

AKEURA

White Paper

Research at the Speed of Outbreak

Embedding Clinical Research and Vaccine Development into Emergency Response

Lessons learned from the Bundibugyo Ebola disease outbreak in Africa

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Index

- Executive Summary 03
- Introduction 04
- A Preparedness Gap With No Easy Fix 05
- Epidemiological Context 06
- Vaccine Development Landscape 06
- Clinical Research Opportunities 07
- Key Challenges in Clinical Development 08
- Lessons Learned From Ebola Case Studies 09
- Strategic Recommendations 12
- Conclusion 13
- About the Authors 14
- About AKEURA 14
- References 15

Executive Summary

The 2026 Bundibugyo virus disease outbreak in the Democratic Republic of Congo and Uganda has created an urgent public health and research priority. In contrast to Zaire Ebola virus disease, no licensed vaccine or approved therapeutic currently exists for Bundibugyo virus disease. By June 2026, more than 1,000 confirmed cases had been reported in the Democratic Republic of Congo, raising concerns about cross-border spread. Population mobility, insecurity, and health-system constraints highlight the need for a coordinated public health response, regional clinical trial readiness, and accelerated vaccine development.

Based on five case studies, we highlight the following tensions:

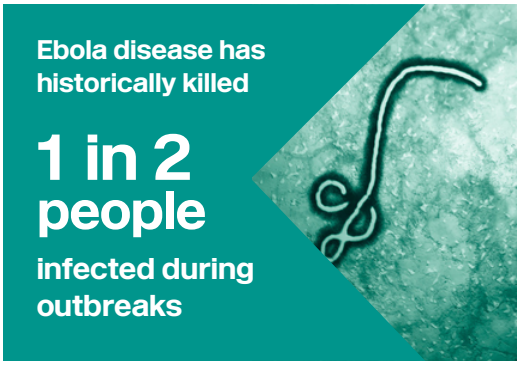
- The need for predictable funding for product development, manufacturing readiness, clinical trial preparedness, and equitable access planning before and during outbreaks.
- Lack of a unified roadmap linking candidate selection, protocol development, regulatory strategy, site activation, community engagement, manufacturing readiness, deployment planning, and post-authorization evidence generation.
- An insufficient number of prequalified outbreak-ready clinical trial sites, trained research teams, emergency standard operating procedures, laboratory networks, cold-chain capacity, mobile data capture, and rapid contracting mechanisms.
- Flexible manufacturing of type-specific vaccines, parallel preclinical and clinical preparation, and early planning for scale-up if safety and immunogenicity data are supportive.
- Regulatory mechanisms such as rolling submissions, reliance and joint review models, emergency review procedures, master protocols, and pre-agreed safety monitoring frameworks for regulatory approval, which maintain participant protection and scientific integrity.
- Community engagement from the start of protocol design to ensure culturally appropriate communication, transparent risk-benefit messaging, and mechanisms for community feedback.

This white paper aims to define priority clinical research opportunities during the 2026 outbreak and explore the operational, regulatory, scientific, and ethical factors that influence rapid trial implementation. It also provides practical recommendations for sponsors, contract research organizations, regulators, funders, and outbreak-response partners to facilitate timely study initiation, strengthen collaboration, and accelerate the generation of evidence needed to support vaccine development and outbreak control.



Introduction

Ebola virus is a filovirus, an enveloped, negative-sense RNA virus in the family Filoviridae [1], that causes Ebola virus disease (EVD), a severe hemorrhagic illness in humans and nonhuman primates. EVD is highly lethal, with case fatality rates of 50% or higher in outbreaks [2]. Human-to-human spread occurs through direct contact with blood, body fluids, tissues, or contaminated objects. Clinically, Ebola attacks the whole body rather than one organ system: high fever, vomiting, diarrhea, coagulopathy, and multiorgan failure are recurrent features [3].



Ebola's recorded history starts in 1976, when outbreaks were recognized almost simultaneously in what is now the Democratic Republic of the Congo and Sudan; the disease's name comes from the Ebola River near Yambuku [4]. The first outbreak in Zaire was contained in under 11 weeks, and it established the basic clinical and epidemiological picture [5].

