

BX-620

Rabivex — a CNS-penetrant lyssavirus polymerase inhibitor for symptomatic rabies.

Rabies kills approximately 59,000 people a year. Once symptoms begin it is effectively one hundred per cent fatal, and it has been that way for the entire history of medicine. Fewer than twenty survivors of symptomatic rabies have ever been documented.

Indication	Symptomatic rabies encephalomyelitis, and failed or delayed post-exposure prophylaxis, including infection with non-rabies lyssaviruses.
Modality	Small-molecule non-nucleoside inhibitor of the lyssavirus L polymerase, intravenous with an intrathecal loading dose
Target	Polymerase (L) protein of the lyssavirus ribonucleoprotein complex
Route and schedule	Intrathecal 25 mg loading dose on day 1, then 250 mg intravenously twice daily for 21 days; the regimen under study is deliberately front-loaded into the central nervous system
Development stage	Phase 1, healthy volunteers
Current study	LANTERN-1 (NCT-BX0620-01) — randomised, double-blind, placebo-controlled single and multiple ascending intravenous dose study, with a separate open-label intrathecal tolerability cohort
Containment	BSL-3 with rabies pre-exposure immunisation for all staff; challenge studies at BSL-3 enhanced
Regulatory pathway	FDA Animal Rule, 21 CFR 314 Subpart I, with a single-arm natural-history comparison

Mechanism of action

Lyssaviruses carry a negative-sense RNA genome that is transcribed and replicated by a single large polymerase protein, L, working with the phosphoprotein P and the nucleoprotein N. BX-620 is a non-nucleoside inhibitor that binds an allosteric pocket at the interface between the polymerase and capping domains of L and prevents the conformational cycling required for processive RNA synthesis. Because the site is structural rather than catalytic, the compound does not require intracellular phosphorylation and is not in competition with host nucleotide pools, which matters in the metabolically compromised neuron. Rabies is a disease of the neuron and of nothing else: the virus travels retrogradely up peripheral axons to the spinal cord and brain, and by the time symptoms appear the infection is behind the blood–brain barrier. BX-620 was selected from its series on a CSF-to-unbound-plasma ratio of 0.61 rather than on potency, and is given with an intrathecal loading dose because the pharmacology has to be in the neuraxis on the first day, not the fourth.

Why this disease

Rabies is the most lethal infection known to medicine. The virus enters through a bite, replicates quietly in muscle, then enters a peripheral nerve and travels to the central nervous system at a few millimetres an hour. The incubation period — weeks to months, occasionally years — is the reason post-exposure prophylaxis works so well: there is time to immunise before the virus is out of reach. The moment it arrives in the brain, that door closes completely.

Post-exposure prophylaxis is close to perfectly effective and is also close to perfectly unavailable where the disease actually is. The great majority of the roughly 59,000 annual deaths occur in children in Asia and Africa, following dog bites, in places where immune globulin is expensive, cold chain is unreliable and the bite was never reported. Prophylaxis failure is not a pharmacological problem. It is a supply problem, and it produces a steady stream of patients for whom medicine currently offers palliation only.

The Milwaukee protocol and its successors have been attempted repeatedly and have not produced reproducible survival. Every published survivor is a case report. A disease with a case fatality of essentially one hundred per cent is unusual in one useful respect: the bar for demonstrating benefit is unambiguous.

The disease at a glance

Feature	Detail	Why it matters
Case fatality	~100% once symptomatic; <20 documented survivors ever	Any reproducible survival is a categorical result, not an incremental one
Annual deaths	~59,000, mostly children	The burden is concentrated where prophylaxis is least available
Reservoir	Domestic dogs (>95% of human cases), bats, wildlife	Elimination programmes work but are decades from completion
Incubation	Weeks to months, occasionally years	Prophylaxis is highly effective; the failure mode is access, not biology
Site of disease	Central nervous system, behind the blood–brain barrier	A peripherally restricted antiviral cannot work, however potent
Current therapy	None. Supportive and palliative care only	There is no comparator to be non-inferior to
Biosafety	Risk Group 3; staff pre-exposure immunised	Tractable containment relative to the filoviruses and arenaviruses

