



Trials of antivirals for Ebola ISARIC Experience

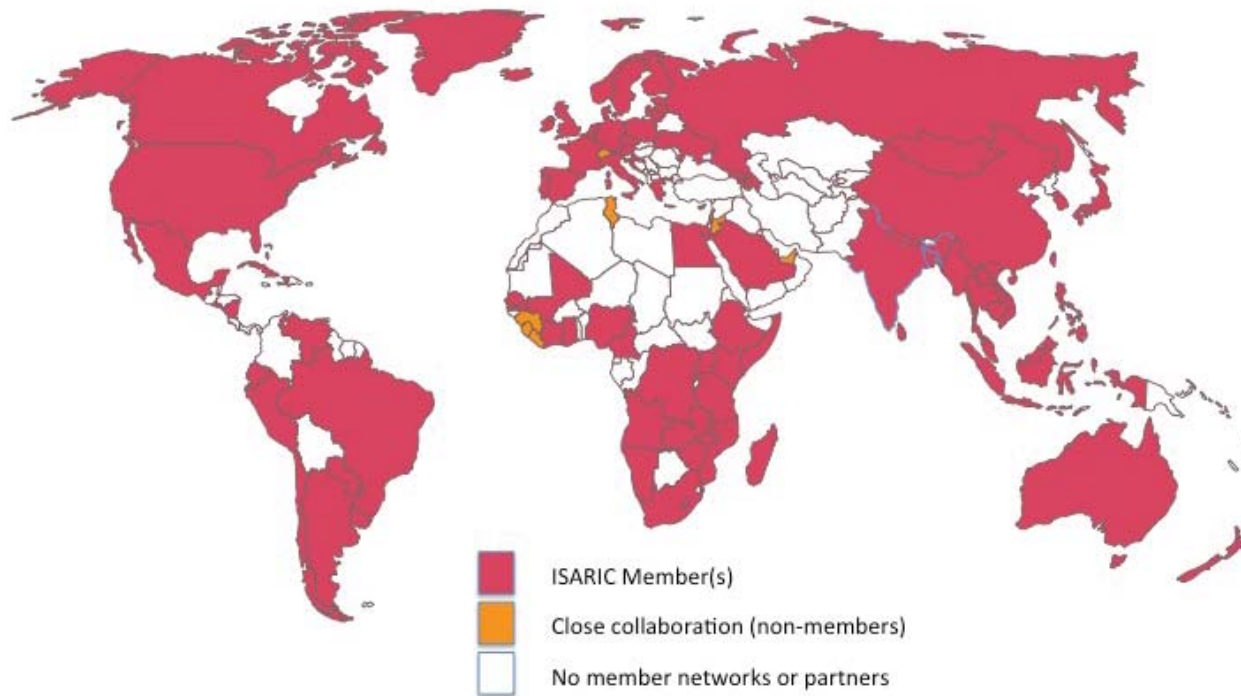
Peter Horby
University of Oxford

9th European Congress on Tropical Medicine and
International Health

Basel, Switzerland, 6-10 September 2015



The International Severe Acute Respiratory and Emerging Infection Consortium
Preparedness through coordinated clinical research



***More than 40
member
networks***

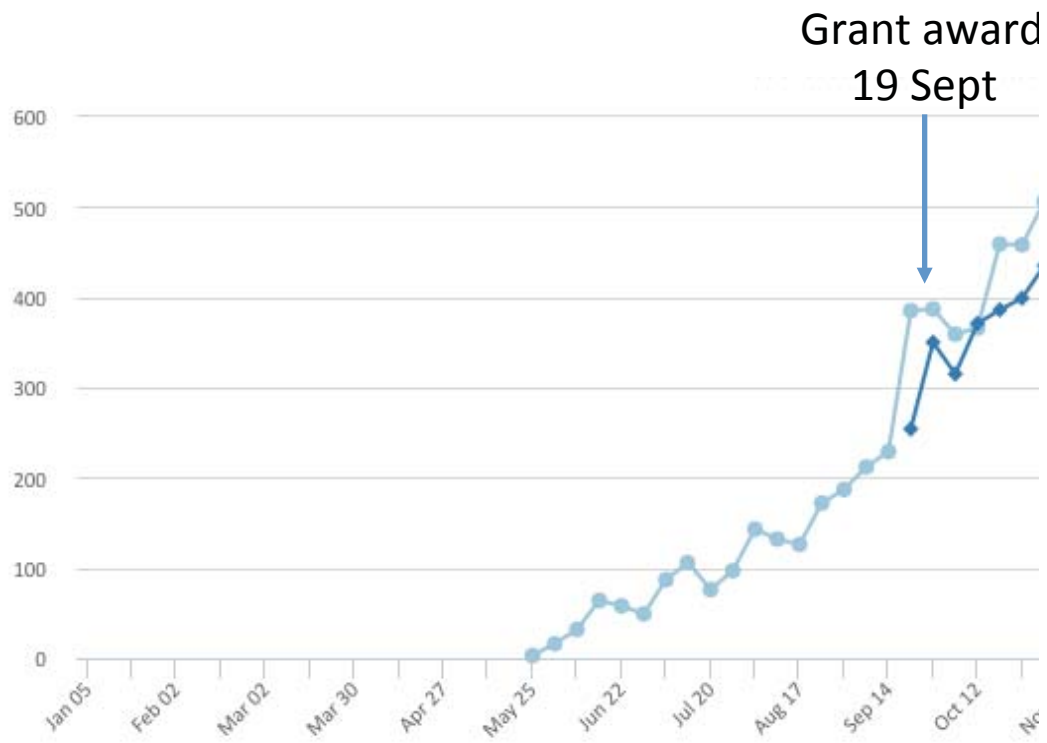
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Ebola trial timelines



