Ebola R&D
Landscape of clinical candidates and trials

Public report
October, 2015

Preamble

As of September 2015, the devastating Ebola outbreak in West Africa has claimed the lives of more than 11,311 people[1]. This outbreak excessively strained the health systems of the affected nations and triggered a truly global response to tackle the epidemic. This response included a rapid scale-up of research and development efforts supported by significant investments from the private sector, governments and foundations, by innovation from regulators, and by researchers working in areas where the epidemic was raging . This R&D effort was made considerably more complicated by the complex and volatile nature of the epidemic. At its start 18 months ago, there were no licensed vaccines against Ebola, no treatments with proven efficacy in humans, and no diagnostics that met WHO's Target Product Profile for a rapid, simple Ebola Virus Disease (EVD) test. While this is still the case today, on all these fronts there has been significant progress and hope that a suite of approved and licensed products will be available in the future.

While efforts for effective vaccine, therapy and diagnostic solutions are still ongoing it is mission critical that scientists openly share, and promote sharing of, information regarding ongoing research activities so that everyone can benefit from the lessons learned (even from studies with negative results) and to reduce unnecessary duplication of effort. Publication of data and findings, in peer-reviewed journals, provides opportunities for further analysis and for determination of next steps. It is an obligation that we as scientists have: towards society, towards science and towards those individuals who volunteered in experimental studies in anticipation of contributing to reducing the burden of EVD.

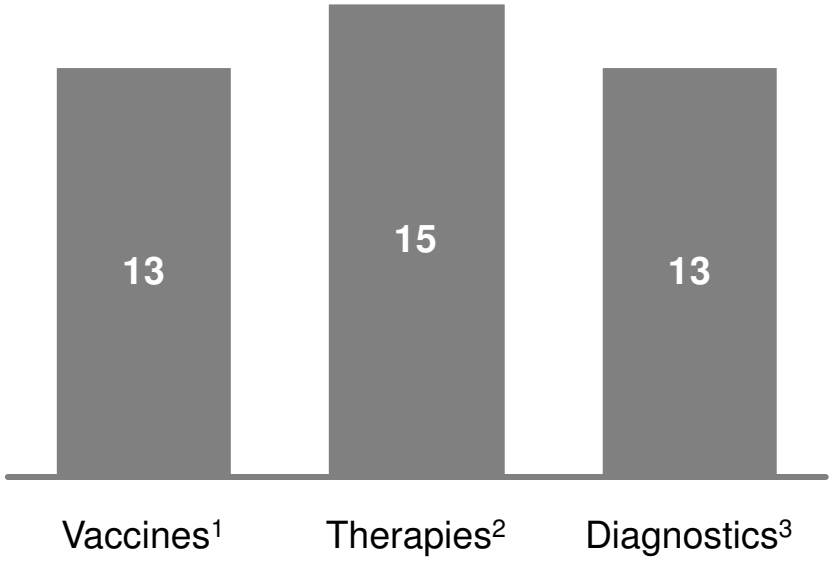
This report was commissioned by the Bill & Melinda Gates Foundation and the Foundation for the National Institutes of Health, with support from the Wellcome Trust and the WHO, following initial discussions at a meeting of the Heads of International Research Organizations (HIROs). This document is an attempt to capture a comprehensive compendium of current clinical activities to develop vaccines, therapies and diagnostics for EVD. The report is not intended to capture all the details of partnerships / grants for these activities. Nor is it meant to provide an assessment of effectiveness, safety or any other interpretation of research data. Such assessments are best left to the usual rigorous scientific review process. This report brings together information from public releases and clinical trial databases, as well as from interviews with more than 50 stakeholders from academic institutions, research organizations, private corporations, regulators and funders. We thank all those who have contributed by helping us compile this information and who have assured us that all information contained here-in is either publically available elsewhere and/or has been disclosed with explicit consent from authorized stakeholders.

Admittedly, the landscape of research is rapidly evolving. The first version of this report captures current information as of August / September 2015. We hope this information will be helpful to many and will trigger individuals and institutions to promote further transparency and sharing of results so that science, and humanity, can be the ultimate beneficiaries.

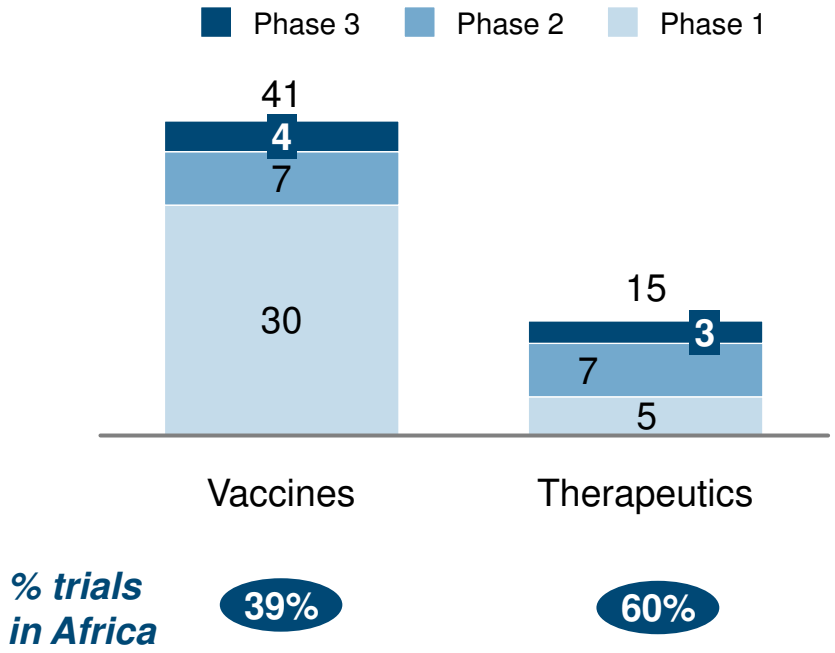
1 WHO Ebola Situation Report; latest data can be accessed at http://apps.who.int/ebola/ebola-situation-reports

High-level summary of Ebola clinical candidates during the 2014-2015 West African outbreak

Ebola vaccine, therapeutic, and diagnostic candidates in clinical development (2014-2015)



Clinical trials for Ebola vaccines and therapeutics[4] (2014-2015)



1 Considering different vaccine combinations/variants as distinct
2 Including therapies only given under compassionate use
3 Products that have received FDA or WHO emergency use listing; up to 80 are in some stage of development
4 Based on triangulation from public sources and stakeholder interviews. If a trial spans multiple phases or is unclassified, classification here is based on the highest phase or the trial's primary outcomes

SOURCE: Clinicaltrials.gov (September 2015), WHO ICTRP portal, Pan-African Trial Registry, Stakeholder interviews, WHO categorization of drugs for Ebola, WHO Diagnostics, FDA Emergency Use Authorizations

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Guide to categories for clinical-stage vaccines

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Category	Vaccine	Manufacturer	Pages
A Vaccines with post-Ph. 1 trials	▪ ChAd3-EBOZ (monovalent)	▪ GSK	5-7
	▪ rVSV-ZEBOV	▪ Merck	
	▪ Ad26.ZEBOV + MVA-BN-Filo	▪ Janssen ▪ Bavarian Nordic	
B Alternative vaccine variants in Phase 1 trials	▪ ChAd3-EBOZ + MVA-EBOZ-EM	▪ GSK ▪ Emergent BioSolutions	8-9
	▪ ChAd3-EBOZ +MVA-BN-Filo	▪ GSK ▪ Bavarian Nordic	
	▪ ChAd3-EBO (bivalent)	▪ Okairos[1]/National Institutes of Health (NIH)	
	▪ ChAd3-EBO (bivalent) + MVA-EBOZ-IDT	▪ Okairos[1]/NIH ▪ IDT Biologika on behalf of NIH	
	▪ ChAd3-EBOZ + Ad26.ZEBOV	▪ GSK, Janssen	
C Other novel vaccines with planned, ongoing or completed Ph 1	▪ EBOV GP	▪ Novavax	10-11
	▪ rVSVN4CT1-EBOV GP	▪ Profectus	
	▪ rVSVN4CT1-EBOV-SUDV-MARV	▪ Profectus	
	▪ Ad5-EBOV	▪ Beijing Institute of Biotechnology, Tianjin Cansino Biotech	
	▪ INO-4212	▪ Inovio	

