ initiated 5 days post-infection survived. These data suggest that a schedule of 2 doses of 50 mg/kg ZMapp™ administered on Days 5 and 8 post infection provides similar efficacy as 3 doses of 50 mg/kg ZMapp™ administered on Days 5, 8, and 11 post infection.

ZMapp™ has not been tested in clinical trials, and there are limited data available for administration of ZMapp™ to human patients. ZMapp™ has been administered under expanded access INDs in the US and compassionate use provisions in Spain, the UK, and Liberia. A total of twenty doses of ZMapp™ have been administered to nine patients. Doses levels have ranged from approximately 42.5-50 mg/kg, and patients have received between 1 and 3 doses. Possible risks and Adverse Events, as well as guidance for ZMapp™ administration are summarized in the following section.

2.3 Possible Risks and Adverse Drug Reactions

ZMapp™ is an investigational drug that has not previously been administered in humans, except in cases of expanded access emergency INDs in the US and compassionate use provisions in other jurisdictions. The recommended dosing and administration are based on efficacy studies in non-human primates and previous clinical experience with monoclonal antibody therapeutics. The primate dose regimen has been mimicked in humans in expanded access INDs (without allometric scaling).

ZMapp™, as with any other mAb treatment administered at a high dose, has the potential to cause severe, including fatal, infusion reactions. Severe reactions typically occur during the first infusion (Lenz, 2007). Symptoms, signs and sequelae include:

- Fever
- Chills
- Nausea
- Urticarial
- Hypotension
- Angioedema

- Hypoxia
- Bronchospasm
- Pulmonary Infiltrates
- Acute Respiratory Distress Syndrome
- Myocardial Infarction
- Ventricular Fibrillation
- Cardiogenic Shock
- Anaphylaxis
- Anaphylactoid Events
- Death

Anaphylactic and other hypersensitivity reactions have been reported following the IV administration of proteins, including antibodies, to patients. Medicinal products for the treatment of hypersensitivity reactions, e.g., epinephrine (adrenaline) and antihistamines should be available for immediate use in the event of an allergic reaction during administration of this product. Steroids (e.g. glucocorticoids) could suppress the patient's own immune response to EBOV, and are not recommended for EBOV infected patients administered ZMapp™.

There are no data on the safety of ZMapp™ in patients with moderate heart failure (NYHA Class III) or severe, uncontrolled cardiovascular disease. The treating physician must be aware that pre-existing ischemic cardiac conditions such as angina pectoris, atrial fibrillation and flutter may become symptomatic. The risk of cardiovascular complications resulting from infusion reactions should be considered before treatment and patients must be closely monitored during administration. Since hypotension may occur during treatment, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the ZMapp™ infusion.

2.4 Guidance for the Investigator

The following are guidelines for ZMapp™ administration and should be adjusted for each patient, as each case will vary in potential for infusion reactions. **Do not administer ZMapp™ as an IV bolus or push.**

2.4.1 Guidance for infusions

First Infusion

The initial intravenous infusion rate shall begin at 50 mg/hour (12.5 mL/hr) for the first 30 minutes. Increase the dose rate by 50 mg/hr every 15-30 minutes to a maximum of 400 mg/hour (100 mL/hr). The infusion will be maintained at this rate (400 mg/hour) until the total study drug dose is met, or until the infusion must be stopped due to persistent infusion reactions of CTCAE grade 2 or above. For severe infusion reactions, stop the infusion until reaction symptoms subside to CTCAE grade 1 levels. Restart the infusion at 50% of the rate at which the reaction was observed. If the reaction does not re-occur, proceed to increase the rate as before. Mild or moderate infusion reactions should be treated by reducing the rate by 50% until symptoms subside to grade 1 levels, and then resume the rate increases as before.

For example, for a patient weighing 70 kg, the total recommended dose (at 50 mg/kg) is 3500 mg, in 875 mL (4 mg/mL solution). If no toxicity is observed, the first infusion using the rate scheme above will take up to approximately 12 hours.

Second and third infusions

In the absence of toxicity during the most recent prior infusion, initiate the infusion at 200 mg/hr (50 mL/hr), and increase the rate by 200 mg increments every 15-30 minutes to a maximum of 800 mg/hr. If no toxicity is observed, the second and third infusions will take ~5 hours.

2.4.2 Patient Monitoring and Assessment

Patients should be monitored closely during each ZMapp™ infusion. At minimum, the following parameters for patient monitoring should be recorded:

- Vital signs and nursing observation every 15 minutes during first 2 hours of infusion. Subsequent frequency of monitoring subject to individual patient response.
- Oximetry monitoring, with supplemental nasal oxygen in the event of drop in percent oxygenation.
- Parenteral glucocorticoids and epinephrine must be available at beside at all times.
- Acetaminophen and antihistamines may be repeated every 4 hours as needed.
- Bronchodilators may be used as needed. Medical and radiological pulmonary assessment, as needed for shortness of breath.
- ECG prior to treatment, repeat in the event of cardiac symptoms.
- Patients with preexisting cardiac or pulmonary pathology must be monitored carefully.

- Plasma viral load should be assessed daily by quantitative PCR. On day of infusion, plasma samples should be taken prior to administration of ZMapp™.
- Additional plasma samples (citrate tubes) should be collected prior to and on a daily basis for one week following administration of ZMapp™ for subsequent testing of ZMapp™ concentration and possible anti-drug antibodies. Additional serum samples 14 days and 28 days post-administration are also requested.

2.5 Selected References

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ZMapp™ Characterization Summary, KBI BioPharma,16 October 2014

Patient Information Sheet: ZMapp^{tm} Triple Monoclonal Cocktail

Sponsor's Name:	LeafBio
Investigational Product Name:	ZMapp^{TM}
Investigational Product Description:	Three chimeric human/murine monoclonal antibodies (13C6-FR1, c2G4 and c4G7; IgG_1 , kappa isotype) against the Ebola (Zaire) surface glycoprotein.

Why ZMapp?

The first experimental treatment to be studied in the protocol will be the use of two or three separate intravenous (given by vein) infusions of ZMapp^{tm}, an investigational product called a "triple monoclonal antibody cocktail" that consists of antibodies raised against a surface protein of the Ebola virus. Antibodies are natural infection-fighting proteins produced by the body that bind to the surfaces of viruses and prevent them from infecting cells. ZMapp^{tm} is called a "cocktail" because it contains more than one type of antibody (in this case, three) against Ebola and they work together to inhibit the virus. In the case of ZMapp^{tm} , the antibodies are produced in, and harvested from, plants genetically altered to produce large quantities of these three different antibodies against Ebola.

In monkey studies this triple cocktail has been shown capable of rescuing infected animals from death when the product was given as late as five days after infection with what would otherwise have been a lethal dose of Ebola virus in those monkeys. In addition, there is now some very limited ("anecdotal") experience with use of this monoclonal cocktail in at least nine different patients with Ebola who received this drug on a "compassionate use" basis in 2014. Of those first nine patients, some of whom also received other experimental treatments plus ZMapp, six survived and three died. However, it is very important to note that we have no way of knowing whether ZMapp was actually responsible for the survival of those six prior patients.

How is ZMapp given?

ZMapp^{tm} is not available in pill form and must be given by slow intravenous infusion over several hours on two or three separate occasions three days apart. The rate of each infusion can be increased slowly over time if the drug continues to be well tolerated, but each infusion may last up to 12 hours in order to give the drug safely and minimize the chances of developing any severe side effects.

What is known about ZMapp in humans?

These first few patients with Ebola who have received ZMapp^{tm} to date have generally tolerated the medication without significant side effects. When side effects have occurred, their severity has generally been lessened by slowing down, or temporarily stopping, the rate in which

the drug has been given by vein. **Some of the side effects that have been reported include: skin flushing (turning red), fast heart rate, chills, a rise or fall in blood pressure, itchiness, edema, fever, chest pain, shortness of breath, brief seizures, and skin rash**. However, in some cases it could not always be determined whether ZMapp^{tm} caused these side effects or whether they were due to Ebola. Regardless, this experience is far too limited to know whether the drug will continue to be safe when given to larger numbers of patients and, in particular, whether either new short term or longer term side effects may be seen as the numbers of patients who receive this experimental therapy increases over time. There is always the risk that the drug may not cause benefit and, in fact, may cause harm that outweighs any potential favorable effect of the drug upon the virus itself. In particular, ZMapp^{tm} is a drug that consists of antibody proteins that are made in plants. Whenever a human receives a drug consisting of protein(s), especially proteins not produced in humans, there is always the chance that they could have a severe allergic reaction (called "anaphylaxis") to the protein. Anaphyaxis can cause a rapid drop in blood pressure, fast heart rate, difficulty breathing, and other serious side effects that, if untreated, can result in death. It cannot always be predicted in advance who might develop this type of severe reaction.

What will happen to me while receiving ZMapp^{tm} ?

If you are assigned to the arm of the study that includes receiving ZMapp^{tm}, you will have baseline blood tests drawn in order to measure the current level of Ebola virus in your bloodstream and to monitor your kidney function, liver function, bone marrow function, and other safety measures. Vital signs will also be checked and then repeated frequently while you are receiving the medication intravenously. An electrocardiogram (EKG) will be performed to monitor your heart. If necessary to prevent or control side effects, you may be given acetaminophen and/or an antihistamine by mouth either prior to, or during, the ZMapp^{tm} infusion. If not already in place, you will have an IV (intravenous line) inserted into an arm vein or other vein to allow your doctors to give the ZMapp^{tm} medication.

The ZMapp^{tm} infusion will be started at a slow rate and then increased if you are not having any significant side effects. If side effects do develop, your doctors may need to slow the infusion rate, temporarily discontinue it until you recover, or administer other medications to reduce the severity of the side effects. For example, if you develop fever your doctors may decide to treat you with acetaminophen to reduce the height of the fever. However, even when given at the highest rate the entire infusion may take up to 12 hours to complete. At the end of each infusion you will continue to be monitored for any side effects that may develop as a result of the infusion.

At the present time we are planning to administer only two separate infusions of ZMapp^{tm} to each individual rather than the three infusions that have often been givenin the past. This is because the latest data from monkey studies suggests that just two infusions may be as effective as three in fighting Ebola in treated animals.

After you receive your treatment course of ZMapp^{tm}, your doctors will continue to monitor the level of Ebola in your bloodstream in order to try to learn whether the ZMapp^{tm} infusions had any effect in lowering that level. Throughout your participation in this study they will continue to provide you with all of the other standard medical measures that have been proven to be effective in helping people recover from Ebola.

A Multicenter Randomized Safety and Efficacy Study of Putative Investigational Therapeutics in the Treatment of Patients with Known Ebola Infection

Short Title:	MCM RCT Protocol
Sponsored by:	Office of Clinical Research Policy and Regulatory Operations (OCRPRO) National Institute of Allergy and Infectious Diseases 5601 Fishers Lane Bethesda, MD 20892

NIH Protocol Number:	15-I-0083
Protocol IND #:	125530
ZMapp™ IND#:	122451
ClincalTrials.gov Number:	NCT02363322

Date:	22 October 2015
Version:	6.0

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CBC	Complete Blood Count
CFR	Code of Federal Regulations (US)
CI	Confidence Interval
CRF	Case Report Form
CSO	Clinical Safety Office
DCR	Division of Clinical Research
DRC	Democratic Republic of Congo
DSMB	Data and Safety Monitoring Board
EBOV	Ebola virus
ECG	electrocardiogram
EVD	Ebola hemorrhagic fever
ETU	Ebola treatment unit
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
HCW	health care workers
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
MCMs	medical countermeasures
NHP	nonhuman primate
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OCRPRO	Office of Clinical Research Policy and Regulatory Operations
OHRP	Office for Human Research Protections
oSOC	optimized standard-of-care
OTC	over-the-counter
PI	Principal Investigator
PK	Pharmacokinetics
POC	point-of-care
SAE	Serious Adverse Event/Serious Adverse Experience
SERF	Safety Expedited Report Form
SMM	Sponsor Medical Monitor
SOC	standard-of-care
SRCP	Safety Review and Communications Plan
SUSAR	Serious Unexpected Suspected Adverse Reactions
UP	Unanticipated Problem
WBC	White Blood Cell Count

ZEBOV	Zaire Ebola virus

PROTOCOL SUMMARY

Full Title:	A Multicenter Randomized Safety and Efficacy Study of Putative Investigational Therapeutics in the Treatment of Patients with Known Ebola Infection
Short Title:	MCM RCT in EBOV
Clinical Phase:	1/2
IND Sponsor:	Office of Clinical Research Policy and Regulatory Operations (OCRPRO)
Conducted by:	Multicenter Trial
Principal Investigator:	Richard T. Davey, Jr., MD
Sample Size:	Up to 100 per arm
Accrual Ceiling:	1000
Study Population:	Patients with known Ebola infection
Accrual Period:	February 2015 – December 2016
Study Design:	Randomized clinical trial
Study Duration:	Start Date: February 2015 End Date: December 2017
Study Agents:	ZMapp^{tm}, convalescent plasma, favipiravir, TKM-Ebola, others
Primary Objective:	• To establish the safety and efficacy of investigational therapeutics in patients with Ebola virus infection
Secondary Objectives:	• Uniform observational database on clinical and virologic parameters associated with severe Ebola virus infection • To evaluate the comparative effects of investigational therapeutics on clinical parameters of Ebola infection • Comparative effects of different investigational agents on immediate plasma viral load kinetics • 24-48 hour pharmacokinetics of investigational therapeutics when possible and appropriate • Comparative frequency of serious adverse events (SAEs) • Duration of hospital stay • Time to viral load clearance • Late onset of any clinical symptoms possibly consistent with delayed virologic relapse
Primary Endpoint:	• Mortality at Day 28
Inclusion Criteria	• Males or females with documented positive PCR for Ebola virus infection within 10 days of enrollment • Willingness of study participant to accept randomization to any assigned treatment arm • Access to oSOC

- All males and females of childbearing potential, must be willing to use highly 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 58 of study
- Ability to provide informed consent personally, or by a legally-authorized representative if the patient is unable to do so.

Exclusion Criteria:

- Any medical condition that, in the opinion of the site investigator, would place the patient at an unreasonably increased risk through participation in this study, including any past or concurrent conditions that would preclude randomization to one or more of the assigned treatment arms.
- Prior treatment with any investigational antiviral drug therapy against Ebola infection, other than experimental vaccines, within 5 half-lives or 30 days, whichever is longer, prior to enrollment

Study Design Principles:

A randomized, controlled adaptive trial, with frequent interim monitoring to facilitate the following: dropping of poorly performing arms, introduction of new candidate therapies and modification of current optimized standard-of-care (oSOC). Comparisons of safety and efficacy will be based on data from concurrently randomized participants. In its simplest iteration, the study can be viewed as a series of 2-arm comparisons whereby the superior treatment, if identified, from each pairwise comparison becomes the basis of the new supportive care backbone (hence the term "optimized SOC", or oSOC, to describe this potentially evolving backbone) common to each future arm of the study and against which additional investigational interventions may then be added to the protocol, tested and compared:
Arm A: optimized SOC alone
Arm B: Investigational treatment X + optimized SOC

- In the <u>initial</u> iteration and at protocol team discretion, the optimized SOC employed in Arm A is expected to consist of aggressive fluid replacement and electrolyte monitoring and replacement to be compared to Arm B in which both investigational therapeutic agent X <u>plus</u> that same optimized SOC are featured.

- If this pairwise comparison shows the superiority of Arm B over Arm A, then investigational treatment X featured in Arm B will be incorporated into the new oSOC common to each future arm of the study (assuming adequate drug supply exists to permit this).
- Conversely, if a given pairwise comparison of Arm A versus Arm B fails to yield a clear statistical winner in terms of the primary endpoint, then subsequent pairwise comparisons will not incorporate the "failed" intervention featured in current Arm B into the new oSOC backbone.

Study Synopsis:

- Informed consent for research participation upon admission into the treatment center
- Baseline determination of clinical status according to standardized CRF
- Baseline collection of plasma for Ebola viral load by PCR to be processed by an appropriate laboratory facility
- Centralized randomization assignment made
- Provision of Arm A or Arm B intervention according to assigned treatment arm and the individual pharmacologic or logistical requirements of the treatment intervention
- 24-48 hour pharmacokinetic measurements of assigned intervention where appropriate and possible
- Daily assessments of clinical status according to standardized CRF and flow sheet
- Serial collection of plasma for viral load determination by PCR for processing in an appropriate laboratory facility, as possible.
- Long term follow-up, when feasible, for any late onset clinical history or symptoms possibly consistent with delayed virologic relapse.

PRÉCIS

Ebola viruses (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 EBOV 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. However, the 2014 West African outbreak significantly exceeds all previous outbreaks in geographic range, number of patients affected, and in disruption of typical activities of civil society.

There is strong consensus that the most important element necessary to improve survival from Ebola infection is the provision of full hemodynamic support in the form of aggressive fluid replacement, ability to diagnose and correct severe metabolic derangements, and other standards of modern medical care available in resource-rich environments. However, against this background, a small series of investigational agents or interventions have also been proposed as putative antiviral strategies of potential utility in treating this infection. Unfortunately, phase 1/2 data supporting the safety and efficacy of these agents is generally lacking, and thus there should be equipoise as to which, if any, of these interventions should be utilized in the treatment of severe infection.

In this multicenter randomized trial, we propose a flexible trial design with frequent interim monitoring to facilitate early elimination of poorly performing treatments as well as the introduction of new candidate therapies. The trial allows for a series of pairwise comparisons of novel interventions against a background of optimized medical care, with the goal of determining whether one or more of these interventions can improve the mortality over that achievable through optimized standard-of-care (oSOC) alone. The primary endpoint of this trial will be comparative mortality at Day 28, with a number of secondary endpoints that hopefully will generate generalizable knowledge about the relative safety and antiviral activity of these adjunctive interventions.

16 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

16.1 Background

16.1.1 Filoviruses

Ebola viruses (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 EBOV outbreaks (Table 8) affecting mostly central Africa, with 2 large outbreaks in 1995 in Kikwit, DRC, and in Gulu, Uganda in 2000-2001. The ongoing West African outbreak significantly exceeds all previous outbreaks in geographic range, number of patients affected, and in disruption of typical activities of civil society.