Candidate therapies - WHO

Product	What is it?	Evidence
ZMapp	Ebola antibody cocktail	Solid protection in monkeys
TKM-Ebola	RNA inhibitor	Solid protection in monkeys
Brincidofovir	DNA polymerase inhibitor	Antiviral activity in cell lines
Favipiravir	RNA polymerase inhibitor	Solid protection in mice. Antiviral in monkeys
Convalescent plasma	Antibodies from recovered patients	Failed in monkeys

Candidate therapies - status

Product	Status September 2014
ZMapp	None available
TKM-Ebola	None available
Brincidofovir	Available
Favipiravir	JIKI trial in preparation
Convalescent plasma	Supporting trials by ITM & Liverpool

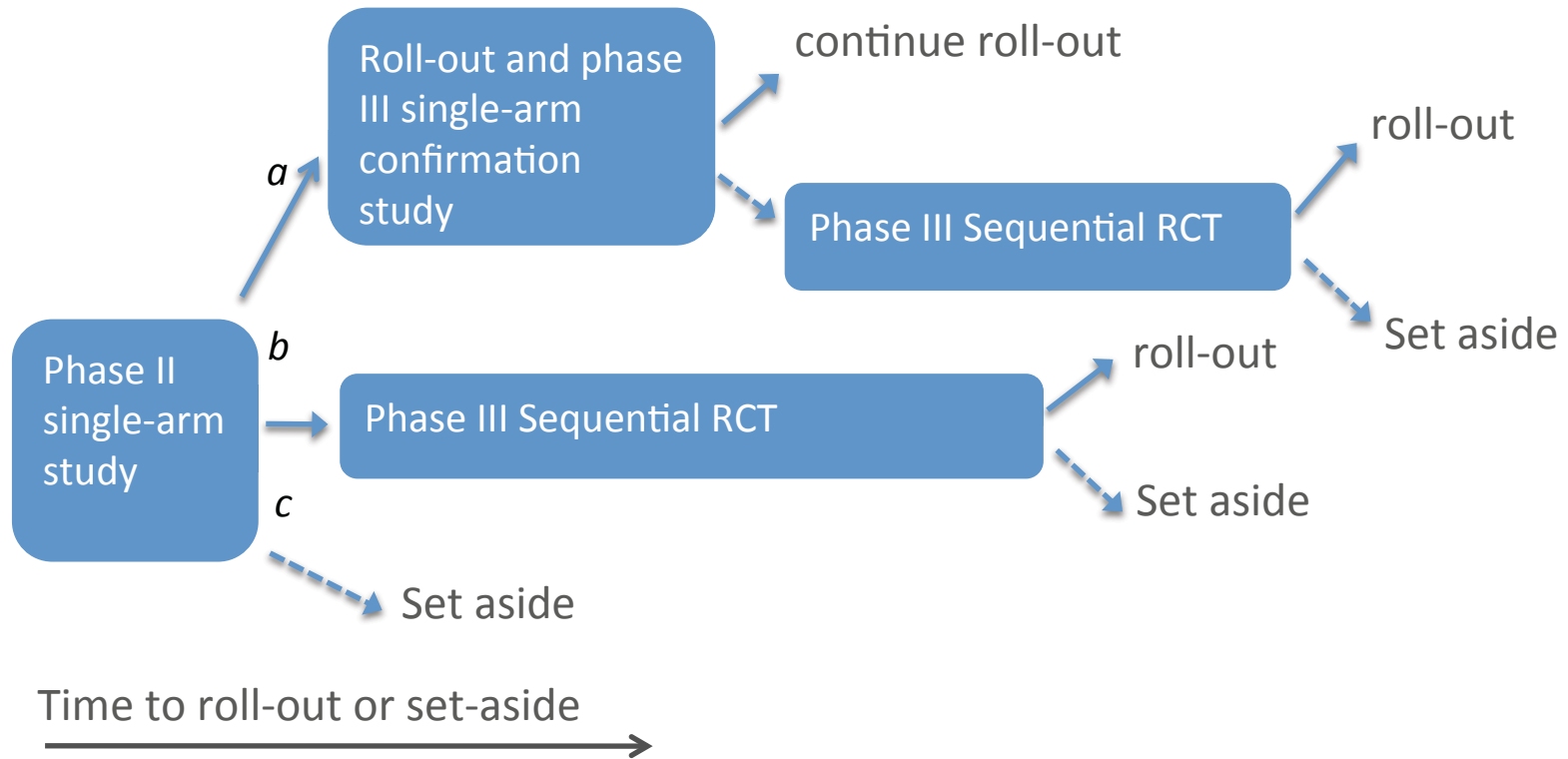
Brincidofovir

- Lipid conjugate of nucleotide analogue cidofovir
- Large and relevant safety database
 - Safety database > 1000 individuals
 - > 400 patients with serious or life-threatening infections
- Phase 3 clinical development ongoing for adenovirus and CMV
- Oral, bi-weekly dosing
- Tablets immediately available for a clinical trial
- Room temperature stable

