

BX-1265

Arenavir — a pan-arenavirus small-molecule fusion inhibitor for the South American haemorrhagic fevers.

Argentine, Bolivian, Venezuelan and Brazilian haemorrhagic fevers are four diseases caused by four closely related viruses, each endemic to a single agricultural region, each with case fatality between 15 and 30 per cent untreated, and none with an approved drug. Individually none of them will ever justify a development programme. Together, with one conserved target, they might.

Indication	New World arenavirus haemorrhagic fever, including Junín (Argentine), Machupo (Bolivian), Guanarito (Venezuelan) and Sabiá (Brazilian) virus infection, with retained activity against Lassa virus and Lujo virus.
Modality	Oral and intravenous small-molecule inhibitor of arenavirus GP2-mediated membrane fusion
Target	The transmembrane–stable signal peptide interface of the arenavirus GP2 fusion machinery
Route and schedule	300 mg intravenously twice daily for 5 days, then 300 mg orally twice daily to complete 14 days
Development stage	Phase 1, healthy volunteers
Current study	CROSSBAR-1 (NCT-BX1265-01) — randomised, double-blind, placebo-controlled single and multiple ascending dose study with an intravenous-to-oral switch cohort
Containment	BSL-4 for Junín, Machupo, Guanarito and Sabiá virus; Risk Group 4 pathogens; federal select agent registration
Regulatory pathway	Conventional randomised controlled trial route in Argentina for the Junín indication; Animal Rule for the remaining species

Mechanism of action

Arenaviruses are unusual among enveloped viruses in retaining a stable signal peptide as a permanent third subunit of the mature glycoprotein spike. That stable signal peptide sits in the membrane and forms an interface with the transmembrane domain of GP2, and the pH-sensing that triggers fusion in the acidified endosome is a property of that interface rather than of GP2 alone. It is also, structurally, a very small pocket that cannot vary much without breaking the machine. BX-1265 binds it and prevents the low-pH conformational change, so fusion does not occur and the genome is not released. The consequence of choosing this site rather than the receptor-binding surface is breadth: New World arenaviruses use transferrin receptor 1 and Old World arenaviruses use alpha-dystroglycan, so a receptor-blocking approach is necessarily species-restricted, whereas the fusion interface is shared. In pseudotype assay BX-1265 inhibits Junín, Machupo, Guanarito, Sabiá, Lassa and Lujo virus glycoproteins within a 6-fold potency range. Breadth was the entire design objective, because the alternative is four separate development programmes for four diseases that occur in four maize-growing regions and would each, on their own, never be funded.

Why this disease

Four South American haemorrhagic fevers are caused by four New World arenaviruses, each carried by a different rodent and each confined to a defined agricultural zone: Junín virus in the Argentine pampas, Machupo virus in the Beni department of Bolivia, Guanarito virus in the Venezuelan llanos, Sabiá virus in São Paulo state. Cases follow the harvest, because that is when people and rodents meet in the same fields.

Argentine haemorrhagic fever has something the others do not: convalescent immune plasma, which reduces mortality from around 15–30 per cent to under 1 per cent when given inside the first eight days. It works. It also depends on a donor registry, cold chain, correct blood group matching and a supply that is entirely outside the control of the treating clinician, and it does not exist at all for Machupo, Guanarito or Sabiá virus. A late-transfusion neurological syndrome occurs in about 10 per cent of recipients.

Each of these diseases produces at most a few hundred cases a year. No one of them will ever support a dedicated development programme, and that is exactly why none of them has a drug. The scientific bet in BX-1265 is that a target conserved across the genus turns four unfundable indications into one fundable one, with the additional property that it also covers Lassa virus and Lujo virus, which are Old World arenaviruses on the other side of the family.

The disease at a glance

Feature	Detail	Why it matters
Case fatality	15–30% untreated across the four New World species	Under 1% for Junín virus where immune plasma is available in time
Geography	Argentina, Bolivia, Venezuela, Brazil — defined agricultural zones	Seasonal, tied to harvest and rodent population cycles
Reservoir	A different rodent species for each virus	Eradication is not achievable; exposure is occupational
Current therapy	Immune plasma for Junín virus only; ribavirin off-label	Supply-limited, donor-dependent, and absent for three of four viruses
Annual cases	Tens to a few hundred per virus	Individually too small to fund; collectively addressable
Target conservation	Stable signal peptide–GP2 interface, conserved genus-wide	One molecule can cover six species including Lassa and Lujo
Biosafety	Risk Group 4, BSL-4, select agents	Live work restricted to registered maximum-containment facilities