1 Subsequently acquired by GSK

PRELIMINARY

Summary of candidate information for vaccines that have progressed past Phase 1 trials

Vaccine candidates	*Highest pre-clin. evidence*	*Early clinical evidence*	*Latest trials (next pg)* [4]
ChAd3-EBOZ	▪ 100% effective in 1 published NHP challenge study (n=8) [a]	▪ A published Phase 1 trial (n=60) in U.K [b] – No SAEs – Fever in 3% of vaccinees, resolved next day – 235-469 GMT[1] ▪ Two additional Phase 1 trials with unpublished data in Mali (n=91), US (n=20), and one Phase 1/2 in Switzerland (n=120) [c]	▪ Three ongoing/near-term Ph. 2 and/or 3 trials in W. Africa
rVSV-ZEBOV	▪ 100% effective in 4 published NHP challenge studies (total n=37) [d,e,f,g]	▪ Two phase 1 trials in U.S. (n=40) published [h] – No SAEs – Fever in 30% of vaccinees, resolved next day – 1300-4079 GMT[2] ▪ Four additional phase 1 trials in Europe and Africa (n=138) published [i] – No SAEs – Fever in 20% of total vaccines – 13 cases of arthritis – 1056-1970 GMT[3] ▪ Two additional phase 1 trials that have not been published	▪ Four[5] ongoing Ph 2 and/or 3 trials in W. Africa. ▪ Published interim results from ring vaccination [j]: – 100% efficacy (p=0.0036) – Possibly 1 vaccine-related SAE, to be confirmed
Ad26. ZEBOV + MVA-BN-Filo	▪ 100% effective in company-publicized NHP challenge study (n=8) [l]. Manuscript submitted	▪ One Phase 1 trial (n=87) in U.K. has completed enrollment and manuscript is being finalized. Company-publicized interim analysis: [l] – 3 groups receiving Ad26 as prime + MVA as boost; 2 groups receiving MVA as prime and Ad26 as boost – No vaccine related SAEs – Objective fever in 3 subjects (2 vaccinated,1 placebo), resolved next day – "robust" antibody response post Ad26 prime (97% responders at D28) further enhanced by boosting: 4274-10573 GMT[6] ▪ One Ph 1 trial in US (n=128) completed enrollment, manuscript being prepared ▪ Two additional ongoing Phase 1 trials in Kenya & Ghana[7] (n=84), Uganda & Tanzania (n=72)	▪ Two ongoing/near-term Ph.2 trials in Europe and Africa ▪ One multi-stage Ph. 3 trial planned in Sierra Leone

NOTE - Different ELISA methods and reporting units have been used for the different vaccines hence the GMT numbers are not "readily" comparable. Taking this into account D28 immunogenicity after 1 dose of rVSV-ZEBOV and ChAd3-ZEBOV are similar

1 GMT of IgG responses at day 28 against EBOV GP using EC90 end-point titration ELISA, after subtraction of prevaccination responses, differs by treatment groups

2 Geometric mean titer of IgG responses at day 28 against Zaire-Kikwit GP using ELISA, differs by treatment groups

3 Geometric mean titer of antibody response at day 28 against ZEBOV GP using ELISA, differs by treatment groups

4 As these candidates are already in Ph. 2, ongoing Ph. 1 trials are not shown in detail; 5 The Guinea trial has two components; these are shown separately on the next page; 6 Geometric mean titer of IgG responses against EBOV GP corresponding to Day 28 schedule; 7 Pending approval in Ghana, Kenya completed enrollment (n=72)

SOURCE: Clinicaltrials.gov, Pan African Clinical Trials Registry (PACTR), Published academic studies, Public releases, stakeholder interviews

VACCINES A

Summary of latest clinical trials for candidates in post-Ph. 1 (1/2)

PRELIMINARY

Original Design

Revised Design

	Trial Description, Short-hand name	Design	Popul a-tion	Location	Phase	Start date	End date[1]	Goal enroll.[2]	Current enroll[2]/ date	Trial Status	Publication Status[3]
ChAd3-EBOZ (mono-valent)	Safety and Immunogenicity in Adults	▪ Randomized, double-blind ▪ Immediate vs. placebo + delayed (6 mo) vaccination	Adults	West Africa[4]	2	Jul 2015	Oct 2016	3,000		Currently recruiting	Intend to publish[5]
	Safety and immunogenicity in pediatrics	▪ Randomized, observer blind[6] ▪ Immediate Vx + Placebo (Meningococcal Vx) at 6 mo vs. Immediate placebo + Vx at mo. 6	Childre n	West Africa[7]	2	Oct 2015	Mar 2017	600		Not yet recruiting	Intend to publish[5]
Multiple vaccines	Safety, immunogenicity, and efficacy (PREVAIL I)	▪ Randomized , double-blind ▪ Placebo: 2 treatment arms (ChAd3-EBOZ or rVSV-ZEBOV), 1 placebo arm ▪ Ph. 2 includes close monitoring	Adults	Liberia	2	Feb 2015	Apr 2016	1500 600		Enrollment complete	Intend to publish
rVSV-ZEBOV	Efficacy and safety (Ring vaccination)	▪ Cluster-randomized, open label ▪ Vaccinees are “rings” (contacts/contacts-of-contacts) of confirmed Ebola cases ▪ Immediate vs. delayed (21 days) vaccination	Adults	Guinea	3	Mar 2015	Feb 2016	10,000	>7651 *As of Jul 20*	Currently recruiting	Methods and interim results published Jul. 2015 [j, k]
	Safety and Immunogenicity (in front-line workers, part of above trial)	▪ Non-random, open-label ▪ Single arm receiving vaccine	Adults	Guinea	2	Mar 2015	Feb 2016	1,200[8]	1200 *Aug 21*	Currently recruiting	Plan to publish when follow-up complete
	Efficacy, safety, & immunogenicity (STRIVE)	▪ Randomized, open-label ▪ Immediate vs. delayed (18-24 weeks) vaccination ▪ Safety sub-study in approx. 400 subjects ▪ Immunogenicity sub-study in approx. 500 subjects	Adults	Sierra Leone	2/3	Apr 2015	Jun 2016	10,000 6,000	>8500 *As of Sep 4*	Currently recruiting; main trial enrollment completed Aug.	Intend to publish
	Safety & immunogenicity of 3 consistency lots and a high-dose lot	▪ Randomized, double-blind ▪ 5 arms: 1 for each of the 3 consistency lots of Vx, 1 high-dose lot of Vx, 1 placebo	Adults	U.S., Canada, U.K., Spain,	3	Aug 2015	Jun 2016	1,125	1125 *As of Sep 18*	Currently recruiting	Intend to publish

1 Final data collection for primary outcome; 2 Total enrollment in all arms of study; 3 In a peer-reviewed journal
4 Approved in Senegal, Mali, Nigeria, and seeking approvals in Cameroon, Ghana; 5 The publication steering committee will decide on scope and timelines of all publications derived from these studies in early 2016; 6 until interim analysis; 7 Planned for Mali, Senegal, Ghana, Cameroon, Nigeria; 8 Additional 2,000 volunteers to be included for the safety database

