

## Overview of candidate Ebola vaccines as of August 19, 2019

Nine candidate Ebola vaccines have undergone or are currently undergoing clinical evaluation at different trial phases. Three vaccines were licensed, three vaccines have completed or are in trials up to Phase 1 phase, two vaccines up to or in Phase 2 stage, and one vaccine has completed Phase 3 stage.

Type of candidate vaccine	Developer	Strain(s) aimed to protect against	a. Current stage of clinical evaluation b. Number of subjects with data analysed to date c. Regulatory status	Proposed vaccination schedule	Proposed indication	Proposed target population for the label indication	Current storage specifications*	Current formulation and presentation (doses per vial)	Number of clinical research grade doses available	Forecasted production capacity
<b>PROPOSED INDICATION: REACTIVE USE DURING OUTBREAKS</b>										
<b>Licensed in country of origin</b>										
Ad5-EBOV (monovalent) <sup>1</sup>	CanSino Biologics Inc. & Beijing Institute of Biotechnology, China	Zaire ebolavirus (Makona)	a. Phase 1 in China and Phase 2 in Sierra Leone b. >681 people enrolled c. Licensed obtained from CFDA in October 2017 to use under national reserves by National Medical Products Administration (NMPA), China in the event of Ebola outbreak Submitted to WHO for Emergency Use Assessment and Listing (EUAL) in July 2018.	1 dose	Reactive	18 to 60 years	+2°C to +8°C for 12 months	Final Formulation: Lyophilized  Presentation: Single dose vial + diluent	20,000 doses	Can produce 150 000 doses per year and potentially scale-up to 500 000 doses/year.
<b>Granted Breakthrough Therapy Designation by the US FDA and PRIME status by the European Medicines Agency (EMA) since 2016</b>										
rVSVΔG-ZEBOV-GP <sup>9</sup>	Merck, USA	Monovalent Zaire (Kikwit 1995)	a. Phase 3 completed in Guinea (2016). b. >200,000 people Over 18,000 people enrolled in clinical trials. Ongoing expanded access protocol in DRC with over 200,000 people vaccinated in affected areas in DRC c. Granted Breakthrough Therapy Designation by the US FDA and PRIME status by the European Medicines Agency (EMA) since 2016 Submitting rolling BLA to US FDA and rolling MAA to EMA for licensure Submitting to WHO for EUAL.	1 dose	Reactive	Active immunization (reactive use) of at-risk subjects ≥ 18 years of age to protect against disease caused by <i>Zaire ebolavirus</i> . [When the required paediatric data are available, will seek an indication for use in subjects ≥ 1 year of age].	60°C to -80°C for 36 months And, 2°C – 8°C for 14 days	Final Formulation: Liquid frozen  Presentation: 10 dose vials.  After licensure single dose vials	500,000 doses currently available for dosing recommended by SAGE  (Corresponds to - 250 000 doses available for dosing proposed for licensure)	For 2020, planned replenishments targets are set to be (display as Guinea dose (2x10 <sup>7</sup> ):  Jan 2020: Approx. 340000 additional doses  April/May: Approx 60000  June-Dec: Approx 900 000 additional doses  Total: Approx. 1300 000
<b>Currently submitting to US FDA to seek licensure under the Animal Rule</b>										
Nanoparticle recombinant Ebola GP vaccine <sup>8</sup>	Novavax, USA	Monovalent Zaire (Makona)	a. Phase 1 b. >182 people enrolled	2 doses with planned boosts for HCW in potential epidemic areas.	Reactive	≥ 18 years	No information available	Final formulation: Liquid Matrix-M1 Adjuvant  Presentation: Separate single-dose vials	No information available	No information available
<b>Ongoing clinical evaluation</b>										
INO-4201 (DNA vaccine) <sup>7</sup>	Inovio Pharmaceuticals, USA	Plasmid of Ebola outbreak strains from 1976-2006	a. Phase 1 b. >230 people enrolled	2 doses	Reactive	≥ 18 years	+2°C to +8°C for 3 years and 25°C for 1 year 37°C for 1 month 60°C for several days	Final Formulation: Liquid  Presentation: Single-dose vials	Potentially have 10,000 doses in bulk remaining of INO-4201.	No information available