After a relatively quiet period in the 1980s and early 1990s, outbreaks reappeared, and new species were discovered in Côte d'Ivoire and Uganda. The virus's ecological reservoir and transmission dynamics remained incompletely understood, but bats emerged as the leading suspected reservoir. The 2014–2016 West African outbreak changed Ebola's public history: it started in Guinea, spread to Liberia and Sierra Leone, and became the largest and deadliest outbreak on record, with 28,616 cases and 11,310 deaths [3].

Before the West African epidemic, no licensed treatment or vaccine were available, only supportive care. Nowadays, treatment has moved from supportive care alone to antibody therapy. Based on the PALM trial in which four investigational therapies for EVD were compared in the Democratic Republic of Congo, during the outbreak in 2018 [6], The World Health Organization (WHO)'s 2022 guideline recommends the use of two monoclonal antibodies, mAb114 and REGN-EB3 [7]. These should be given as soon as possible after laboratory confirmation. Supportive care still matters a lot: the WHO guidance and reviews both emphasize early diagnosis, fluid and electrolyte replacement, symptom control, and broader optimized supportive care as major survival drivers [7, 8].

Ebola prevention now rests on one licensed vaccine –Ervebo– for EVD itself, plus outbreak-focused ring vaccination and targeted vaccination of people at highest risk. Ring vaccination involves vaccinating the people around a confirmed Ebola case, not the whole population. In practice, that usually includes household members, caregivers, health workers, and others who had direct or indirect exposure, with vaccination offered quickly after a case is identified. When contact tracing is difficult, programs may use a targeted geographic strategy instead, vaccinating everyone in a neighborhood or village. Protective efficacy was demonstrated in an open-label, cluster-randomized ring vaccination trial in the communities of Conakry, Guinea, and Sierra Leone [9, 10].

The analysis included a total population of 11 841 individuals, assigned to 117 clusters (rings) vaccinated either immediately or after a 21-day delay. rVSV-ZEBOV showed up to 100% efficacy, with no cases of EVD as of 10 days after immunization, compared to 23 cases in yet unvaccinated subjects [9]. In fact, new cases of EVD were not diagnosed from six days after vaccination, indicating the rapid onset of protective immune responses considering that exposure may have occurred prior to immunization [10].

A two-dose Ebola vaccine regimen was developed for the prevention of Ebola virus disease, combining Zabdeno (Ad26.ZEBOV-GP – prime dose) and Mvabea (MVA-BN-Filo – boost dose). Zabdeno initially received EU marketing authorization under exceptional circumstances on 1 July 2020. Although its authorization was initially granted for five years and converted to unlimited validity in 2025, the vaccine was never marketed in the European Union. On 1 May 2026, at the request of the marketing authorization holder, the European Commission withdrew the marketing authorization. As Zabdeno was intended to be administered together with Mvabea as part of the complete vaccination regimen, the marketing authorization for Mvabea was also withdrawn.

The 2026 Bundibugyo virus outbreak is particularly significant because it has emerged in settings where emergency response, surveillance, community engagement, and clinical research must operate simultaneously [11-14]. While effective vaccines exist for Ebola disease caused by Zaire ebolavirus, those products do not show evidence of protection against Bundibugyo virus disease, and the available evidence does not support routine use of Zaire-specific vaccines as a substitute outside controlled research settings [9, 15-18].



UP TO
100% *vaccine efficacy in the ring vaccination trial*

No cases reported 10 days or more after immunization, compared with 23 cases among individuals not yet vaccinated

Historically, Ebola disease case fatality rates have varied widely by virus species, outbreak setting, timeliness of detection, access to supportive care, and quality of infection prevention and control. The Bundibugyo outbreak therefore requires a dual approach: immediate outbreak control through proven public health measures and rapid clinical research to close the countermeasure gap for a less-studied Ebola virus species.

A Preparedness Gap with No Easy Fix

Absence of licensed Bundibugyo-specific vaccines and therapeutics

The central challenge is the absence of licensed vaccines or specific approved therapeutics for Bundibugyo virus disease. This creates an immediate need to accelerate candidate vaccines while maintaining appropriate standards for safety, ethics, regulatory oversight, and community trust.

Transmission in complex operating environments

The outbreak is unfolding in environments where insecurity, population movement, strained health infrastructure, and cross-border transmission risks may complicate case detection, isolation, contact tracing, referral pathways, and trial implementation.