SOURCE: Clinicaltrials.gov, PACTR, Stakeholder interviews; public releases

VACCINES A

Summary of latest clinical trials for candidates in post-Ph. 1 (2/2)

PRELIMINARY

Original Design

Revised Design

	Trial Description, Short-hand name	Design	Popula-tion	Location	Pha-se	Start date	End date[1]	Goal enroll.[2]	Current enroll[2]/ date	Trial Status	Publication Status[3]
Ad26. ZEBOV + MVA-BN-Filo	Safety, Tolerability, and Immunogenicity	▪ Randomized, observer-blind ▪ Receive Ad26.Ebov or placebo, followed by MVA-BN-Filo or placebo ▪ Three groups (different timings for the second shot)	Adults	U.K. France	2	July 2015	July 2016	612	TBD *TBD*	Currently recruiting in UK	Intend to publish
	Safety, Tolerability, and Immunogenicity	▪ Randomized, observer-blind ▪ Receive Ad26.Ebov or placebo, followed by MVA-BN-Filo or placebo ▪ Healthy adults and elderly population divided into three groups (different timings for the second shot) ▪ Children and HIV+ subjects divided into 2 groups ▪ Staggered enrollment of special populations	Adults (incl. HIV+ subjects) and children	Ivory Coast, Burkina Faso, Kenya, Uganda, Ghana Rwanda	2	Oct 2015[4]	Aug 2016 (adults only)	1,188	0 *Sep 25*	Not yet recruiting	Intend to publish
	Safety, immunogenicity, and efficacy (in stages) (EBOVAC-Salone)	▪ Open-label. An IDMC will give guidance on advancing through groups and stages ▪ Stage 1 + 2a: single arm receiving vaccine. ▪ Stage 2b: Extended safety & immunogenicity—design TBD	Adults only (stage 1); Adults & children (stages 2a,2b)	Sierra Leone	2	Sep 2015[4]	Aug 2017	440[5] TBD[6]	0 *Sep 25*	Not yet recruiting	Intend to publish
		▪ Open-label, cluster randomized ▪ This portion of trial depends on outbreak status and is currently on hold	Adults & children	Sierra Leone	3	TBD	TBD	TBD	0 *Sep 25*	Not yet recruiting	Intend to publish, if this stage occurs

1 Final data collection for primary outcome
2 Total enrollment in all arms of study
3 In a peer-reviewed journal
4 Pending Regulatory Approval
5 For stage 1+2a
6 For stage 2b

SOURCE: Clinicaltrials.gov, PACTR, Stakeholder interviews; public releases

PRELIMINARY

Summary of candidate information for alternative vaccine variants in Ph 1 clinical trials

Vaccine+ Boost Candidate	*Highest pre-clinical evidence*	*Early clinical evidence*	*Latest trials (next pg)*
ChAd3-EBOZ + MVA-EBOZ-EM	▪ Vaccine and MVA boost 100% effective in 1 published NHP study (n=4) using researcher-produced MVA[1] [a]	▪ No completed studies	▪ Two Ph. 1s ongoing
ChAd3-EBOZ +MVA-BN-Filo		▪ No completed studies	▪ Two Ph. 1s ongoing
ChAd3-EBO (bivalent)	▪ Unboosted bivalent vaccine 50% or 100% effective (depending on dose range, total n=8) in 1 published NHP study [a]	▪ One published preliminary report (n=20) of an ongoing Ph. 1 trial in U.S. [m] – No SAEs – Fever in 2 pts, resolved by next day – 331-2037 GMT[2]	▪ Two Ph. 1s ongoing
ChAd3-EBO (bivalent) + MVA-EBOZ-IDT			▪ Two Ph. 1s ongoing
ChAd3-EBOZ + Ad26.ZEBOV	▪ Two vaccines have been studied separately, but not as a booster combination	▪ No completed studies	▪ One Ph. 1 ongoing

1 MVA used in this study is similar to the manufactured MVA products, but not identical
2 Geometric mean titer of antibody response to Zaire GP at 4 weeks using ELISA, number differs by treatment groups

SOURCE: Clinicaltrials.gov, Pan African Clinical Trials Registry (PACTR), Published academic studies, Public releases

VACCINES B

Summary of latest clinical trials for alternative vaccine variants in Ph 1 clinical trials

PRELIMINARY

Original Design

Revised Design

	Trial Description	Design	Popula-tion	Location	Phase	Start date	End date[1]	Goal enroll.[2]	Trial Status	Publication Status[3]
ChAd3-EBOZ + MVA-EBOZ-EM	Safety and immunogenicity	▪ Non-random, open-label ▪ 1 group receives MVA-EBOZ only (two dose levels) ▪ 3 groups receive ChAd3-EBOZ followed by MVA-EBOZ (different timings)	Adults	U.K.	1a	Apr 2015	Oct 2015	38	Enrollment complete Sep. 2015	Manuscript under development
	Safety and immunogenicity	▪ Randomized, open-label ▪ 2 groups: both receive ChAd3-EBOZ + MVA-EBOZ a week later, but vaccine administered differently	Adults	Senegal	1b	July 2015	Jan 2016	40	Enrollment complete	Manuscript under development
ChAd3-EBOZ + MVA-BN-Filo	Dose-escalating safety & immunogenicity	▪ Non-random, open-label ▪ 7 groups: different dosage levels and timings ▪ In 3 of these groups, a subset receive ChAd3-EBOZ only (no boost)	Adults	U.K.	1a	Sep 2014	Dec 2015	92	Enrollment complete Sep. 2015	Prelim. Results submitted
	Dose-escalating safety & immunogenicity (sub-study[4])	▪ Randomized, double-blind ▪ 2 groups: following ChAd3-EBOZ, participants received MVA-BN-Filo or placebo	Adults	Mali	1b	Oct 2014	Sep 2015	52	Enrollment complete	Submitted
ChAd3-EBO (bivalent)[5]	Dose-escalating safety, tolerability, and immunogenicity	▪ Non-random, open-label ▪ Part 1: 2 dosage groups of bivalent vaccine ▪ Part 2: 1 group receives high-dose bivalent Vx, 1 dose receives monovalent Vx (randomized dosage level), 2 group (from a prior trial) receive bivalent Vx boost	Adults	U.S	1/1b	Aug 2014	Dec 2015	150	Enrollment complete	Prelim. Report published [m]; final report under development (NEJM)
	Safety, tolerability, and immunogenicity	▪ Randomized, open-label ▪ 1 group with: 2 subgroups receiving monovalent Vx and 2 subgroups receiving bivalent Vx ▪ 1 group (from a prior trial) receive bivalent Vx	Adults	Uganda	1b	Jan 2015	July 2016	90	Enrollment complete	Intend to publish
ChAd3-EBO (bivalent) + MVA-EBOZ-IDT	Dose, safety, and immunogenicity	▪ Randomized, open-label ▪ 7 groups: 2 receive MVA-EbolaZ only, 1 receives ChAd3-EBO +MVA-Ebola Z, 4 receive MVA-Ebola Z (and received ChAd3-EBO or –EBOZ in a prior trial)	Adults	U.S	1/1b	Mar 2015	Dec 2016	160	Currently recruiting	Intend to publish
	Safety, tolerability, and immunogenicity	▪ Randomized, Double-blind ▪ All receive ChAd3-EBO (either low or high dose), followed by either MVA-EBOZ-IDT or placebo	Adults	Mali	1b	Mar 2015	Jan 2016	60	Enrollment complete	Manuscript under development
ChAd3-EBOZ + Ad26.ZEBOV	Safety and immunogenicity	▪ Randomized, open-label ▪ 2 groups receive ChAd3-EBOZ, then Ad26.ZEBOV ▪ 2 groups receive Ad26.ZEBOV, then ChAd3-EBOZ	Adults	U.K	1	July 2015	Apr 2016	32	Currently recruiting	Intend to publish

