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Public Health Threats

POSITION PAPER ON CLINICAL DEVELOPMENT OF BUNDIBUGYO VACCINES

Following the meeting hosted by AMA-EMA-WHO on 24 August 2026, EMA-ETF and AMA have agreed to define the minimum requirements for rapid advancement of Bundibugyo virus (BDBV) vaccines into clinical trials that would allow an efficient and timely start of ring vaccination clinical trial for potential authorization.

The focus of the document is around the type of vaccines that were presented at the 24 August 2026 meeting, i.e. viral vectored and mRNA vaccines.

While some of the key principles could be applied for other vaccine constructs, it cannot be excluded that additional considerations may apply pending consultation with regulatory bodies.

PRECLINICAL TESTING

Safety studies

It is a well-established regulatory principle that in public health emergency situations, non-clinical toxicology studies can be deferred to expedite clinical development and swift deployment of countermeasures, provided that safety of clinical trial participants is not compromised.

For vaccines with well characterised platform data, repeat-dose toxicity studies are not needed to support Phase I or Phase II clinical trials and should be further deferred or waived when the same platform technology has already generated preclinical toxicity data across multiple vaccine candidates, demonstrating that different antigens do not adversely affect the overall safety profile.

In addition, the availability of preclinical and clinical safety data from filovirus-specific vaccines developed using the same platform technology would further support the justification for waiving such preclinical studies.

Platform technologies such as adenovector-based, vesicular stomatitis virus-based and mRNA vaccines have already generated sufficient data to document that the toxicological profile of new vaccine candidates is mainly driven by attributes of the technology itself and may not be significantly impacted by the antigenic composition of new vaccine candidates. For example, it is generally recognised that for mRNA vaccines, the immunostimulatory effect of the lipid nanoparticle formulations is the main driver of the findings in preclinical toxicity studies.

It is considered that in the circumstances mentioned above, which could be applicable e.g. to VSV, ChAdOX1 and mRNA vaccines, a product-specific repeat-dose toxicity study for a BDBV vaccine is unlikely to provide additional information relevant to the human safety risk assessment even beyond early trials; therefore, a waiver of these studies appears scientifically justified.

Biodistribution studies could be also waived based on prior knowledge. However, immunogenicity data in animals, e.g. small rodents, would be needed before the start of clinical trials to ensure that the vaccine is sufficiently immunogenic.

Also, the proposed Phase I and Phase II trials are small-scale, highly controlled studies and are specifically designed to monitor safety and reactogenicity in humans. Because these trials start with low doses and small, closely monitored cohorts, any unexpected human reaction to a new antigen will be caught quickly. This makes the risk of bypassing redundant animal models acceptable.

However, preclinical testing may be needed with an established platform if:

- The new antigen has a known inherent toxicity or mimics a human protein that could trigger severe autoimmunity.
- The vaccine candidate uses a drastically higher dose or a different route of administration than previously tested.
- The formulation includes a new adjuvant that has not qualified with the platform before.

BDBV challenge models

Cynomolgus macaques model represents the gold standard animal model to investigate filovirus vaccines. This model is stringent and conservatively mimics human disease, with similar pathophysiology but accelerated disease progression, with very high mortality, which is 100% with Ebola, Ebola Sudan or Marburg viruses, but is around 60-80% with BDBV based on the few studies reported in the literature (Falzarano 2011, Mire 2013, O'Donnell 2026).

Due to the paucity of BSL4 laboratories able to conduct such studies, there is currently a delay in the availability of these data for BDBV vaccines in development. Therefore, alternative models have been investigated, in particular the ferret model that confers uniform lethality and could be seen as an additional/alternative model to the macaque model, at least to support decisions on advancing candidates into late-stage clinical trials. To what extent vaccine immunity in ferrets resembles human immune responses remains unclear.

Data from non-human primates (NHPs), particularly cynomolgus macaques, is considered very relevant because of the reasons indicated above, and in principle should be generated for all vaccine candidates before initiating ring vaccination clinical trials. However, they are not required for starting Phase I/II clinical trials. The design of such studies should be discussed with regulatory authorities, and the focus would be to investigate the efficacy of a single vaccine administration given 14-28 days before challenge. Vaccination closer to challenge, e.g. 3 or 7 days earlier, would provide additional information.

The extent to which ferret data could replace NHP studies should be discussed on a case-by-case basis, taking into account the level of prior knowledge of the platform with respect to protection for other filoviruses. If filovirus vaccines with the same platform technology failed to demonstrate protection in NHP studies, it will be required to generate NHP data with BDBV specific challenge.

Acceptance of the ferret model could occur on a case by case based on the justification above, including:

- **Susceptibility:** Ferrets are highly susceptible to wild-type BDBV without the need for viral adaptation.
- **Pathology:** They can accurately recapitulate human BDBV disease, including viremia, coagulopathy (abnormal clotting), and uncontrolled viral replication in major organs.
- **Advantages:** Because they are a small-animal model, they are more cost-effective, allow for larger sample sizes, and help relieve the extreme demand for NHPs resources.