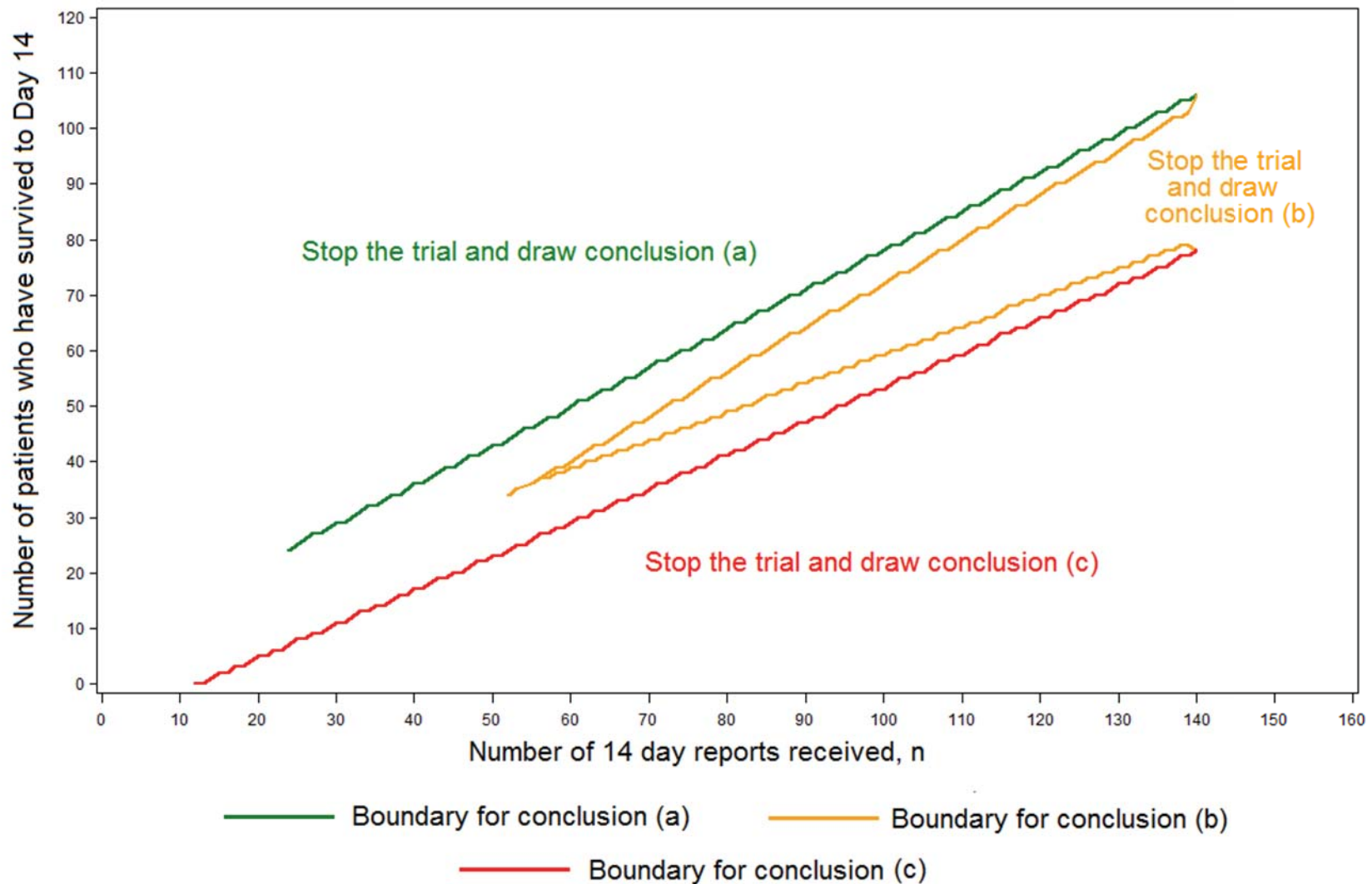
Trial design considerations

- *Ongoing humanitarian crisis + trial involves risks*
 - Need to identify any useful therapeutic quickly
 - Need to discard any useless agents quickly
- *High death rate + volatile conditions*
 - Unclear if randomisation to standard care would be acceptable
- A common approach to developing drugs for patients with solid tumours is a small single-arm phase II trial followed, if promising, by a larger randomised phase III comparison with a standard control treatment

Multi Stage Design



	Survival	Conclusion	Outcome
(a)	80%	Very effective	Maximize benefits
(b)	67%	Promising	Justification for RCT
(c)	50%	Ineffective	Minimize wasted effort



Sequential design

Data analysed each time a patient reaches Day 14.

Maximum sample size = 140

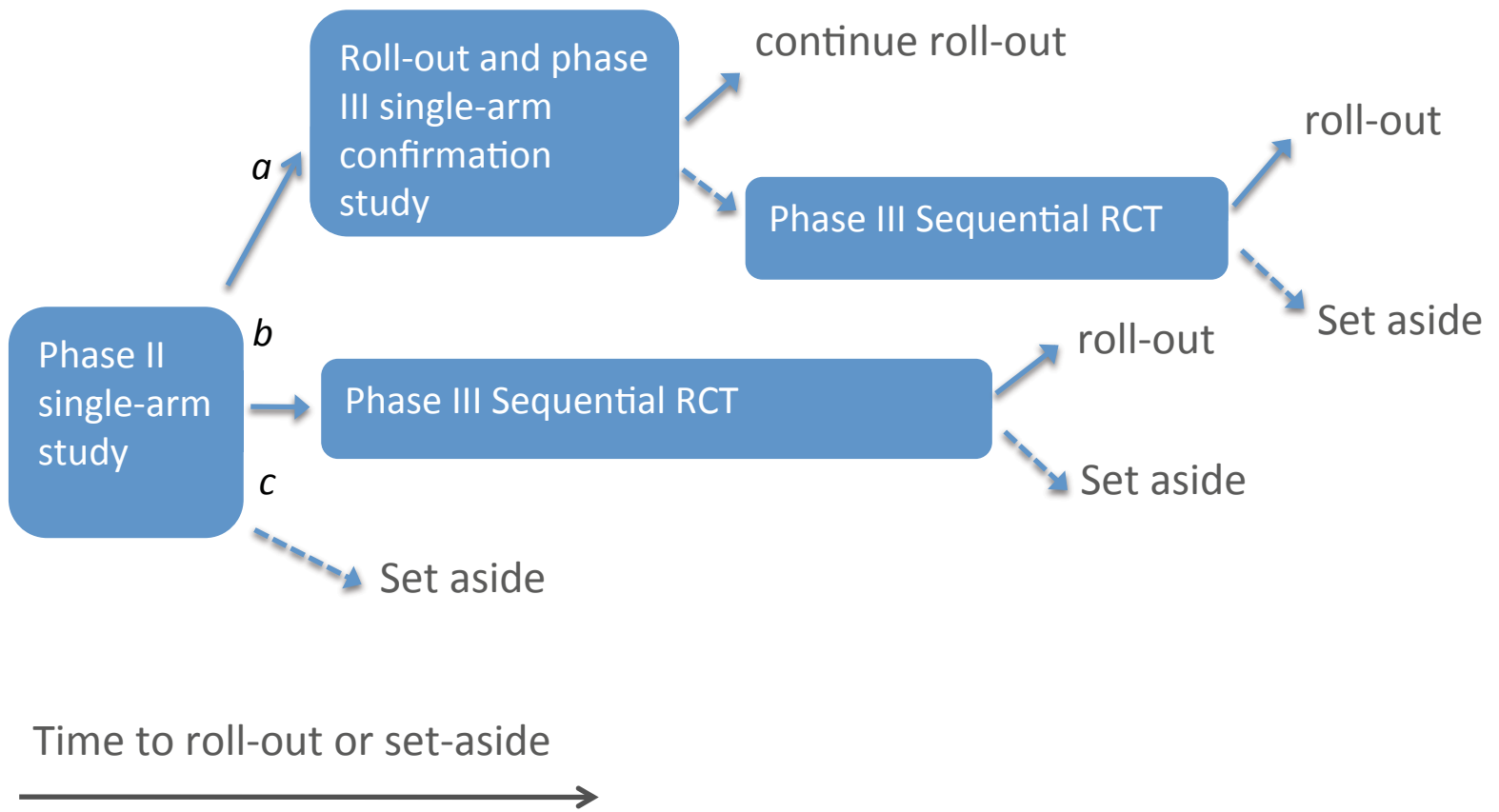
24 straight successes → (a)