Table 8: Ebola Virus Outbreaks

Viral species	Year	Outbreak location	# of human cases (% fatality)
	1976	Yambuku, Zaire (DRC)	318 (88%)
Zaire Ebola virus	1977	Tandala, Zaire (DRC)	1 (100%)
	1994	Ogooue-Invindo province, Gabon	51 (60%)
	1995	Kikwit, Democratic Republic of Congo	315 (79%)
	1996	Mayibout, Gabon	37 (57%)
	1996	Booue, Gabon and Johannesburg, South Africa	61 (74%)
	2001-02	Ogooue-Invindo province, Republic of Congo (RC)	124 (79%)
	2002-03	Cuvette region, RC and Ogooue-Invindo province, Gabon	143 (90%)
	2003	Mboma and Mbandza, Republic of Congo	35 (83%)
	2005	Etoumbi and Mbomo, Republic of Congo	12 (75%)
	2007	Kasai Occidental province, Democratic Republic of Congo	25 (not determined)
	2008/2009	Democratic Republic of the Congo	32 (47%)
Sudan Ebola virus	1976	Nzara, Maridi, Tembura, Juba, Sudan	284 (53%)
	1979	Nzara, Yambio, Sudan	34 (65%)
	2000-01	Gulu, Masindi, Uganda	425 (53%)
	2004	Yambio, Sudan	17 (41%)
	2011	Uganda (Luwero District)	1 (100%)
Taï	1994	Tai forest, Ivory Coast	1 (0%)
Ebola Virus	1995	Liberia, Liberia	1 (0%)
Reston Ebola virus	1989	Reston, VA, USA	4 (0%)
	1992	Siena, Italy	0
	1996	Alice, TX, USA	0
	2008	Philippines	0

Bundibugyo Ebola virus	2007/2008	Uganda	131 (37%)

16.1.2 Therapy

To date the standard treatment of Ebola hemorrhagic fever (EVD) during the present 2014 outbreak has been strictly supportive, involving largely oral fluid and electrolyte replenishment and pain reduction. 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 have neither been available nor tested in most patients. However, in the few centers where such measures were able to be employed, a substantial reduction in mortality has been reported. Thus, substantial planning efforts are currently geared towards identification, standardization, and deployment of the most successful standard-of-care (SOC) measures that potentially could be introduced into these previously resource-poor areas where the majority of patients have been treated. In addition to ongoing epidemiologic measures to limit the spread to uninfected populations, there is widespread consensus that improved SOC measures could represent the single most effective means of reducing the substantial mortality rates associated with the disease in the affected regions.

In contrast, in the United States and other developed nations to which a small number of infected health care workers (HCW) have been medically evacuated, aggressive intravenous 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 optimized standard of care (oSOC) there 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 late fall, 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. The reported distribution of investigational agents in these individuals was as follows:

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

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 extremely difficult to discern. In addition, to date 6 medically evacuated HCWs brought back to the United States following a serious percutaneous exposure to Ebola virus while in country, but without documented infection at the time of transfer, also received 1 putative MCM each: Tekmira siRNA in one case and the investigational VSVΔG-ZEBOV vaccine in the remaining five. It should be emphasized that in 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 humans 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 in rodent models, but either failed testing or were not thoroughly tested in the nonhuman primate (NHP) model, which is 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 current outbreak and, in fact, was also used in a limited number of patients during the Kikwit 1995 ZEBOV outbreak. However, its earlier success remains a matter of dispute (1). Experimentally, passive immunization with horse serum resulted in protection of Hamadryl baboons (2), whereas it only delayed death in Cynomolgus macaques (3, 4). Certain monoclonal antibody treatments have also been successful in rodent models (5-7) but have failed in preliminary nonhuman primate studies (8), indicating possible evasion of antibody neutralization as an escape mechanism of the virus. Other, more recent monoclonal antibody cocktails may avoid this limitation. However, it remains fair to say, at least at this time, that the therapeutic role of convalescent plasma or monoclonal preparations as treatment adjuncts remain as unsubstantiated in this disease as do direct antiviral agents.

16.2 Rationale for Study

The current state of medical science with respect to the treatment of filovirus infections such as Ebola does not adequately address the role of therapeutic adjuncts beyond supportive care in the successful management of these infections. In many cases, our understanding of the role that these adjunctive therapies may play is greatly hampered by lack of an adequate phase 1 safety and toxicity database of the lead drug candidates, or by lack of data concerning even how the candidates in more advanced development may perform in this particular patient population. The tragic dimensions of the ongoing Ebola epidemic in West Africa afford little time to explore these issues according to a more conventional time frame of traditional drug development, and argue strongly for an accelerated exploration of the safety, toxicity, and potential preliminary efficacy of lead agents in a controlled research setting.

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:

- Even in highly-resourced medical environments such as those available in the US, Europe, or other developed regions, the past record of being able to generate important

and generalizable knowledge concerning the role of experimental therapies for infectious diseases of public health importance when those agents have been made available under single-use emergency IND, Emergency Use Authorization (EUA), or similar mechanisms has been disappointing at best. A consolidated multicenter approach to study lead candidates according to a single research protocol offers a potential opportunity to improve upon this record.

- Even if concentrated efforts to generate important comparative efficacy assessments between individual treatment interventions falls short, 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 receiving oSOC.

- Optimized SOC must be the mainstay of therapy and remain the backbone to which experimental treatment modalities must be introduced and compared.

- Depending upon site and resources, invariably differences in oSOC may occur that may obscure the potential additional contribution of experimental therapeutics. Therefore, every effort must be made to standardize the oSOC that exists as the backbone to this experimental treatment protocol. In situations where this may not be fully possible, i.e. in comparing in-country oSOC versus oSOC available in intensive care settings within developed nations, this difference must be taken into account when comparing outcome in different patient cohorts.

- Questions of equity concerning the ethics of allowing potentially beneficial experimental treatments to be studied in places where fully optimized supportive care may be possible, and not in places where optimized care has not been introduced to date, are certainly reasonable, heartfelt, and compelling but, if taken to their logical extreme when involving drugs in extremely limited supply and of unknown safety, could prevent their scientific study altogether and result in no generalizable knowledge being generated about the value of these agents in any setting, an outcome that would disadvantage society as a whole.

- A unique and presently unavoidable factor in establishing pairwise comparisons identified for this trial is the limited, intermittent, or absent drug supply that may exist for several of the lead candidates proposed for study. The current flexible treatment design is an attempt to overcome this unpredictable element.

- As present knowledge of the potential toxicity of lead candidates in this patient population is as limited as knowledge of their potential therapeutic value, investigators should and must be able to maintain equipoise as to the introduction and role of individual agents in treating patients severely ill with Ebola infection.

- A key ethical feature and justification for this approach, based upon the current and foreseeable circumstances, is that there is a significant degree of ‘acceptability of [trial

drug] risk,' in the face of unprecedented individual and community risk for morbidity and mortality.

- The use of a common protocol is recommended for the following reasons:
    - This design can accommodate the study of more than 1 investigational therapy using a single shared control group.
    - As mentioned above, this design can accommodate staggered and intermittent availability of limited supplies of the anti-Ebola investigational drugs.
    - This design can also provide a more equitable means of allocating scarce product through randomization (much like a lottery) while also allowing critically important data to be gathered on the safety and efficacy of these investigational products that will benefit patients (i.e., knowledge of whether an investigational product is actually helping, hurting, or of no consequence).
    - Having a randomized concurrent control group is essential to maximize the likelihood that the conclusions drawn from the trial are correct. Site-specific case fatality rates (CFR) have varied substantially both between different treatment centers as well as even chronologically within the same centers over the course of the present epidemic, making the use of historical controls fixed in time or place fraught with significant hazard.
    - A single trial design allows for having a data safety monitoring board (DSMB) and stopping rules in place. The stopping rules should be reasonable, and if one of the products is found to be effective at an interim time point but there is not a sufficient supply of the product that has been found to be effective, it may still be ethical to continue the common protocol. When sufficient supplies of the product become available, that product might be incorporated into the revised oSOC, as discussed earlier. If there are insufficient supplies of a product, even if efficacy has been shown, one may be able to argue that providing the scarce supplies of drug through a clinical trial is more equitable than other potential approaches in addition to allowing continued comparative data generation to improve the understanding of its appropriate use.

17 STUDY OBJECTIVES

17.1 Primary Objective

- To establish the safety and efficacy of investigational therapeutics in patients with Ebola virus infection.

17.2 Secondary Objectives

- To create a uniform observational database on clinical and virologic parameters associated with severe Ebola virus infection

- To evaluate the comparative effects of investigational therapeutics on clinical parameters of Ebola infection
- To study the comparative effects of different investigational agents on immediate plasma viral load kinetics
- To obtain 24-48 hour pharmacokinetics of investigational therapeutics when possible and appropriate*
- To determine the comparative frequency of serious adverse events (SAEs)
- To describe infusion related adverse reactions
- To compare the duration of hospital stay
- To compare the time to viral load clearance
- Long term follow-up for any late onset clinical history or symptoms possibly consistent with delayed virologic relapse.

* 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 and transport 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.

18 STUDY DESIGN

18.1 General

Study size: up to 1000 patients
Study duration: 24 months
Study duration of individual subjects: Initially for 30 days following the primary endpoint (mortality at Day 28), or for a total of 58 days. Interested subjects will also be offered the opportunity, where and whenever feasible, to participate in long term follow-up (up to 1 year or more depending upon need) past Day 58 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 CNS or the male testes).
Sex distribution: males and females
Age range: unrestricted

A randomized, controlled clinical trial of experimental Ebola virus disease therapies compared to current oSOC. Treatment efficacy evaluations are based on outcome comparisons between treatment arms from concurrently enrolled subjects. The study can be conceptualized as a series of 2-arm comparisons between different therapeutic interventions: oSOC versus an experimental therapy plus oSOC. It is intended that the oSOC will be updated to incorporate an experimental therapy when the latter's efficacy has been demonstrated. While the updated oSOC should be the comparator for unproven therapies, this may not always be practical (e.g., when supply of the new drug is limited). Whether the updated oSOC is always added as optimized background therapy to existing unproven/experimental therapies will depend on

practical considerations, including drug availability and the appropriateness of combining specific therapies. However, the intent is that the study will continue enrolling and employ the next selection of available medical countermeasure in the comparison if there is a temporary shortage of the present countermeasure being studied.

Stage 1: the initial phase (see Figure 5)
Randomization to the following:

Arm A: $oSOC_1$** alone
or
Arm B: Investigational treatment X + $oSOC_1$**

*The subscript "1" indicates the first or current "optimized standard-of-care." In the initial iteration and at protocol design team discretion, Arm A will be an oSOC alone arm to be compared to Arm B in which both an investigational therapeutic agent (i.e. Drug "X") plus oSOC are combined.

** In developed countries, oSOC is defined as the application of aggressive fluid resuscitation, hemodynamic and respiratory support, metabolic corrections, diagnostic evaluation, and other modalities of advanced critical care that are generally available in most academic centers capable of caring for critically ill patients. In areas where such advanced methods may not be fully available (i.e., in advanced medical care units to be built and supported in the affected countries of West Africa by the USG and other government entities), this definition should apply to the optimal standards of care possible in those settings.

If and when a statistical difference is shown between the 2 arms supporting superiority of one intervention over the other, the superior ("winning") intervention is then used as the basis of a modified oSOC in which incorporation of that intervention as an addition to the prior oSOC becomes the new basis of comparison. This is assuming that sufficient drug supply exists to permit the incorporation of that superior therapy into a new oSOC backbone and fuel additional comparisons. If that is not the case, then subsequent comparisons will have to revert back to the previous oSOC until such time as additional quantities of the superior therapy can be made available. If, however, incorporation into a new oSOC is possible, then that modified arm can then compared to new Arm C (i.e., consisting of a new therapeutic intervention not previously tested) so that the pairwise comparisons can continue until the list of favored treatment explorations is exhausted and/or until an optimal regimen appears clear. This can be summarized as follows:

Stages 2-K: the post-initial phase with up to K additional therapies.

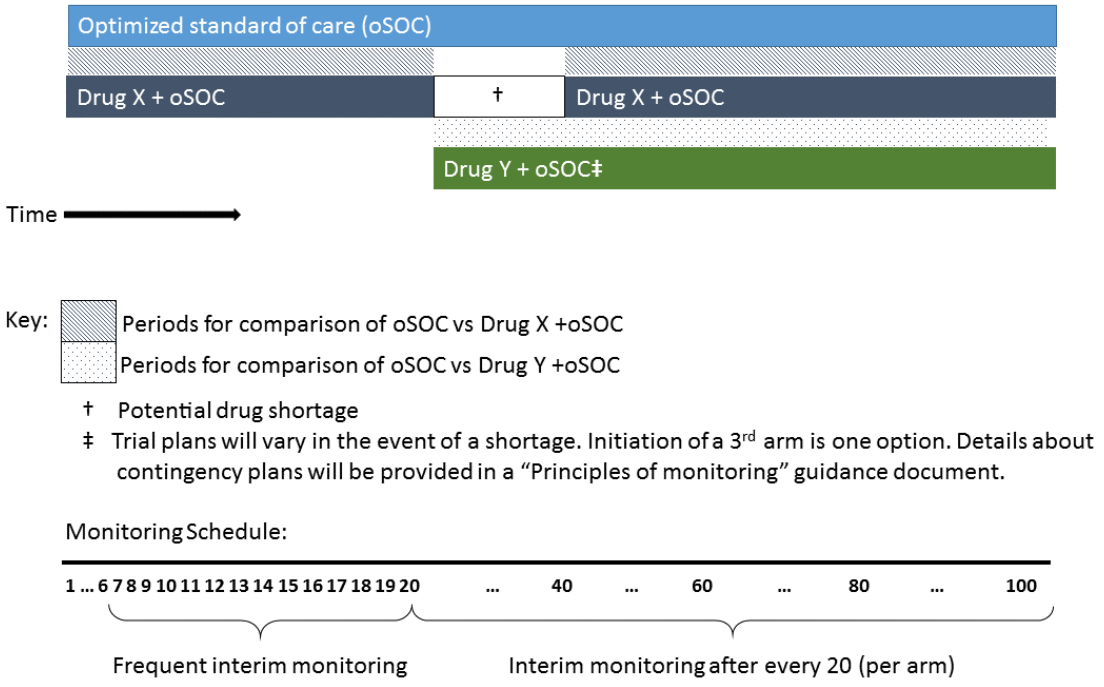
Randomization to the following:
Control arm: Updated current oSOC ($oSOC_{k;\ where}$ k=2,…, K to indicate the possible updated oSOCs)

Experimental arm: Investigational therapy + best oSOC, where the best oSOC may be the most current oSOC or the previous oSOC, depending on drug availability, appropriateness of combination therapy, etc. as determined by the study team in concordance with the DSMB.

Advisory stopping boundaries for efficacy (and futility) will be provided to the DSMB to guide decisions about when an experimental arm is deemed superior (or not worthy of further investigation). A description of these boundaries is provided in the statistics section (Section 22). Specifics about these boundaries will be provided in a DSMB statistical analysis plan.

While for illustrative purposes, the strategy is described with sequential pairwise comparisons, in practice, it can be adapted for more than 2 pairwise comparisons. The study might be modified accordingly, if there is compelling scientific interest to study more than 2 different interventions simultaneously ("Drug Y" example in Figure 5). Success at being able to demonstrate statistical difference between comparator arms will of course depend upon being able to enroll sufficient numbers into each arm to power these comparisons.

Figure 5: Example of Possible Clinical Trial Design Schematic for the Common Protocol – First Phase



18.2 Study Endpoints

Study endpoints will be evaluated by comparing randomized groups.

18.2.1 Primary Endpoint

- 28-day survival

18.2.2 Secondary Endpoints

- 58 day survival time
- Change in Ebola virus threshold cycle within first 72 hours after randomization
- Rate of Ebola viral clearance, quantified as change in threshold cycle per day
- Time from randomization to first negative Ebola PCR
- Cumulative incidence of serious adverse events (SAEs)
- Cumulative incidence of adverse events (AEs) as assessed by laboratory monitoring
- Incidence of infusion related adverse reactions
- Frequency of clinically significant study agent administration or infusion reactions
- Duration from time of symptom onset to discharge from treatment unit or hospital
- Cumulative incidence of progression to severe disease (hemorrhage, multi-organ failure, seizures)
- Cumulative incidence from the time of randomization to resolution of gastrointestinal symptoms (vomiting and diarrhea).

- Cumulative incidence from time of randomization to resolution/progression of individual clinical symptoms
- Maximal serum creatinine in first 14 days
- Pharmacokinetics of investigational therapeutics
- Long term follow-up, when feasible, for any late onset clinical history or symptoms possibly consistent with delayed virologic relapse.

18.3 Overview of Study Drugs

By the fall of 2014 preclinical studies, and/or past use of interventions with anecdotal evidence, had identified a number of lead candidate therapeutic interventions that might be considered as prime candidates for further study in patients with known Ebola infection. With time it was thought possible that additional antiviral or immune-enhancing agents with preclinical supporting data may be identified and added to this list. Conversely, emerging toxicity data, failure to replicate previous supportive findings in additional preclinical animal model testing, emerging data from other recent therapeutic trials in West Africa, or similarly negative factors conceivably could also lead to narrowing of this list over time. Further, if inclusion were to be expanded to patients with high-risk exposures but no documented infection, the list of putative MCMs could be broadened even further and would likely include putative vaccine candidates. However, confining this proposed RCT to just enrollees with documented infection, the likely lead candidates initially identified for consideration of study included:

- Convalescent or post-immunization plasma harvested from recent Ebola infection survivors:
    - In time it is possible that this category could potentially be expanded to include plasma donors who have participated in phase 1 anti-Ebola vaccine testing and whose plasma shows high neutralizing activity against the virus in animal or *in vitro* assays.
- ZMapp™ triple monoclonal antibody cocktail from Mapp Biopharmaceutical:
    - A combination of 3 different humanized monoclonal antibodies against the Ebola glycoprotein.
- Tekmira siRNA (or "TKM-Ebola") from Tekmira Pharmaceuticals Corp:
    - A combination of small interfering RNAs targeting 2 of the 7 proteins in Ebola: Zaire Ebola L polymerase and Zaire Ebola polymerase complex protein (VP35), formulated with Tekmira's lipid nanoparticle technology. Targeting of the initial product was subsequently optimized against the prevalent Guinea strain of the 2014 virus.
- Favipiravir from Toyama Chemical Co., LTD:
    - A selective inhibitor of RNA-dependent RNA polymerase with activity against a wide variety of viruses.
- BCX4433 from BioCryst
    - viral RNA-dependent RNA polymerase (RdRp) inhibitor
- AVI-7537 from Sarepta
    - phosphorodiamidate morpholino oligomer

This list was not intended to be exhaustive, and future inclusion of other drug candidates (e.g. different monoclonal antibody cocktails targeted at epitopes identical to those in ZMapp™) was not prohibited by these examples.

