

BX-1330

Riftavir — a fixed-sequence antibody and polymerase inhibitor pair for Rift Valley fever.

Rift Valley fever moves with rainfall. Epizootics follow heavy rain across East Africa and the Arabian peninsula, livestock abort in large numbers, and the people who handle them become infected. Most recover; a minority develop retinitis, encephalitis or a haemorrhagic syndrome with case fatality above 50 per cent. There is a licensed veterinary vaccine and nothing at all for humans.

Indication	Severe Rift Valley fever in humans, including the haemorrhagic, encephalitic and ocular forms, and post-exposure prophylaxis after occupational exposure.
Modality	Co-administered pair: a human IgG1 monoclonal antibody against the Gn glycoprotein, and a small-molecule bunyavirus L-polymerase inhibitor, both intravenous
Target	Rift Valley fever virus Gn glycoprotein head domain; and the L polymerase endonuclease domain
Route and schedule	Single 20 mg/kg antibody infusion on day 1, with 400 mg polymerase inhibitor intravenously twice daily for 10 days
Development stage	Phase 1, healthy volunteers
Current study	HEADWATER-1 (NCT-BX1330-01) — randomised, double-blind, placebo-controlled study evaluating each component alone and in combination, in ascending dose cohorts
Containment	BSL-3 enhanced with vector containment; select agent registration; staff vaccinated where available
Regulatory pathway	FDA Animal Rule for the severe human forms, 21 CFR 314 Subpart I, with an outbreak-activated randomised protocol

Mechanism of action

Rift Valley fever virus has a tripartite negative-sense genome and two envelope glycoproteins, Gn and Gc, arranged in an ordered lattice on the virion surface. Gc carries the class II fusion machinery; Gn caps it and carries the principal neutralising epitopes. The antibody component of BX-1330 binds the Gn head domain and locks the lattice, preventing the Gc rearrangement required for fusion in the endosome, and it does so at an epitope conserved across the East African, West African and Arabian peninsula lineages that have caused human outbreaks. It clears circulating virus efficiently and it does not enter the eye or the central nervous system in useful concentration, which is the reason for the second component. The small-molecule component inhibits the endonuclease domain of the L polymerase, the activity the virus uses to cap-snatch host messenger RNA, and it is a small, lipophilic molecule with an unbound brain-to-plasma ratio of 0.55 and measurable vitreous penetration. Rift Valley fever kills through hepatic necrosis and haemorrhage and it blinds and disables through retinitis and encephalitis, and those are pharmacologically different problems. The programme is a fixed pair because neither component alone addresses both.

Why this disease

Rift Valley fever is a climate-driven disease in the most literal sense. Unusually heavy rainfall floods depressions where Aedes eggs have lain dormant for years, the eggs hatch already carrying the virus, and an epizootic begins in livestock within weeks. Sheep and cattle abort almost universally and newborn lambs die at close to one hundred per cent.

Human cases follow the animal cases, and they follow them through the hands of herders, abattoir workers, veterinarians and the women who handle obstetric material.

Most human infection is a self-limiting febrile illness. The problem is the minority. A few per cent develop late-onset retinitis, which frequently leaves permanent macular scarring and visual loss; a smaller proportion develop encephalitis, sometimes weeks after the acute illness has resolved; and around one per cent develop a haemorrhagic hepatic form with case fatality above 50 per cent. Because the denominator is large, the absolute number of severely affected people in a major outbreak is substantial — the 2006–2007 East African epidemic produced hundreds of deaths across Kenya, Somalia and Tanzania.

There is a licensed veterinary vaccine and it is genuinely useful. There is nothing licensed for humans: no vaccine, no antiviral, no antibody. Care is supportive, and the ocular and neurological forms in particular receive no specific treatment at all. The disease is also expanding — it reached the Arabian peninsula in 2000 — and its driver is rainfall, which is not moving in a favourable direction.

The disease at a glance

Feature	Detail	Why it matters
Case fatality	>50% in the haemorrhagic hepatic form; ~1% overall	A large denominator makes the absolute severe-case burden significant
Severe forms	Haemorrhagic hepatitis, encephalitis, retinitis	Three different compartments, requiring different pharmacology
Sequelae	Permanent visual loss after retinitis	Survival is not a sufficient endpoint for this disease
Transmission	Aedes and Culex mosquitoes; direct contact with livestock tissue	Occupational exposure is predictable and prophylaxis is plausible
Trigger	Heavy rainfall and flooding; dormant infected Aedes eggs	Outbreaks are forecastable weeks in advance from rainfall data
Geography	East, West and Southern Africa; Arabian peninsula since 2000	Expanding range; a WHO priority pathogen
Veterinary vaccine	Licensed and effective	Animal control works but does not reach every herd in time
Human countermeasures	None licensed — no vaccine, no therapeutic	Supportive care only, including for the ocular and neurological forms
Biosafety	Risk Group 3 enhanced; select agent; vector containment required	Arthropod work adds a containment dimension the viral programmes do not have

Preclinical and pharmacology package

- Antibody component: terminal half-life 26 days at 20 mg/kg; serum neutralising titre above the in vitro IC90 for 45 days, which supports a single-visit post-exposure prophylaxis regimen for abattoir and veterinary workers ahead of a forecast epizootic.
- Polymerase inhibitor component: unbound brain-to-plasma ratio 0.55; measurable vitreous penetration in the rabbit at 0.3 of unbound plasma — the property that justified carrying a second component at all.