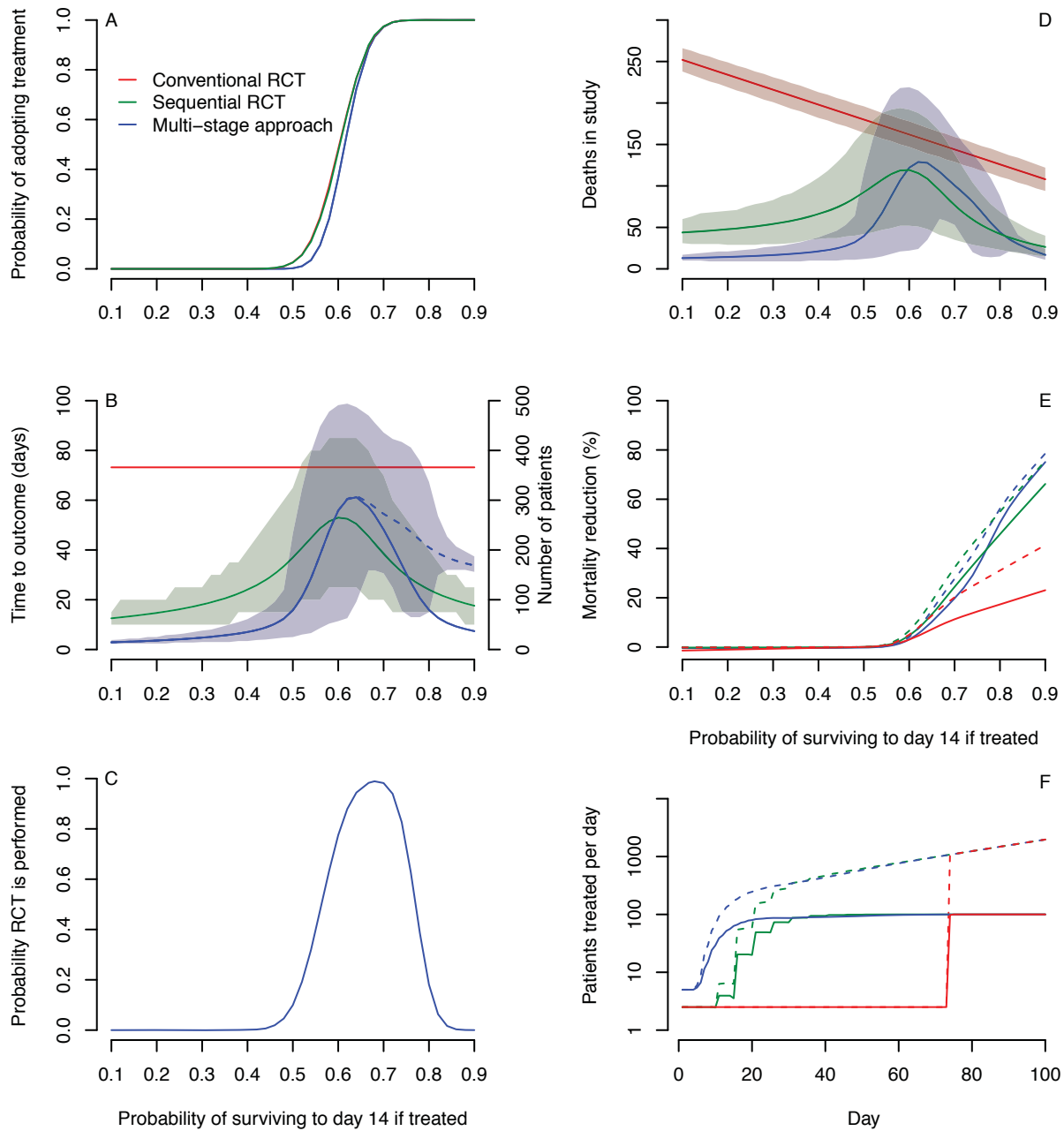
12 straight failures → (c)

Design 1. RCT without interim analysis

Design 2. Sequential RCT (up to 20 interim analyses)

Design 3. Multi-stage approach (MSA)





Cooper B et al. PLoS Med. 2015 Apr 14;12(4):e1001815.