18.4 Considerations in Choice of Study Drugs

Several factors influencing choice and sequence of study drugs/interventions to be compared in this protocol must be considered:

- Willingness of both the pharmaceutical sponsors and the FDA to allow each of these drugs to be studied according to this proposed trial design
- Sufficient and dedicated supply of individual agents to allow them to be available for study over the projected timeline of the trial
- Ongoing equipoise of the investigators that
  - No available individual agent has yet been demonstrated to be superior to oSOC
  - No available individual agent has yet been demonstrated to be superior to other agents
- No compelling safety/toxicity concern has emerged with respect to individual agents to favor their removal from consideration as study interventions
- The status of eIND access to these interventions during the projected timeline of this trial that may preclude, or circumvent, interest in enrollment of patients into this RCT.

With these considerations in mind, the starting choice of interventions to be entered into and compared in this trial was determined by a consensus of the site investigators performing this study at their individual treatment centers. The most recent deliberations of this group are reflected in Appendix A of this protocol.

18.5 Definitions for the Purpose of this Study

Enrolled

For the purpose of collecting data and samples, and reporting SAEs, a subject will be considered enrolled beginning from when the informed consent form is signed until the subject is considered either “discontinued”, or “completed”.

Discontinued

Subjects are considered discontinued when they meet 1 or more of the following criteria:

- Subject withdraws consent after being dosed and prior to the completion of Day 28 (see Section 19.5)
- Subject is withdrawn after enrollment by investigator (see Section 19.6) including lost to follow-up

Completed

Subjects are considered completed for the main study endpoint when they 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 scheduled for that time. Patients willing to undergo extended follow-up for one year or more (i.e. to determine the incidence of any late onset history or symptoms potentially c/w virologic relapse) will still be considered as having

completed the study if a) they decline this extended follow-up, or 2) choose to discontinue extended follow-up prior to reaching one year past Day 58.

19 STUDY POPULATION

19.1 Research Subject Recruitment

Persons with confirmed Ebola virus infection at participating health centers may participate in the trial so long as the site can provide enhanced supportive care including the provision of fluid resuscitation (preferably intravenously, but potentially orally through nasogastric tubes), hemodynamic monitoring, and laboratory monitoring of fluid and electrolyte disturbances coupled with the ability to correct such abnormalities as they are detected.

19.1.1 Participation of Site Employees

Site employees who meet inclusion 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.

19.2 Inclusion Criteria

- Males or females with documented positive PCR for Ebola virus infection within 10 days of enrollment
- Willingness of study participant to accept randomization to any assigned treatment arm
- Access to oSOC
- All males and females of childbearing potential, must be willing to use highly effective methods of contraception [e.g. absolute abstinence from potentially reproductive sexual activity, hormonal, surgical or multiple barrier/combined], from time of enrollment for the duration of study participation.
- Must agree not to enroll in another study of an investigational agent prior to completion of last required protocol visit (Day 58)
- Ability to provide informed consent personally, or by a legally-authorized [per applicable local laws and regulations] representative [LAR] if the patient is unable to do so.

19.3 Exclusion Criteria

- Any medical condition that, in the opinion of the site investigator, would place the patient at an unreasonably increased risk through participation in this study, including any past or concurrent conditions that would preclude randomization to one or more of the assigned treatment arms.
- Prior treatment with any investigational antiviral drug therapy against Ebola infection, other than experimental vaccines, within 5 half-lives or 30 days, whichever is longer, prior to enrollment.

19.4 Vulnerable Populations

19.4.1 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 infection than from the study medications themselves, pregnant women will be permitted entry into the study. However, there may still be certain study medications (e.g., favipiravir) with known teratogenic potential to which pregnant women should not be assigned, and these considerations must be reviewed on a case-by-case basis with study investigators. For example, if favipiravir happens to be the drug currently under study, pregnant women should not be enrolled in the trial during the period this particular drug is being tested.

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 Ebola Treatment Unit (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.

19.4.2 Inclusion of Children

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 study participation.

19.5 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.

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

19.6 Discontinuation of Subject by Investigator

The investigator has the right to withdraw subjects from the study. Subjects may be withdrawn from the study for any of the following reasons:

- The investigator believes that continuation in the study would be detrimental to the subject. 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. If in the investigator's best judgment discontinuation is in the subject's best interest.

The reason for withdrawal from the study is to 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.

19.7 Discontinuation of Study

The National Institute of Allergy and Infectious Diseases (NIAID), each institution's Institutional Review Board (IRB), or the Food and Drug Administration (FDA) may terminate this study at any time. 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
- Investigators do not adhere to the protocol or applicable regulatory guidelines in conducting the study

20 TREATMENT

20.1 Randomization and Blinding

This study follows an open-label randomization design. A randomization scheme will be generated by the Data Management Center prior to the initiation of the study.

20.2 Study Drugs

Every attempt will be made to pre-position the study drugs under active study at the participating sites' pharmacies in advance of enrollments. Randomization of individual patients to a given study drug will only occur when there is sufficient quantity of that drug to complete a full treatment course for those individuals.

21 STUDY PROCEDURES

21.1 Personnel for Study Procedures

Assessments and study procedures may be performed by members of the investigative team and clinical team as noted on the Delegation of Responsibilities log.

The study will be conducted in accordance with the protocol, GCP, and all applicable US and West African regulations.

21.2 Site-Specific Considerations

The reality of the 2014-15 outbreak of Ebola infection is that patient care has been, and will likely continue to be, provided in a wide variety of different clinical settings, some of which have been fortunate to be comparatively resource-rich and others of which have faced significant resource challenges. Accordingly, the capability of individual sites to conduct the full spectrum of clinical research components outlined in this protocol will almost certainly vary widely depending upon such factors as staffing, available

equipment, and current operational, clinical, and safety practices. With this consideration in mind, as long as sites can fulfill the minimal standards of oSOC as outlined in Section 3.1 and obtain the necessary information to inform the primary endpoint, it is appropriate that 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. The inability of a site to collect the full optimal frequency of assessments as outlined below due to unavoidable resource limitations will not constitute a protocol deviation.

21.3 Schedule of Evaluations

The day when the subject is enrolled and randomized to their assigned treatment arm is denoted as Study Day 0. The first day after randomization is Study Day 1. 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 past Day 58 to determine the incidence of potential virologic relapse will either be seen in person or contacted via phone on a periodic basis; all study days past Day 58 will be considered Extended Follow-Up assessments. If necessary, and with the patient's verbal consent at the time they agree to extended follow-up, 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 a late onset virologic relapse syndrome. The expected frequency of such periodic assessments will be every 1-3 months up to one full year past Day 58, subject to the patients' wishes and the logistics and feasibility of contacting individual participants on a serial basis.

Table 9: Schedule of Evaluations

Evaluation / Procedure	***Screen***	***Baseline***	***Follow Up***										
Day +/- Window	**−1 to 0**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8+** while hospitalized	**28-35**	**58 ±7**	**Ext. F/U (Q 1-3 mo.)**
ELIGIBILTY/RANDOMIZATION													
Informed consent	X												
Demographics	X												
Ebola PCR	-10 to 0												
Randomize subject		X											
STUDY DRUG ADMINISTRATION													
ZMapp™ (if randomized to receive ZMapp™)		X (Day 0 if possible)			+ 3 days from 1st dose			+ 3 days from 2nd dose					
Investigational agents #2		*Other investigational agents per the adaptive trial design, refer to most recent SOP*											
MINIMUM STUDY PROCEDURES *(only obtained while in treatment unit)*													
Vital signs		X	X	X	X	X	X	X	X	X	X	X	
Record of Optimized Supportive Care		X	X	X	X	X	X	X	X	X			
Assessment of current symptoms/conditions		X	X	X	X	X	X	X	X	X	X	X	X
Ebola PCR with ct	X		X			X			Every 2-3 days until 1 negative				
Creatinine, Potassium	X		X			X			X				
OPTIMAL 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 PCR with ct		X	X	X	X	X	X	X	X	until 2 negative	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			
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		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	

6.2.1 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 and time when signed. The informed consent process will occur on or before Day 0.

6.2.2 Demographics

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

- Age
- Sex
- Ethnicity
- Race
- Country of Birth

6.2.3 Medical History

The following information should be recorded:

- Focused Medical history regarding EVD, including all prior PCR results
- Current Symptoms
- Current participation in any recent research protocols

6.2.4 Clinical Data

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

6.2.7 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 (or told directly if found ineligible during screening evaluation), and the reason for ineligibility will be discussed. If desired by the subject, and if applicable for the reason for ineligibility, the results will be shared with their outside health care provider.

21.4 Day 0

21.4.1 Baseline Evaluation

Within 24 hours prior to randomization, a baseline clinical evaluation will be performed with documentation of current symptoms and clinical conditions including vital signs.

The list of symptoms and signs to assess includes: fever, sore throat, cough, fatigue, weakness, dizziness, confusion, hearing loss, headache, myalgia, arthralgia, loss of appetite, vomiting, diarrhea, symptoms, abdominal pain, trouble urinating, chest pain, breathing difficulties, shortness of breath, hiccups, rash, edema, conjunctivitis, oral ulcers/thrush, hemorrhage, multi-organ failure, convulsions.

21.4.2 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).

21.4.2.1 Minimum Baseline Requirements:

- Creatinine
- Potassium
- Ebola PCR with threshold cycle (ct)
    - Although any positive Ebola PCR collected up to 10 days prior to informed consent provides eligibility, a baseline specimen should be collected on Day 0 if the prior specimen was collected >24 hours, as the viral load may have substantially changed.

21.4.2.2 Optimal Baseline Laboratories

- CBC with differential
- Acute/hepatic/mineral chemistry panels as available via POC testing, defined as:
    - Metabolic Panel = Na, K, Cl, HCO_3, blood urea nitrogen, creatinine, glucose, Ca, Mg
    - Hepatic Panel = AST/SGOT, ALT/SGPT, Alkaline phosphatase, t-Bilirubin,
    - Lactate
    - Albumin
    - ionized Calcium
- Ebola PCR with threshold cycle (ct) and/or quantitative copies/mL
- PT/aPTT/INR
- D-Dimer
- Urinalysis (evaluating RBC, protein, and glucose) if available as POC test
- Serum or urine pregnancy test (females of childbearing potential only) if available as POC
- Specimen storage

21.4.3 Randomization

Randomization occurs on Day 0 with the site communicating with the regional operations center for the randomization.

21.4.4 Study Drug Administration Timing

It is possible that Study Day 0 may be consumed by longitudinal determination of a patient's overall clinical status, implementation of oSOC provisions, assessment for study eligibility, and study randomization. Therefore, it is possible that actual administration of an investigational study intervention (if part of the assigned treatment arm) may be deferred until Study Day 1. Refer to the Pharmacy SOP for specific administration details.

21.5 Follow Up Study Days

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

21.5.1 Follow-up Daily Assessment and Optimized Supportive Care

This will include documentation of:

- Current Symptoms or conditions
- Vital signs
- Optimized Supportive Care received
- Study agent administration, as applicable
- Laboratory (as performed)
- Urinalysis (as performed, optional)
- Imaging and Resuscitation (as performed, optional)
- Any Serious Adverse Events
- Discharge / Outcome information, as appropriate

21.5.2 Pharmacokinetic Sampling

- 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

21.5.3 Clinical Safety Laboratory Testing

21.5.3.1 Minimum Requirements:

- Creatinine
- Potassium
- Ebola PCR with threshold cycle (ct)

For the frequency of required minimum lab testing, refer to the Schedule of Evaluations in Section 6.2

21.5.3.2 Optimal Daily Laboratory Monitoring

Refer to Schedule of Evaluations (Table 9**)** in Section 21.2. Testing should be performed during hospitalization and thereafter additionally as clinically indicated:

- CBC with differential
- Chemistry panels as available via POC testing, as defined in Section 6.3.2
- Ebola PCR with threshold cycle (ct)
  - After two negative Ebola PCRs, testing may be discontinued.
  - Consideration of other bodily fluid sampling as clinically appropriate
  - Date of first PCR negative result
- PT / aPTT / INR
- D-Dimer
- Urinalysis, if available as POC test
- Specimen Storage

21.5.4 Special Follow-up Assessments

21.5.4.1 Day of Discharge

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

21.5.4.2 Day 28

As the primary endpoint is 28-day mortality, the Day 28 visit is essential for data needed for this endpoint. All efforts should be made to ensure timely completion of this study visit.

21.5.4.3 Pregnancy

Any pregnant women enrolled into this study will be followed through term and for 6 months after delivery as able and with the consent of the subject.

21.5.4.4 Extended Follow-Up

Patients will be contacted either in person or by telephone to answer questions according to a special CRF dedicated to eliciting a history of signs or symptoms potentially c/w late onset of a virologic relapse, with particular focus on neurologic symptoms that may represent re-emergence of virus from a CNS source.

22 STATISTICAL METHODS

22.1 Background

A statistically valid plan for conducting a randomized trial of limited and unproven treatment options for Ebola virus disease is not straightforward. Such a trial is unlike most others in several respects: 1) the mortality rate of the "control" arm, i.e., best supportive care arm, is not well known, nor are the factors associated with improved outcome, 2) the oSOC may change as a result of accumulating results from the trial, 3) although the target number of patients is 100/arm, the actual number may be much smaller because the supply of one or more treatments may be severely limited and intermittent, superiority of one arm over another might be established with lesser numbers, and/or the epidemic itself may resolve . However, rather than precluding a randomized controlled trial (RCT), these circumstances favor it, for an

RCT is the most efficient and accurate means of evaluating the benefits of alternative therapies. Nonetheless, an unusual amount of flexibility in trial design is needed to seamlessly accommodate changing circumstances. Flexibility is critical for many reasons. For example, if evidence supports updating the existing oSOC (and dissemination of the new standard is feasible), this change should be implemented seamlessly. If however, the new standard requires a drug with a supply that is nearly depleted (and will remain so for some time), immediate changes to the oSOC may not be possible. Continuation of randomization to the treatment (with the nearly depleted supply) versus the initial standard may be the preferred strategy to allocate the limited supply. Plans for every potential scenario are not possible to specify *a priori*, which leaves such decision making to the domain of the study team in consultation with the DSMB. The present study design attempts to maximize the informational content of the limited data generated, given the above considerations.

22.2 Design

The trial will commence with randomization to oSOC (i.e., best supportive care) versus an experimental arm receiving oSOC plus treatment. Randomization will use permuted blocks with variable but small block sizes, and will be stratified by baseline Threshold cycle (CT) value on PCR ($\leq$22 versus > 22) and site of treatment (western Africa versus the United States/Europe). The PCR resulted nearest the time of randomization should be used for the stratification.

The trial primary endpoint is mortality by 28 days. The high mortality rate of Ebola virus disease and the uncertainty associated with the oSOC efficacy, mandate aggressive interim monitoring, which is described in the next section. If more than 2 treatment strategies are evaluated, the design will follow the same stopping rules outlined below, but randomization will proceed with equal probability to each of the arms. Strict control of the type I error rate would require adjustment of boundaries for comparison of multiple arms. We recommend against such adjustments, given the exigent circumstances surrounding the Ebola epidemic. Intention-to-treat analyses will be employed. Each patient will undergo only a single randomization in the study.

22.3 Interim Monitoring

Methods of monitoring clinical trials generally require knowledge of the total amount of information at trial's end. Boundaries are then constructed to guide decisions to control the probability of falsely declaring a treatment benefit at one or more interim analyses, including the final analysis. Such boundaries correspond to scenarios in which the level of evidence in support of treatment efficacy (or the lack thereof) exceeds some pre-determined threshold. Early boundaries are usually very difficult to cross, while boundaries at the end of the trial are similar to what they would be in the absence of monitoring. Our setting requires a somewhat different paradigm because although the target sample size is 100/arm, circumstances beyond our control may lead to a smaller number of patients. Moreover, we would like the flexibility of modifying the oSOC arm quite early if results show the superiority of an experimental agent plus oSOC, for example. We recommend monitoring beginning with 6 participants in an experimental arm and 6 in the best supportive care arm, and continuing after every additional

patient per arm, if necessary, up to 20. After that, monitoring would be after every 20 patients per arm until the target number of 100/arm is reached or the trial ends for other reasons. Any decision to curtail for other reasons will be made by a group blinded to trial results. The boundary we recommend is motivated from a Bayesian perspective. Bayesians formulate their prior opinion about the size of the treatment effect through a `prior' distribution, which is updated to a `posterior' distribution after observing data. We give details of the specification of the prior distribution and the construction of the boundary later. What are most important are the boundary itself and its statistical properties such as type I error rate (the probability of crossing the boundary inappropriately, i.e., when the 2 arms are equally effective) and power (the probability of crossing the boundary appropriately, i.e., when one arm is superior to the other).

Table 10 illustrates the design's flexibility by showing the boundaries assuming that factors beyond our control result in only 20 participants per arm by trial's end instead of the planned 100 per arm (stopping boundaries for 100 subjects per arm are included in Appendix B). For example, with 6 people evaluated in each arm, we declare superiority of one arm over the other only if all 6 die in one arm and none die in the other. On the other hand, with 10 people per arm, we cross the boundary if the numbers of deaths out of 10 in the 2 arms are as follows:

5. 7 or more and 0,
6. 8 or more and 1
7. 9 or more and 2
8. 10 and 3

Notice that the boundaries at the end of the trial are more lenient than interim boundaries: interim boundaries use a probability level of 99.9%, whereas the final boundary uses a level of 97.5%. This reinforces the need for a blinded group to make stopping recommendations for reasons other than safety or efficacy; otherwise, inflation of the type I error rate could result from lowering the boundary for the final analysis. Boundaries for a sample size of 100 per group will be generated following this same procedure and will be distributed to the DSMB.