Fragmented research and response systems

A rapid response requires alignment between ministries of health, regulators, ethics committees, sponsors, vaccine developers, implementing partners, community leaders, and funders. Without a unified roadmap, clinical development may be delayed by sequential decision-making, duplicative approvals, unclear data-sharing arrangements, and insufficient operational readiness.

Epidemiological Context

Outbreak response timelines leave little room for delayed evidence generation, as the 2026 Bundibugyo outbreak demonstrates. The outbreak was confirmed in May 2026 following laboratory identification of Bundibugyo virus in the Democratic Republic of Congo, with Uganda reporting related cases shortly thereafter. WHO declared the event a public health emergency of international concern, and response measures have included enhanced surveillance, case management, infection prevention and control, contact tracing, cross-border preparedness, deployment of medical supplies, and community engagement [11-14, 19-21].

By late June 2026, the outbreak had expanded across affected provinces in the Democratic Republic of Congo, with additional confirmed cases in Uganda. Case counts remain subject to change as surveillance and laboratory confirmation continue. The outbreak has also underscored the importance of rapid data flows, active case finding, community-based surveillance, and safe referral pathways.

Key epidemiological and operational features include delayed recognition of early transmission, possible circulation before formal outbreak declaration, cross-border movement, transmission in highly mobile mining and commercial corridors, risks to healthcare workers, variable contact tracing coverage, and the need for sustained community trust. These factors influence where and how clinical research can be initiated without disrupting the emergency response.

Diagnostic readiness is also central to the response. Frontline Ebola diagnostic tools used in previous outbreaks have often been optimized for Zaire ebolavirus, while Bundibugyo virus detection may require pan-filovirus or Bundibugyo-capable assays available through reference or specialized laboratory networks. Delays in confirmation can prolong transmission windows, slow isolation, and reduce the feasibility of contact-based research approaches [12-14, 19-21].

Vaccine Development Landscape

Existing Ebola vaccines and their limitations

At the time of the Bundibugyo outbreak, licensed Ebola vaccines were designed for Ebola disease caused by Zaire ebolavirus. Ervebo has demonstrated high effectiveness against Zaire ebolavirus disease, while the Ad26.ZEBOV/MVA regimen has been used for prophylactic prevention strategies; however, neither product is licensed for Bundibugyo virus disease. WHO guidance indicated that evidence for cross-protection against Bundibugyo virus is limited and insufficient to support routine programmatic use outside controlled research settings. This limitation creates a clear need for Bundibugyo-specific vaccines and broader pan-ebolavirus vaccine strategies [9, 15-18].

Emerging Bundibugyo vaccine candidates

The Coalition for Epidemic Preparedness Innovations (CEPI) has announced accelerated support for three investigational Bundibugyo ebolavirus vaccine candidates, using a portfolio approach to increase the likelihood that at least one candidate can progress rapidly toward clinical evaluation [22, 23].

Platform	Developer / Partner	Strategic Rationale
rVSV-based Bundibugyo vaccine	International AIDS Vaccine Initiative (IAVI) partners	Builds on the platform used for the licensed Zaire ebolavirus vaccine and has the strongest relevant preclinical rationale among the early candidates, although human clinical evaluation is still required.
ChAdOx1 viral vector	University of Oxford / Serum Institute of India	Uses a well-characterized viral vector platform with potential for rapid manufacturing, clinical-grade dose production, and scale-up in an outbreak setting.
mRNA vaccine	Moderna	Provides rapid design adaptability, scalable manufacturing potential, and a platform suited to accelerated response when a new viral target is identified.

The multi-platform approach is strategically important because no single vaccine development pathway is guaranteed to succeed. Advancing rVSV, ChAdOx1, and mRNA candidates in parallel increases the likelihood that at least one candidate can progress toward human trials, while also strengthening preparedness for future outbreaks caused by other filoviruses [16, 17, 22, 23].

Clinical Research Opportunities

1 | Rapid Adaptive Trial Designs

Adaptive and platform trial designs can support the evaluation of multiple investigational products under a shared operational framework [24-27]. Such designs may reduce duplication, accelerate decision-making, and allow candidates to be added, modified, or discontinued based on emerging evidence. Seamless Phase I/II approaches may also help compress timelines while preserving safety oversight and data integrity. The US Food & Drug Administration [28] and the European Medicines Agency [29] provide guidance on the appropriate use of adaptive designs for clinical trials to provide evidence of the effectiveness and safety of drugs or biologics, including vaccines.