1 Final data collection for primary outcome; 2 Total enrollment in all arms of study; 3 In a peer reviewed journal;4 Sub-study here is part of larger Ph. 1 study (n=91) for ChAd3-EBOZ; 5 Trials also tested the monovalent ChAd3-EBOZ

SOURCE: Clinicaltrials.gov, PACTR, Stakeholder interviews; public releases

PRELIMINARY

Summary of other novel vaccines with planned, ongoing or completed Phase 1 studies

Vaccine Candidate	*Highest pre-clinical evidence*	*Early clinical evidence*	*Latest trials (next pg)*
EBOV GP	▪ 100% effective in company-publicized studies: 3 in NHP, (n=11) with full lethal controls; one in mice (n=9) [n,o]	▪ One ongoing Ph. 1 trial has in company-publicized top-line results [p]: – Well-tolerated – highly immunogenic	▪ One Ph. 1 trial ongoing
rVSVN4CT1-EBOV GP	▪ 100% effective in published NHP study (n=4) [q]	▪ No completed Ph. 1	▪ One Ph.1 trial planned
rVSVN4CT1-EBOV-SUDV-MARV	▪ 100% effective in company-publicized NHP study (n=10 challenged with Ebola)	▪ No completed Ph. 1	▪ One Ph.1 trial planned
Ad5-EBOV	▪ 100% effective in unpublished guinea pig study [r] ▪ 100% protective (IM) in NHP challenge study (July 2015) - 2 dose ranges and 2 route of admin – IM and intranasal); Manuscript being prepared	▪ Ph. 1 trial with completed enrollment in China, Published prelim. results (n=120) [r]: – No SAEs – 18% had mild fever – 683-1306 GMT[1]	▪ Two Ph. 1 trials completed ▪ One ongoing Ph. 1 trial for boost regimen ▪ One Ph. 2 planned
INO-4212	▪ 100% effective in published study in protecting guinea pigs (n=15) and mice (n=10) [s] ▪ Unpublished ongoing NHP challenge study	▪ No completed Ph. 1	▪ One Ph. 1 initiated May 2015

1 Antibody responses to Zaire strain glycoprotein, as measured as Geometric Mean Titers, at day 28, by ELISA; number varies by dose groups

SOURCE: Clinicaltrials.gov, Published academic studies, Public releases

Summary of latest trials for other novel vaccines

PRELIMINARY

Original Design

Revised Design

	Trial Description	Design	Popula-tion	Location	Pha-se	Start date	End date[1]	Goal enroll.[2]	Trial Status	Current enroll.[2]	Publication Status[3]
EBOV GP	Immunogenicity and safety	▪ Randomized, observer-blind ▪ 13 study arms, spanning different dosing, adjuvant, and placebo combinations	Adults	Australia	1	Feb 2015	Apr 2016	230	Enrollment complete	230 *Final Count*	TBD
rVSVN4CT1-EBOV GP	Safety, tolerability, and immunogenicity	▪ Randomized, double-blind ▪ 3 dose-escalating cohorts each with an active and a placebo arm ▪ Receive one shot and another at 28 days	Adults	U.S.	1	Nov 2015	Jan 2016	39	Not yet recruiting	0 *Aug 31*	Intend to publish
rVSVN4CT1-EBOV-SUDV-MARV	Safety, tolerability, and immunogenicity	▪ Randomized, double-blind ▪ 3 dose-escalating cohorts each with an active and a placebo arm ▪ Receive one shot and another at 28 days	Adults	U.S.	1	Mar 2016	June 2016	39	Not yet recruiting	0 *Aug 31*	Intend to publish
Ad5-EBOV	Safety, tolerability, and immunogenicity	▪ Randomized, double-blind ▪ 2 groups: 1 for low-dose vaccine, 1 for high-dose ▪ In each group, 40 receive vaccine, 20 receive placebo	Adults	China	1	Dec 2014	Feb 2015	120	Complete	120 *Final Count*	Prelim. Results published Mar 2015 [r]
	Safety and immunogenicity	▪ Randomized, double-blind ▪ Participants in above trial receive a second shot (as a booster) of what they previously received	Adults	China	1	Aug 2015	Nov 2015	120	Currently recruiting	110 *Aug 20*	Intend to publish
	Safety, side-effect profile, immunogenicity	▪ Non-randomized, open label ▪ 2 groups: 1 for low-dose vaccine, 1 for high-dose ▪ No placebo	Adults	China	1	Mar 2015	July 2015	61	Complete	61 *Final Count*	Intend to publish
	Extended safety and immunogenicity	▪ Randomized, double-blind ▪ 3 groups: 1 receive high dose Vx, 1 receive low-dose Vx, 1 receives placebo	Adults	Sierra Leone	2	Oct 2015	July 2016	600 (pending finalization)	Ethics committee approved; pending regulatory approval	0 *Aug 20*	Intend to publish
INO-4212	Safety, tolerability and immunogenicity	▪ Non-randomized, open-label ▪ 5 groups: 1 receiving INO-4212, 3 receiving INO-4201 or INO-4202 (the components of INO-4212) – Intramuscular and Inter-dermal, 1 receiving INO-4212 and INO-9012 as immune response boost ▪ All receive electroporation after Vx	Adults	U.S.	1	May 2015	Dec 2016	75	Currently recruiting	TBD	Intend to publish

1 Final data collection for primary outcome; 2 Total enrollment in all arms of study; 3 In a peer reviewed journal

SOURCE: Clinicaltrials.gov; public releases, stakeholder interviews

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Guide to categories for clinical-stage therapies

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Category	Treatment	Manufacturer	Pages
D **Therapies with recent formal trials examining efficacy**	▪ ZMapp	▪ Mapp Biopharmaceutical	14-16
	▪ Favipiravir (Avigan)	▪ Toyama Chemical (subsidiary of Fujifilm)	
	▪ TKM-130803	▪ Tekmira	
	▪ Brincidofovir	▪ Chimerix	
	▪ Convalescent Plasma	▪ N/A—not a commercialized product ▪ Cerus Corp.'s INTERCEPT system[2] used in 3 trials	
	▪ Convalescent Blood	▪ N/A--not a commercialized product	
	▪ Interferon beta 1a	▪ Several[1]	
E **Therapies with Ph. 1 trials for the goal of treating Ebola**	▪ BCX4430	▪ Biocryst	17-18
	▪ MIL77	▪ Institute of Basic Medical Sciences (IBMS) & MabWorks	
F **Therapies that have been given to humans outside of formal trials**	▪ Amiodarone	▪ N/A—generic	19
	▪ Artesunate-amodiaquine	▪ N/A—generic	
	▪ Atorvastatin + irbesartan (+/- clomifene)	▪ N/A—generic	
	▪ FX06	▪ F4 Pharma	
	▪ ZMAb	▪ Defyrus	
	▪ Lamivudine	▪ N/A—generic[3]	

1 Product used in trial donated from Biogen; 2 Licensed in U.S. and Europe for acquired coagulopathy; 3 marketed as Epivir in the U.S. by GSK
NOTE: Information for earlier-stage candidates can be found at: http://www.who.int/medicines/ebola-treatment/cat_prioritization_drugs_testing/en/

PRELIMINARY

Summary of candidate information for therapies/procedures in trials examining efficacy