Type of candidate vaccine	Developer	Strain(s) aimed to protect against	a. Current stage of clinical evaluation b. Number of subjects with data analysed to date c. Regulatory status	Proposed vaccination schedule	Proposed indication	Proposed target population for the label indication	Current storage specifications*	Current formulation and presentation (doses per vial)	Number of clinical research grade doses available	Forecasted production capacity
<b>PROPOSED INDICATION: PREVENTIVE USE</b>										
<b>Licensed in country of origin</b>										
EpivacEbola <sup>5</sup>	FBRI SRC VB VECTOR, Rospotrebnadzor, Russia	Monovalent Zaire (Makona)	a. Phase 1 and 2/3 in Russia b. >300 people enrolled a. Licensed in Russia since 2016	2 doses (prime + boost on 28 days)	Preventive	18 to 55 years	2-8°C for 1 year  Can extend shelf-life to 2 years	Final Formulation: Liquid  Presentation: Single dose vial	20 000 doses currently available	Can produce a million doses in a few weeks, no additional data
GamEvac-Combi and GamEvac-Lyo <sup>6</sup>	Gamaleya Research Institute of Epidemiology and Microbiology, Russia	Monovalent Zaire (Makona)	a. Ongoing Phase ½ in Russia and Phase 3 in Guinea (Kindia) Phase 4 reported in Russia b. >2,000 people enrolled c. Licensed in Russia for emergency use in the event of an EVD outbreak	2 doses (prime + boost on 21 days)  1st dose: rVSV-GP  2nd dose: rAd5-GP	Preventive	18 to 55 years	16°C to -20°C for 12 months 4°C for lyophilized formulation	Final Formulation: Liquid frozen and Lyophilized  Presentation: Single-dose vials	No information available	Can produce 20 000 doses per year and potentially scale-up to 100 000 doses/year.
<b>Currently submitting to US FDA to seek licensure under the Animal Rule and/or to European Medicines Agency.</b>										
Ad26.ZEBOV & MVA-BN-Filo (2-dose regimen, VAC52150) <sup>2</sup>	Janssen Vaccines & Prevention B.V, The Netherlands	Zaire ebolavirus (Mayinga)	a. Phase 1: Four studies completed in Europe, the United States and Africa Phase 2/3: Six Phase 2/3 studies in Europe, USA and Africa (partially) unblinded; two Phase 2/3 studies in Africa ongoing b. >6,500 people enrolled c. Negotiating with the US FDA to obtain licensure using the Animal Rule Filing at EMA under conditional approval or approval under exceptional circumstances Collaborative review with WHO (PQ) and African NRAs planned d. Submitted file to WHO for EUAL. Received request for additional evidence.	2 doses  1st dose: Ad26.ZEBOV (EBOV GP)  2nd dose on day 56: MVA-BN-Filo (EBOV/SUD V/MARV GP, TAFV NP)	Preventive	Adults and children ≥ 1 year of age	Ad26.ZEBOV: 20°C or 60°C for up to 60 months and  +2 to +8°C for up to 12 months  MVA-BN-Filo: 20°C or 60°C for up to 60 months and  +2 to +8°C for up to 6 months	Final Formulation: Liquid frozen  Presentation: Single-dose vials	50,000 labelled regimens ready to be used.  1.5 million regimens in vials, QC-released, need to be labelled.  Depending on urgency 45,000 or more additional regimens available each month	500 000 per year depending on the demand
Nanoparticle recombinant Ebola GP vaccine <sup>8</sup>	Novavax, USA	Monovalent Zaire (Makona)	a. Phase 1 b. >182 people enrolled	2 doses with planned boosts for HCW in potential epidemic areas	Preventive	≥ 18 years	No information available	Final Formulation: Liquid Matrix-M1 Adjuvant  Presentation: Separate single-dose vials	No information available	No information available
<b>Ongoing clinical evaluation</b>										
ChAd3 (monovalent Zaire) <sup>3</sup>	Sabin Vaccines Institute / National Institute of Allergy and Infectious Diseases (NIAID), USA	Monovalent: Zaire (Mayinga)	a. Phase 2 in Cameroon, Senegal, Mali, Liberia, Nigeria b. >5,600 people enrolled c. GSK has sublicensed the investigational product to Sabin ( <a href="#">press release</a> ).	1 dose	Preventive	Adults and Children		Final Formulation: Unknown  Presentation: Single dose vials	450,000 doses	No information available