2 | Outbreak-Embedded Trials

Outbreak-embedded trials should be designed to complement not compete with the emergency response. Ring vaccination, targeted prophylaxis, healthcare worker cohorts, and high-risk contact studies may provide practical pathways for evaluating safety, immunogenicity, and early effectiveness signals where ethically and operationally appropriate. Five case studies are discussed below.

3 | Biomarker and Immunogenicity Studies

Immunogenicity studies are essential to identify potential correlates of protection and to understand cross-reactive immune responses across orthoebolavirus species. These studies can support future regulatory decisions, dose selection, booster strategies, and development of broader vaccine candidates. So far, Ebola appears to have candidate correlates, not a universally accepted one: neutralizing or binding anti-GP antibody responses, plus some cellular-response signatures, are the main contenders [30-32], while the strongest validation still comes from animal-model and immunogenicity data rather than a confirmed human protective cutoff.

4 | Multi-Strain and Pan-Ebolavirus Vaccine Development

The outbreak strengthens the case for investment in vaccines that provide broader protection across Ebola virus species. Research priorities include pan-ebolavirus antigens, broadly neutralizing antibodies, heterologous prime-boost strategies, and platform technologies that can be rapidly adapted to new viral threats.

5 | Real-World Evidence Generation

Outbreak data can generate real-world evidence to support regulatory assessment, public health decision-making, and implementation planning. This requires harmonized data standards, rapid ethics approvals, secure data-sharing agreements, and integration between surveillance systems and clinical research platforms.

6 | Therapeutic and Post-Exposure Prophylaxis Research

Although this paper focuses primarily on vaccine development, therapeutic and post-exposure prophylaxis studies are also important. Candidate monoclonal antibodies [33], antiviral agents [34, 35], and combination regimens may provide opportunities to reduce mortality among confirmed cases or prevent disease among high-risk contacts, provided that trials are ethically designed and integrated into clinical care pathways.

Key Challenges in Clinical Development

Scientific Challenges

Scientific uncertainties include genetic diversity across Ebola virus species, limited human efficacy data for Bundibugyo-specific vaccines, incomplete understanding of immune correlates of protection, limited knowledge of Bundibugyo reservoirs and spillover dynamics, and potential variability in immune responses across populations at risk.

Operational Challenges

Operational constraints may include insecurity, limited access to affected communities, displacement, highly mobile populations, workforce shortages, cold-chain requirements, limited laboratory capacity, data connectivity gaps, contact tracing limitations, and the need to align trial procedures with outbreak-response workflows.

Regulatory and Ethical Challenges

Rapid trial launch requires accelerated but rigorous ethics and regulatory review, clear informed consent processes, community engagement, safety oversight, adverse event reporting pathways, and transparent governance for data access and interim analyses.

Economic and Funding Challenges

The commercial market for Bundibugyo-specific countermeasures is limited, which increases dependence on public, philanthropic, and multilateral financing. Sustainable progress will require predictable funding for product development, manufacturing readiness, clinical trial preparedness, and equitable access planning before and during outbreaks.

Lessons Learned From Ebola Case Studies

◆ Case Study 1: Ebola ça Suffit Ring Vaccination Trial, Guinea

The Ebola ça Suffit trial in Guinea used a cluster-randomized ring vaccination design to evaluate rVSV-ZEBOV during the West Africa Ebola outbreak. Rather than recruiting the general population, the trial enrolled individuals linked socially or geographically to a confirmed Ebola case, including contacts and contacts of contacts. Rings were randomized to immediate vaccination or delayed vaccination, allowing the trial to generate evidence while also supporting transmission interruption. The design was particularly valuable because it followed the epidemic, concentrated recruitment among people at higher risk, and allowed interim analyses as transmission patterns changed [9, 18].

Implication for clinical evidence generation during outbreak response:

Ring-based or contact-network trial designs may be appropriate where transmission chains are identifiable, and contact tracing is functioning. For Bundibugyo vaccine candidates, such designs could prioritize high-risk contacts, healthcare workers, and contacts of contacts while aligning trial activities with outbreak-control operations.