Type I Error Rate

Table 11 shows the probability of crossing the boundary and declaring a treatment difference if we begin monitoring after 6 patients per arm and continue monitoring after each additional patient in both arms up to 20/arm, then every 20 per arm up to 100/arm. This probability of crossing the boundary depends on the true mortality probabilities in each arm, but the maximum value when the event probabilities in the 2 arms are equal is approximately 6% for a trial with 100 participants per arm. Even though the Bayesian methodology does not explicitly aim to control the type I error rate, that rate is controlled at close to the conventional level of 0.05. The first 5 rows of numbers in Table 11 also show type I error rate if circumstances beyond our control result in a final sample size of 20, 40, 60, or 80 per arm.

Power and Sample Size

The last 6 rows of numbers in Table 11 show scenarios with event probabilities differing in the 2 arms. With 100 per group, power is 88% to detect a difference if the true mortality probabilities in the 2 arms are 0.20 and 0.40, a 50% relative reduction. The selected sample

size of 100/arm also gives reasonably high power (83%) to detect a difference if the true mortality probabilities are 0.30 and 0.50, a 40% relative reduction.

Table 12shows the average sample size, taking into account the possibility of stopping early, for the scenarios with a treatment effect. If the true mortality rates in arms A and B are 0.3 and 0.5, respectively, and a sample size of 100 is targeted, then the study will stop for efficacy, on average, with only 76 patients (per arm).

Table 10: Flexibility of Trial Design

The top row gives the number of patients per arm, and the boundaries in parentheses are the numbers of deaths in the 2 arms, with + indicating that number or greater (e.g., in the “8” column, 7+ means 7 or 8).

6	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
(6,0)	(6+,0)	(7+,0)	(7+,0)	(7+,0)	(7+,0)	(7+,0)	(7+,0)	(8+,0)	(8+,0)	(8+,0)	(8+,0)	(8+,0)	(8+,0)	(4+,0)
	(7,1)	(8,1)	(8+,1)	(8+,1)	(9+,1)	(9+,1)	(9+,1)	(9+,1)	(10+,1)	(10+,1)	(10+,1)	(10+,1)	(10+,1)	(6+,1)
			(9,2)	(9+,2)	(10+,2)	(10+,2)	(10+,2)	(11+,2)	(11+,2)	(11+,2)	(11+,2)	(11+,2)	(12+,2)	(8+,2)
				(10,3)	(11+,3)	(11+,3)	(11+,3)	(12+,3)	(12+,3)	(12+,3)	(13+,3)	(13+,3)	(13+,3)	(9+,3)
					(11,4)	(12,4)	(12+,4)	(13+,4)	(13+,4)	(13+,4)	(14+,4)	(14+,4)	(14+,4)	(11+,4)
						(12,5)	(13,5)	(13+,5)	(14+,5)	(14+,5)	(15+,5)	(15+,5)	(15+,5)	(12+,5)
							(13,6)	(14,6)	(15,6)	(15+,6)	(15+,6)	(16+,6)	(16+,6)	(13+,6)
									(15,7)	(16,7)	(16+,7)	(16+,7)	(17+,7)	(14+,7)
										(16,8)	(17,8)	(17+,8)	(18+,8)	(15+,8)
											(17,9)	(18,9)	(18+,9)	(16+,9)
												(18,10)	(19,10)	(17+,10)
													(19,11)	(17+,11)
														(18+,12)
														(19+,13)
														(19+,14)
														(20,15)
														(20,16)

Table 11: Probability of Crossing the Boundary for Different Mortality, Probabilities, and Sample Sizes in the 2 Arms

		Simulated Type I Error Rate*				
Mortality probability treatment A (P_A)	Mortality probability treatment B (P_B)	20 per group	40 per group	60 per group	80 per group	100 per group
0.1	0.1	0.038	0.039	0.042	0.050	0.048
0.2	0.2	0.049	0.052	0.049	0.049	0.053
0.3	0.3	0.046	0.051	0.052	0.054	0.055
0.4	0.4	0.042	0.057	0.056	0.054	0.057
0.5	0.5	0.041	0.061	0.061	0.055	0.063
		Simulated Power				
Mortality probability treatment A (P_A)	Mortality probability treatment B (P_B)	20 per group	40 per group	60 per group	80 per group	100 per group
0.1	0.3	0.36	0.63	0.80	0.90	0.96
0.1	0.4	0.61	0.90	0.98	1.00	1.00
0.1	0.5	0.82	0.99	1.00	1.00	1.00
0.2	0.4	0.27	0.50	0.67	0.80	0.88
0.2	0.5	0.50	0.82	0.94	0.98	1.00
0.3	0.5	0.23	0.46	0.62	0.74	0.83

*These type I error rates refer to comparisons of two arms and do not reflect the study-wise type I error rate.

Table 12: Average Final Sample Size per Arm using Stopping Criteria Defined Above

Mortality probability treatment A (P_A)	Mortality probability treatment B (P_B)	Targeted sample size (per arm)			
		40	60	80	100
		Average final sample size (per arm)			
0.1	0.3	39	54	67	75
0.1	0.4	35	44	48	49
0.1	0.5	29	32	32	32
0.2	0.4	38	56	70	82
0.2	0.5	35	47	53	56
0.3	0.5	38	56	71	84

The frequency of monitoring can be altered. For example, if patient heterogeneity is large, one may not conduct the first interim analysis until more patient outcome data has accrued (e.g., 10 per arm). Regardless of the monitoring frequency, the data and safety monitoring board's recommendation to stop or continue an ongoing trial will be based on consideration of multiple factors. The Bayesian perspective allows calculation of `credibility' intervals (analogous to confidence intervals) for the difference in mortality probabilities between arms whether or not advisory boundaries are crossed.

Comparison to Other Boundaries

Even though the boundaries were motivated from a Bayesian perspective, they are actually quite similar to Haybittle-Peto boundaries using either Fisher's exact test or Barnard's test. Suppose circumstances beyond our control limit the total sample size to 20 participants per arm. A comparison of the 3 boundaries is shown, in Figure 6 and Figure 7 for interim analyses after 10 and 15 participants, and in Figure 8 at the final analysis after 20 participants per arm. The proposed boundary is quite similar to, but slightly less conservative than, Barnard's test. Fisher's exact test is slightly more conservative.

Figure 6: Interim Analysis after 10/Arm

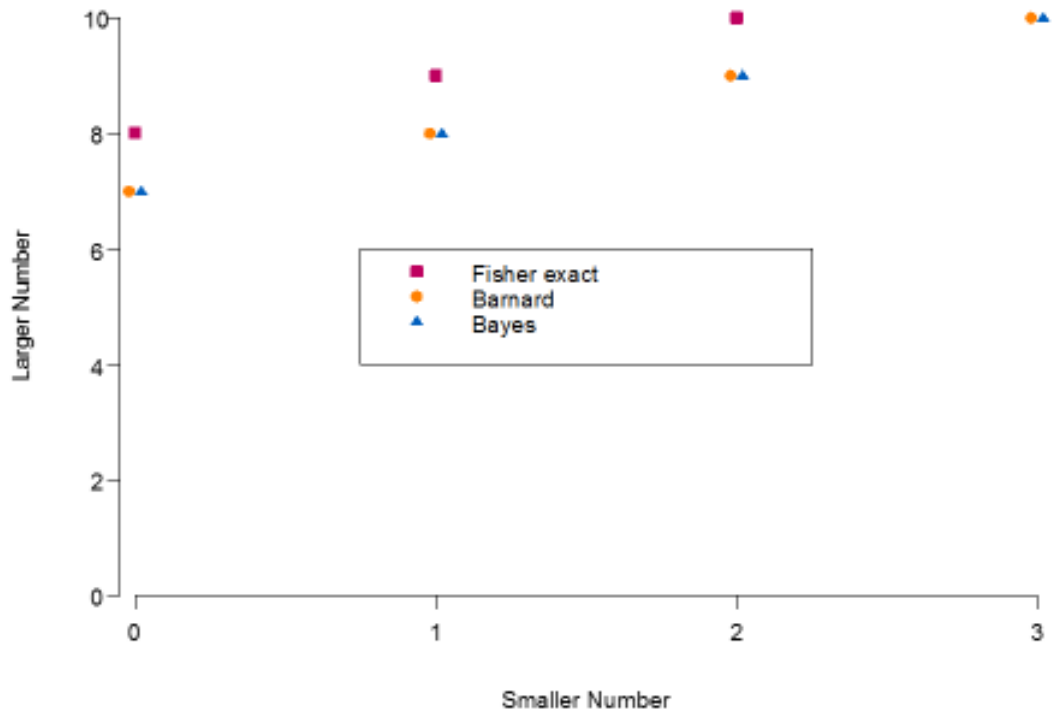


Figure 7: Interim Analysis after 15/Arm

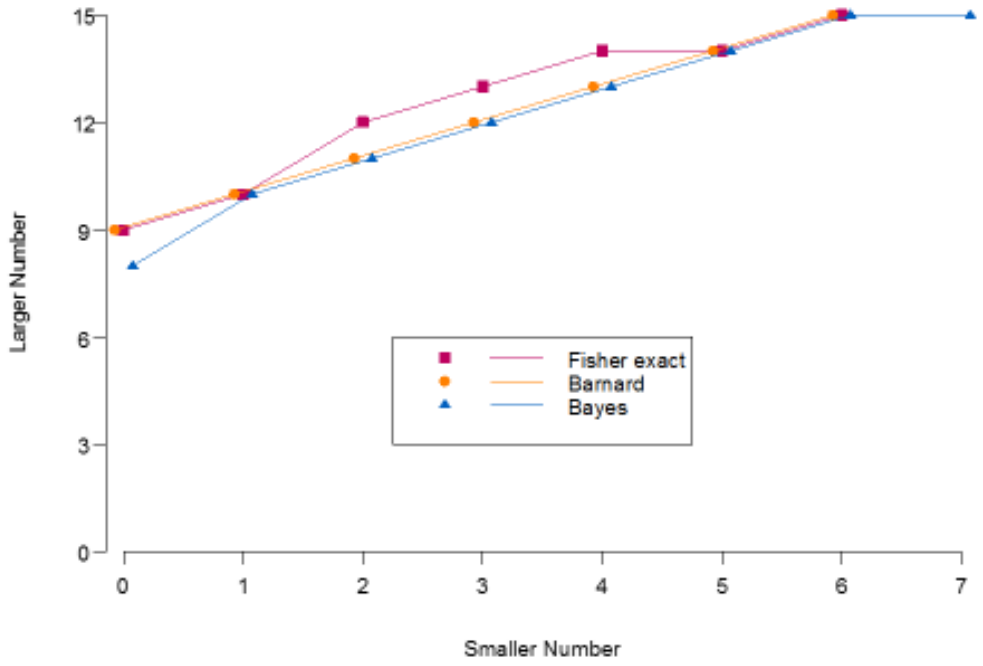
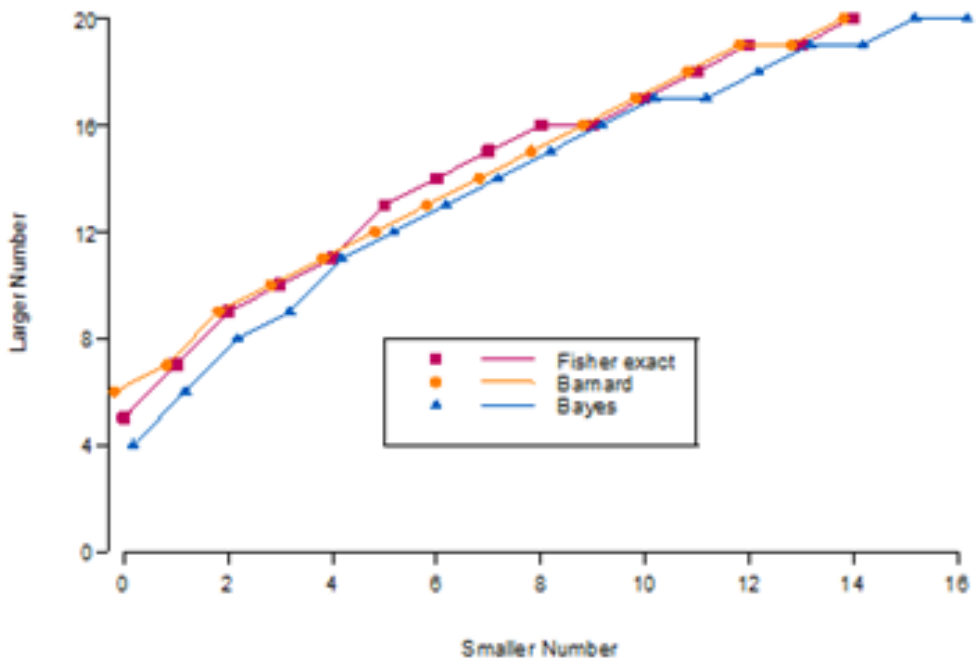


Figure 8: Interim Analysis after 20/Arm



Advisory Futility Boundaries

Advisory boundaries for futility will be computed using the conditional probability of reaching a statistically significant result at the end of the trial with 100 per arm, given the results observed at an interim analysis (called conditional power). Serious consideration for stopping a treatment for futility will be given if the conditional power is less than 20% even assuming the relative treatment benefit for remaining patients is 50%.

Technical Details of Boundary Construction

Thoughtful specification of the prior distribution is crucial in Bayesian analysis. We want conclusions to depend primarily on data from the trial, not on prior opinion. This argues for a skeptical prior distribution that does not already assume that a treatment works. Let *p* denote the probability of survival in a given arm. Our prior distribution on *p* can be formulated by imagining having data on 2 people treated with a given agent, and observing that exactly 1 of the 2 survived. The probabilistic equivalent is to assume a beta prior distribution on *p* with parameters 1 and 1, equivalent to a uniform distribution on the interval (0,1). This is consistent with an overall survival probability of 0.50 for the current Ebola outbreak, but with wide variability reflecting substantial uncertainty about *p*. Moreover, a uniform distribution for p ensures very little influence of our prior opinion on conclusions. The observed data very quickly dominate in decision-making. For instance, if 20 people are given the treatment and 12 of them survive, the posterior distribution for the survival probability is beta with parameters 13 and 9. In other words, combining our prior opinion with the observed data equates to observing 13+9=22 people, 13 of whom survived. Our prior opinion constitutes only 2 of the 22

people, and therefore has very little effect on the conclusions. Also, we use the same prior distribution in different arms. That way, our prior opinion does not favor any treatment over oSOC. If p_A and p_B denote the survival probabilities in arms A and B, respectively, we use independent beta posterior distributions in the 2 arms to calculate the probability that $p_A<p_B$, namely that the survival probability in arm B exceeds that in arm A. At any interim analysis preceding the final analysis, we declare arm B superior if this probability exceeds 99.9%. At the final analysis, we declare superiority of arm B if this probability exceeds 97.5%.

22.4 Analyses

Differences in mortality probabilities between an experimental arm and the best supportive care arm will be estimated using 95% Bayesian credibility intervals akin to confidence intervals. The treatment effect will be expressed in both an absolute and relative terms, and will be estimated in the overall group and in the pre-defined strata: baseline threshold cycle (CT) value on PCR ($\leq$22 versus > 22) and where the patient was treated (western Africa versus the United States/Europe). The posterior probability that the relative treatment benefit differs by strata will be calculated; if this probability exceeds 97.5% that will be taken as evidence of a differential treatment effect by strata.

As noted earlier, Bayesian analysis with the non-informative prior distribution specified above is very similar to classical statistical analysis using Barnard's test. To highlight this point, we will also present classical confidence intervals for the absolute and relative treatment benefit based on Barnard's test.

Some patients may receive MCMs other than the randomized treatment. This will be documented in the record, but it is extremely problematic statistically to try to account for the effect of supplementary treatment that may be administered in response to a patient's failing health. A sensitivity analysis will be conducted by treating such patients as if they would have died by 28 days in the absence of the additional MCMs.

Similar sensitivity analyses will be conducted for patients missing the primary endpoint of 28 day mortality.

The analyses of the symptom histories obtained in extended follow-up of patient are intended to be observational and descriptive in nature, will apply to patients in all treatment arms, and are designed to provide some additional information as to whether there is a detectable increase in delayed virologic relapse in trial participants over a period of one year or more following recovery and initial clearance of virus from the plasma.

23 RISKS AND BENEFITS

23.1 Potential Risks

23.1.1 Unknown Risks

The primary risks to participants are due to study interventions whose human safety profile is either absent or, in most cases, early and accumulating, due to ongoing animal and/or early/first in human trials. Generally these are either still in early phase 1 testing, have not yet entered phase 1 testing, or, for those interventions in more advanced development, have not yet been tested in a human population infected with Ebola virus. Thus, unlike conventional phase 2 trials in which a safety database has already been generated to guide the dosing and schedule of study drug administration, it is presently unknown what toxicities these agents could cause when used in this critically ill patient population or, for that matter, in any humans at all.

It is anticipated that additional animal safety and toxicity studies will be in-progress at the time of trial initiation for some agents. Results will be made available to the study investigation team and pertinent regulatory bodies for review promptly, as they are available. In addition, in some cases phase 1 testing of lead candidates in normal human volunteers may commence during the same interval of time that this trial is conducted. Should it be concluded from any of these studies that there are additional significant risks to study subjects, participants will be informed and additional administration of study product may be suspended until review by the FDA as well as by each institution's IRB.

23.1.2 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.

23.1.3 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.

23.2 Potential Benefits

There is no definite expectation of benefit to participants or to society at large. However, the agents likely to be investigated 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 conceivable that one or more interventions may subsequently be shown to offer evidence of a greater reduction in morbidity and mortality than that 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 very early stage of testing. However, even if no experimental treatment intervention is shown 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.