Probabilities of reaching each conclusion for the phase II trial of treatment

Exact probabilities for Phase 2 with 140 cases

$p = \text{true probability of surviving for 14 days}$

p	description	Probability of reaching conclusion:		
		(a)	(b)	(c)
0.800	very effective	0.908	0.092	0.000
0.667	promising	0.034	0.950	0.016
0.500	ineffective	0.000	0.100	0.900

RAPIDE Rapid Assessment of Potential
Interventions & Drugs for Ebola

Brincidofovir trial

Government of Liberia

University of Liberia-Pacific Institute for Research and Evaluation



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Scientific Title	Open-label, non-randomised single arm trial to investigate the efficacy of Brincidofovir compared to historic controls or Ebolavirus Disease in an outbreak setting in West Africa
Clinical Phase	2
Trial Design	Open-label, non-randomised, single arm trial
Trial Participants	Patients with confirmed Ebolavirus disease attending the participating treatment centre
Planned Sample Size	Up to 140 adult participants, paediatric enrolment according to presentation over the same recruitment period
Investigational Medicinal Product	Brincidofovir (BCV)
Formulation, Dose, Route of Administration	Patients ≥ 50 kg: 200 mg initial dose, then 100 mg twice weekly for 4 doses Patients < 50 kg: 4mg/kg initial dose, then 2 mg/kg twice weekly for 4 doses
Treatment duration	2 weeks
Follow up duration	30 days follow-up

BUSINESS

Chimerix Scraps Testing of Experimental Ebola Drug in Liberia

Declining Ebola Infection Rate Contributed to Company's Decision

By **PETER LOFTUS**

Jan. 31, 2015 4:18 p.m. ET

Chimerix Inc. scrapped testing of its experimental antiviral in Ebola patients in Liberia, saying the number of infections had dropped in recent weeks, and that only a handful of patients had been enrolled in the Liberian study.

The abrupt reversal in Chimerix's plans could raise questions about whether the declining number of Ebola infections in West Africa could be a problem for other experimental drugs and vaccines currently undergoing testing in the region for safety and efficacy. The World Health Organization said this week the incidence of the deadly disease continues to fall in the three countries that were hardest hit last year—Guinea, Liberia and Sierra Leone.

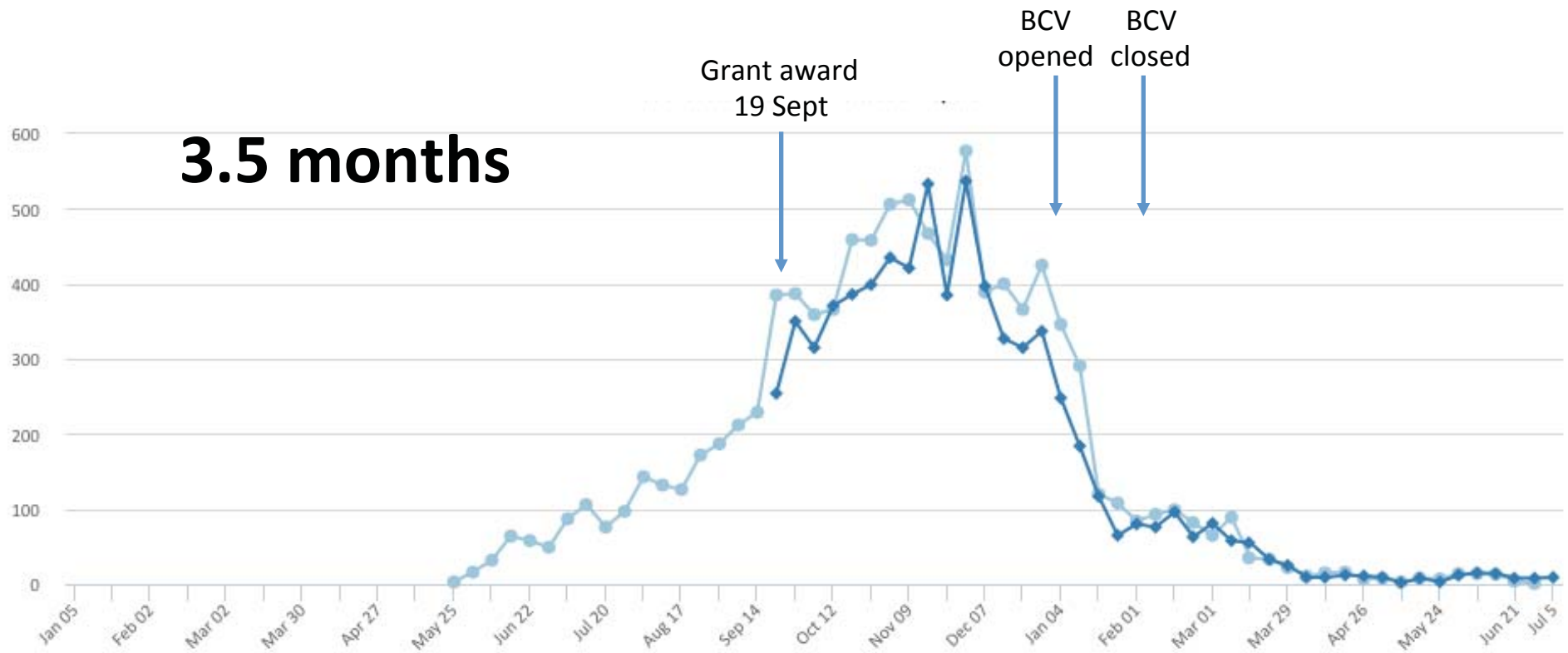
More than 22,000 people had been infected with Ebola and more than 8,800 had died as of Jan. 25, primarily in the three West African countries, according to WHO.

