

BX-308

Prionex — an intrathecal PRNP antisense oligonucleotide for Creutzfeldt-Jakob disease.

Creutzfeldt–Jakob disease is invariably fatal, usually within four to six months of symptom onset in the sporadic form. Prions resist conventional decontamination and no treatment has ever been approved. Prionex is an investigational substrate-reduction approach in the VIGIL-0 Phase 1 study.

Indication	Sporadic and genetic Creutzfeldt–Jakob disease, fatal familial insomnia and Gerstmann–Straussler–Scheinker syndrome; an asymptomatic PRNP-variant registry is also in scope.
Modality	Intrathecal PRNP-directed antisense oligonucleotide (chemically modified gapmer)
Target	PRNP messenger RNA and the normal cellular prion protein it encodes
Route and schedule	Lumbar intrathecal loading doses on days 1, 15 and 29, followed by maintenance every 12 weeks; cerebrospinal-fluid sampling at each visit
Development stage	Phase 1, healthy volunteers
Current study	VIGIL-0 (NCT-BX0308-01) — open-label single and multiple ascending dose study with staggered cohorts and cerebrospinal fluid pharmacodynamic sampling
Containment	Containment level 3 with dedicated prion practice; single-use instruments and validated inactivation
Regulatory pathway	Cleared US IND; conventional clinical development route under evaluation

Mechanism of action

Prionex is a chemically modified gapmer antisense oligonucleotide complementary to PRNP messenger RNA. After hybridisation, the DNA-like segment recruits endogenous RNase H1, which cleaves the RNA strand of the duplex and lowers production of normal cellular prion protein. The misfolded prion is not a virus and has no genome to inhibit; it propagates by templating its conformation onto normal cellular prion protein. Every known prion strain requires that cellular protein as substrate, whether the disease is sporadic, inherited or acquired. Lowering substrate is therefore a strain-agnostic strategy in principle, but it is not the same as clearing existing misfolded protein and no clinical efficacy has been established. Intrathecal delivery is used because the relevant biology is in the central nervous system, where systemic exposure may be limited. Cerebrospinal-fluid prion protein provides a pharmacodynamic readout at each visit; the site reports 38 per cent lowering at 40 mg, which is a biomarker observation rather than a clinical outcome.

Why this disease

Creutzfeldt–Jakob disease is a transmissible spongiform encephalopathy caused by conformational conversion of normal cellular prion protein. It is not a virus or bacterium: there is no genome to attack and no immune response that can simply be boosted. Sporadic disease accounts for most cases, while a smaller proportion is genetic, including fatal familial insomnia and Gerstmann–Straussler–Scheinker syndrome; acquired forms are rare.

The incidence of sporadic CJD is approximately one to two cases per million people per year. It presents with rapidly progressive dementia, ataxia, myoclonus and other neurological signs, and is universally fatal. Median survival is four to six months from symptom onset, although the course varies. There is no approved treatment and supportive care

cannot alter the underlying propagation process.

Prions are unusually durable. They resist standard autoclaving, alcohol, formaldehyde and ionising radiation, which is why contaminated neurosurgical instruments may be destroyed or treated with 1N sodium hydroxide and a 134°C extended steam cycle. VIGIL-0 takes a substrate-reduction approach: it asks whether lowering normal PRNP protein can be achieved safely in the central nervous system. The study is not designed to claim a change in the natural history of prion disease.

The disease at a glance

Feature	Detail	Why it matters
Incidence	Approximately 1–2 cases per million people per year	The disease is rare, so conventional large trials are not feasible.
Main form	Sporadic CJD accounts for most recognised cases	A candidate must address disease biology rather than one outbreak strain.
Inherited forms	PRNP variants cause genetic CJD, fatal familial insomnia and GSS	Genetic counselling and family context matter to enrolment.
Clinical course	Rapid dementia, ataxia, myoclonus and other neurological decline	Diagnosis and referral often occur after substantial disease progression.
Case fatality	Approximately 100%; median survival 4–6 months	There is no established disease-modifying treatment.
Agent	Misfolded host prion protein; no genome	Antisense substrate reduction differs from antiviral or immunological approaches.
Durability	Resists standard autoclave, alcohol and formalin	Dedicated decontamination is required for tissue and instruments.
Readout	CSF prion protein lowering; 38% at 40 mg reported on site	The biomarker is pharmacodynamic and is not a clinical efficacy result.