23.3 Alternatives

The alternative to participating in this protocol is not to participate and to receive access either to supportive care measures or to experimental therapies through other approved regulatory means.

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

24.1 Intended Use of the Samples/Specimens/Data

Samples and data collected under this protocol will be used to determine the interventional agent safety, anti-viral effects, development of anti-drug antibodies, effects on immune response, and pharmacokinetics. Viral specific items of interest include: diagnostics and viral pathogenesis.

24.2 Storage of Samples/Specimens/Data

Samples obtained in this study must adhere to national regulations for long term storage. For U.S. sites, CDC regulations governing 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 at NIH and outside) may wish to study these samples and/or data. In that case, IRB approval must be sought prior to any sharing of samples. Any clinical information shared about the sample with or without patient identifiers would similarly require prior IRB approval.

The research use of stored, unlinked or unidentified samples 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.

24.3 Storage of Genetic Samples

No samples are being stored for genetic testing on the subjects.

24.4 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) will be reported to the institution's IRB and to the protocol team.

25 REMUNERATION PLAN

Subjects will not be compensated for the time and inconvenience of study participation, including for any outpatient assessments that may occur following hospital discharge.

26 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.

26.1 Documenting, Recording, and Reporting Adverse Events

At each contact with the subject, information regarding serious adverse events will be elicited by appropriate questioning and will be:

- documented in the subject's medical record/source document,
- recorded on the Serious Adverse Event Case Report Form (SAE CRF), and
- reported to relevant regulatory authorities by the principal investigator or designee as outlined below

26.2 Definitions

Adverse Event (AE)

An adverse event 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.

Serious Adverse Event (SAE)

A Serious Adverse Event is an AE that results in one or more of the following outcomes:

- death
- a life threatening (i.e., an immediate threat to life) event

- prolongation of the existing hospitalization (or re-hospitalization)
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect
- a medically important event*

* Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but they may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

Protocol Deviation: 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

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

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

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

4. 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
5. Continuing: Non-compliance that is recurring
6. Minor: Non-compliance that, is neither serious nor continuing.

26.3 Assessment of Safety

Safety data in this study will be limited to the collection of targeted symptoms (daily, while hospitalized or in an ETU) and SAEs. Until participants are discharged from the hospital or ETU, items on the targeted list do not additionally need to be reported as SAEs.

The Data Coordinating Center will grade the severity of laboratory values according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, 2014.

26.4 Investigator Assessment of Serious Adverse Events

Due to severity of critical illness in Ebola disease and expected clinical progression, for clinical events, investigators will capture only SAEs and a targeted list of current symptoms and conditions. The Investigator will evaluate all SAEs with respect to **Seriousness** and **Causality** (relationship to study agent and relationship to research) as defined below.

26.4.1 Causality

The likelihood that the SAE is related to the study agent will be assessed by the investigator considering by 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

26.5 Investigator Reporting Responsibilities to the Sponsor

26.5.1 Serious Adverse Events

All SAEs must be reported on the Serious Adverse Event case report form (SAE CRF). Deaths and immediately life threatening SAEs must be reported within 1 business day after the site becomes aware of the event to the Data Coordinating Center. All other SAEs must be reported within 3 business days of site awareness. All deaths must be reported as SAEs.

The medical monitor, in consultation with the site investigator, will determine the expectedness of all SAEs.

26.5.2 Unanticipated Problems

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

4. unexpected in terms of nature, severity, or frequency in relation to
   c. the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents;
   d. the characteristics of the subject population being studied (persons with life threatening EEbola infection); and

5. possibly, probably, or definitely related to participation in the research; and
6. 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 at the University of Minnesota, and local IRB 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 sent by e-mail no later than 7 calendar days of site awareness of the event.

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

26.5.3 Pregnancy

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

Pregnancy outcome data (e.g., delivery outcome, spontaneous or elective termination of the pregnancy) will be on a protocol-specified form. Pregnant participants should be advised to notify their obstetrical care provider of study agent exposure, if applicable.

26.6 Reporting Procedures to the IRB

26.6.1 Expedited Reporting to the IRB

SAEs, Serious and non-serious Unanticipated Problems, and deaths will be reported per institutional requirements. Please refer to the Manual of Operations, Reporting SOP about site specific requirements.

26.6.2 Annual Reporting to the IRB

Annual reporting will occur in accordance with institutional requirements.

26.7 Follow-Up of Serious Adverse Events

SAEs that have not resolved by the end of the initial follow-up period are followed until final outcome is known. This includes pregnancy. 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.

26.8 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.

26.9 Safety Oversight

26.9.1 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

26.9.2 Sponsor Medical Monitor (SMM)

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

26.9.3 Data and Safety Monitoring Board (DSMB)

An independent DSMB 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 PI will submit the written DSMB summary open reports with the DSMB recommendations to the IRB.

- The DSMB will monitor safety closely throughout the trial and may pause enrollment in the event of 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 continuing the study as planned, modifying the study, or terminating the study.

27 CLINICAL MONITORING STRUCTURE

27.1 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." Monitors under contract to the NIAID/Office of Clinical Research Policy and Regulatory Operations (OCRPRO) will 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 will be: 1) to verify the existence of signed informed consent

documents and documentation of the Informed Consent Form (ICF) 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 will 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 will be available to discuss the study progress and monitoring visit.

28 ETHICS/PROTECTION OF HUMAN SUBJECTS

28.1 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 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.

The participants will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. 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, a photograph or scanned image of the informed consent signature page will be stored. No paper copy will be retained.

28.2 Subject Confidentiality

All records will be kept confidential to the extent provided by federal, state and local law. 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, or the sponsor's designee.

29 DATA MANAGEMENT AND MONITORING

29.1 Data Management Responsibilities

The 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 collected in the electronic data system, and must 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.

29.2 Data Capture Methods

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

29.3 Types of Data

Source documents include, but are not 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.

29.4 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 source documents created at the bedside and in the 'hotzone' will be incinerated and not be retained. Where possible, photographs or digital scans will be obtained.

29.5 Record Retention

The investigator is responsible for retaining all essential documents listed in the ICH Good Clinical Practice Guideline. All essential documentation for all study subjects are to be maintained by the investigators in a secure storage facility for a minimum of 3 years per NIAID policies. 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 law.

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STATISTICAL APPENDIX

Power Tables

More extensive power tables: Table 13 shows the approximate power for a range of sample sizes and mortality probabilities in the 2 arms, while Table 14 shows the sample sizes required for approximately 80% and 90% power.

Table 13: Approximate Power under Different per Arm Sample Sizes (n) when the Larger and Smaller Mortality Probabilities are p_A and p_B, Respectively

Powers of 80% or higher are boldfaced.

P_A	P_B	n=20	n=30	n=40	n=50	n=60	n=70	n=80	n=90	n=100
0.2	0.1	0.14	0.16	0.24	0.27	0.32	0.38	0.42	0.47	0.51
0.3	0.1	0.35	0.49	0.63	0.72	0.79	**0.86**	**0.90**	**0.93**	**0.95**
	0.2	0.10	0.14	0.18	0.21	0.24	0.27	0.30	0.34	0.37
0.4	0.1	0.61	0.79	**0.90**	**0.95**	**0.98**	**0.99**	**1**	**1**	**1**
	0.2	0.27	0.39	0.50	0.60	0.67	0.74	**0.80**	**0.84**	**0.88**
	0.3	0.08	0.12	0.15	0.18	0.20	0.23	0.26	0.29	0.31
0.5	0.1	**0.82**	**0.95**	**0.99**	**1**	**1**	**1**	**1**	**1**	**1**
	0.2	0.49	0.69	**0.82**	**0.89**	**0.94**	**0.97**	**0.98**	**0.99**	**1**
	0.3	0.22	0.35	0.46	0.55	0.62	0.67	0.73	0.79	**0.83**
	0.4	0.08	0.12	0.16	0.18	0.20	0.22	0.24	0.26	0.31
0.6	0.1	**0.94**	**0.99**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
	0.2	0.73	**0.90**	**0.97**	**0.99**	**1**	**1**	**1**	**1**	**1**
	0.3	0.45	0.66	**0.80**	**0.88**	**0.92**	**0.95**	**0.97**	**0.98**	**0.99**
	0.4	0.21	0.35	0.46	0.54	0.61	0.67	0.72	0.75	**0.83**
	0.5	0.08	0.12	0.16	0.18	0.20	0.22	0.24	0.26	0.31
0.7	0.1	**0.99**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
	0.2	**0.90**	**0.99**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
	0.3	0.71	**0.90**	**0.96**	**0.99**	**1**	**1**	**1**	**1**	**1**
	0.4	0.45	0.66	**0.80**	**0.88**	**0.92**	**0.95**	**0.97**	**0.98**	**0.99**
	0.5	0.22	0.35	0.46	0.55	0.62	0.67	0.73	0.79	**0.83**
	0.6	0.08	0.12	0.15	0.18	0.20	0.23	0.26	0.29	0.31

Table 14: Sample Sizes required for 80% and 90% Power for Different Values of the Larger and Smaller Mortality Probabilities, p_A and p_B.

p_A	p_B	n_{80}	n_{90}
0.2	0.1	198	264
0.3	0.1	61	81
	0.2	293	392
0.4	0.1	31	40
	0.2	81	109
	0.3	357	476
0.5	0.1	19	26
	0.2	39	52
	0.3	95	126
	0.4	392	520
0.6	0.1	13	17
	0.2	23	30
	0.3	41	57
	0.4	97	128
	0.5	392	520
0.7	0.1	10	12
	0.2	15	20
	0.3	22	31
	0.4	41	57
	0.5	95	126
	0.6	357	477

APPENDIX A: Historical Background on Protocol Development

On November 11, 2014, a meeting was held that included investigators from the 3 high containment patient care units (Emory University Hospital, University of Nebraska Medical Center, and the NIH Clinical Center) in the United States who have cared for individuals medically evacuated from West Africa as well as representatives of various US government agencies (NIH, FDA, BARDA/ASPR, CDC, and various constituencies within the DoD) who have been involved in the US response to the 2014 Ebola crisis. This meeting was conducted in follow up to a prior meeting of these groups on October 27, 2014, in which the attendees endorsed the concept of performing a randomized clinical trial of adjunctive medical countermeasures of potential utility in treating patients with documented Ebola virus infection, whether seen here in the US, Europe, or in 1 of the affected countries in West Africa. Two major outcomes of that initial meeting had been:

1. The group concluded that it was both ethical and scientifically desirable to attempt to conduct an RCT in which one of the initial comparator arms would be optimized standard-of-care (oSOC) alone, acknowledging that the level of supportive care that defines oSOC would almost certainly vary between the different geographic regions who might participate in such a study. While available resources, personnel, and other constraints will likely not permit the level of oSOC achievable in West Africa to approach that currently available in the United States and other developed nations within a short time frame, the hope was that the provision of additional outside resources currently planned might improve the level of oSOC in some of the ETUs operating, or planned to open in, some regions of the affected West African countries and that these units might then be able to support the performance of clinical research in addition to their primary commitment to clinical care.
2. While the investigators had at least some familiarity with most of the MCMs proposed for study in the context of an RCT, overall they felt that there were significant gaps in the group's mutual understanding of the preclinical and early clinical trial results supporting the potential utility of individual agents. Accordingly, they felt it was critical that the group undertake a comprehensive review of the available *in vitro*, animal (NHP and other animal model data) and early clinical data that the manufacturers have compiled about these individual agents in terms of their activity against Ebola virus.

With this background, the investigator group reconvened on November 11, 2014, and invited company representatives of the lead candidates with putative antiviral or immune-enhancing activity against EBOV to present their products' supportive data, toxicity data, and early in-man experience. Over the course of that meeting 7 different products, including convalescent plasma, were individually reviewed and discussed with the sponsors, and then afterwards a closed session was held in which the investigators discussed which of the products they felt had the strongest preclinical and early clinical data to support prioritizing its study within the context of an RCT in EBOV patients. Important elements of this discussion included the following:

8. It was again reiterated that the only scientific approach with a reasonable likelihood of being able to determine conclusively the potential therapeutic benefit or harm of a given

experimental therapeutic adjunct is one in which that adjunct can be compared to a backbone of oSOC.

9. There were no decisions made at this time to exclude any of the reviewed products for further consideration of inclusion within an RCT.
10. Some of the products were less far advanced in terms of their preclinical development, and could potentially benefit from further animal and toxicity testing before being prioritized for immediate study within the proposed RCT.
11. Not all of the data from ongoing or recently completed preclinical testing was available for each agent, and in at least 1 case allusion was made to preliminary animal test results that reportedly did not support activity of the agent in that particular animal model. Hence, subsequent, more complete knowledge of those findings could likely influence the prioritization of individual agents within the study queue.
12. The molecular drift of the current circulating Guinea strain of EBOV from the previous Zaire strain may not necessarily be optimized as a target for all of the agents, and modifications of product towards this newest strain may be necessary in some cases.
13. The available or predicted drug supply of each of the agents varied from product to product, and the potential limited availability of certain agents would likely be an important factor in planning pairwise comparisons of product against oSOC at least in the near term.
14. The likelihood of quickly raising the oSOC available in West African ETUs to the level currently afforded in most US or European hospitals was deemed quite low. However, it was again emphasized that the most important outcome comparison to be made in an RCT was between the backbone oSOC available in the individual setting into which an experimental MCM was being introduced as an adjunct to that oSOC, not the comparison between different levels of oSOC available in different treatment settings.

With the considerations above in mind, the investigators concluded that they would be most supportive of initiating an MCM RCT beginning with ZMapp^{tm} triple monoclonal antibody cocktail as the lead candidate for study. This was concluded despite the absent supply of this agent currently as well as the likelihood that only fairly limited quantities of this product would be capable of being produced until early in 2015. ZMapp^{tm} is produced by Mapp Biopharmaceutical, Inc./LeafBio, Inc. and consists of a triple monoclonal antibody product that is manufactured in *Nicotiana benthamiana* (tobacco species) and that is directed against the surface glycoprotein (GP) of Ebola virus. There are compelling data from an infectious challenge model in NHPs (*Rhesus macaques*) showing that the drug cocktail may be capable of rescuing infected animals from death when the product is administered as late as 5 days after what would otherwise be a lethal challenge in that animal model. In addition, there is now anecdotal experience with use of 1-3 treatment doses of this monoclonal cocktail in 8 different patients with EBOV who received this drug under the auspices of eIND or compassionate use mechanisms thus far in 2014. Of those 8 patients, some of whom received additional MCMs, 6 survived to resolution of their illness, whereas 2 died.

As a fallback to consideration of use of ZMapp^{tm} as the lead study candidate, however, the investigators also recommended that convalescent plasma be prioritized as the second lead candidate for inclusion in the RCT. In addition to anecdotal experience overseas with the use of convalescent plasma in both prior and the current Ebola virus outbreaks, current experience

with using plasma in patients medically evacuated to the United States equals or exceeds that of other MCMs. Currently, 8 of 9 patients with EBOV treated in the US have survived, and of those 8 survivors, 6 have received either infusions of whole blood or convalescent plasma as part of their adjunctive therapy in addition to other MCMs. These infusions have occurred at different times in their clinical illnesses, and from different sources of donor plasma. However, 4 of the more recent 6 convalescent plasma recipients have received plasma infusions from the same donor patient. To date these infusions have generally been well tolerated according to the investigators involved with their administration.

Unfortunately, standardization of donor units according to anti-Ebola antibody titers, including neutralizing activity, has not occurred on a uniform basis and, in the case of the most frequent plasma donor, plasma has been obtained from different points in his convalescent period. A reliable, consistent, and well-characterized source of plasma to fuel an RCT would be a significant challenge to incorporation of this strategy into an RCT unless additional measures were undertaken to identify and collect a sufficient supply of this material in advance. In this regard, it was suggested that post-immunization plasma harvested from individuals who have received 1 of the current Ebola vaccines currently in phase 1 and early phase 2 testing might conceivably be an acceptable alternative to convalescent plasma given its expected abundance and relative ease of procurement from normal volunteer vaccine recipients. However, from the standpoint of a broadly protective response in individuals with established infection, it could also be argued that the more restricted, likely oligoclonal, antibody response generated by these GP-based vaccines may or may not be comparable to the broader polyclonal response induced by natural infection and presumably present in convalescent plasma. The current vaccine trials are actively evaluating the degree of both humoral and cell-mediated immunity induced by the 2 major vaccine constructs under study, and consideration should be given to evaluating plasma from vaccine recipients in a post-exposure prophylaxis model.

These 2 choices recommended for research prioritization in an RCT are obviously immune-based approaches, a strategy for which there is substantial precedent in other viral diseases. The investigator group briefly also touched upon the issue of which of the available directly-acting antiviral agents under consideration might be recommended as the third or fourth category of agents to be entered into such a study. As part of this consideration, the potential ease with which candidate agents could be introduced and studied within a research setting lacking reliable access to parenteral therapy should be a significant factor in this choice. However, no single agent was uniquely identified for prioritization from the discussion that ensued, and clearly more discussion of this topic within the group is warranted in the very near term.

Addendum:

The prospect of the first new lot of ZMapp™ becoming available during the first week of February 2015 but in only very limited quantities prompted additional discussion of what the second choice of investigational agent should be in the event that the ZMapp™ supply proved inadequate to sustain continuous enrollment. As above, prior discussion had pinpointed convalescent plasma in this capacity. In this regard, in the United States both Emory and

Nebraska have been engaged in an ongoing effort with the Cerus Corporation over the past few months to collect and store units of plasma harvested from a small number of donors who have recovered from Ebola infection. As of 9 February 2015, at least 20 such units have been collected. In West Africa, the Gates Foundation has been particularly active in collecting convalescent plasma from recovered victims of Ebola infection in both Sierra Leone and Liberia. However, in neither situation have the donated units been standardized according to their level of antibody content or the degree of neutralizing activity present, presumably making them a completely heterologous mixture of plasma.