Preclinical and pharmacology package

- CSF-to-unbound-plasma ratio 0.61 at steady state; CSF concentration exceeded the in vitro EC90 for rabies virus across the full dosing interval at 250 mg twice daily.
- Intrathecal 25 mg produced CSF concentrations approximately 40-fold the EC90 within two hours, the basis for the loading-dose design.
- Oral bioavailability 11 per cent — too low to develop; the programme is deliberately parenteral.
- In vitro activity retained against rabies virus street isolates from four continents and against European bat lyssavirus 1 and Australian bat lyssavirus; reduced against phylogroup II lyssaviruses.
- No genotoxic signal; no cardiovascular liability at the exposures tested; 28-day toxicology complete in rat and dog with a dedicated neuropathology assessment of the intrathecal route.
- Hamster and non-human primate challenge models established; treatment initiated at onset of clinical signs rather than at inoculation, which is the only design that answers the clinical question.

Clinical development — LANTERN-1

Design	Randomised, double-blind, placebo-controlled single and multiple ascending intravenous dose study, with a separate open-label intrathecal tolerability cohort
Population	Healthy adult volunteers aged 18–55 for the intravenous cohorts; the intrathecal cohort enrolls volunteers already undergoing lumbar puncture for an unrelated indication under separate consent.
Sites	Two, United States
Enrolment	18 of 42 as of 31 July 2026
Doses studied	50 mg to 500 mg intravenously; 5, 15 and 25 mg intrathecally
Primary objective	Safety and tolerability, with a prespecified neurological examination battery
Key secondary	Cerebrospinal fluid concentration at 2, 6 and 24 hours; plasma pharmacokinetics; CSF-to-unbound-plasma ratio; absence of arachnoiditis on protocol-defined criteria
Status	Recruiting; intravenous cohorts 1–4 complete, first intrathecal cohort complete

Safety observed to date

Most frequent ($\geq 20\%$): headache, dizziness, nausea. Post-lumbar-puncture headache occurred in 4 of 9 intrathecal participants and resolved within 72 hours. Grade ≥ 3 observed in 7 per cent of participants: ALT increased. No dose-limiting toxicity observed to 500 mg intravenously or 25 mg intrathecally.

Warnings and monitoring in the protocol

Investigational agent. Intrathecal administration carries the risks of lumbar puncture and of chemical arachnoiditis; the intrathecal cohorts are conducted only at sites with neurology cover and are reviewed dose by dose. Observed events at intravenous doses have been grade 1 to 2 headache, dizziness and transient transaminase elevation. Weekly hepatic monitoring through day 28. Not to be used outside a clinical trial or an authorised expanded access or emergency use framework. BX-620 does not replace wound care, rabies immune globulin or vaccination after an exposure, and must never be presented to a patient as a reason to delay them.

Development milestones

Date	Milestone	Status
Q4 2026	LANTERN-1 multiple ascending dose completion	Planned
Q4 2026	Second intrathecal tolerability cohort with neuropathology review	Planned
Q1 2027	Hamster post-onset treatment study readout	Planned
Q3 2027	Non-human primate post-onset treatment study	Planned
2027	Emergency-use framework discussion with the FDA	Planned
2028	Natural-history comparison protocol with reference centres	Under discussion

Regulatory status and pathway

Investigational New Drug application cleared in January 2026. There is no approval of any kind in any jurisdiction. Symptomatic rabies cannot be studied in a conventional randomised trial: the cases are few, geographically scattered, and the outcome without treatment is not in doubt. The intended route is therefore 21 CFR 314 Subpart I supported by a prospectively defined natural-history comparison assembled with reference centres, alongside an emergency-use framework for individual patients. Orphan drug designation has been requested. Designations are not approvals and none has yet been granted.

Biosafety and handling

Rabies virus is a Risk Group 3 organism. All staff working with live virus are pre-exposure immunised and titre-monitored. Challenge studies are performed at BSL-3 enhanced under federal registration. Clinical sites handle no infectious material. Clinicians should be clear with patients and families that BX-620 is investigational, that it does not replace wound washing, rabies immune globulin or vaccination after an exposure, and that nothing about this programme is a reason to delay standard post-exposure prophylaxis by a single hour.

For volunteers in LANTERN-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-620 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-620 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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