Chimerix, of Durham, N.C., said in a news release issued late Friday that after discussions with the U.S. Food and Drug Administration, the company “is ceasing further participation in all current and future clinical studies of brincidofovir” for Ebola virus disease. This includes a study in Liberia sponsored by the U.K.'s University of Oxford, which began in January.

Peter Horby, an Oxford researcher who was helping to run the study, said the decision to halt it “arose from bilateral discussions between Chimerix and the FDA.” He said he wasn't aware of any reasons for the decision beyond declining case numbers. An FDA representative couldn't immediately be reached.

The company said the number of new cases of confirmed Ebola virus disease in Liberia “has decreased significantly, with only a handful of patients enrolled to date” in the

Ebola trial timelines



RAPIDE Rapid Assessment of Potential
Interventions & Drugs for Ebola

TKM-Ebola-Guinea Trial

Government of Sierra Leone

College of Medicine and Allied Health Sciences, Sierra Leone



Public Health
England

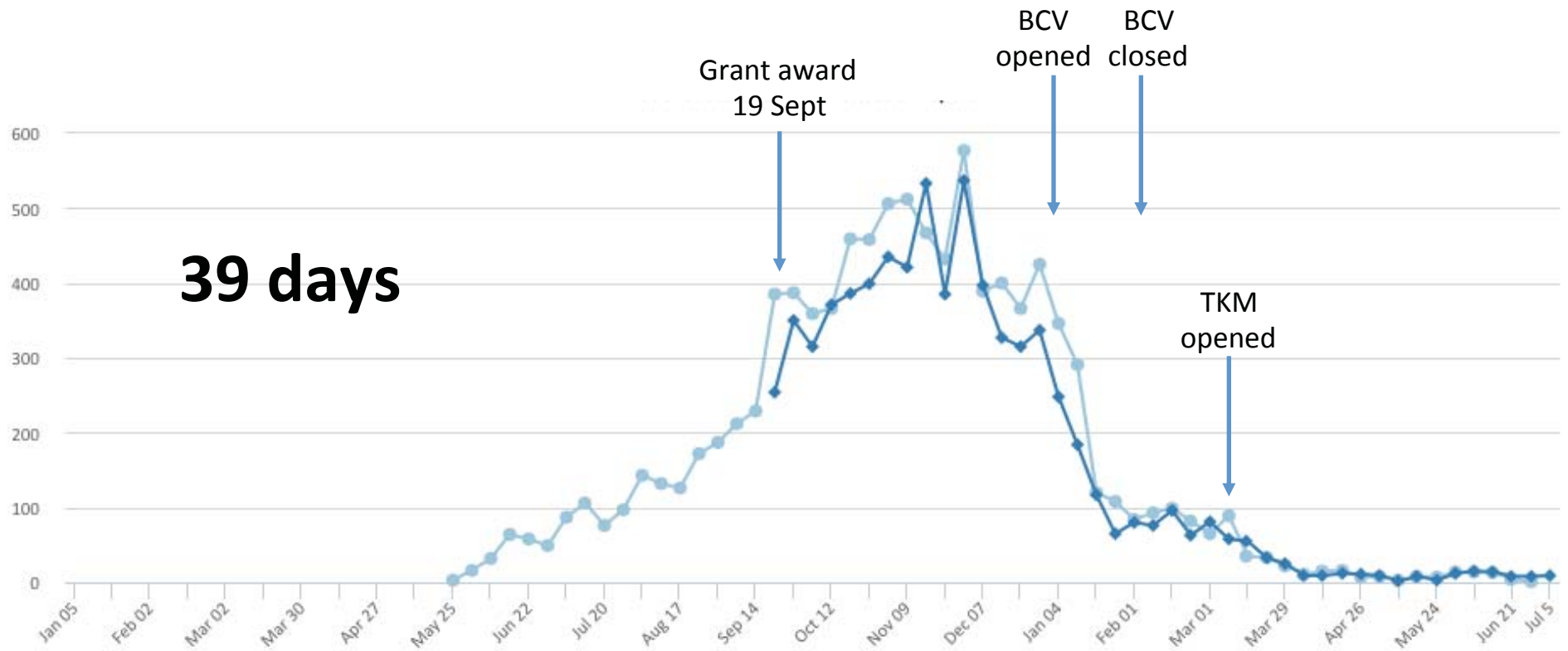


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Moving on quickly



siRNA Proof-of-Concept Non-Human Primates



THE LANCET

Postexposure protection of non-human primates against a lethal Ebola virus challenge with RNA interference: a proof-of-concept study

Thomas W Geisbert, Amy C H Lee, Marjorie Robbins*, Joan B Geisbert, Anna N Honko, Vandana Sood, Joshua C Johnson, Susan de Jong, Iran Tavakoli, Adam Judge, Lisa E Hensley, Ian MacLachlan*

Summary

Background We previously showed that small interfering RNAs (siRNAs) targeting the Zaire Ebola virus (ZEBOV) RNA polymerase L protein formulated in stable nucleic acid-lipid particles (SNALPs) completely protected guineapigs when administered shortly after a lethal ZEBOV challenge. Although rodent models of ZEBOV infection are useful for screening prospective countermeasures, they are frequently not useful for prediction of efficacy in the more stringent non-human primate models. We therefore assessed the efficacy of modified non-immunostimulatory siRNAs in a uniformly lethal non-human primate model of ZEBOV haemorrhagic fever.