Preclinical and pharmacology package

- RNase H1 recruitment and PRNP transcript cleavage are quantified in human neuronal and glial cell systems, with normal prion protein measured separately from the antisense strand.
- Cerebrospinal-fluid and plasma pharmacokinetics are modelled after lumbar delivery, including persistence through the 12-week maintenance interval.
- The 20 mg, 40 mg and 60 mg bands are assessed for CSF prion protein lowering, neurological examination findings and procedure-related tolerability; the reported 38% at 40 mg is a pharmacodynamic observation.
- Non-clinical distribution studies examine spinal cord and brain regions, because a lumbar dose must reach the relevant central nervous system compartments without relying on systemic exposure.
- Off-target RNA binding, complement activation, platelet effects and innate immune stimulation are assessed for the modified gapmer sequence.
- Prion-handling validation covers CSF collection, sealed transport, instrument segregation and the site's sodium-hydroxide and extended steam decontamination process.

Clinical development — VIGIL-0

Design	Open-label single and multiple ascending dose study with staggered cohorts and cerebrospinal fluid pharmacodynamic sampling
Population	Adults aged 18–75 with early symptomatic sporadic or genetic prion disease, plus an asymptomatic PRNP-variant registry cohort. VIGIL-0 does not involve deliberate exposure to infectious material.
Sites	Two, United States
Enrolment	12 of 24 as of 31 August 2026
Doses studied	20 mg, 40 mg and 60 mg by lumbar intrathecal injection over one to three minutes; loading on days 1, 15 and 29 followed by maintenance every 12 weeks
Primary objective	Safety and tolerability of repeated lumbar intrathecal administration
Key secondary	Cerebrospinal-fluid prion protein concentration; pharmacokinetics in CSF and plasma; neurological examination; functional measures; platelet count, coagulation and procedure-related adverse events
Status	Recruiting; 20 mg and 40 mg cohorts open; 12 of 24 participants enrolled

Safety observed to date

Most frequent ($\geq 20\%$): post-lumbar-puncture headache, back pain, nausea. Grade ≥ 3 observed in 8 per cent: headache, aseptic meningitis (one participant, resolved).

Warnings and monitoring in the protocol

Investigational agent. Post-lumbar-puncture headache occurred in 34 per cent of procedures. Monitor platelet count and coagulation before each dose. Cerebrospinal fluid protein elevation is expected and is not by itself a reason to withhold treatment. Not to be used outside a clinical trial. Because prion disease is transmissible through central nervous system tissue, all cerebrospinal fluid handling follows the site's prion protocol, including single-use instruments and 1N sodium hydroxide plus 134 degree Celsius extended-cycle steam for anything reusable.

Development milestones

Date	Milestone	Status
Q4 2025	PRNP substrate-reduction candidate nominated; intrathecal formulation selected	Complete
Q1 2026	VIGIL-0 cleared under a US IND and first site opened	Complete
Q2 2026	20 mg cohort completed; CSF sampling and procedure review accepted	Complete
Q3 2026	40 mg cohort open; 12 of 24 participants enrolled	Current
Q4 2026	60 mg cohort and repeat-dose safety review	Planned
2027	Longitudinal CSF pharmacodynamic analysis and protocol decision	Planned

Regulatory status and pathway

Prionex is being evaluated under a cleared US Investigational New Drug application. The programme uses a conventional clinical development route because intentional human infection is impossible and unethical, while the disease has a defined clinical diagnosis and a cerebrospinal-fluid pharmacodynamic marker. VIGIL-0 is Phase 1 and is designed to characterise intrathecal safety, exposure and PRNP-related biomarker change; it is not powered to establish clinical efficacy. Any later study would need to address the short natural history, diagnostic delay and heterogeneity of sporadic and genetic disease. Prionex has not been approved by any regulatory authority and is not available on prescription.

Biosafety and handling

Prion work is performed under containment level 3 with a dedicated prion practice. Cerebrospinal fluid and tissue are treated as potentially infectious; instruments are single-use where possible, and reusable items require 1N sodium hydroxide plus a 134°C extended-cycle steam process. VIGIL-0 does not expose participants to infectious material. The 29 August 2026 public statement, 'Statement on a containment failure' (ref BXRA-PS-2026-08), confirms only that an event occurred, was found by Baxtra's own staff, that work stopped, an independent review is open, and authorities were notified. It declines to name the programme, suite, material, quantities, dates or individuals, and states there is no identified risk outside the facility. Please do not write to ask.

For volunteers in VIGIL-0

- 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-308 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-308 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.

Cleared for external publication by the Disclosure Review Board · DRB-2026-0308 · public revision 3 of 12 · issued 31 August 2026. Queries to disclosure@baxtra.pages.dev.