On 9 February 2015 members of the core protocol team from NIAID, Emory, UNMC, WRNNMC, FDA (CDER and CBER), BARDA, ASPR, and other constituencies within DoD convened by teleconference to again discuss this issue of proposed second- and third-line agents for consideration in the trial. The concerns with convalescent plasma were discussed and remained quite similar to the previously-discussed limitations cited above: i.e. different donors providing plasma at different stages of their recovery, no current standardization of these donated units, no commonly accepted standards for what level of antibody and/or neutralizing activity should be present, and possible differences between the U.S. and West Africa in terms of ready access to available units. Unfortunately, while several groups have collected plasma from various donors for laboratory study, currently there do not appear to be any robust and comprehensive efforts underway to immediately remedy the clinical situation by providing the appropriate infrastructure and resources to test and characterize donated units according to their perceived activity level. If such studies are underway, no one on the call was aware of any recent illuminating data resulting from those efforts. Given the heterogeneous nature of the available supply, the point was made that it would take a very large trial to compensate for these unit-to-unit differences in antibody activity, and that attempting to study them within the context of a smaller trial would likely introduce considerable error. Rather, in the absence of better standardization at the plasma level, it was suggested that it might be preferable to consider dedicating these harvested units to the production of an IVIG product downstream whose antibody content could be better characterized and standardized, both for NHP testing and conceivably even for future human trials.

With these concerns in mind, the group generally agreed that it would be preferable to target one of the two most prominent directly-acting antiviral agents (favipiravir and TKM-Ebola-Guinea) for higher prioritization in the study. The concerns and limitations of each were reviewed in detail, some of which can be summarized as below:

Favipiravir:

- Some supportive NHP virology data, but also some unexplained GI toxicity
- Reportedly supportive clinical data from recent INSERM trial, but inadequate control group for comparison
- Clinical experience generally supporting safety, but in uncontrolled studies
- Sponsor hesitancy to select a single dose for further study and preference for a dose-comparison trial instead
- Hence, no definitive dose selected for an Ebola indication as yet, which would be an essential requirement for inclusion into the MCM RCT trial
- Possibly favorable antiviral activity shown in recent INSERM trial, but data not available directly to study team as yet

- Oral administration an obvious plus

TKM-Ebola Guinea:

- Stronger NHP data concerning rescue from lethal challenge
- Unclear if safety profile for Guinea product will be identical to prior product, although no reason to suspect otherwise
- Cytokine storm syndrome commonly seen at higher dose (0.5 mg/kg) and with higher infusion rate
- Company's recommendation to drop dose to 0.3 mg/kg and slow infusion rate may result in fewer adverse events related to cytokine storm (needs validation)
- No current plan for study of product in competing RCT
- Current plans are to have approximately 50 treatment courses available at end of March
- Parenteral administration, as with ZMapp™

The consensus of the group was that each product has supportive science behind it, with perhaps TKM-Ebola Guinea having a slight edge in that respect from the NHP data. However, the recent announcement of potentially encouraging virologic data from the INSERM trial of favipiravir (being submitted as a late-breaker abstract to the CROI meeting in Seattle later this month) suggested to the group that we should await release and review of those data prior to making any definitive rank-ordering of drug #2 and drug #3. Meanwhile, however, each of the two sponsors (Medivector and Tekmira) should be approached and informed of the study team's renewed interest in their products, hopefully discouraging them from pursuing additional uncontrolled studies of these drugs that will not actually answer the question of efficacy. The FDA should also approach Medivector about the possibility of being able to make a dose selection decision as soon as possible based upon available experience rather than awaiting a dose comparison trial that may not be possible to conduct within the context of the current outbreak.

APPENDIX B: Adaptive Trial Design Stopping Boundaries

Stopping Boundaries based upon 6-15 Subjects per Arm

Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm	
6		7		8		9		10		11		12		13		14		15	
Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm	
Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*
6	0	6	0	7	0	7	0	7	0	7	0	7	0	7	0	8	0	8	0
		7	1	8	1	8	1	8	1	8	0	8	0	8	0	9	1	9	0
						9	2	9	2	9	1	9	1	9	1	10	1	10	1
								10	3	10	2	10	2	10	2	11	2	11	2
										11	4	11	3	11	3	12	3	12	3
												12	5	12	4	13	5	13	4
														13	6	14	6	14	5
																		15	7
	* Note that number of deaths given in arm B refers to the given number OR FEWER for the corresponding number of deaths in arm A.																		

Stopping Boundaries based upon 16-100 Subjects per Arm

Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm		Number of subjects per arm	
16		17		18		19		20		40		60		80		100	
Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm		Number of deaths by arm	
Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*	Arm A	Arm B*
8	0	8	0	8	0	8	0	8	0	9	0	9	0	9	0	5	0
9	0	9	0	9	0	9	0	9	0	10	0	10	0	10	0	6	0
10	1	10	1	10	1	10	1	10	1	11	1	11	0	11	0	7	1
11	2	11	2	11	2	11	1	11	1	12	1	12	1	12	1	8	1
12	3	12	2	12	2	12	2	12	2	13	2	13	1	13	1	9	2
13	4	13	3	13	3	13	3	13	3	14	2	14	2	14	2	10	3
14	5	14	4	14	4	14	4	14	4	15	3	15	2	15	2	11	3
15	6	15	6	15	5	15	5	15	5	16	4	16	3	16	3	12	4
16	8	16	7	16	7	16	6	16	6	17	4	17	4	17	3	13	4
		17	9	17	8	17	7	17	7	18	5	18	4	18	4	14	5
				18	10	18	9	18	8	19	6	19	5	19	5	15	6
						19	11	19	10	20	6	20	6	20	5	16	7
								20	12	21	7	21	6	21	6	17	7
										22	8	22	7	22	6	18	8
										23	9	23	8	23	7	19	9
										24	10	24	8	24	8	20	10
										25	11	25	9	25	9	21	10
										26	12	26	10	26	9	22	11
										27	13	27	11	27	10	23	12
										28	14	28	12	28	11	24	13
										29	15	29	12	29	11	25	13
										30	16	30	13	30	12	26	14
										31	17	31	14	31	13	27	15
										32	18	32	15	32	14	28	16
										33	19	33	16	33	15	29	17
										34	21	34	17	34	15	30	18
										35	22	35	18	35	16	31	18
										36	24	36	19	36	17	32	19
										37	25	37	20	37	18	33	20
										38	27	38	21	38	19	34	21
										39	29	39	22	39	20	35	22
										40	31	40	23	40	20	36	23
												41	24	41	21	37	24
												42	25	42	22	38	25
												43	26	43	23	39	25
												44	27	44	24	40	26
												45	28	45	25	41	27
												46	29	46	26	42	28
												47	30	47	27	43	29
												48	32	48	28	44	30
												49	33	49	29	45	31
												50	34	50	30	46	32
												51	35	51	31	47	33
												52	37	52	32	48	34
												53	38	53	33	49	35
												54	40	54	34	50	36
												55	41	55	35	51	37
												56	43	56	36	52	38
												57	44	57	37	53	39
												58	46	58	38	54	40
												59	48	59	39	55	41
												60	51	60	41	56	42
														61	42	57	43
														62	43	58	44
														63	44	59	45
														64	45	60	46
														65	47	61	47
														66	48	62	48
														67	49	63	49
														68	50	64	50
														69	52	65	51
														70	53	66	52
														71	55	67	53
														72	56	68	54
														73	57	69	55
														74	59	70	56
														75	61	71	57
														76	62	72	58
														77	64	73	59
														78	66	74	60
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																99	93
																100	95

SUMMARY of AMENDMENTS TO PROTOCOL

Amendment Label	IRB Approval Date	Amendment Summary
A	3/9/15	addition of the Liberian Principal Investigator and study sites. Updated information has been included regarding ZMAPP product and infusion details (three infusion set three days apart). An update of the ongoing conversations of Investigators from all sites has been added to Appendix A.
B	4/6/15	Clarification of the site-specific considerations have been added to the protocol (section 6.15) based on the resources available. Further information from Liberian Ebola Treatment Units has preliminarily identified a correlation between baseline Cycle Threshold (CT) value on Ebola PCR and patient outcomes. This has prompted the Study Team to change the stratification for the randomization procedures of this study
C	4/20/15	The main purposes of the amendment are to acknowledge that the ability of individual sites to perform full spectrum of clinical research components outlined in prior versions protocol varied widely depending upon such factors as staffing, available equipment, and current operational, clinical, and safety practices. Therefore this version of the protocol

		attempts to define the minimal standards for assessment of efficacy and safety as well as allow full detailed assessments to obtain full longitudinal data collection when sites are able.
D	7/13/15	An updated Investigator's Brochure and an updated version of the ZMAPP Patient Information Sheet was added which will be given to participants at the time of consent.
E	11/23/15	Added long-term follow-up. The DSMB strongly recommended long-term follow-up of enrolled subjects be considered (within reasonable limits of access and feasibility) given reports of the recurrence of Ebola virus disease in some patients. Interested subjects will be offered the opportunity, where and whenever feasible, to participate in long term follow-up (up to 1 year or more depending upon need) past Day 58 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.

Data Analysis Plan for MCM RCT

31 1 STUDY OVERVIEW

The study protocol serves as the master protocol for the evaluation of multiple candidate countermeasures for the treatment of Ebola virus disease (EVD). The initial phase of the trial will focus on the evaluation of ZMapp and the order of additional treatments to be evaluated is still to be determined.

Participants in the initial phase will be randomized in a 1:1 allocation ratio to optimized standard of care (oSOC) or oSOC plus ZMapp. A maximum of 200 subjects will be randomized (100 per treatment arm) but frequent interim monitoring will be used to allow termination of the trial if a definitive result is achieved early in the trial.

The primary objective of this trial is to establish the safety and efficacy of investigational therapeutics in patients with Ebola virus infection. The primary endpoint for this trial is 28-day survival. Other key efficacy endpoints include: overall survival and time-to-viral load clearance. Safety endpoints

32 2 SUMMARY OF REPORTS

Table A3.1. Type of reports and their distribution

Reports	Prepared by*	Distribution	Frequency†	Distributed to		
				Protocol co-chairs, blinded biostatisticians	*DSMB*	*LeafBio*
Open Report to the DSMB	S	Electronic ‡	M	**X**	**X**	**X**
Closed Report to the DSMB	S	Electronic ‡	M		**X**	
Study Progress Reports	S, DM	Web site	Updated daily	**X**		**X**
SAE Reports						
By trt group	S	DSMB report	M		**X**	
Pooled **	S	Email	Upon request	**X**		
SAEs related to treatment	S, SO	Electronic	Event-driven		**X**	**X**
Safety Reports	S, SO	Electronic	Event-driven	**X**	**X**	**X**

* Prepared by: DM = data manager, S = Independent biostatisticians,
SO = Safety office at the Statistical and Data Management Center (SDSMB), blinded to study arm

† Frequency: M = Prior to each DSMB meeting

‡ Reports to the DSMB will be available for download from a secure server; upon request, DSMB members will also receive a hard copy. The open report will be posted on the study web site after the DSMB meeting.

** Reports are blinded to study arm assignment. All information will also be provided to the DSMB as part of the closed reports, by treatment group.

Abbreviations: SAE = serious adverse event

3 OPEN REPORT TO THE DSMB

The open report to the DSMB includes reports on accrual, eligibility violations, baseline characteristics, and data completeness as described below. The data are presented pooled across study groups. Open reports will be produced by the independent biostatisticians, under direction of the protocol principal investigators and blinded statisticians.

The open reports will be distributed as indicated in table A3.1, and posted to the study web site after each DSMB review together with the DSMB summary recommendations.

3.1 Accrual

The following reports will be provided:

- Enrollment, by calendar time, geographic location (United States vs. West Africa) and treatment site.

3.2 Eligibility violations

Number (N) and percent (%) of participants who were enrolled in violation of inclusion/exclusion criteria will be reported for each inclusion/exclusion criterion separately and total. Reports will be overall, geographic location (United States vs. West Africa) and by treatment site.

3.3 Baseline Characteristics

The following baseline data will be summarized, overall, by geographic location (United States vs. West Africa) and by treatment site:

- Demographics: Age, sex, race, country of birth, work involving contact with a person with Ebola or decedents (N and %), and role (e.g., doctor, nurse, ambulance driver, laboratory) and enrollment in any other studies related to Ebola
- Clinical Information: Results of pregnancy test, weight, height, blood pressure, pulse, body temperature, respiratory rate and oxygen saturation
- Illness Information: days since onset of symptoms, cycle threshold (actual value and dichotomized as CT > 22 vs. CT ≤ 22), country where EVD diagnosis was confirmed
- Symptoms: Fever, sore throat, cough, etc.
- Chemistries: creatinine and potassium are required, all other chemistries are optional. Optional data will be summarized for subjects where data is available.
- Hematology and Coagulation: optional data summarized as provided.
- Urinalysis: optional data, summarized for subjects where data is available.
- Imaging and Resuscitation: optional data, summarized for subjects where

data is available.

Summaries for continuous-valued outcome will include N and mean, SD or median, IQR. Summaries for categorical outcomes will include N and %.

3.4 Data Completeness

The following reports will be provided, overall, by geographic location (United States vs. West Africa) and by treatment site:

- Withdrawal of consent (N and %)
- Required forms:
    - Number (and % of expected) of completed baseline forms
    - Number (and % of expected) for each item on the baseline form
    - Number (and % of expected) of daily follow-up forms (overall and by study day)
    - Number (and % of expected) for each item on the daily follow-up form (overall and by study day)
    - Number (and % of expected) of current symptom forms (overall and by study day)
    - Number (and % of expected) for each item on the daily follow-up form (overall and by study day)
    - Number (and % of expected) of daily chemistries forms
    - Number (and % of expected) for each item on the daily chemistries form (overall and by study day)
    - Number (and % of expected) of ZMapp forms (overall and by study day)
    - Number (and % of expected) of completed day 28 forms received, according to the following categories: completed, still in follow-up period, withdrawn and lost to follow-up
    - Number (and % of expected) of completed day 58 forms received, according to the following categories: completed, still in follow-up period, withdrawn and lost to follow-up
    - Number (and % of expected) of discharge forms
    - Number (and % of expected) of death forms
- Optional forms:
    - Number (and % of maximum possible) of completed daily hematology forms
    - Number (and % of maximum possible) of daily urinalysis forms
    - Number (and % of maximum possible) of daily resuscitation forms

4 CLOSED REPORT TO THE DSMB

Closed reports are by treatment group, unless otherwise noted. Treatment groups will be labeled by letters. A sealed envelope to break the blind of the treatment groups will be provided with the report to the DSMB Chair.

4.1 Baseline Characteristics

Baseline characteristics provided in the open report will be summarized by treatment group in the closed report section. Summaries for continuous-valued outcomes by treatment group will include N and mean, SD or median, IQR. Summaries for categorical outcomes will include N and %.

P-values for comparisons of baseline characteristics between treatment groups will not be provided.

4.2 Data Completeness

Data completeness reports in the open report section (see 3.4) will be provided by treatment group in the closed section. The proportion of patients for which the day 28 form is available from among those who have completed the 28-day follow period will be compared between treatment groups using Fisher's exact's test.

4.3 Patient Profiles

A one page patient profile will be provided for each patient in the trial. This will provide a basic summary of their current status in the trial (i.e. treatment group, current study day, if they have been discharged, etc.). In addition, for each day, we will provide the CT value, vital signs, required chemistries (creatinine and potassium), days which infusions occurred and any SAEs.

4.4 Primary Outcome

The primary endpoint for this trial is 28-day mortality. All comparisons between treatment groups will follow the intent-to-treat principle, unless otherwise noted.

4.4.1 Primary analysis at study completion

Inference relating to the primary endpoint will quantify the probability that the 28-day mortality rate is lower (or higher) under ZMapp relative to oSOC using the Bayesian paradigm. A uniform(0,1) prior will be used for the 28-day mortality rate in both groups. The following summaries will be presented:

1. Basic summaries of 28-day survival (N and %) for each group, broken down into the following categories: dead, alive and still in follow-up period.
2. Point estimate (all point estimates derived from Bayesian inference will use the posterior mean) and 95% credible interval (all credible intervals derived from Bayesian inference will use quantiles of the posterior distribution; i.e. 2.5^{th} and 97.5^{th} percentile) for the absolute difference in 28-day mortality rate between the two treatment arms.
3. Point estimate and 95% credible interval for the relative risk of 28-day mortality between the two treatment arms.
4. The posterior probability that arm A is superior to arm B, given the observed data.
5. Graphical displays of the updated posterior distribution for the absolute difference and relative risk, given the observed data.

The difference in 28-day mortality will be considered statistically significant if the posterior probability that the 28-day mortality rate in arm A is greater than the 28-day mortality rate in arm B is greater than 0.975 or vice versa.

Additional details about the computation of the posterior probabilities required for inference can be found in the following two documents: "Thumbnail sketch of Ebola

Treatment Trial Monitoring, with Examples” and “Monitoring a Trial of MCMs for Ebola Virus Disease.”

4.4.1.1 INTERIM MONITORING AND ANALYSES

Interim analyses will first occur after the primary outcome is available for 12 subjects. Thereafter, interim analyses will be completed every 2 subjects until outcomes are available for 40 subjects, at which points interim analyses will occur after every 40 subjects. Ideally, the treatment groups would be balanced at the interim analyses (i.e. 6/group, 7/group, etc.) but, in practice, slight imbalances are expected at any point during the trial and this will have minimal impact on the operating characteristics of the proposed interim monitoring procedure.

The following summaries will be presented at all interim analyses:

1. Basic summaries of 28-day survival (N and %) for each group, broken down into the following categories: dead, alive and still in follow-up period.
2. Point estimate and 99.8% credible interval for the absolute difference in 28-day mortality rate between the two treatment arms.
3. Point estimate and 99.8% credible interval for the relative risk of 28-day mortality between the two treatment arms.
4. The posterior probability that arm A is superior to arm B, given the observed data.
5. Graphical displays of the updated posterior distribution for the absolute difference and relative risk, given the observed data.

The difference in 28-day mortality will be considered statistically significant at the interim analyses if the posterior probability that the 28-day mortality rate in arm A is greater than the 28- day mortality rate in arm B is greater than 0.998 or vice versa.

Conditional power will be included in DSMB reports after outcomes are available for 40 subjects. The conditional probability will be computed as the probability of a significant result at the end of the trial, as defined in Section 4.3.1, given the current data.

