

BX-733

Hantrelvir — a host-directed endothelial stabiliser for hantavirus cardiopulmonary syndrome.

Andes orthohantavirus kills between a third and a half of the people it infects, and it kills them by flooding the lungs within hours. The virus itself does very little cytopathic damage. The lethal event is the loss of the endothelial barrier, and that is a host process, which means it is a target.

Indication	Hantavirus cardiopulmonary syndrome caused by Andes orthohantavirus and related New World hantaviruses, including Sin Nombre virus.
Modality	Small-molecule selective S1PR1 agonist, intravenous with oral step-down
Target	Sphingosine-1-phosphate receptor 1 on pulmonary microvascular endothelium
Route and schedule	8 mg intravenously on day 1, then 8 mg orally once daily for 7 days, started at the transition from the febrile to the cardiopulmonary phase
Development stage	Phase 1, healthy volunteers
Current study	RIDGELINE-1 (NCT-BX0733-01) — randomised, double-blind, placebo-controlled single and multiple ascending dose study with a dedicated cardiac monitoring package
Containment	BSL-3 for Sin Nombre and Andes virus culture; BSL-4 practices for rodent-derived material
Regulatory pathway	Conventional 505(b)(1) development with a randomised controlled trial at South American sites

Mechanism of action

Hantavirus cardiopulmonary syndrome is not a cytopathic disease. The virus infects pulmonary microvascular endothelium and, rather than lysing it, dysregulates it: VEGFR2 signalling is amplified, VE-cadherin at the adherens junction is internalised, and the barrier fails. Plasma enters the alveolus. A previously well young adult can go from mild fever to refractory hypoxaemia and cardiogenic shock in under twelve hours, and the outcome is decided in that window rather than by viral clearance. Sphingosine-1-phosphate signalling through S1PR1 is the principal endogenous brake on that process: it drives Rac1-dependent cortical actin assembly, stabilises VE-cadherin at the junction and directly antagonises VEGFR2-mediated permeabilisation. BX-733 is a selective S1PR1 agonist with minimal activity at S1PR3, the receptor responsible for most of the cardiac liability of first-generation compounds in this class. It restores barrier function without touching the virus, which is an unusual thing to offer for an infectious disease and is the reason the programme is designed around a physiological endpoint rather than a virological one.

Why this disease

Hantaviruses are carried by rodents and reach people through aerosolised excreta — a shed, a woodpile, a grain store. In the Americas the resulting illness is hantavirus cardiopulmonary syndrome, and it has an unusual clinical shape: three to six days of fever, myalgia and gastrointestinal upset that looks like influenza, then an abrupt transition to pulmonary oedema, shock and death, frequently in people in their twenties and thirties with no comorbidity at all.

Andes orthohantavirus, found in Argentina and Chile, is the only hantavirus for which person-to-person transmission is well documented, including clusters among household contacts and healthcare workers. That single property moves it

from the category of rare rodent-borne illness into the category of outbreak pathogen, and it is the reason the programme prioritised Andes over Sin Nombre despite the latter being the North American agent.

Care is entirely supportive: intubation, vasopressors, and in the best-equipped centres extracorporeal membrane oxygenation, which does work and is available to almost none of the people who need it. There is no antiviral and, given how little of the damage the virus does directly, an antiviral arriving at the point of diagnosis would probably be too late anyway. Stabilising the endothelium is the intervention that fits the timeline of the disease.

The disease at a glance

Feature	Detail	Why it matters
Case fatality	35–40% (Andes); ~38% (Sin Nombre)	Deaths occur in young, previously healthy adults
Reservoir	Long-tailed pygmy rice rat (Andes); deer mouse (Sin Nombre)	Exposure is environmental and largely unavoidable in endemic areas
Transmission	Aerosolised rodent excreta; person to person for Andes virus	The only hantavirus with documented human-to-human spread
Incubation	Typically 9–24 days	Long enough that the exposure is often forgotten by presentation
Clinical course	Abrupt transition to pulmonary oedema and shock	The therapeutic window is measured in hours, not days
Mechanism of death	Endothelial barrier failure, not viral cytopathology	The lethal step is a host process and therefore druggable
Current therapy	Supportive care; ECMO where available	No pharmacological intervention exists
Biosafety	Risk Group 3; BSL-4 practices for rodent-derived material	Culture is restricted; serology and PCR are widely available