◆ Case Study 2: STRIVE Vaccine Trial, Sierra Leone

The Sierra Leone Trial to Introduce a Vaccine Against Ebola, known as STRIVE, was an individually randomized phase II/III trial of rVSV-ZEBOV among healthcare and frontline response workers. Conducted during and immediately after the West Africa outbreak, STRIVE enrolled more than 8,600 participants and required rapid development of trial infrastructure, including vaccination sites, participant follow-up systems, data centers, reliable power supply, cold-chain capacity, and clinical research training for national staff. The trial also demonstrated the importance of sustained communication, community engagement, and rumor management before and during recruitment [36-38].

Implication for clinical evidence generation during outbreak response:

Trial readiness cannot depend solely on protocol approval. Successful execution requires operational investment in people, power, cold chain, mobile communication, participant follow-up, training, and community engagement. For the Bundibugyo response, regional site networks should be activated with practical readiness packages before vaccine candidates enter the field.

Case Study 3: PALM Therapeutics Trial, Democratic Republic of Congo

The PALM trial evaluated investigational Ebola therapeutics during the 2018–2019 outbreak in North Kivu and Ituri, Democratic Republic of Congo. The study randomized patients with laboratory-confirmed EVD to receive investigational therapies alongside enhanced supportive care. It was implemented in Ebola treatment units despite insecurity, resource constraints, and operational complexity. Independent data and safety monitoring enabled interim review, and the trial generated actionable evidence that identified therapies associated with improved survival [6].

Implication for clinical evidence generation during outbreak response:

Randomized studies can be ethically and operationally feasible during Ebola outbreaks when they are embedded in treatment units, supported by strong clinical care, and governed by independent safety oversight. For Bundibugyo, therapeutic, prophylaxis, and vaccine trials should be designed with clear interim decision rules, harmonized standard-of-care packages, and operational integration into case management.

Case Study 4: Community Engagement Lessons from EBOVAC-Salone & PREVAC

Ebola vaccine trials in Sierra Leone, including EBOVAC-Salone and PREVAC, reinforced that community engagement is not only a recruitment function but a core ethical and operational requirement. Community liaison and social science teams helped identify rumors, community concerns, and participant information needs, then adapted communication approaches through reciprocal dialogue, locally relatable messaging, respectful engagement, and relationship-building. These experiences highlight the importance of combining clinical operations with social science and community feedback loops [37, 38].

Implication for clinical evidence generation during outbreak response:

Community engagement should be treated as a trial-critical workstream with dedicated staff, budget, social science input, rumor tracking, and local-language communication. This is particularly important where mistrust, stigma, insecurity, or prior negative experiences with emergency response may affect participation and retention.

Case Study 5: WHO R&D Blueprint and Preparedness-Based Research

The WHO R&D Blueprint was developed in response to the recognition that research systems must be prepared before epidemics escalate. Lessons from the West Africa Ebola epidemic showed that vaccine and therapeutic development could be accelerated when candidate products, trial designs, ethical pathways, regulatory coordination, funding, and partnerships were mobilized rapidly. The Blueprint model emphasizes priority pathogen roadmaps, product profiles, coordinated governance, data-sharing, and the integration of research into public health emergency response [6, 9, 16-18, 36-38].

Implication for clinical evidence generation during outbreak response:

Preparedness should be operationalized before candidate products arrive at trial sites. This includes pre-positioned master protocols, ethics and regulatory reliance mechanisms, site-readiness checklists, laboratory qualification plans, data-sharing agreements, pharmacovigilance systems, and rapid funding triggers.

Case Study	Core Lesson	Application to Bundibugyo Trial Execution
Ebola ça Suffit, Guinea	Ring vaccination designs can generate evidence while supporting outbreak control [9, 18].	Use contact networks, contact-of-contact mapping, and high-risk cohorts to prioritise enrolment while supporting outbreak control.
STRIVE, Sierra Leone	Infrastructure, training, cold chain, follow-up systems, and communication must be built rapidly and locally [36-38].	Activate regional site-readiness packages and invest in trained national research teams.
PALM, DRC	Randomised trials can be embedded in Ebola treatment units during insecurity when clinical care and safety oversight are strong [6].	Embed study procedures into clinical care workflows, ensure independent safety monitoring, and use adaptive decision rules for interim evidence.
EBOVAC-Salone and PREVAC, Sierra Leone	Trust requires reciprocal communication, local relationships, respect, and social science feedback [37, 38].	Deploy community engagement teams before recruitment, maintain rumour-management systems, and tailor consent communication to local concerns.
WHO R&D Blueprint	Preparedness before escalation reduces delays during emergency research [16, 17].	Pre-position master protocols, regulatory reliance pathways, site-readiness packages, data systems, laboratory networks, and rapid funding mechanisms.