CLINICAL TESTING

Early clinical development

The focus of the early clinical trials is safety and immunogenicity in healthy adult participants to select an appropriate dose to be moved into late-stage clinical trials in the shortest possible timeframe.

Prior knowledge from the same platform technology, in particular with other filovirus vaccines would allow to focus the doses to be tested in early clinical trials so to allow a rapid progression of dose selected.

Single dose vaccines should be the target of these studies to potentially allow rapid deployment in outbreak settings. However, 2 dose-schedules, if considered relevant, could be tested in parallel, provided this is not causing delays with the advancement of candidate vaccines.

The study should be ideally conducted in the African region to ensure a smooth transition to Phase III efficacy/safety demonstration (ring vaccination study).

In case the first-in-human study is planned in other regions, set up of clinical trials in Africa either as separate clinical trial or as part of a seamless Phase I/II/III trial, needs to be considered and advanced swiftly.

Rapid approval from NRAs in countries is instrumental to ensure timely initiation of these clinical trials.

The early Phase I clinical trials should be controlled, with a placebo arm. Inclusion should be for healthy individuals with no underlying conditions that could affect the results of the trial, e.g. immunocompromised subjects.

Safety should be the primary endpoint. Safety collection should include solicited adverse events (AE)s in the first 7 days, unsolicited AEs over the first month after last dose and collection of serious SAEs and AEs of Special Interest (AESIs) to be agreed with regulators over 6 months following last dose.

In order to advance vaccines into late-stage clinical trials, safety data over the first 2-4 weeks for vaccines for which there is sufficient prior knowledge can be considered sufficient.

The sample size for these studies can be limited to e.g. 20-30 subjects per arm. However, the actual minimal number required may vary depending on the prior knowledge on the platform technology and plans to conduct further clinical trial before starting the Phase III clinical trial.

Staggered dose escalation process with safety review from Independent Safety Monitoring Team should be considered based on safety data up to Day 7. Depending on the platform data, it could be justified to run different dose levels in parallel. In addition, also depending on the available data, the need for sentinel dosing with safety checks after few participants are recruited in each arm and safety data up to 48h are available should be considered.

Immunogenicity should be a secondary endpoint. Humoral response in terms of binding and neutralising antibodies (GMTs/GMCs and seroconversion) should be measured at least on Day 14 and Day 28 after last dose (Day 7-10 could be considered in addition but should not be on the critical path for advancing the vaccines). If 2 doses are included, immunogenicity before second dose should be also measured. Sera should be retained for additional exploratory analyses such as for other type of functional antibodies. Longer term immunogenicity testing after e.g. 6 and 12 months should also be included in the protocol.

Dose selection should be based on safety and immunogenicity data at 4 weeks after last dose.

Developers need to discuss and agree with regulatory authorities their selected dose.

In case the clinical data from the Phase I clinical trial(s) leave significant uncertainties with respect to the dose selection for pivotal Phase III clinical trial, larger Phase I/II clinical trials might be needed. Timely consultation with regulatory authorities is critical.

As children are affected by Bundibugyo disease (BVD) with high mortality reported, it is necessary to generate as early as possible data in the full paediatric age range, so as to allow their inclusion in ring vaccination trial to the extent possible. Prior knowledge should inform the initial doses to be tested in younger children.

In this sense, clinical trials to measure safety, immunogenicity and to determine dose selection in children should be initiated as soon as possible, once preliminary results at 4 weeks in adults' clinical trial(s) are available.

However, to execute the above, paediatric specific stopping rules must be clearly defined. Since the trial transitions immediately from adults to children based on preliminary 4-week adult safety data, explicit and non-negotiable regulatory thresholds for stopping or pausing the trial must be codified. These rules must specifically account for paediatric-focused adverse events, such as severe injection site reactions, persistent crying, systemic high fevers, or neurological changes.

Age strata should be defined and customised based on previous knowledge from the platform technology, e.g. adolescents 12-17, children 6-11 and younger children 1-3 and 3-5. Alternative age-grouping or pooling age groups may be possible or necessary, if justified by the knowledge accumulated on a specific platform and based also on adult data. At least 20 children per dose of the investigational vaccine in each age bracket should be included. In terms of comparator, the preferred option would be administration of another clinically indicated vaccine such as a conjugated typhoid vaccine. Administration of placebo could be possible, pending agreement by NRAs and Ethics Committees that must approve the clinical trial. Alternative study design should be timely discussed with regulators.

Safety and immunogenicity assessment should follow the same requirements as for adults. Recruitment could occur in parallel across age cohorts, at least for adolescents and children 6-11. For younger children, a staggered inclusion based on at least 7 days reactogenicity and safety data in older children and based on specific platform technology considerations should be considered.

These recommendations may have to be adjusted in case there are specific safety concerns with any of the candidate vaccines.

Regulatory and ethics review of clinical trial protocols should be accelerated to the extent possible considering the emergency.