## Notes

### <sup>1</sup> Ad5-EBOV (monovalent)

- Ad5-EBOV is a replication-defective recombinant human type 5 adenovirus expressing Zaire (Makona, 2014) Ebola virus envelope glycoprotein.
- After re-constitution, each dose includes two vials (0.5ml/vial) with a total volume of 1ml, containing  $8 \times 10^{10}$  VP of the replication-defective recombinant human type 5 adenovirus expressing the Ebola virus envelope glycoprotein.
- Three clinical studies of Ad5-EBOV were completed, including a randomized, double-blinded, placebo-controlled Phase Ia clinical trial of 120 Chinese subjects, an open Phase Ib clinical trial of 61 Africans in China (PMID: [25817373](#), [28017642](#), [2870962](#)) and a Phase 2 clinical trial of 500 Africans in West Africa (PMID: [28017399](#)). Total 156 subjects were inoculated according to the registration specification ( $8 \times 10^{10}$  VP/dose), 78 subjects were inoculated by  $4 \times 10^{10}$  VP/dose and 355 subjects were inoculated by  $1.6 \times 10^{11}$  VP/dose.
- Two Phase 1 trials in China (120 and 61 healthy adults) and one Phase 2 trial in Sierra Leone (500 healthy adults) were completed. The investigators reported good safety (the most common adverse events (AEs) reported included fever and mild injection site pain and no vaccine-related serious adverse events (SAEs) recorded) and immunogenicity profile (the geometric mean titre (GMT) of anti GP antibody peaked around 28 days after vaccination with a responder rate of 96% (95% CI: 91%-99%) but the vaccine-elicited antibody responses decreased on 168 days with a responder rate of 76% (95% CI: 67%-83%)) of Ad5-EBOV (PMID: [28017399](#)).
- This vaccine is licensed to use under national reserves by NMPA, China in the event of Ebola outbreak or emergency to prevent the Ebola virus disease caused by the Ebola virus (Zaire).
- EUAL application was submitted to WHO in July 2018 and is currently under review.