	Highest pre-clinical evidence	*Early clinical evidence*	*Latest trials (next page)* [1]
ZMapp	▪ 100% survival in one published NHP study (n=18) [t]	▪ Ph. 1 in healthy volunteers planned but not yet started	▪ One clinical endpoint study ongoing
Favipiravir	▪ 100%[2] survival in mice (n=11) [u,v]	▪ No Ph. 1 for goal of treating Ebola ▪ Phase 1 and 2 studies for influenza – Safe and well tolerated – Statistically and clinically beneficial effect on influenza symptoms and cessation of viral shedding	▪ One Ph. 2 trial ongoing. Informally shared interim results (Feb. 2015, n=80) show [w,x] – Unlikely to be effective in patients who start treatment with very high viral load (CT<20) – Possible efficacy for patients who begin treatment with CT ≥20
TKM-130803	▪ siRNA has 67 or 100% survival in NHP (n=10)[3] [y, z]	▪ Incomplete safety assessment in healthy subjects ▪ Ph. 1 (using different formulation, TKM-100802) terminated, results not published	▪ One Ph. 2 trial has completed enrollment
Brincidofovir	▪ No animal studies. Company-publicized in vitro activity against Ebola [aa]	▪ No Ph. 1 for goal of treating Ebola ▪ Studied for other indications, some gastrointestinal side effects	▪ One Ph. 2 trial was stopped
Convalescent plasma (CP)	▪ Although human plasma hasn't been studied, related studies show: – 100% in NHP (n=3), using igG[4] [ab] – 0% in NHP (n=4) using whole blood transfusion[ac]	▪ No completed Ph. 1 for goal of treating Ebola ▪ Safely used to treat other diseases in past 50 years ▪ 8 patients received whole blood transfusion in published informal study, 7 survived [ad] ▪ One patient received human sera (and interferon) in published informal study and survived [ae]	▪ One Ph. 2/3 CP trial ongoing in Sierra Leone ▪ One Ph 2/3 trial in Guinea – enrollment stopped ▪ One Ph. 1/2 trial of CP with enrollment paused in Liberia ▪ One Ph. 2 trial of CP ongoing in U.S.
Convalescent blood			▪ One unclassified trial of whole blood
Interferon beta 1a	▪ Published NHP study shows significantly delayed death (0% survival) [af]	▪ No Ph. 1 for goal of treating Ebola ▪ Approved for other indications ▪ One patient received interferon (and human sera) in published informal study and survived [ae]	▪ One Ph 1/2 ongoing

1 As these candidates are in efficacy trials, Ph. 1 trials are not shown in detail; 2 If administered within 6 days post-infection; 3 Survival differed by study groups (different number of treatments); 4 study used IgG (post-fractionation), human plasma has not been studied in NHP;
SOURCE: Clinicaltrials.gov, Pan African Clinical Trials Registry (PACTR), Published academic studies, Public releases

Summary of clinical trials examining efficacy (1/2)

PRELIMINARY

Original Design

Revised Design

	Trial Description	Design	Popula-tion	Location	Phase	Viral load[1]	Start date	End date[2]	Goal enroll.[3]	Current enroll[3]/ date	Trial Status	Publication Status[4]
ZMapp	Safety and efficacy study (PREVAIL II)	▪ Randomized, open-label ▪ 2 arms: ZMapp+optimized Std of Care vs. oSOC only ▪ oSOC includes Favipiravir in Guinea	Adults & children	U.S., Liberia, Sierra Leone, Guinea[5]	Clinical end-point study	✓[6]	Feb 2015	TBD[7]	200[8]	~60 *Aug 01*	Currently recruiting	Intend to publish (once study completes)
Favi-piravir	Safety and efficacy in reducing mortality (JIKI)	▪ Non-random, open-label ▪ Single arm, historical controls	Adults & children	Guinea	2	✓	Dec 2014	Jun 2015 *(estimated[9])*	225[9]	126 *Aug '15*	Enrollment ongoing[9]	Intend to publish
TKM-130803	Safety and efficacy (RADIPE-TKM)	▪ Part of a multi-Stage trial design with boundaries based on historical / contemporary controls with results guiding subsequent trial design ▪ Non-random, open-label ▪ Single arm, historical controls	Adults	Sierra Leone	2	✓	Mar 2015	Jun 2015	upto 100	TBD *Final*	Trial completed Jun 2015 (reached statistical endpoint)	Submitted
Brinci-dofovir	Safety and efficacy (RAPIDE-BCV)	▪ Part of a multi-Stage trial design with boundaries based on historical / contemporary controls with results guiding subsequent trial design ▪ Non-random, open-label ▪ Single arm, historical controls	Adults & children	Liberia	2	✓	Jan 2015	Jan 2015	140	4 *Final*	Trial stopped (manu-facturer withdrew) Jan 2015	Submitted

1 Viral load is an outcome; 2 Final data collection for primary outcome; 3 Total enrollment in all arms of study; 4 In a peer reviewed journal; 5 Study began in Guinea in July 2015 with Guinean MoH and INSERM as new partners; 6 Viral load may be tested but not required; 7 will enroll until DSMB advises to stop; 8 No fixed original goal enrollment, as study design is adaptive; 9 Clinicaltrials.gov accessed Oct 21

SOURCE: Clinicaltrials.gov, PACTR, Stakeholder interviews; public releases

Summary of clinical trials examining efficacy (2/2)

PRELIMINARY

Original Design

Revised Design

	Trial Description	Design	Popula-tion	Location	Phase	Viral load[1]	Start date	End date[2]	Goal enroll.[3]	Current enroll[3]/ date	Trial Status	Publication Status[4]
Convale-scent plasma (CP)	Safety and efficacy of CP for early EVD in Sierra Leone	▪ Non-random (based on CP availability), open-label ▪ 2 arms: Control is crystalloid infusion	Adults & children	Sierra Leone	2/3	✓	Mar 2015	After out-break end	130[5] 300	4 *Aug 7*	Currently recruiting	Manuscript under development
	Safety and efficacy of CP for EVD in Guinea	▪ Non-random (based on CP availability), open-label ▪ 2 arms: Control is SOC only[6]	Adults[7] & children	Guinea	2/3	✓	Feb 2015	Oct 2015	130 200	102 *Final*	Enrollment stopped	Submitted
	Safety and efficacy of CP for EVD in Liberia	▪ Non-random (based on CP availability), open-label ▪ 2 arms: Control is SOC only	Adults & children	Liberia	1/2	✓	Nov 2014	May 2015[8]	70	>6 *Jul 17*	Enrollment paused	TBD
	Safety and efficacy of INTERCEPT Plasma from convalescent donors	▪ Non-random, open-label ▪ Single arm receiving transfusion ▪ Study also enrolling donors to collect plasma	Adults & children	U.S.	2	✓	Dec 2014	Dec 2015	12	0 *Aug 23*	Currently recruiting	Intend to publish
Convales cent whole blood	Efficacy of blood transfusions[9]	▪ Non-random (depends on blood avail.and consent), open-label ▪ 2 arms: Control is SOC only	Adults & children	Sierra Leone	N/A[10]	✓	Nov 2014	Feb 2015	100	71 *Jun 29*	Enrollment finished, analyzing results	Manuscript under development
Inter-feron beta 1a	Safety and Efficacy of IFN β-1a in Ebola patients[8]	▪ Non-random, open-label ▪ Single arm, historical controls	Adults only	Guinea	1/2	✓	Mar 2015	After out-break end	30 50	<30 *Jun 18*	Actively enrolling	Manuscript under development

1 Viral load is an outcome; 2 Final data collection for primary outcome; 3 Total enrollment in all arms of study; 4 In a peer reviewed journal; 5 Goal of 12 cases for rich sampling (increased PK/PD and biomarker investigation); 6 Historical controls will be used if needed, as all enrolled so far have been in treatment arm; 7 Including pregnant women; 8 Unless enrollment resumes (pending outbreak status); 9 Not a publically registered trial; 10 No phase classification given;

SOURCE: Clinicaltrials.gov, PACTR, ISCRTN registry, Stakeholder interviews; public releases

Summary of candidate information for therapies/procedures in early-clinical-stage trials