Preclinical and pharmacology package

- Oral bioavailability 74 per cent; terminal half-life 31 hours, supporting once-daily oral step-down after an intravenous first dose.
- S1PR1 selectivity over S1PR3 greater than 300-fold, which is the design point that separates BX-733 from earlier compounds in this class and their cardiac liability.
- Heart rate nadir occurred 3.5 hours after the first oral dose, mean reduction 9 beats per minute at 8 mg, with full recovery by 24 hours and complete attenuation on repeat dosing.
- Ex vivo permeability assay: serum from participants dosed at 8 mg reduced Andes-virus-induced monolayer permeability by 61 per cent, the programme's translational pharmacodynamic marker.
- Efficacy demonstrated in the Syrian hamster Andes virus model with treatment started at onset of tachypnoea; survival 8 of 12 treated against 1 of 12 control.
- No genotoxic signal; 28-day toxicology complete in rat and dog with dedicated ophthalmic and cardiac assessments.

Clinical development — RIDGELINE-1

Design	Randomised, double-blind, placebo-controlled single and multiple ascending dose study with a dedicated cardiac monitoring package
Population	Healthy adult volunteers aged 18–55 with no history of arrhythmia or conduction abnormality.
Sites	Three, United States
Enrolment	29 of 48 as of 31 July 2026
Doses studied	1 mg to 16 mg orally; 2, 4 and 8 mg intravenously; 7-day courses in the multiple-dose cohorts
Primary objective	Safety and tolerability, with continuous telemetry for the first 6 hours after the first dose
Key secondary	Heart rate nadir and time to nadir; pharmacokinetics; lymphocyte count kinetics; pulmonary function; ex vivo endothelial permeability assay on participant serum
Status	Recruiting; oral cohorts 1–5 complete, intravenous cohort 2 open

Safety observed to date

Most frequent ($\geq 20\%$): bradycardia (asymptomatic, first dose), headache, fatigue. Grade ≥ 3 observed in 6 per cent of participants: symptomatic bradycardia in one participant at 16 mg, resolved without intervention; ALT increased in two. The 16 mg dose was not carried forward.

Warnings and monitoring in the protocol

Investigational agent. S1PR1 agonism causes a first-dose reduction in heart rate and, less commonly, atrioventricular conduction delay; all participants undergo six hours of continuous telemetry after the first dose. Dose-dependent peripheral lymphocyte count reduction is an expected pharmacodynamic effect of receptor internalisation and is monitored, not treated. Macular oedema and hepatic enzyme elevation are class effects and are screened for. Not to be used outside a clinical trial or an authorised expanded access or emergency use framework. This is a host-directed agent: it does not reduce viral load and is not antiviral therapy.

Development milestones

Date	Milestone	Status
Q4 2026	RIDGELINE-1 intravenous cohort completion and cardiac safety package	Planned
Q1 2027	Multiple ascending dose readout and permeability biomarker analysis	Planned
Q2 2027	Non-human primate Andes virus model, post-onset treatment	Planned
Q4 2027	Phase 2 protocol and site activation, Argentina and Chile	Planned
2028	Randomised controlled Phase 2 in confirmed hantavirus cardiopulmonary syndrome	Planned

Regulatory status and pathway

Investigational New Drug application cleared in March 2026. There is no approval of any kind in any jurisdiction. Unlike the filovirus and henipavirus programmes, BX-733 is not an Animal Rule candidate: Andes virus produces a steady

annual case load at identified referral hospitals in Argentina and Chile, and a randomised controlled trial with a mortality and ventilator-free-days endpoint is feasible. The programme is being developed conventionally under 505(b)(1), with a Phase 2 protocol under design with South American investigators. Orphan drug designation has been requested.

Biosafety and handling

Andes and Sin Nombre viruses are Risk Group 3 organisms, handled at BSL-3, with BSL-4 practices applied to rodent-derived material because of the aerosol risk. Hamster challenge studies are performed under federal registration in a dedicated animal BSL-3 suite. Clinical sites handle no infectious material. Clinicians managing a suspected case should apply droplet and contact precautions — which for Andes virus, unusually among hantaviruses, are genuinely necessary for household and healthcare contacts.

For volunteers in RIDGELINE-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-733 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-733 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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