Strategic Recommendations

To advance clinical evidence generation during outbreak response, we have turned the lessons learned into six strategic recommendations.

Establish an Integrated R&D-to-Access Framework

Stakeholders should align on a unified roadmap linking candidate selection, protocol development, regulatory strategy, site activation, community engagement, manufacturing readiness, deployment planning, and post-authorization evidence generation.

Strengthen Regional Clinical Trial Capacity

Investment should prioritize prequalified outbreak-ready clinical trial sites, trained research teams, emergency standard operating procedures, laboratory networks, cold-chain capacity, mobile data capture, and rapid contracting mechanisms across affected and at-risk countries.

Accelerate Platform-Based Vaccine Development

Sponsors and funders should support platform technologies that enable rapid antigen substitution, flexible manufacturing, parallel preclinical and clinical preparation, and early planning for scale-up if safety and immunogenicity data are supportive.

Implement Adaptive Regulatory Pathways

Regulators and ethics committees should consider implementing agile oversight mechanisms that accelerate outbreak-embedded research while maintaining participant protection and scientific integrity. Practical approaches include emergency review or emergency-use pathways where legally available, rolling data submissions, joint or reliance-based review models, master protocols and pre-positioned protocol templates, master agreements, and pre-agreed pharmacovigilance, safety monitoring, and reporting frameworks.

Prioritize Community Engagement and Trust

Community engagement should be embedded from the earliest stages of protocol design. Trial teams should work with local leaders, survivors, healthcare workers, and civil society groups to ensure culturally appropriate communication, transparent risk-benefit messaging, and mechanisms for community feedback.

Operational Strategy for Executing Clinical Trials in Outbreak Settings

Experience from previous Ebola outbreaks demonstrates that clinical trials can be implemented during emergencies when research is integrated into the public health response rather than treated as a parallel activity.

Conclusion

The 2026 Ebola disease outbreak caused by Bundibugyo virus highlights a persistent preparedness gap: global vaccine progress has not advanced evenly across all Ebola virus species. The absence of licensed Bundibugyo-specific vaccines and therapeutics requires a coordinated response that integrates public health fundamentals with accelerated clinical research.

If implemented effectively, outbreak-embedded research can do more than address the 2026 Bundibugyo emergency. It can generate evidence for next-generation Ebola vaccines, strengthen African clinical research infrastructure, improve diagnostic and therapeutic readiness, reinforce regulatory preparedness, and build durable systems for future epidemic threats.



About the Authors

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Sobe brings over 18 years of experience in the planning, execution, and oversight of clinical research across Sub-Saharan Africa. His experience includes leading clinical operations across multiple African countries and building strong partnerships with global sponsors, national regulatory authorities, and ethics committees. His therapeutic experience spans multiple high-burden diseases, including Ebola, tuberculosis, malaria, and Lassa fever.

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Laurence brings more than two decades of experience in vaccine R&D and clinical leadership. Her senior roles at large and small biopharma companies, as well as in clinical research, have enabled her to contribute to high-impact vaccine programs for HPV, Zika, and Norovirus. Her expertise spans regulatory, medical, and strategic functions across infectious disease pipelines.

About AKEURA

AKEURA is a specialist contract research organization (CRO) helping sponsors advance medicines across their full lifecycle. Our dual expertise in early- through late-phase clinical development and real-world evidence is delivered by hands-on clinicians, scientists, and epidemiologists, drawing on more than 25 years of experience.

We're built on the belief that a team of the right people, giving everything they've got to the needs of the study, will outperform any other approach. Our team of more than 500 experts spanning five continents has delivered more than 1,000 studies in over 75 countries, including regions where patients are hardest to reach. AKEURA exclusively focuses on three therapeutic areas: neuroscience, infectious diseases and vaccines, and cardiometabolic diseases. Across each, we bring the experience, reach, and hands-on expertise to give every promising medicine the study it deserves.

For more information, visit **akeura.com**.

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