	Highest pre-clinical evidence	*Early clinical evidence*	*Latest trials (next page)*
BCX 4430	▪ 100% (n=6, 25 mg/kg BID) or 67% effective (n=6, 16 mg/kg BID) in company-publicized NHP study (Rhesus macaques) when treatment initiated within 2 hrs of infection with EBOV [ag] ▪ Not effective in NHP (cynomolgus macaques) at 16 mg/kg BID (n=6) when initiated at 48 hr post-infection [ah] ▪ 100% effective in mice (n=10) [ai]	▪ Single ascending dose portion of phase 1 study completed	▪ One Ph. 1 study ongoing
MIL77	▪ MIL77 appears at least as effective as ZMapp in a limited number of NHP; manuscript in preparation	▪ No completed Ph. 1 ▪ Also given under compassionate use to 2 Ebola patients in U.K. and Italy	▪ One Ph. 1 study planned

SOURCE: Clinicaltrials.gov, WHO Drug Prioritization Table, Published academic studies, Public releases, stakeholder conversation

Summary of trials for therapies/procedures in early clinical stages

PRELIMINARY

Original Design

Revised Design

	Trial Description	Design	Popula-tion	Location	Phase	Start date	End date[1]	Goal enroll.[2]	Current enroll.[2]	Trial Status	Publication Status[3]
BCX 4430	Safety, tolerability, and pharmaco-kinetics	▪ Randomized, double-blind ▪ Part 1 (single dose): 6 ascending dose cohorts. Per cohort, 6 subjects receive drug, 2 receive placebo ▪ Part 2 (multiple dose): Up to 4 ascending dose cohorts. Per cohort, 8 subjects receive drug, 2 receive placebo	Adults only	U.K.	1	Dec 2014	Dec 2015	88	~48 *As of Aug 14*	Currently recruiting, Part 1 complete	Manuscript under development
MIL77	Safety, tolerability, and pharmaco-kinetics	▪ Randomized, open-label, placebo-controlled ▪ 3 dose-escalation groups	Adults only	China	1	*Dates TBD—trial pending regulatory approval*		32	0 *As of Aug 19*	Not yet recruiting, IND submitted	Intend to publish

1 Final data collection for primary outcome
2 Total enrollment in all arms of study
3 In a peer reviewed journal

SOURCE: Clinicaltrials.gov, public releases,

Summary of other therapies used in the outbreak

PRELIMINARY

	Treatment	Description of use	Comments
Therapies with approved compassionate use or historical observational studies	Amiodarone	▪ Compassionate use in 65 patients in Lakka, Sierra Leone	▪ Reported mortality of 63% ▪ Known toxic side effects ▪ One Ph. 2/3 trial was planned but did not launch
	Artesunate-amodiaquine (ASAQ)	▪ Retrospective analyses in Liberia ▪ During a shortage of the first-line anti-malarial, some patients were prescribed ASAQ	▪ 64-65% (total n=257) of those not receiving ASAQ died ▪ 51% (total n=71) of those receiving ASAQ died
	ZMAb	▪ Given to 4 patients under compassionate use	▪ Results not known
	FX06	▪ Given to 2 patients under compassionate use	▪ 1 treated patient survived
Therapies that lack sufficient details on protocol and/or results	Atorvastatin + irbesartan (+/- clomifene)	▪ Reportedly given to ~100 patients under compassionate use in Sierra Leone	▪ Non-verified, non-peer-reviewed mortality claim of 2% ▪ No formal documentation of treatment results
	Lamivudine	▪ Given to 15 patients under compassionate use in Liberia	▪ No clinical confirmation of Ebola in treated patients ▪ Non-verified, non-peer-reviewed mortality claim of 13%

Source: Public releases; WHO Categorization of Ebola drugs; published academic literature

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WHO Emergency Guidance on Selection and use of Ebola in vitro diagnostic assays available at:
http://www.who.int/csr/resources/publications/ebola/ivd-assays/en/

DIAGNOSTICS

Diagnostic products with FDA and/or WHO emergency use authorization

Technology:
- PCR
- Antigen lateral flow device

	Product	Manufacturer	Targets	Manufacturer Claims LOD	Manufacturer Claims Sensitivity	Manufacturer Claims Specificity	Independent evaluation results LOD	Independent evaluation results Sensitivity	Independent evaluation results Specificity	Time to result (hrs)
FDA EUA and WHO EUAL	ReEBOV	Corgenix	ZEBOV	1 million PFU/ml	78-96%	73-91%	211 mllion copies/ml[1]	91.8%	84.6%	<0.5
	Xpert Ebola	Cepheid	ZEBOV	232.4 copies/ml	90-100%	100%	1,340-4,230 copies/ml	n/a	n/a	1.5
	BioThreat-E	BioFire	ZEBOV	600,000 PFU/ml	96%	100%	4,059 copies/ml[1]	n/a	n/a	1.25
WHO EUAL only	Liferiver	Shanghai BioTech	ZEBOV + 3 other EV	n/a	n/a	n/a	42,300 copies/ml	n/a	n/a	<4-6
	RealStar Filovirus	Altona	ZEBOV + 4 other EV	1.39[2] copies/mL	n/a	n/a	1 PFU/ml[3]	n/a	n/a	<4-6
	SQ Q Line Ebola Zaire Ag	SD Biosensor Inc.	ZEBOV	n/a	n/a	n/a	31.3 ng/ml[4] 3.9 ng/ml[5] 62.5 ng/ml[6]	84.9%	99.7%	<0.5
FDA EUA only	RealStar Ebolavirus	Altona	ZEBOV + 4 other EV	1 PFU/ml	100%	100%	n/a	n/a	n/a	<4-6
	NGDS BT-E	BioFire	ZEBOV	10,000 PFU/ml	87-92%	100%	n/a	n/a	n/a	1.25
	LightMix	Roche	ZEBOV	4,781 PFU/ml	97.8%	100%	n/a	n/a	n/a	4-6
	EZ1	US DoD	ZEBOV	1,000-5,000 PFU/ml[7]	100%	100%	n/a	n/a	n/a	4-6
	CDC NP	CDC	ZEBOV	30 $TCID_{50}$ / reaction	98-100%[8]	100%	n/a	n/a	n/a	4-6
	CDC VP40	CDC	ZEBOV	30 $TCID_{50}$ / reaction	100%	94-100%[8]	n/a	n/a	n/a	4-6
	OraQuick	OraSure technologies Inc.	ZEBOV + 2 other EV	1,640,000 $TCID_{50}$/mL[9] 1.06 ng/test[10]	84%	98%	n/a	n/a	n/a	<0.5

1 As performed by BNITM; 2 As claimed by manufacturer per WHO report; 3 As demonstrated in FDA EUA testing; 4 Recombinant ZEBOV GP; 5 Recombinant ZEBOV NP; 6 Recombinant ZEBOV VP40; 7 1,000 PFU/ml with live-virus spiked in Trizol-inactivated whole blood and 5,000 PFU/ml with Trizol inactivated whole blood or plasma; 8 Lower value for contrived urine specimens and 100% for contrived whole blood specimens; 9 For Zaire Ebola inactivated Virus; 10 Using recombinant VP40 antigen;

SOURCE: WHO Selection Of IVD Guidance (Accessed September 2015), FDA Emergency Use authorizations (Accessed Sep 2015), Device labels