A detailed description of the interim monitoring for this trial, including the rationale and operating characteristics, can be found in a separate document entitled, “Monitoring a Trial of MCMs for Ebola Virus Disease.”

4.4.1.2 PARTIALLY OBSERVED OBSERVATIONS

The analysis described above only utilizes subjects for which the primary endpoint has been fully observed (i.e. death or 28-day survival). At the interim analyses, there will be subjects that have been enrolled and randomized but have yet to complete the 28-day follow-up period. In this case, we will complete a sensitivity analysis to determine how the results of the analysis presented in Section 4.3.1.1 would change depending on the outcomes for these subjects. Specifically, we will present the summaries described in Section 4.3.1.1 assuming that all remaining subjects in group A will survive, while all subjects in group B will die and assuming that all remaining subjects in group B will survive, while all subjects in group A. This will provide a “worst-case-scenario” for how

much the results of our primary analysis could change based on the outcomes of the partially observed subjects.

4.4.1.3 EARLY TERMINATION FOR EXTERNAL REASONS

There are several scenarios where the trial may terminate early for external reasons (end of the epidemic, inadequate drug supply, etc.). This situation is discussed in more detail in guidance document provided to the DSMB. In the event that the trial is terminated for external reasons, we will summarize the difference in 28-day mortality rate by group as described in Section 4.3.1 and the difference between groups will be declared statistically significant if the posterior probability that the 28-day mortality rate in arm A is greater than the 28-day mortality rate in arm B is greater than 0.975 or vice versa.

4.4.2 Additional analyses

4.4.2.1 STRATIFIED ANALYSIS

In addition to the above grouped summaries, we will also complete a stratified analysis by the location of treatment (West Africa vs. U.S.) and CT value (> 22 vs. ≤ 22). Stratified analyses will be completed separately for the two stratification factors and will be completed once data are available for the two stratum. Analyses will be completed assuming the Bayesian paradigm with uniform(1,1) prior distributions for the 28-day mortality rate in each stratum. The following summaries of the stratified analyses will be reported:

1. Basic summaries of 28-day survival (N and %) for each group within a stratum, broken down into the following categories: dead, alive and still in follow-up period.
2. Point estimate and 99.8% credible interval for the relative risk of 28-day mortality between the two treatment arms for each stratum.
3. The posterior probability that the relative risk in stratum 1 is greater than the relative risk in stratum 2. The relative risks will be considered significantly different if the posterior probability is greater than 0.975 or less than 0.025.

4.5 Secondary Outcomes

4.5.1 Overall Survival

Overall survival, defined as the time from randomization to death, will be summarized by Kaplan-Meier curves for the two treatment groups for the overall study population and stratified by location (West Africa vs. U.S.) and CT value (> 22 vs. ≤ 22). Overall survival will be compared between treatment groups using the Cox proportional hazards regression model stratified by location and CT value.

In addition, we will also provide basic summaries of survival at discharge and 58-day survival (N and %) for each group, broken down into the following categories: dead, alive and still in follow- up period.

4.5.2 Time-to-viral load clearance

Time-to-viral load clearance will be summarized by treatment group as follows: mean (SD) for subjects with an observed time-to-viral load clearance, N (%) of patients that died before clearance and N (%) of patients that remain unresolved (i.e. patients that are still being followed). Time-to-viral load clearance will be compared between groups using both the

Wilcoxon and chop-lump test. In both cases, we will order subjects first by time-to-viral load clearance (shortest to longest), followed by subjects that died before clearance (longest to shortest). This treats any death as a worse outcome that than the longest time-to-viral load clearance and will allow us to include all data in a single hypothesis test.

4.5.3 Change in CT value within first 72 hours after randomization

The change in CT value within the first 72 hours will be summarized by treatment group by the mean (SD) and compared using the two-sample t-test. The number and percent of patients that died within 72 hours will also be reported.

4.5.4 Daily Outcomes

The following will be summarized by treatment group as described:

- Vital Signs: blood pressure, pulse, body temperature, respiratory rate, oxygen saturation – summarized daily by treatment group
- Summary of optimized supportive care provided: electrolytes and intravenous fluids, other treatments (ventilation, ECMO, supplemental oxygen, etc.) – summarized daily by treatment group
- Current symptoms – summarized daily by treatment group
- Chemistries: creatinine and potassium are required and will be summarized for each 3- day window (i.e. days 1- 3, days 4 – 6, etc.) by treatment groups, all other chemistries are optional and will be summarized as available
- PCR: summarized for each 3-day window (i.e. days 1- 3, days 4 – 6, etc.) by treatment groups
- Hematology and coagulation: optional data – summarized as available
- Urinalysis: optional data – summarized as available
- Imaging and resuscitation: optional data – summarized as available

Summaries for continuous-valued outcomes by treatment group will include N and mean, SD or median, IQR. Summaries for categorical outcomes will include N and %.

4.6 Safety outcomes

4.6.1 SAEs

SAEs will be summarized and compared between treatment groups as follows:

- Number and percent of patients experiencing SAEs by treatment group. Test of statistical significance will use Fisher's exact test.
- Counts of SAEs by treatment group. The rate of SAEs will be formally compared using a zero-inflated negative binomial model.
- Kaplan-Meier cumulative event curves by treatment group; p-values will be provided for comparing the active treatment groups to placebo using the log-rank test

- For SAEs that are assessed as related to study drug, counts by treatment groups and p- value from zero-inflated negative binomial model.

4.6.2 Safety listings

Line listings by treatment group will be provided for SAEs and "unanticipated problems". Listings will include the SID, treatment group label, diagnosis, relatedness to treatment, date of onset, time from treatment to onset, event status (recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, death), date of resolution or death, and EVD status.

4.6.3 Pregnancies

The number of pregnancies reported during the 58-day follow-up period after randomization, and the outcomes of these pregnancies, will be summarized by treatment group.

4.6.4 Infusion Reactions

The number and percent of patients experiencing infusion reactions will be summarized for patients randomized to ZMapp. 95% CIs for the rate of infusion reactions will also be provided. Infusion reactions will also be broken down by the specific infusion reactions reported on the ZMapp infusion form and summarized by the number and percent experiencing each infusion reaction.

4.6.5 Infusion Interruptions

The number and percent of patients for which infusion interruptions occurred will be summarized for patients randomized to ZMapp. 95% CIs for the rate of infusion interruptions will also be provided.

4.6.6 Unanticipated problems

Incidence of "unanticipated problems" will be tabulated for each of the treatment groups. Reports will have similar format as the summary reports for SAEs.

5 DAILY STUDY PROGRESS REPORTS ON THE WEB

Progress reports include reports on accrual, baseline characteristics, and data completeness. These data summaries are pooled across study groups. The reports are similar to those described in the open report section.

These reports will be available on the study web site (controlled access), updated daily. Additional reports may be provided to study leadership on request.

6 SAE REPORTS TO LEAFBIO

Listings for SAEs that are assessed as related to the studied treatment will be provided to LeafBio. Reports will be as described in the protocol.

7 SHELLS FOR TABLES AND FIGURES

Shells for key tables and figures are provided in this section. For example, a shell for Kaplan- Meier curves for the primary endpoint is shown; similar Kaplan-Meier curves will also be provided for several secondary endpoints, as described earlier.

Final Data Analysis Plan for PREVAIL II
Ebola Virus Disease Medical Countermeasures (EVD MCM) Trial

January 20, 2016

Table of Contents

1 Introduction

This document describes the content proposed for the primary statistical analysis of PREVAIL II, the randomized controlled trial of ZMapp in acute Ebola virus disease (EVD). The focus is on analyses that address the major randomized comparisons for key safety, tolerability and efficacy outcome measures, including those needed to address the study's primary objective as well as the main secondary objectives. This analysis plan therefore includes the key analyses for presentation or publication of the primary conclusions of the study.

2 Study Overview

The study protocol is a master protocol for the evaluation of multiple candidate countermeasures for the treatment of EVD. Given the waning epidemic, the initial (and, to date, only) phase of the trial was focused only on the evaluation of ZMapp, although the study was designed to provide flexibility to introduce additional treatments under certain situations that are described in the protocol. The Primary Objective of this study was to establish the safety and efficacy of ZMapp in patients diagnosed with Ebola virus infection.

Patients were randomized in the United States, Liberia, Sierra Leone, and Guinea in a 1:1 allocation ratio to optimized standard of care (oSOC) versus oSOC plus ZMapp. A maximum of 200 subjects were to be randomized (100 per treatment arm) in this trial. The primary endpoint for the trial is survival as assessed at Day 28.

Following the first randomized patient on March 13, 2015, the Data and Safety Monitoring Board (DSMB) reviewed interim data on 7 occasions. Following each review, the DSMB indicated that they had no safety concerns and recommended the study continue.
In anticipation of study closure due to the absence of EVD, pooled (both treatment groups combined and blinded) outcome data were provided to the U.S. study team by the unblinded statisticians, Dr. Joe Koopmeiners and Ms. Jacquie Nordwall, on November 25, 2015. These data were used to update the data analysis plan that was prepared prior to the beginning of the trial. The pooled data were updated on December 31, 2015 following submission of 28 day follow-up data for the last person randomized on November 21, 2015.
On January 8, 2016, a provisional draft of the updated data analysis plan was shared with the Food and Drug Administration, Mapp Biopharmaceutical, INSERM, and other participating site investigators. The final data analysis plan detailed in the present document considers the comments that were received concerning that January 8th proposal. The document retains some of the information from the original analysis plan concerning the format and content of open and closed DSMB reports.
As of January 14, 2016, 42 days after the last case of EVD in Liberia was discharged, all three countries in West Africa had been declared Ebola-free. Accordingly, the study was planned for closure to new accrual as of that date. Subsequent to that determination there has been a potential resurgence of EVD reported in Sierra Leone; the scope and duration of that recent outbreak, as well as whether any potential new cases may be referred for enrollment, are unclear at this time. If additional enrollments do occur, this will delay the timeline for implementing the final study analysis as summarized in this document. As of the original

planned date of closure on 1-14-2016 there have been a total of 72 patients randomized on the protocol.

3 PLANNED Analyses

Unless otherwise stated, all tables, figures, and listings will show results by randomized arms. For tables with categorical variables, the number (%) will be presented. For tables with continuous variables, the mean, standard deviation, median, 25th and 75th percentiles, min and max will be presented. The number with missing values will also be shown. In calculation of percentages, subjects with missing data will not be included in the denominator. Data presented as listings or figures will be specifically noted.

3.1 Analysis Populations

The primary population includes all randomized patients, with the exception of one individual who fled from the ETU on the first day. This is the only subject for whom there is missing primary outcome data. (Sensitivity analyses will also be performed including this individual in his/her assigned group, as described below).
The primary analyses will be performed on all subjects regardless of baseline covariates. The study stratified randomization based on cycle threshold (CT > 22 vs. CT ≤ 22) and geographic location, and analyses will be presented accordingly. In addition, some analyses will specify age subgroups defined as: adults ≥ 18 years vs. children aged <18 years.

3.2 Subject Accrual

The following information about accrual will be summarized:

- Number randomized: overall and by month/year. Dates of first and last randomizations.
- Number randomized by geographic location (United States, Liberia, Sierra Leone, Guinea), country, and site
- Number randomized by cycle threshold (CT ≤ 22 versus > 22)
- Number randomized by children versus adults

3.3 Eligibility violations

Number (N) and percent (%) of any participants who were enrolled in violation of inclusion/exclusion criteria will be reported for each inclusion/exclusion criterion separately and total. Reports will be overall, by geographic location (United States vs. West Africa) and by treatment site.
Listing: Description of violations of eligibility criteria among randomized subjects.

3.4 Baseline Characteristics

The following baseline data will be summarized overall and by treatment assignment, geographic location (United States, Liberia, Sierra Leone and Guinea) and treatment center:

- Demographics: Age, sex, race, country of birth, work involving contact with a person with Ebola or decedents (N and %), and role (e.g., doctor, nurse, ambulance driver, laboratory) and enrollment in any other studies related to Ebola
- Clinical information: Results of pregnancy test, weight, height, blood pressure, pulse, body temperature, respiratory rate and oxygen saturation
- Illness information: days since onset of symptoms, cycle threshold (actual value and dichotomized as CT > 22 vs. CT ≤ 22), country where EVD diagnosis was confirmed
- Symptoms: Fever, sore throat, cough, etc.
- Chemistries: measurement of serum creatinine and potassium were required, all other chemistries were considered optional. Optional data will be summarized for subjects where data is available.
- Hematology and Coagulation: optional data summarized as provided.
- Urinalysis: optional data, summarized for subjects where data is available.
- Imaging and Resuscitation: optional data, summarized for subjects where data is available.

3.5 Data Completeness

The following reports will be provided overall and by treatment assignment, geographic location and treatment center:

- Withdrawal of consent (N and %)
- Required forms:
    - Number (and % of expected) of completed baseline forms
    - Number (and % of expected) for each item on the baseline form
    - Number (and % of expected) of daily follow-up forms (overall and by study day)
    - Number (and % of expected) for each item on the daily follow-up form (overall and by study day)
    - Number (and % of expected) of current symptom forms (overall and by study day)
    - Number (and % of expected) for each item on the daily follow-up form (overall and by study day)
    - Number (and % of expected) of daily chemistries forms
    - Number (and % of expected) for each item on the daily chemistries form (overall and by study day)
    - Number (and % of expected) of ZMapp forms (overall and by study day)
    - Number (and % of expected) of completed day 28 forms received, according to the following categories: completed, still in follow-up period, withdrawn and lost to follow-up

- Number (and % of expected) of completed day 58 forms received, according to the following categories: completed, still in follow-up period, withdrawn and lost to follow-up
- Number (and % of expected) of discharge forms
- Number (and % of expected) of death forms

- Optional forms:
  - Number (and % of maximum possible) of completed daily hematology forms
  - Number (and % of maximum possible) of daily urinalysis forms
  - Number (and % of maximum possible) of daily resuscitation forms

3.6 Optimized Supportive Care Descriptions

- Optimized supportive care provided by study day:
  - Intravenous fluids as total volume (continuous variable) and % receiving fluids
  - Intravenous fluids will also be presented by combining all fluids (normal saline and lactated ringers, etc) and presenting in ml/kg to adjust for differences in age and body mass.
  - Other treatments (electrolytes, ventilation, ECMO, supplemental oxygen, medications etc.) as %
- The number of days with supportive care infusions until discharge/death will be summarized.
- Also, for 3-day windows: 1-3, days, 4-6 days, etc. supportive care infusions will be summarized.
- Data will be analyzed both by geographic region and, where applicable, by incorporation of Favipiravir as oSOC.

3.7 ZMapp Infusion Summaries

Note: for patients assigned to the ZMapp group, ZMapp was to be started immediately following randomization. The 2nd dose was to be given 3 days after the 1st dose; the 3rd dose was to be given 3 days after the 2nd dose.

- The distribution of the number of infusions per patient (0, 1, 2, 3)
- Time elapsed between randomization and first dose
- Study day of infusion of each dose will be summarized
- Duration (minutes and mean) by study day
  - additional separate tables for adults and children
- Volume received (mean and ml/kg) by study day.
- Percent receiving prepared volumes of 95% or greater.
- Calculated dose (mg/kg) of ZMapp Dose actually administered
- Number and percent of patients experiencing infusion reactions
  - Total N (%)
  - N (%) categorized by the specific infusion reactions reported
  - N (%) which required intervention
    - N% by intervention taken
- Number and percent of patients experiencing infusion interruptions

- Total N (%)
- Pre-treatments administered before infusions to ameliorate reactions
- Other problems with the infusion noted on the case report form.
- Listing of other problems related to infusion
- Listing of subjects assigned to ZMapp who did not receive all doses before death: subject ID, site, days from randomization to first dose, days from first ZMapp to death, total doses given

3.8 Primary Outcome

The primary outcome is death within 28 days from randomization, and the primary population includes all randomized patients, with the exception of one individual who fled from the ETU on the first day and for whom no other primary data were subsequently captured.
Note: as a sensitivity analysis to assess the impact of the single subject with unknown vital status following randomization, the primary analysis described below will be performed assuming the subject was alive at 28 days and repeated assuming the subject was dead at 28 days.

Primary analysis

Inference relating to the primary endpoint will quantify the probability that the 28-day mortality rate is lower (or higher) under ZMapp relative to oSOC using the Bayesian paradigm as follows:

A. The prior distribution of 28-day mortality probabilities, p_0 and p_1, in the oSOC and ZMapp arms is that of independent uniforms on [0,1].
B. The posterior distributions of p_0 and p_1 after observing x_0 and x_1 deaths among n_0 and n_1 people in the two arms is that of independent betas with respective parameters (x_0+1, n_0-x_0+1) and (x_1+1, n_1-x_1+1).
C. The posterior probability that $p_1<p_0$ will be computed: if this probability is 0.975 or greater, ZMapp will be declared superior to oSOC, whereas if the probability is 0.025 or less, ZMapp will be declared inferior to oSOC.
D. Treatment effect estimates and 95% credible intervals will be computed for both the relative risk p_1/p_0 and absolute risk difference p_1-p_0. The medians of the posterior distributions of p_1/p_0 and p_1-p_0 are used to estimate these quantities. 95% credible intervals are computed as follows.
    a. For p_1/p_0, compute lower and upper limits (L and U, respectively) satisfying $P(p_1/p_0<L \text{ given } x_0,x_1)=0.025$ and $P(p_1/p_0>U \text{ given } x_0,x_1)=0.025$.
    b. For p_1-p_0, compute lower and upper limits (L and U, respectively) satisfying $P(p_1-p_0<L \text{ given } x_0,x_1)=0.025$ and $P(p_1-p_0>U \text{ given } x_0,x_1)=0.025$.

Additional Supportive Analyses Using Primary Outcome:

Alternative test statistics:

The following alternative test statistics will be performed on the primary outcome as secondary analyses.

- Barnard's unconditional test will be performed using a one-tailed test of $p_1=p_0$ versus $p_1<p_0$.
  A. The first alpha level used is 0.025 (one-sided). As with the Bayesian analysis, the overall type 1 error rate including monitoring may exceed 0.025.
  B. The second alpha level is adjusted using the Haybittle-Peto monitoring procedure: $\alpha=0.025-(0.001)k$, where k is the number of interim looks at the data.