Preclinical and pharmacology package

- Oral bioavailability 68 per cent; terminal half-life 14 hours; intravenous-to-oral switch established without a dose adjustment.
- Pseudotype inhibition within a 6-fold potency range across Junín, Machupo, Guanarito, Sabiá, Lassa and Lujo virus glycoproteins — the breadth result the target site was selected to deliver.
- Authentic-virus plaque reduction in maximum containment confirmed for Junín and Machupo virus, consistent with the pseudotype ranking.
- Escape selection over 25 passages against Junín virus produced a single GP2 transmembrane substitution with a 9-fold potency loss and a substantial fitness cost.

- QTcF increase up to 8 milliseconds at 600 mg twice daily; no increase above baseline variability at the 300 mg regimen carried forward.
- Efficacy demonstrated in the guinea pig Junín virus model with treatment started at day 5 after inoculation; survival 11 of 14 treated against 2 of 14 control.
- No genotoxic signal; 28-day toxicology complete in rat and dog.

Clinical development — CROSSBAR-1

Design	Randomised, double-blind, placebo-controlled single and multiple ascending dose study with an intravenous-to-oral switch cohort
Population	Healthy adult volunteers aged 18–55. No participant is exposed to any arenavirus at any point.
Sites	Three, United States
Enrolment	31 of 54 as of 31 July 2026
Doses studied	50 mg to 600 mg orally twice daily; 150 and 300 mg intravenously; 10-day courses
Primary objective	Safety and tolerability
Key secondary	Pharmacokinetics by both routes and the intravenous-to-oral switch; food effect; QT assessment; ex vivo pseudotype neutralisation across six arenavirus species
Status	Recruiting; oral cohorts 1–5 complete, switch cohort open

Safety observed to date

Most frequent ($\geq 20\%$): headache, nausea, dizziness. Grade ≥ 3 observed in 6 per cent of participants: ALT increased, and one asymptomatic QTcF prolongation above 480 milliseconds at the highest dose level. No dose-limiting toxicity at or below 450 mg twice daily.

Warnings and monitoring in the protocol

Investigational agent. Observed events in dose escalation have been grade 1 to 2 headache, nausea, dizziness and transient transaminase elevation. A dose-dependent QTcF increase of up to 8 milliseconds was observed at 600 mg twice daily and that dose was not carried forward; electrocardiographic monitoring is protocol-mandated. Weekly hepatic monitoring through day 28. Not to be used outside a clinical trial or an authorised expanded access or emergency use framework. Where immune plasma is available and indicated for Argentine haemorrhagic fever, it remains the standard of care and this product does not displace it.

Development milestones

Date	Milestone	Status
Q4 2026	CROSSBAR-1 intravenous-to-oral switch cohort completion	Planned
Q1 2027	Full multiple ascending dose and QT package readout	Planned
Q2 2027	Non-human primate Junín virus efficacy study	Planned
Q3 2027	Machupo and Guanarito virus animal efficacy, maximum containment	Planned

Date	Milestone	Status
Q4 2027	Phase 2 protocol with Argentine national reference institute	Under discussion
2028	Randomised controlled Phase 2 in Argentine haemorrhagic fever, immune plasma as background therapy	Planned

Regulatory status and pathway

Investigational New Drug application cleared in May 2026. There is no approval of any kind in any jurisdiction. Argentine haemorrhagic fever is the one indication in this group where a randomised controlled trial is realistic: cases are concentrated, the season is predictable, and a national reference institute already manages the immune plasma programme. Any such trial would be designed with immune plasma as background therapy rather than as a comparator to be withheld, because withholding an effective treatment would be indefensible. For Machupo, Guanarito and Sabiá virus the route is 21 CFR 314 Subpart I. Orphan drug designation has been requested for all four indications. Designations are not approvals and none has yet been granted.

Biosafety and handling

Junín, Machupo, Guanarito and Sabiá viruses are Risk Group 4 organisms and United States select agents. All authentic-virus plaque reduction, escape selection and animal challenge work is performed inside the Palm Coast maximum-containment suite under federal select agent registration, in positive-pressure suits, behind an airlock, with effluent decontamination. Pseudotype work is performed at BSL-2. Clinical sites handle no infectious material of any kind. Clinicians managing a suspected case should apply standard viral haemorrhagic fever precautions and contact their national reference laboratory before sending samples.

For volunteers in CROSSBAR-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-1265 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-1265 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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