Ease of use: High, Medium, Low

Emergency authorized products span a wide range of ease-of-use

PRELIMINARY

Product	Manufacturer	Technology	Platform(s)	Other materials required[1]		Emergency list date[2]		Sample
				Equip.	Other	WHO	FDA	
ReEBOV	Corgenix	Antigen lateral flow device	None	High	High	Feb 19, 2015	Feb 24, 2015	Blood, plasma
Xpert Ebola	Cepheid	rRT-PCR	GeneXpert	Medium	High	May 08, 2015	Mar 23, 2015	Venous blood
BioThreat-E	BioFire Defense	Multiplex rRT-PCR	FilmArray	High	High	N/A	Oct 25, 2014	Blood, urine
Liferiver	Shanghai ZJ BioTech	rRT-PCR	ABI 7500 Fast Dx, LightCycler 480 II, CFX96, SLAN 96	Medium	High	Apr 27, 2015	N/A	Blood
RealStar Filovirus	Altona Diagnostics	rRT-PCR	ABI 7500 Fast/SDS, Light Cycler 480 II, CFX96	Low	High	Nov 25, 2014	N/A	Plasma
SQ Q Line Ebola Zaire Ag	SD Biosensor Inc.	Antigen lateral flow device	None	High	High	Sep 8, 2015	N/A	Blood, plasma, serum
RealStar Ebolavirus	altona Diagnostics	rRT-PCR	ABI 7500 Fast Dx, LightCycler, CFX96	Low	High	N/A	Nov 10, 2014	Plasma
NGDS BT-E	BioFire Defense	Multiplex rRT-PCR	FilmArray	High	High	N/A	Oct 25, 2014	Blood, plasma, serum
LightMix	Roche	rRT-PCR	LightCycler 480 II, cobas Z 480	Low	Low	N/A	Dec 23, 2014	Whole blood
EZ1	US DoD	rRT-PCR	ABI 7500 Fast Dx, LightCycler, JBAIDS	Low	High	N/A	Aug 05, 2014	Blood, plasma
CDC NP	CDC	rRT-PCR	ABI 7500 Fast Dx, CFX96	Low	Low	N/A	Oct 10, 2014	Blood, plasma, serum, urine
CDC VP40	CDC	rRT-PCR	ABI 7500 Fast Dx, CFX96	Low	Low	N/A	Oct 10, 2014	Blood, plasma, serum, urine
OraQuick	OraSure technologies Inc.	Antigen lateral flow device	None	High	High	N/A	July 31, 2015	Blood, plasma,

1 Number of materials that are required but not provided with product - first column describes lab instruments/lab requirements and second describes reagents and consumables; 2 If multiple reauthorizations exist, original date is shown here

SOURCE: WHO Diagnostics, FDA Emergency use authorizations, Device instructions

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Acknowledgments

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Acronyms used

- Centers for Disease Control and Prevention (CDC)
- Centre National de Recherche et de Formation sur le Paludisme (CNRFP)
- Foundation for Innovative New Diagnostics (FIND)
- London School of Hygiene & Tropical Medicine (LSHTM)
- National Institute of Allergy and Infectious Diseases (NIAID)
- World Health Organization (WHO)

ID numbers for trials detailed in this report (in order of appearance)

ChAd3-EBOZ	NCT02485301 & PACTR201504001092179
	NCT02548078 & PACTR201507001154522
Multiple vaccines	NCT02344407
rVSV-ZEBOV	PACTR201503001057193
	NCT02378753 & PACTR201502001037220
	NCT02503202
Ad26.ZEBOV + MVA-BN-Filo	NCT02416453
	NCT02564523
	NCT02509494 & PACTR201506001147964
ChAd3-EBOZ+ MVA-EBOZ-EM	NCT02451891
	NCT02485912
ChAd3- EBOZ + MVA-BN-Filo	NCT02240875
	NCT02267109
ChAd3-EBO (also cAd3-EBOZ)	NCT02231866
	NCT02354404
ChAd3 EBO + MVA-EBOZ-IDT	NCT02408913
	NCT02368119
Chad3-EBOZ + Ad26.ZEBOV	NCT02495246

EBOV GP	NCT02370589
rVSVN4CT1-EBOV GP	No protocol online
rVSVN4CT1-EBOV-SUDV-Marv	No protocol online
Ad5-EBOV	NCT02326194
	NCT02533791
	NCT02401373
	No protocol online
INO-4212	NCT02464670
ZMapp	NCT02363322
Favipiravir	NCT02329054
Tekmira (tkm-130803)	PACTR201501000997429
Brincidofovir	NCT02271347; PACTR201411000939962
Convalescent plasma	ISRCTN13990511
	NCT02342171
	NCT02333578
	NCT02295501
Convalescent whole blood	No protocol online
Interferon beta 1a	No protocol online
BCX 4430	NCT02319772
MIL77	No protocol online

SOURCE: ClinicalTrials.Gov, Pan-African Clinical Trials Registry, ISRCTN Registry

References for vaccine candidates (1/3)

PRELIMINARY

Candidate		Source letter and citation	Date
ChAd3 vaccines		NIAID: "Ebola Vaccine Trial Opens in Liberia"	Feb 2015
		NIAID: "NIAID/GSK Experimental Ebola Vaccine Appears Safe, Prompts Immune Response"	Nov 2014
		NIAID: "Rapid and Durable Protection Against Ebola Virus With New Vaccine Regimens"	Sep 2014
		"Reflections on Clinical Research" by E. Higgs at Gates Global Partners Forum	May 2015
		"Update on Ph. 1 Program", GSK presentation at WHO	Jan 2015
	a	Stanley et al, "Chimpanzee adenovirus vaccine generates acute and durable protective immunity against Ebola virus challenge," Nature Medicine.	Sep 2014
	b	Rampling et al, "A Monovalent Chimpanzee Adenovirus Ebola Vaccine – Preliminary Report," New England Journal of medicine and supplementary appendix	Jan 2015
	c	"GSK/NIH Ebola Vaccine Development," GSK update to FDA (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM448003.pdf)	May 2015
		Supplementary Appendix to Rampling et al 2015	Jan 2015
		"GSK and J&J/Bavarian Nordic take Ebola candidates to Senegal, Europe," Fierce Vaccines	Jul 2015
	m	Ledgerwood et al, "Chimpanzee Adenovirus Vector Ebola Vaccine--Preliminary Report," New England Journal of Medicine	Nov 2014
rVSV-ZEBOV	d	Geisbert and Feldmann, "Recombinant Vesicular Stomatitis Virus – Based Vaccines Against Ebola and Marburg Virus Infections," Journal of Infectious Diseases	Nov 2011
	e	Geisbert et al, "Vesicular stomatitis virus-based vaccines protect nonhuman primates against aerosol challenge with Ebola and Marburg viruses," Vaccine	Dec 2008
	f	Qiu et al, 'Mucosal Immunization of Cynomolgus Macaques with the VSVΔG/ZEBOVGP Vaccine Stimulates Strong Ebola GP-Specific Immune Responses," PLOS.	May 2009
	g	Jones et al, "Live attenuated recombinant vaccine protects nonhuman primates against Ebola and Marburg viruses" Nature Medicine	June 2005

References for vaccine candidates (2/3)

PRELIMINARY

Candidate	Source letter and citation		Date
rVSV-ZEBOV *(contd.)*	h	Regules et al, "A Recombinant Vesicular Stomatitis Virus, Ebola Vaccine – Preliminary Report," New England Journal of Medicine	Apr 2015
	i	Agnandji et al, "Phase 1 Trials of rVSV Ebola Vaccine in Africa and Europe – Preliminary Report," New England Journal of Medicine	Apr 2015
		Supplementary Appendix to Agnandji et al 2015	Apr 2015
		NIAID release: "Ebola Vaccine Trial Opens in Liberia"	Feb 2015
		"Reflections on Clinical Research" by E. Higgs at Gates Global Partners Forum	May 2015
		Rottingen et al, "Ebola vaccine trial in Guinea," correspondence in The Lancet	May 2015
		John Konz, "rVSV-ZEBOV-GP Vaccine (V920): Development Update," FDA website (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM448006.pdf)	May 2015
	j	Henao-Restrepo et al, " Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial" The Lancet	July 2015
	k	*Ebola ça Suffit* Ring Vaccination Trial Consortium. "The ring vaccination trial: a novel cluster randomized controlled trial design to evaluate vaccine efficacy and effectiveness during outbreaks, with special reference to Ebola. *BMJ*; **351:** h3740	July 2015
Ad26.ZEBOV + MVA-BN-Filo	l	Van Hoof, "Janssen Ebola Vaccine Program Update," FDA Advisory Committee Update (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM448005.pdf)	May 2015
		"Bavarian Nordic announces that the Oxford Vaccines group has initiiated a Phase 2 study of the Ebola prime-boost regimen combining MVA-BN-Filo and Janssen's Advac technology," Company releases	Jul 2015
		"Bavarian Nordic announces Preliminary Phase 1 results," Company releases	May 2015