Geisbert et al, Lancet 2010; 375: 1896-905

TKM-Ebola (TKM-100802) Anti-viral Efficacy

NHP Inoculated with Lethal Dose of Ebola Virus Zaire 1995 Kikwit Survival to Day 41

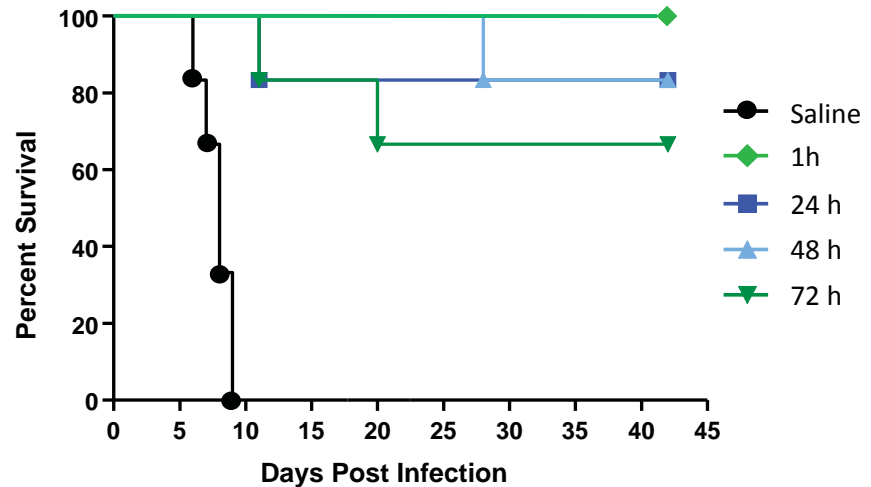
- Newer (2011) formulation lyophilized LNP protect 100% using a 4-fold lower dose than second generation LNP (1 h tx delay)
- 83% protection with delay of up to 48 h, 67% @ 72h.
- Significant survival advantage at 10 fold lower dose (67% @ 0.2 mg/kg).



X 7 daily doses



Rhesus Macaque



Product details: TKM-130803

- siRNA cocktail adjusted to Guinea strain
- Wet formulation
- IV once daily infusion over two hours
- Seven days treatment

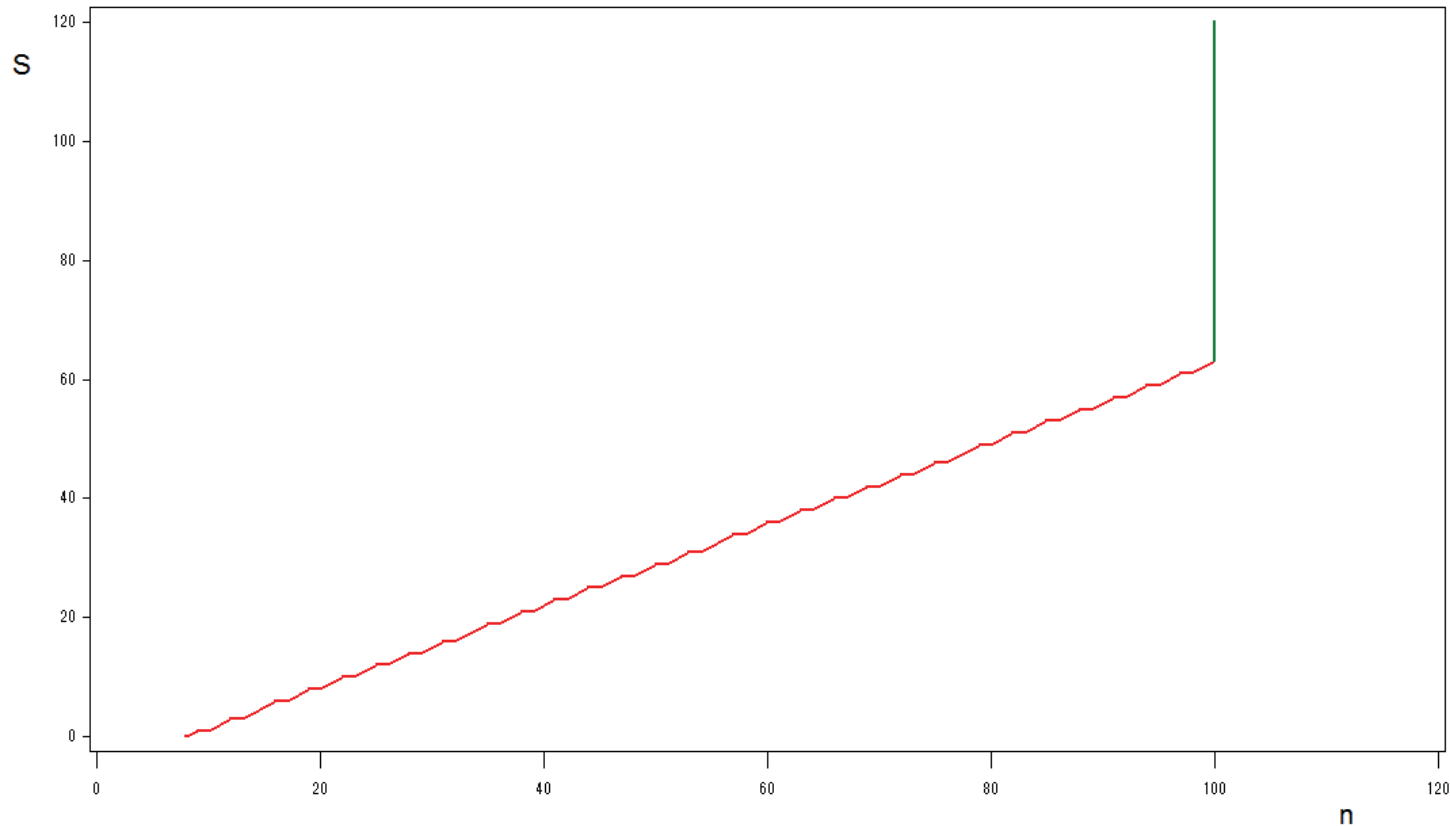


TKM-130803 trial constraints

- Limited supply: only 100 treatment courses available
- Limited cases: waning epidemic