### <sup>2</sup> Ad26.ZEBOV & MVA-BN-Filo (2-dose regimen, VAC52150)

- Ad26.ZEBOV is a monovalent replication-incompetent adenoviral vector serotype 26 (Ad26) vaccine, which encodes the full-length GP of the EBOV Mayinga variant, and is produced in the human PER.C6® cell line. MVA-BN-Filo is a multivalent Modified Vaccinia Ankara (MVA)-BN vaccine, which encodes the EBOV Mayinga GP, the Sudan virus (SUDV) Gulu GP, the Marburg virus (MARV) Musoke GP, and the Tai Forest virus (TAFV, formerly known as Côte d'Ivoire ebolavirus) nucleoprotein (NP). It is manufactured in chicken embryo fibroblast cells derived from specific pathogen-free eggs.
- The formulation of Ad26.ZEBOV, MVA-BN-Filo is liquid frozen. The vaccine regimen consists of an immunization with Ad26.ZEBOV ( $5 \times 10^{10}$  vp) as the first dose, followed by MVA-BN-Filo ( $1 \times 10^8$  Inf U) as a second dose 56 days later. The proposed target population includes adults and children aged  $\geq 1$  year.
- Efficacy of the vaccine was demonstrated in an EBOV animal model where vaccination with the clinical dose provided 100% protection. Partial protection was observed when the doses of the vaccines were reduced. A shorter interval between doses as well as an inverted dose-order were also associated with lower protective efficacy rates.
- Four Phase 1 trials were completed: 87 healthy adults in Europe (PMID: [27092831](#), [28291882](#)), 164 healthy adults in the United States ([NCT02325050](#)) and 72 and 72 healthy adults in Africa ([NCT02376426](#), [NCT02376400](#)). Three Phase 2 trials were completed: 423 healthy adults in Europe ([NCT02416453](#)), 200 healthy adults and 200 HIV-infected adults in the United States and Africa ([NCT02598388](#)), and 669 healthy adults, 142 HIV-infected adults, 132 healthy adolescents and 132 healthy children in African countries ([NCT02564523](#)). Two Phase 3 trials in the United States (144 and 329 healthy adults) ([NCT02543567](#), [NCT02543268](#)) were completed. One Phase 3 study in an Ebola-affected region (Sierra Leone) (445 healthy adults, 192 healthy adolescents and 193 healthy children) (PMID: [27821112](#)) with the aim of establishing safety and immunogenicity in adults, followed by an expanded safety and immunogenicity study in adults and children was partially unblinded. In addition, one Phase 1/2/3 trial on healthy children and adults aged less than 71 years in multi-countries in the United States, Europe and Africa ([NCT02661464](#)) are ongoing. One additional trial was started in 2017, PREVAC (in partnership with NIAID, INSERM, LSHTM) ([NCT02876328](#)), to evaluate the safety and immunogenicity of the vaccine regimen in previously affected countries (Guinea, Liberia, and potentially Sierra Leone). Finally, in August 2018, a safety and immunogenicity trial in health care and frontline workers was started in Uganda ([NCT04028349](#)).
- To date more than 6,500 people have been enrolled. The available (partially) unblinded and analyzed clinical studies (4 Phase 1, 3 Phase 2, and 3 Phase 3) evaluating the 2-dose Ad26.ZEBOV, MVA-BN-Filo regimen in different intervals (14 to 84 days) in adults did not reveal any safety concerns. An unblinded safety review on pooled data from 1932 adults (of which 118 HIV+) revealed only mild to moderate AEs of short duration with no sequelae. Unblinded pediatric safety data are available for 649 children aged  $\geq 1$  year receiving active vaccination (253 adolescents 12-17 years old; 252 children 4-11 years old and 144 toddlers 1-3 years old) and 189 children receiving at least one dose of placebo/control. Overall, the safety profile consists of mild to moderate AEs of short duration with no sequelae, with no relevant differences compared with adult participants. No safety signals were identified.
- Following phase 1 vaccine development, phase 2 and 3 studies confirm the robust immunogenicity of the vaccine regimen, including long term persistence of the immune response up to at least two years. The vaccine has been demonstrated to be immunogenic in all populations evaluated.
- In the absence of clinical efficacy data, and as agreed with regulatory agencies EMA and FDA, the likelihood of protection of the Ad26.ZEBOV, MVA-BN-Filo 0, 56 vaccine regimen is inferred by immunobridging. For this, human immunogenicity is assessed against an animal model that describes the relationship between immunogenicity and survival after a challenge with Ebola virus.
- Ad26.ZEBOV/MVA-BN-Filo has not been licensed yet. Agreements on the approach to demonstrate the protective effect of the vaccine were achieved with FDA (licensure under Animal Rule) and EMA (conditional approval or licensure under exceptional circumstances). WHO PQ and African country registrations are planned to be achieved via parallel review with EMA.
- A file in support of WHO EUAL was submitted to WHO in a rolling manner including CMC, non-clinical and clinical Phase 1/2/3 data in July/September 2016 and in subsequent annual updates.

### <sup>3</sup> ChAd3 (monovalent Zaire)

- ChAd3 (monovalent Zaire) vaccine consists of ChAd3-EBOZ glycoprotein Zaire drug substance
- ChAd3 (monovalent Zaire) has been administered to over 5000 adults and children
- A Phase 1 trial was conducted in Mali (91 healthy adults) ([NCT02267109](#)). A Phase 1/1b trial has been completed in 143 adults in the U.S. ([NCT02231866](#)). A Phase Ib trial has been completed in 90 adults in Uganda ([NCT02354404](#)). The investigators reported acceptable safety profile of ChAd3 (monovalent Zaire)
- A Phase 1/2 trial was conducted in 120 healthy adults in Switzerland ([NCT02289027](#))
- Three Phase 2 trials were conducted and completed in Cameroon, Nigeria, Senegal, Mali (3013 adults and 600 children), and Liberia (1500 adults) ([NCT02485301](#); [NCT02548078](#); [NCT02344407](#)). The investigators reported acceptable safety profile of ChAd3 (monovalent Zaire)
- ChAd3 (monovalent Zaire) has been licensed to GSK and sublicensed to Sabin Vaccine Institute ([press release](#)).
- No EUAL submission was initiated and no WHO prequalification has been obtained.