References for vaccine candidates (3/3)

PRELIMINARY

Candidate		Source letter and citation	Date
Ebov GP	n	Smith, "Recombinant EBOV/Makona Glycoprotein (GP) Nanoparticle Vaccine Produced in Sf9 Insect Cells,"ISBioTech meeting (http://www.novavax.com/download/file/Novavax%20EBOV%20GP%20Vaccine%20ISBIO%20GSmith%20final.pdf)	Mar 2015
	o	Smith, "Recombinant EBOV/Makona Glycoprotein (GP) Nanoparticle Vaccine Produced in Sf9 Insect Cells," for International Symposium on Filoviruses (http://www.novavax.com/download/file/1015_Smith%20Novavax%20Filovirus%2028March15%20-FINAL.pdf)	No date
	p	“Novavax Announces Positive Top-Line Data from Phase 1 Ebola Vaccine Trial on WHO Teleconference” company releases	July 2015
rVSV N4CT1	q	Mire et al, "Single-dose attenuated Vesiculovax vaccines protect primates against Ebola Makona virus," Nature	Apr 2015
Ad5-EBOV	r	Zhu et al, "Safety and immunogenicity of a novel recombinant adenovirus type-5 vector-based Ebola vaccine in healthy adults in China: preliminary report," Lancet.	June 2015
		Wu et al, "Prediction and identification of mouse cytotoxic T lymphocyte epitopes in Ebola virus glycoproteins,” Virol J	June 2012
INO-4212	s	Shedlock et al, "Induction of Broad Cytotoxic T Cells by Protective DNA Vaccination against Marburg and Ebola," Molecular Therapy	Nov 2012

References for therapeutic candidates (1/4)

PRELIMINARY

Candidate	Source letter and citation		Date
ZMapp	t	Qiu et al, "Reversion of advanced Ebola virus disease in NHP with Zmapp". Nature	Oct 2014
		"Reflections on Clinical Research" by E. Higgs at Gates Global Partners Forum	May 2015
		"Liberia-U.S. Clinical Research Partnership Opens Trial to Test Ebola Treatments," NIAID	Feb 2015
		"Zmapp Information sheet," MappBio	ND
Favi-piravir	u	Smither et al, "Post-exposure efficacy of Oral T-705 (Favipiravir) against inhalational Ebola virus infection in a mouse model," Antiviral Research	Jan 2014
	v	Oestereich et al, "Successful treatment of advanced Ebola virus infection with T-705 (favipiravir) in a small animal model," Antiviral Research	Feb 2014
	w	"Preliminary results of the JIKI clinical trial to test the efficacy of favipiravir in reducing mortality in individuals infected by Ebola virus in Guinea," Medecins sans Frontieres	Feb 2015
	x	"Favipiravir in patients with Ebola Virus Disease: early results of the JIKI trial in Guinea" Presentation at CROI conference	Feb 2015
		"JIKI Synopsis": Protocol for trial	ND
		"MediVector Completes Patient Enrollment in Two Phase 3 Studies of Favipiravir for Influenza," MediVector public release	Feb 2015
		"First Patient Enrolled in Northern Hemisphere for Phase 3 Study of Favipiravir for Influenza," PRNewsWire	Jan 2014
TKM-130803		"Tekmira Provides Update on TKM-Ebola-Guinea," Tekmira public release	Jun 2015
		Geisbert et al.,"Postexposure protection of non-human primates against a lethal Ebola virus challenge with RNA interference: a proof-of-concept study," Lancet	May 2010
		"About Investigational TKM-Ebola Therapeutic," Tekmira public release	ND
		FDA Modifies Partial Clinical Hold on Tekmira's TKM-Ebola IND to Allow Multiple Dosing of Healthy Volunteers	Apr 2015

References for therapeutic candidates (2/4)

PRELIMINARY

Candidate		Source letter and citation	Date
TKM-130803 *(contd.)*	y	Geisbert et al.,"Postexposure protection of non-human primates against a lethal Ebola virus challenge with RNA interference: a proof-of-concept study," Lancet	May 2015
	z	Thi et al.,"Lipid nanoparticle siRNA treatment of Ebola-virus-Makona-infected non-human primate," Nature	May 2015
Brincid-ofovir		"Chimerix Focusing Efforts on CMV and Adenovirus Pivotal Trials," Chimerix public release	Jan 2015
		"NIH Ebola Update: Working Toward Treatments and Vaccines," NIH Public Page	Oct 2014
	aa	"Chimerix's Brincidofovir Has in Vitro Activity Against Ebola," Company release	Sep 2014
		"Chimerix Initiates Phase 3 SUPPRESS Trial of Brincidofovir (CMX001) for Prevention of CMV in HCT Recipients," Company release	Sep 2013
		"Chimerix Provides Update on Brincidofovir Pivotal Phase 3 AdVise Trial for the Treatment of Adenovirus," Company release	Jan 2015
		Butler, D. "First trials of blood-based Ebola therapy kick off," in Nature News	Dec 2014
Conva-lescent Plasma/ blood	ab	Dye et al., "Postexposure antibody prophylaxis protects nonhuman primates from filovirus disease," PNAS	Feb 2012
	ac	Jahrling et al, "Ebola Hemorrhagic Fever: Evaluation of Passive Immunotherapy in NHP," Journal of Infectious Diseases	Nov 2007
	ad	Mupapa et al., "Treatment of Ebola Hemorrhagic Fever with Blood Transfusions from Convalescent Patients," Journal of Infections Diseases	Feb 1999
	ae	Edmond et al, "A Case of Ebola Virus Infection," British Medical Journal.	Aug 1977
		"Blood transfusions show early promise as possible Ebola cure," AlJazeera	Feb 2015
		Griensven, J. "The use of Ebola Convalescent Plasma to treat Ebola Virus Disease in resource constrained settings: A perspective from the field," Clinical Infectious Diseases.	Aug 2015
		"Ebola vaccines, therapies, and diagnostics," World Health Organization	
		"Position Paper on Collection and Use of Convalescent Plasma or Serum as an Element in Filovirus Outbreak Response," WHO Blood Regulators Network	Nov 2014

References for therapeutic candidates (3/4)

PRELIMINARY

Candidate	Source letter and citation	Date
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BCX4430	ag "BioCryst Announces Study Results for BCX4430 in a Non-Human Primate Model of Ebola Virus Infection," Biocryst public release	Dec 2014
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Candidate	Source letter and citation	Date
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References for diagnostic products and additional references

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Candidate	Source letter and citation	Date
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	Device labels for listed devices	various
	"Situational Review of Ebola Diagnostics," FIND Diagnostics	Nov 2014
	FDA Emergency Use Authorizations (http://www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm)	No date
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	WHO Emergency Use Assessment and Listing (EUAL) Procedure for Ebola Virus Disease (IVDs)	No date
Overview documents	"Regulatory Pathways for Licensure and Use of Ebola Virus Vaccines During the Current Outbreak FDA Perspective," WHO Consultation on Ebola Virus Vaccines	Sep 2014
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