- No pharmacokinetic interaction between components in the combination cohorts; exposure of each within 1.1-fold of its single-agent value.
- Neutralisation retained across East African, West African and Arabian peninsula lineages; the Gn epitope is conserved in all 41 sequenced human outbreak isolates examined.
- Efficacy demonstrated in the Wistar rat and the common marmoset models with treatment started after onset of viraemia; the marmoset model reproduces both the hepatic and the neurological forms.
- Escape selection against the antibody component alone produced two Gn substitutions, both of which remained susceptible to the polymerase inhibitor — a secondary argument for the fixed pair.
- No genotoxic signal for the small molecule; 28-day toxicology complete in rat and dog with a dedicated ophthalmic package.

Clinical development — HEADWATER-1

Design	Randomised, double-blind, placebo-controlled study evaluating each component alone and in combination, in ascending dose cohorts
Population	Healthy adult volunteers aged 18–60. No participant is exposed to Rift Valley fever virus.
Sites	Three, United States
Enrolment	25 of 60 as of 31 July 2026
Doses studied	Antibody 2, 6 and 20 mg/kg; polymerase inhibitor 100 mg to 600 mg twice daily; three combination cohorts
Primary objective	Safety and tolerability of each component alone and of the combination
Key secondary	Pharmacokinetics of both components and the absence of interaction; immunogenicity; ophthalmic assessment; ex vivo neutralisation against East African, West African and Arabian peninsula lineages
Status	Recruiting; single-agent cohorts complete for both components, first combination cohort open

Safety observed to date

Most frequent ($\geq 20\%$): headache, nausea, infusion-site discomfort. Grade ≥ 3 observed in 5 per cent of participants: ALT increased with the polymerase inhibitor at 600 mg twice daily, which was not carried forward. No ophthalmic finding attributable to either component. No participant discontinued for a treatment-related event.

Warnings and monitoring in the protocol

Investigational agent, and an investigational combination. Infusion-related reactions to the antibody component occurred in 8 per cent of participants, all grade 1 to 2. The polymerase inhibitor produced grade 1 to 2 headache, nausea and transient transaminase elevation, with weekly hepatic monitoring through day 28. Because retinitis is a feature of the disease itself, a full ophthalmic assessment including optical coherence tomography is performed at baseline and at follow-up so that treatment-emergent and disease-related findings can be distinguished. Not to be used outside a clinical trial or an authorised expanded access or emergency use framework. Human infection is frequently acquired from livestock tissue; this product is not a substitute for protective equipment during slaughter, obstetric handling or necropsy.

Development milestones

Date	Milestone	Status
Q4 2026	HEADWATER-1 combination cohort 1 completion and interaction analysis	Planned
Q1 2027	Remaining combination cohorts and full ophthalmic safety package	Planned
Q2 2027	Common marmoset combination efficacy readout, hepatic and neurological forms	Planned
Q3 2027	Post-exposure prophylaxis regimen selection for occupational use	Planned
Q4 2027	End-of-Phase-1 meeting; Animal Rule package alignment	Planned
2028	Outbreak-activated randomised protocol with East African partners	Under discussion

Regulatory status and pathway

Investigational New Drug application cleared in June 2026, filed as a combination under a single application with each component also characterised alone. There is no approval of any kind in any jurisdiction. Rift Valley fever outbreaks are, unusually, partly forecastable: rainfall anomaly data gives weeks of warning, which makes a pre-positioned, outbreak-activated randomised protocol more realistic here than for any other programme in the portfolio. That protocol is being developed with East African partners alongside an Animal Rule package under 21 CFR 314 Subpart I for the severe forms. Orphan drug designation has been requested. Designations are not approvals and none has yet been granted.

Biosafety and handling

Rift Valley fever virus is a Risk Group 3 organism handled at BSL-3 enhanced under federal select agent registration, with staff vaccinated where a vaccine is available to them and titre-monitored. Work involving infected mosquitoes is performed in a dedicated arthropod containment facility with its own entry controls, because the containment problem for a vector-borne agent is not the same problem as for a respiratory one. Clinical sites handle no infectious material. Clinicians should note that human infection is most often acquired from livestock tissue rather than from mosquito bite, and that protective equipment during slaughter, obstetric handling and necropsy is the single most effective intervention currently available.

For volunteers in HEADWATER-1

- No participant is exposed to the target pathogen or to any infectious material at any point.
- Screening includes medical history, physical examination, laboratory tests and an electrocardiogram.
- Participation involves scheduled clinic visits or a residential period, and serial blood sampling.
- A safety follow-up visit takes place approximately 30 days after the last dose.
- Taking part is voluntary; a participant may withdraw at any time, for any reason or none.
- All study procedures and study medicine are provided at no cost, and reasonable travel expenses are reimbursed.
- Suspected side effects can also be reported directly to the FDA through MedWatch.

Important. BX-1330 is an investigational medical countermeasure. It has not been approved by any regulatory authority, and its safety and efficacy have not been established. This document is for information only. It is not medical advice, not biosafety guidance, not an offer to sell or a solicitation to buy securities, and not a promise that this programme will succeed. BX-1330 is not available on prescription. Requests for expanded access or emergency use in a confirmed or strongly suspected case can be made by a treating physician through the medical information route at baxtra.pages.dev/patients.html.

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