  A confidence interval will be computed for the absolute risk difference using Barnard test methodology and confidence level 1-2α. This will be done for each of the two alpha levels specified above.
- The same approach specified above for Barnard's test, including the two separate alpha levels, will also be performed for Fisher's exact test. A confidence interval for the odds ratio will be computed using the non-central hypergeometric distribution.
- An analysis of time to death will be performed using a log-rank test. In addition, a stratified log-rank test will be performed with 4 strata defined by location and cycle threshold. (See description of stratification variables below). This will be done for each of the two alpha levels specified above. Tests of treatment by subgroup interaction will be performed.

Stratification and subgroup analyses

- Additional analyses will be performed within two strata defined by cycle threshold: ≤22 versus >22 for all subjects. To assess whether there is a treatment by cycle threshold interaction, we will compute the posterior probability that the treatment effect (absolute or relative) differs by cycle threshold.
- Analysis combining the United States, Liberia, and Sierra Leone as one location stratum, while Guinea constitutes the other location stratum. (The standard of care in Guinea typically included favipiravir, which was not the case in the other countries). Note that the protocol initially specified stratified randomization for the USA. However, only one patient in the USA was randomized, which is why the location strata have been changed to USA/Liberia/Sierra Leone vs Guinea. To assess whether there is a treatment by location interaction, we will compute the posterior probability that the treatment effect (absolute or relative) differs by location. An additional sensitivity analysis will exclude the lone patient treated in the United States. The treatment effect within the United States cannot be estimated with only one patient, and the differential oSOC in the United States versus West Africa could make interpretation of results more difficult. For example, if the patient was assigned to oSOC and survived, that may simply reflect better oSOC in the United States.
- A stratified analysis of odds ratios by the 4 strata defined by location (USA/Liberia/Sierra Leone versus Guinea) and cycle threshold (≤22 versus >22) will also be performed using the Mantel-Haenszel test and estimator. The corresponding alpha levels are as specified above. Separate tests of whether the treatment effect differs by location and by cycle threshold will be conducted.
- Subgroup analysis will repeat the above analyses (main analysis, then divided by CT and geographic area) for adults and children

- All other subgroup analyses (e.g. age, duration of symptoms, baseline risk score [see description below]) will follow the strategies above
- A baseline risk stratification analysis using a risk score for mortality. This analysis is motivated by the following hypothesis: some individuals will enroll who are at a stage of disease where a fatal outcome can no longer be prevented. However, exclusion of patients in each treatment group who die shortly after randomization would be biased because deaths could be due to the toxicity of ZMapp. A modified intention to treat analysis in which patients who did not receive at least one dose of ZMapp were excluded would also be problematic because early deaths would only be excluded from one of the treatment groups. To address this hypothesis we will carry out subgroup analyses that are protected by randomization based on the risk (or propensity) of death at the time of randomization. With this approach, baseline predictors of death in the first 3 days following randomization and in the first 8 days following randomization (all deaths occurred within 8 days) will be determined using separate logistic models. With the estimated parameters from the logistic models, the probability of 3- and 8-day mortality will be determined for each patient. This probability or "risk score" for each person will be used to stratify/subgroup patients according to high/medium/low risk of death (approximate tertiles) and within each subgroup the two treatment groups will be compared. The primary goal is to determine whether the treatment effect differs by risk of early death. Development of the risk score will be conducted using the pooled (i.e. blinded) data. This will ensure validity of a permutation test, include a larger number of events, and allow a more thorough search for relevant baseline predictors.

  The following baseline predictors will be considered: age, gender, geographic location, CT value, duration of symptoms at enrollment, and type of symptoms (e.g.: systemic symptoms [fever, myalgias, arthalgias], fluid loss [diarrhea, vomiting, blood loss], respiratory compromise [SOB, hypoxia, elevated respiratory rate >24, supplemental oxygen requirement], hemodynamic instability [systolic BP <90, pulse >100, pressor support requirement], renal compromise [anuria, serum creatinine > 2x ULN], and CNS compromise [confusion, seizures, coma]. We hypothesize based on these analyses that benefits of ZMapp on mortality (compared to oSOC) will be greater among patients with a medium to low risk of early (1^{st} 3 days) death, relative to those for whom it is high. Since there may be some patients who enter the trial with a very low risk of death (e.g., no matter the intervention, they were likely to survive), we also hypothesize that the benefits of ZMapp on mortality (compared to oSOC) will be greater among patients whose risk of death *within 8* days is medium or high compared to those from whom it is low.
- Figures:
  - Forest plots of above mortality rates according to the following subgroups:
    - CT≤22/>22
    - Geographic area
    - Adults vs children
    - Sex
    - Duration of time from onset of symptoms to randomization
    - Baseline risk stratification score (as defined above)
  - Kaplan-Meier plots will be made for the following:

- Treatment group
- Treatment group and adults and children
- Treatment group and CT ≤22 versus >22 for all subjects
- Treatment group and duration of time from onset of symptoms to randomization

3.9 Secondary Outcomes

Major secondary outcomes:

This section prioritizes the secondary analyses. The study has limited power—the end of the epidemic means the study will close prior to accruing its targeted sample size. As a result, prioritization of secondary endpoints is needed. We also feel it is important to carefully consider the strengths and limitations of the secondary outcomes prior to unblinding. It is recognized that the secondary endpoint analyses described below will be difficult to interpret if the primary analysis does not demonstrate that ZMapp significantly reduces mortality compared to oSOC alone.

Two endpoints are under consideration: time-to-viral clearance (clearance is defined as the first negative PCR result) and time-to-discharge. One could give different arguments for which is a better choice. Time to discharge undoubtedly encompasses several aspects simultaneously: clearance of virus, amelioration of symptoms, etc. However, there is the possibility of a treatment-associated bias in this outcome. For example, if some patients who were given ZMapp were discharged later to make sure there were no drug-related safety issues, then ZMapp may appear less favorable using this endpoint. Also, we have heard reports that patients were kept in a treatment unit after recovery for a variety of reasons, including waiting for discharge kits containing food supplies and other household items or the presence of a relative undergoing treatment for Ebola at the same unit. These issues make time-to-discharge a less precise indication of how a patient feels or functions.

Time-to-viral clearance is a more objective outcome, but it is also not free of problems. Specifically, it is unclear whether this assay was adequately standardized across sites in this study, leading to concerns about measurement variability. Further, samples were taken on half or fewer of participants on many of the days. Nonetheless, failure to measure PCR is likely to have occurred equally in the two arms and the time interval between a positive and negative PCR was within 3 days for 39 of 50 patients (78%) and within 5 days for 47/50 (94%) of patients . Therefore, it is felt that **time to viral clearance should be the more important secondary outcome**, although both outcomes will be analyzed. Note that, for either outcome, death must be taken into account.

1. Viral clearance/death

Unless otherwise stated, viral clearance is defined by the occurrence of a negative PCR.

A. The first analysis of viral clearance/death is a rank test in which patients who die within 28 days receive worse ranks than survivors, with earlier deaths given worse ranks than later deaths. Among 28-day survivors, patients with longer times to viral clearance will be given worse ranks. Average ranks will be used in the case of ties. A permutation test will be used to determine a p-value for this test.

An additional analysis will use the van Elteren stratified Wilcoxon test on the four strata defined by location (USA/Liberia/Sierra Leone versus Guinea) and cycle threshold (≤22 versus >22). An interaction test will be conducted to determine whether the treatment effect differs by each of these subgroups, and subgroups defined by age, gender, and duration from onset of symptoms to randomization. Subgroup results will be presented using a forest plot. [Ref: Van Elteren, P.H. (1960). On the combination of independent two-sample tests of Wilcoxon. *Bulletin of the International Statistical Institute* **37**, 351-361.]

B. The second analysis of viral clearance/death is based on Fisher's exact test with outcome being death or time to viral clearance exceeding 10 days (i.e., 11 or more days). The rationale for this secondary analysis is as follows. It may be that ZMapp prevents very long times to viral clearance, but has no effect on intermediate times. If we knew the right threshold constituting a "long time to viral clearance," we would select that number. To determine the appropriate threshold, we examined data blinded to treatment assignment. If we select a threshold that is too small, then exceeding the threshold may not represent a bad outcome. On the other hand, if the threshold is too large, the number of people exceeding it may be very small. In that case, the test of whether the proportion of people dead or with large time to viral clearance differs by treatment arm will be nearly the same as the test of whether the proportion of people dead differs by treatment arm. Therefore, the key is to choose a threshold that is among the higher times, but not so high that very few people exceed it. Figure 1 (below) shows the plot of days to viral clearance. Approximately one quarter (13/49=26.5%) of the observations are longer than 10 days. This threshold seems to balance the above concerns. Therefore, the second analysis of viral clearance/death will use Fisher's exact test on outcome: death within 28 days or time to viral clearance exceeding 10 days (i.e., 11 or more days). Note that Fisher's exact test is a permutation test, and permutation tests remain valid even if the threshold is determined after examining blinded data.

An additional analysis will use the Mantel-Haenszel estimator and test to stratify by the 4 strata defined by location (USA/Liberia/Sierra Leone versus Guinea) and cycle threshold (≤22 versus >22). An interaction test will be conducted to determine whether the treatment effect differs by each of these subgroups, and subgroups defined by age, gender, and duration from onset of symptoms to randomization. Subgroup results will be presented using a forest plot.

2. Discharge/Death

A. The first analysis of discharge/death will be the same rank-based method as for viral clearance/death, but substituting "discharge" for "viral clearance." An unstratified and stratified test (van Elteren test) will be performed, where the four strata are defined by location (USA/Liberia/Sierra Leone versus Guinea) and cycle threshold (≤22 versus >22).

B. The second analysis of discharge/death uses Fisher's exact test with outcome being death or time to discharge exceeding 16 days (i.e., 17 or more days). The rational for this threshold is as follows. Figure 2 (below) is a blinded display of times to discharge. A threshold of greater than

16 days again separates approximately the highest 25% of times (13/49=26.5%). This threshold is also a reasonable choice to minimize overlap between this analysis and that of time to viral clearance. Figure 3 (below) shows the threshold lines (plotted at 10.5 for time to viral clearance and 16.5 for time to discharge). Although there is substantial overlap, represented by the upper right region, there are also 5 people meeting the >10 days to viral clearance, but not the >16 days to discharge. Likewise, there are 5 people meeting the >16 days to discharge, but not the >10 days to viral clearance.

As with the corresponding analysis of time to viral clearance, a stratified analysis will also be performed using the Mantel-Haenszel estimator and test on the four strata defined by location (USA/Liberia/Sierra Leone versus Guinea) and cycle threshold (≤22 versus >22). An interaction test will be conducted to determine whether the treatment effect differs by each of these subgroups, and subgroups defined by age, gender, and duration from onset of symptoms to randomization. Subgroup results will be presented using a forest plot.

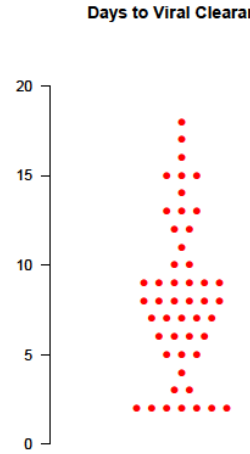

Figure 1. Distribution of days to viral clearance for all subjects who cleared Ebola virus

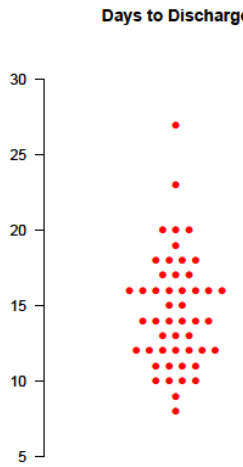

Figure 2. Distribution of days to discharge for all discharged subjects

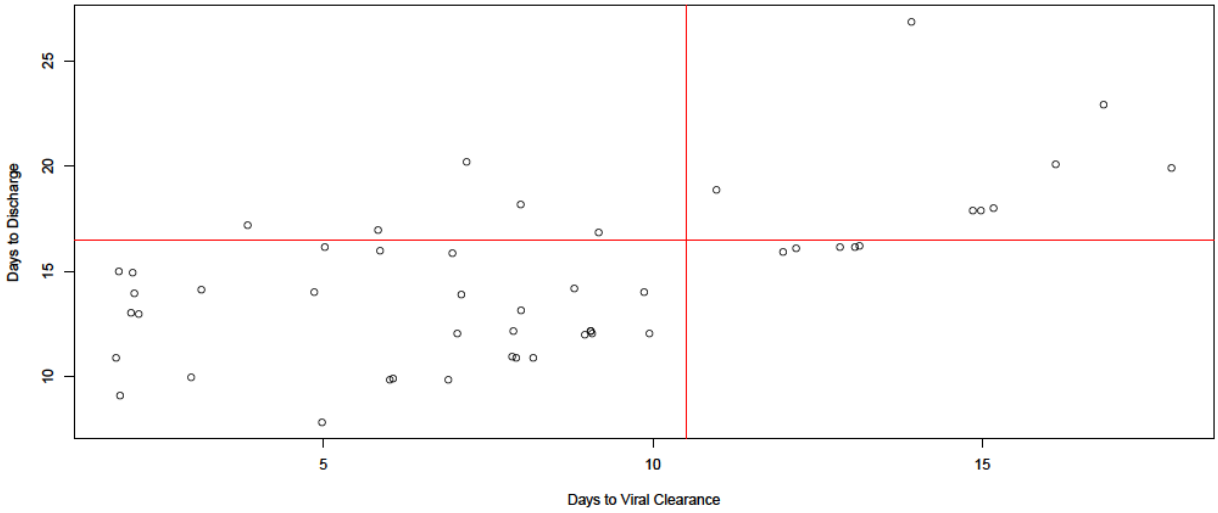

Figure 3. Scatter plot of days to discharge versus days to viral clearance for all surviving subjects

3.9.1 Other Secondary Outcomes

In addition to those parameters described in Section 3.6 above, the following will be summarized by treatment group as described:

- Vital Signs: blood pressure, pulse, body temperature, respiratory rate, oxygen saturation – summarized daily by treatment group

- Current symptoms –
  Two analyses will be performed to compare the number of symptoms across groups:

1. The first analysis of symptoms will compute the average number of symptoms per day during the first 28 days for each patient as well as the average number of days with symptoms. Days with no information on symptoms, including days following the death or discharge of a patient, will be excluded. The groups will be compared using the Wilcoxon rank-sum test. An additional analysis will be conducted using the van Elteren stratified Wilcoxon test on the four strata defined by location (USA/Liberia/Sierra Leone versus Guinea) and cycle threshold (≤22 versus >22).

2. The second analysis of symptoms will be identical to the above analysis, but only during the first 3 days. The rationale is that analyses over the entire 28-day period may be difficult to interpret because some patients will be discharged and others may die. Furthermore, the proportion discharged and proportion dying may differ by arm. Restricting attention to the first 3 days will focus the analysis on the initial stage which is free from discharges and some of the deaths.

    - Percent with any symptom
    - Daily summary of number of reported symptoms
    - Summarized for 7 day intervals by treatment group
    - Symptoms at day 28 and day 58 are also summarized.

- Chemistries: measurement of serum creatinine and potassium were required and will be summarized for each 3-day window (i.e. days 1- 3, days 4 – 6, etc.) by treatment groups, all other chemistries were considered optional and will be summarized as available
    - Additional subgroup analysis will repeat the above for adults and children
- PCR: blood (note- any CT 40.0 or greater will be treated as negative)
    - summarized for each 3-day window (i.e. days 1- 3, days 4 – 6, etc.)
        - if more than one PCR is available in a 3 day period for a given subject, the mean result will be used.
    - summarized as change from baseline for each 3-day window
    - Both of the above will be presented as quantitative (continuous) and qualitative
    - Improvement or worsening of the CT value within the first 72 hours
    - Figure: Kaplan-Meier plot of time to negative Ebola PCR
        - Kaplan-Meier plot repeated for adults and children
    - Individual PCR curves will be presented

- PCR – urine (as available)
    - summarized for each 3-day window (i.e. days 1- 3, days 4 – 6, etc.) by treatment groups
    - presented as % positive
        - additional separate tables for adults and children
- Hematology, chemistries, and coagulation: optional data – summarized as available
    - summarized for each 3-day window (i.e. days 1- 3, days 4 – 6, etc.)
    - summarized as change from baseline for each 3-day window
    - additional separate tables for adults and children

- Urinalysis: optional data – summarized as available
- Imaging and resuscitation: optional data – summarized as available

32.1.1

3.9.2 Safety-Related Outcomes

- SAEs will be summarized and compared between treatment groups as follows:
    - Number and percent of patients experiencing SAEs by treatment group. Test of statistical significance will use Fisher's exact test.
    - For SAEs that are assessed as related to study drug, counts by treatment groups and p-value from zero-inflated negative binomial model.
- Safety line listings by treatment group will be provided for SAEs and "unanticipated problems". Listings will include treatment group label, diagnosis, relatedness to treatment, date of onset, time from treatment to onset, event status (recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, death), date of resolution or death, and EVD status.
- Unanticipated problems

Incidence of "unanticipated problems" will be tabulated for each of the treatment groups. Reports will have similar format as the summary reports for SAEs.

3.9.3 Pregnancies

- a listing of subjects pregnant at enrollment
- listing of pregnancies that occurred on study (from randomization to day 58)

3.9.4 Late Clinical Symptoms:

Subjects will be followed for 1 year to evaluate for late symptoms and/or complications. This analysis will be performed at a separate time from the above stated analyses since it must await completion of the one-year follow-up data.

- Number (and % of expected) of subjects with follow up data between day 56 and 365 (i.e. had any follow up visit)
    - Total, and by country
- Number (and % of expected) of subjects with follow up data at Day 365 (i.e. had 1 year follow-up)
    - Total, and by country
- Number (%) with symptoms at 3 month, 6 months, and 1 year
    - Table of symptoms present
- Number (%) with complications
- Listings of complications (if any)
- Pregnancies

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