- Sought to use all 100 available doses of experimental treatment if the accumulating results are favourable
- Futility stopping rule only

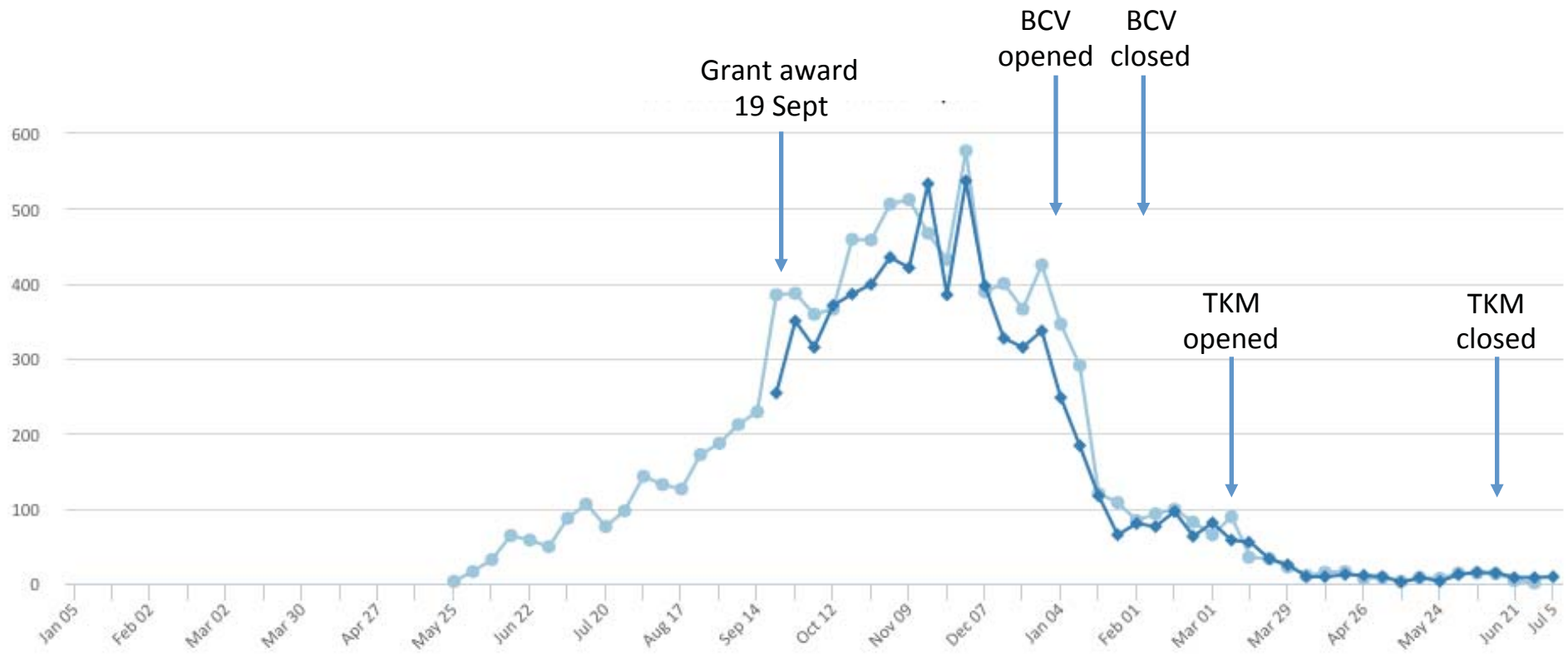
Stopping rule for futility or harm



The probability of declaring TKM to be promising with survival of 0.55 is set at 0.025. Recommending a treatment associated with such a probability of survival to D14 would be considered a type I error, and the risk of this has been set at the conventional value of 0.025. The power of correctly identifying TKM as promising when $p = 0.70$ is 0.827.

	Objectives	Outcome Measures
Primary	To evaluate the impact of TKM treatment on early mortality in EVD	Mortality at D14 (in those that survive first 48 hours after admission)
Secondary	<p>1. To evaluate the impact of TKM-130803 treatment for adults on:</p> <ul style="list-style-type: none"> a) Overall morality at D14 b) Time to recovery c) Late mortality d) Ct value and viral load e) EVD symptoms f) EVD antibody response g) Long term clinical recovery <p>2. i) To assess the safety of TKM treatment for adults.</p> <p>ii) To measure the pharmacokinetics (PK) of TKM following repeat dosing</p>	<p>1.</p> <ul style="list-style-type: none"> a) D14 mortality in all patients allocated to TKM-130803 treatment (not excluding deaths in first 48 hours). b) Time to meeting ETC discharge criteria. c) Mortality at D30 and months 3,6,12 after first dose of study treatment d) Ct value and viral load e) Presence and duration of symptoms (SDs 1-14) f) Convalescent anti-Ebolavirus IgG titer (D30) g) Clinical assessment at months 3,6,12. <p>2.i) Frequency of SARs, key adverse events (SDs 1-14) and monitoring of vital signs (pulse rate, blood pressure, respiratory rate, temperature) pre, during and at 0, 1, 2, 4 and 8 hours post end of infusion</p> <p>ii) PK pre-dose and at the end of infusion on SDs 1, 3, 5 and 7</p>

Ebola trial timelines



Lessons and challenges

- Clinical trials can be executed in a crisis
- European coordination was good
- Time is the biggest enemy
- Shifting epidemiology is a challenge
- Unfinished product pipeline was a hindrance:
 - Availability
 - Incomplete and evolving data
- Ethical framework is inadequate
 - Polarised views of what was ethical / unethical
 - Implications of acute high case fatality
 - Competing trials – no overarching perspective of ethics

Thank you