### <sup>4</sup> ChAd3 (bivalent)

- ChAd3 (bivalent) vaccine consists of cAd3-EBO glycoprotein Zaire and cAd3-EBO glycoprotein Sudan drug substances.
- One dose of ChAd3 (bivalent) is targeting adults aged 18 to 50 years.
- One Phase 1 trial of ChAd3 (bivalent) in the United States (20 healthy adults) ([25426834](#)) was completed. The investigators reported acceptable safety profile of ChAd3 (bivalent).

- ChAd3 (bivalent Zaire+Sudan) has been licensed to GSK No EUAL submission was initiated and no WHO prequalification has been obtained.

#### <sup>5</sup> EpiVacEbola

- EpiVacEbola is a polyepitope vaccine, for the prevention of Ebola fever, based on peptide antigens conjugated to a carrier protein and adsorbed to an aluminium-containing adjuvant.
- The vaccine contributes to the development of protective immunity against the Zaire strain of Ebola virus following two subcutaneous administrations, spaced 21 to 28 days apart.
- A Phase 1 trial was conducted in Russian (60 healthy adults). A Phase 2-3 trial has been completed in 240 healthy adults in Russia.
- Two subcutaneous 100-µg doses (0.5 mL) given 28 days apart are well tolerated by adults aged 18-60. Low frequency of local and systemic reactions suggests good tolerance and low reactogenicity of the vaccine. Physical examinations as well as clinical and biochemical assays of blood and urine demonstrated no pathologic changes, which suggest a high safety profile of the vaccine. The vaccine induced Ebola-specific antibodies and virus-neutralizing antibodies in 78% and 71% of cases, respectively.

#### <sup>6</sup> GamEvac-Combi and GamEvac-Lyo

- GamEvac-Combi and GamEvac-Lyo consist of live-attenuated recombinant vesicular stomatitis virus (VSV) and adenovirus serotype-5 (Ad5) expressing Ebola envelope GP of Zaire Ebola virus species (Makona).
- The formulation of GamEvac-Combi is liquid frozen but that of GamEvac-Lyo is lyophilized. The vaccine regimen consists of a priming immunisation with VSV followed by a boosting immunisation with Ad5 21 days later. The proposed dose of VSV and Ad5 are 0.5ml per dose targeting adults aged 18 to 55 years.
- One Phase I/II trial in Russia (84 healthy adults) (PMID: [28152326](#)) and one Phase 4 trial in Russia (60 healthy adults) ([NCT02911415](#)) were completed for GamEvac-Combi. The investigators reported good safety (the most common AE reported was injection site pain and no vaccine-related SAEs recorded) and immunogenicity profile (antigen-specific response was detected in 93% (half dose) and 100% (full dose) on 28 days after vaccination, and 100% on 42 days) of GamEvac-Combi (PMID: [28152326](#)).
- There is one Phase 3 trial of GamEvac-Combi in Guinea, Africa (2000 healthy adults) ([NCT03072030](#)) and one Phase I/II trial of GamEvac-Lyo in Russia (220 healthy adults) ([NCT03333538](#)) on-going.
- GamEvac-Combi has been licensed by the Ministry of Health of the Russian Federation for emergency use in the territory of the Russian Federation in December 2015 (registration number: LP-003390). The emergency license was based on Phase 1 and II clinical data of safety and immunogenicity (PMID: [28152326](#)).
- No EUAL submission was initiated.
- Regarding WHO prequalification the company stated that a decision to submit will be made after completion of the Phase 3 GamEvac-Combi clinical trial in Guinea.