Phase II/III ring vaccination clinical trial (Core protocol Bundibugyo clinical trial)

Developers are encouraged to consider and support ongoing efforts to conduct platform trials (e.g. Core protocol Bundibugyo clinical trial) for Phase II/III. This includes an evaluation of whether the platform is suitable for obtaining the evidence needed to support a benefit risk evaluation for the specific candidate and how remaining evidence needs may be addressed within the overall development program, including where appropriate, during earlier phases (see above). Consideration should also be given to the extent to which specific objectives (e.g. additional endpoints specific to the candidate) can be accommodated without unduly complicating or compromising the platform's design and efficient conduct. Where participation in a platform is warranted, design aspects specific to the candidate vaccine should be laid out in a candidate specific sub-protocol or amendment.

For any other proposed pivotal clinical trial, prospective formulation of a precise estimand in terms of intervention, target population, endpoint, summary measure and handling of intercurrent events can facilitate planning, analysis, interpretation, and communication of eventual results and should be included in the protocol. The suitability of the study design and statistical analysis should be justified, and potential misalignment and corresponding limitations discussed. Where an alternative development or trial strategy is envisaged, early engagement with regulators is encouraged to ensure alignment on the proposed design, analysis, and evidentiary considerations.

Where the Phase II component is to be embedded in a seamless Phase II/III trial (e.g. ring vaccination platform trial), safety should be the main objective. Immunogenicity determination should be attempted as well, notwithstanding the on-the-ground complexity of collecting, storing and shipping samples from potentially infected individuals. Cohorts should mirror the age brackets described above. The clinical trial protocol should provide specific decision time points/criteria for proceeding from the

Phase 2 to the Phase 3 part to facilitate swift and unambiguous decision making, while including appropriate measures to protect the study integrity.

In general, a ring vaccination prospective randomized clinical trial with identification of contacts and individual randomization within the ring of direct contacts to immediate vaccination or placebo is an acceptable approach to accrue evidence on the efficacy of BDBV vaccines that could support regulatory approval. Administration of vaccine to participants initially assigned to placebo e.g. at day 28 can be acceptable where it does not interfere with primary endpoint assessment and corresponding effect size evaluation.

The planned timing of interim and final analyses and the corresponding decision criteria should be described explicitly. In particular, the target event numbers triggering interim analyses and the final analysis should be pre-specified. Sample size considerations for other endpoints should be explored to obtain sufficient additional information on the vaccine efficacy profile, but also to explore additional outcomes e.g. mortality and severity of disease.

As more than one vaccine could be included in the trial, potentially at different time points, restricting the analysis of trial results corresponding to individual vaccines to concurrent controls is recommended. Each candidate vaccine may require a matched control arm. Pooling of control arm data can be acceptable but requires justification, as differences between vaccine candidates in terms of in-/exclusion criteria or other characteristics, may hamper comparability and require that comparisons are restricted to matched controls only. In general, appropriate measures must be implemented to protect study integrity when interim analyses are conducted, including when investigational arms may be added or dropped.

A single independent monitoring committee should be established not only for the whole platform clinical trial but also possibly covering for the ongoing post-exposure prophylaxis clinical trial (EBO-PEP).

As sample size, endpoint, and other design and analysis considerations may differ between candidates investigated in the platform, they should be guided by the best available knowledge for the specific candidate, as well as prespecified in a per-candidate sub-protocol or amendment.

Adjustment by primary contact / ring should be considered, especially if attack rates across rings is highly heterogeneous. More importantly, adjustment for potentially predictive covariates should be considered, as presence of heterogeneous treatment effects could adversely affect power.

Immunogenicity testing, to the extent possible, should be conducted so to investigate correlates of protection.

Inclusion of paediatric age subjects should occur as soon as possible, pending safety data availability from the dedicated early clinical trials discussed above.

Inclusion of pregnant women should be allowed in the clinical trial, provided there is sufficient evidence from a platform technology perspective based on previous preclinical DART studies and clinical experience that the vaccine does not negatively affect the foetus. To further expand regulatory considerations to ensure maternal-foetal safety, immunogenicity could be estimated.

In the event that a vaccine (e.g. Ervebo) is established as an effective intervention against BDBV disease, the trial may use or transition to an active-controlled design using the vaccine as the comparator. This will require that success criteria are reconsidered, including non-inferiority or superiority comparisons of the candidate vaccines to the new, active control. The latter aspects would

need to be discussed in a timely manner with relevant regulators. Also, the impact of any intervention successful in the post-exposure prophylaxis clinical trial(s) would have to be considered in terms of impact on clinical trial design, reiterating the criticality of timely discussion of adapted study design with regulators.

A demonstration of efficacy based on non-inferiority comparisons requires prospective justification of assay sensitivity and the constancy assumption, in order to determine an appropriate non-inferiority margin. This can be challenging especially as efficacy of the comparator may be limited and, or corresponding effect size estimates uncertain. Options to use non-concurrent control data to justify assay sensitivity of a non-inferiority comparison and quantify vaccine efficacy compared to placebo could be considered. This will require justification that potential time trends in event rates and treatment effects are unlikely. Approaches to analytically quantify and adjust for potential time trends should be considered. In case no suitable non-inferiority margin can be determined, demonstrating superiority to an active control may be acceptable to also conclude superiority to placebo. However, the smaller expected treatment difference compared with an active comparator can substantially increase sample size requirements, while uncertainty regarding the active comparator's effect may complicate sample size planning.