#### <sup>7</sup> INO-4201 (DNA vaccine)

- DNA vaccine INO-4201 is a synthetic DNA plasmid construct expressing Ebola GP designed from consensus DNA sequences of Ebola outbreak strains from 1976-2006.
- The formulation of INO-4201 is liquid; two doses with proposed 2mg per dose intradermally administered in an interval of 4 weeks; targeting to adults aged over 18 years.
- One Phase 1 trial in the United States (75 healthy adults in the initial study) ([NCT02464670](#)) was completed. Final analysis ([JID](#)) showed acceptable safety profile (the most common AEs reported included injection site pain, redness, swelling and itching and no vaccine-related SAEs recorded). Humoral and cellular levels were similar to the rVSV vaccine (Tebas *et al*, *JID* 2019)
- No EUAL submission was initiated and no WHO prequalification has been obtained.

#### <sup>8</sup> Nanoparticle recombinant Ebola GP vaccine

- The nanoparticle vaccine is based on purified recombinant full-length and unmodified 2014 Guinea EBOV GP trimers that self-assemble into distinct nanoparticle structures of approximately 30 to 40 nm diameter. The baculovirus/Sf9 insect cell system was used to clone and express the recombinant EBOV GP protein.
- A Phase 1, randomized, observer-blinded, dose-ranging study to evaluate the immunogenicity and safety of EBOV GP Vaccine with or without Matrix-M1 adjuvant in healthy subjects (≥ 18 to < 50 years of age) was conducted in Australia and completed through 1 year follow-up in April 2016 ([NCT02370589](#)). This study demonstrated the safety of single (Day 0) and repeat doses (Days 0 and 21) of the EBOV GP Vaccine (antigen doses of 6.5, 13, 25, or 50 µg) administered IM alone or in combination with Matrix-M1 adjuvant (50 µg) in healthy volunteers.
- No EUAL submission was initiated and no WHO prequalification has been obtained.

#### <sup>9</sup> rVSVΔG-ZEBOV-GP

- rVSVΔG-ZEBOV-GP consists of a live, attenuated recombinant vesicular stomatitis virus-based vector expressing the envelope GP gene of Zaire Ebola virus (Kikwit 1995 strain).
- The formulation of rVSVΔG-ZEBOV-GP is liquid frozen; one dose with proposed 1ml per dose targeting adults. In the context of the ongoing outbreak in DRC, SAGE recommended to administer 0.5 mL per dose to increase the number of doses available.
- Eight Phase 1 trials in Europe and Africa (115 and 185 healthy adults and 40 healthy children aged 6 to 17 years) (PMID: [26248510](#), [29627147](#), [25830326](#), [28985239](#)), Canada (40 healthy adults) (PMID: [28630358](#)), and the United States (78 and 512 healthy adults) (PMID: [25830322](#), [28606591](#)), one Phase 2 trial in Africa (1000 healthy adults) ([NCT02344407](#)), one Phase II/III trial in Africa (8673 healthy adults) (PMID: [27387395](#), [29788345](#)), and two Phase 3 trials in Africa (5837 healthy adults) (PMID: [26215666](#), [26248676](#), [28017403](#)), and in the United States, Canada and Europe (1197 healthy adults) (PMID: [28549145](#)). The investigators reported acceptable safety profile (the most common AEs reported included injection site pain, headache, pyrexia, fatigue, myalgia and chills and few vaccine-related SAEs recorded) and 100% (95% CI: 69%-100%) efficacy (PMID: [28017403](#)) of rVSVΔG-ZEBOV-GP in the ring-vaccination Guinea trial. The GMT were sustained with minimal change through 360 days after vaccination (PMID: [28606591](#)).
- Two Phase 2 trials on populations aged from 13 to 65 years in Africa and Canada ([NCT03031912](#)) and older than 1 year in Africa ([NCT02876328](#)) are ongoing.
- Granted Breakthrough Therapy Designation from FDA and PRIME status from EMA since 2016.
- The developer submitted an application for licensure to the US FDA and the EMA; the expected timeline to obtain regulatory approval is early 2020. There is ongoing discussion with both regulatory authorities to shorten the timelines.
- EUAL application was submitted to WHO in 2015, and is currently under review.
- No WHO prequalification has been obtained.