NEW MECHANISM FINDINGS OFFER INSIGHTS INTO XARANETIDE'S PHASE 2 SIGNAL IN MORE SEVERE STROKE

KEY HIGHLIGHTS

- ***Xaranetide targets multiple pathways involved in acute brain injury.*** *Laboratory studies strengthen the evidence for xaranetide's ability to target several pathways involved in brain injury, supporting its potential to interrupt multiple parts of the injury process.*

- ***Xaranetide potently inhibits two subunits of the N-methyl-D-Aspartate (NMDA) receptor, which can allow damaging amounts of calcium into brain cells when excessively activated following brain injury[1].*** *Further testing of the NMDA 1/2A subtype supports a voltage-dependent, non-competitive open-channel blocking mechanism. Newly reported findings also demonstrate inhibition of ASIC1a, which responds to tissue acidity, and CaV2.2, which helps control calcium entry and the rele*ase of chemical signals between brain cells.

- ***Xaranetide's NMDA-blocking effect showed partial reversibility in laboratory testing,*** *with channel activity recovering after drug removal and a change in membrane voltage. Reversibility matters because NMDA receptors also support normal brain signalling, learning and plasticity—the ability of connections between brain cells to adapt. An acute neuroprotectant should limit harmful receptor activity without persistently suppressing these essential functions.*

- ***Targeting several injury pathways increases the probability of success*** *and may be particularly relevant in large ischaemic strokes with poor collateral blood supply. Reduced blood flow can cause glutamate to accumulate and excessively activate NMDA channels[2,3],* ***potentially helping explain xaranetide's encouraging signals in more severely affected patients in exploratory Phase 2 analyses.***

Perth, Australia; 20 October, 2026 - Argenica Therapeutics Limited (ASX: AGN) ("Argenica" or the "Company"), a biotechnology company developing novel therapeutics to reduce brain tissue death after stroke and other acute neurological conditions, is pleased to announce

[1] Reinhart KM, et al. (2024). Journal of Neurochemistry, 168(5), 855–867.
[2] Boers AMM, et al. (2017). *J Cereb Blood Flow Metab.* **37**(11):3589–3598.
[3] Rossi DJ, et al. (2000). *Nature.* **403**:316–321.

results of pharmacology studies that strengthen the evidence for xaranetide's multi-target mechanism of action.

The studies show that xaranetide inhibits several channels on the cell surface that are involved in brain injury. They also explain how its effect on one important channel, the NMDA channel, responds to high levels of glutamate and changes in electrical voltage across the cell membrane. Together, the results strengthen the scientific rationale for xaranetide as a novel treatment to protect vulnerable brain tissue following injury.

Argenica CEO and Managing Director, Dr Liz Dallimore, commented: "*the proposed mechanism targets NMDA channels once they open, potentially limiting damaging calcium entry. Further, studies show a multi-target activity targeting other channels implicated in stroke, being the ASIC1a and CaV2.2 channels. This could be particularly relevant in more severe strokes where still-living tissue is under substantial stress resulting in channel opening, and offers a possible explanation for our exploratory Phase 2 signals. Activity against multiple channels strengthens the rationale for addressing several contributors to brain injury with one therapy. This data continues to build on the compelling body of evidence we are accumulating on xaranetide as a novel therapy for brain injury*."

WHY THE MECHANISM MATTERS FOR NEUROPROTECTION

Acute ischaemic stroke and TBI trigger a cascade of damaging biological processes that can begin within minutes and continue over hours to days. Glutamate can accumulate and excessively activate receptors on neurons, particularly NMDA receptors, allowing calcium to enter and build up within the cells. The resulting calcium overload can damage mitochondria and activate processes that lead to neuronal death. This process is known as excitotoxicity[4,5]. NMDA receptors are major mediators of excitotoxicity, with other receptors and ion channels also contributing to brain cell injury[6].

Reducing excessive NMDA receptor activity may interrupt this injury cascade before further damage occurs. In stroke, the therapeutic aim is to preserve viable but threatened tissue around the infarct core, known as the penumbra, while blood flow is restored. The new studies provide mechanistic support for this approach.

The Stroke Treatment Academic Industry Roundtable (STAIR), an international expert forum, has recommended prioritising therapies that act on multiple injury pathways and proposed that this approach could improve the likelihood of successful brain protection. Xaranetide's inhibitory activity across NMDA, ASIC1a and CaV2.2 channels is consistent with this

[4] Rossi DJ, Oshima T, Attwell D. Glutamate release in severe brain ischaemia is mainly by reversed uptake. Nature. 2000;403:316-321
[5] Schinder AF, et al. (1996). J Neurosci. 16(19):6125–6133.
[6] Lai K, et al. (2024). *Nature.* **631**:826–834.

development rationale, supporting its potential to address several contributors to brain cell injury[7].

PHARMACOLOGY RESULTS

Argenica has completed a series of *in vitro* pharmacology studies evaluating the mechanistic target of xaranetide by determining the inhibition of ion channels associated with modulation of glutamate-associated excitotoxicity, including the major mediator of excitotoxicity, the NMDA receptor, as well as voltage-gated calcium channel (CaV2.2) and acid-sensing ion channel 1a (ASIC1a). Studies were conducted at ApconiX (UK) and B'SYS (Switzerland) and evaluated the inhibitory potential, kinetics, mechanism and voltage dependence of xaranetide on NMDA receptor currents.

In these studies, electrophysiological recordings were made from Human Embryonic Kidney (HEK) cell lines stably expressing the full-length ion channel and for each ion channel, a positive control was tested in parallel.

The NMDA studies showed xaranetide reduced activity in both receptor subunits tested, with greater inhibition as concentration increased. At 1.2 µM, the measured onset time constants were approximately five seconds for both subtypes, showing that inhibition developed rapidly once the peptide was applied in these laboratory experiments.

Inhibition persisted despite increasing glutamate

A follow-up B'SYS study examined GluN1/GluN2A receptors in the presence of 0.014 µM (14 nM) xaranetide. Increasing glutamate concentrations from 100 µM to 300 µM and then to 1 mM did not overcome the inhibition. The findings are consistent with inhibition that does not depend on competition at the glutamate binding site. This is relevant to the neuroprotective rationale because glutamate can accumulate during brain ischaemia: xaranetide retained inhibitory activity even under the high-glutamate conditions tested.

Partial reversibility and relevance to recovery

After xaranetide exposure and a voltage step to +40 mV, mean current measured back at -80 mV recovered from approximately 50% to 83% of the initial response. This demonstrated partial reversal of inhibition under that protocol.

Reversibility is relevant because NMDA receptors help strengthen connections between brain cells, supporting learning and adaptation during recovery[8]. The therapeutic aim is to limit excessive activity during acute injury while retaining the signalling needed for recovery. The B'SYS result demonstrates partial reversal under the tested conditions.

[7] STAIR XI: *Top Priorities for Cerebroprotective Studies—A Paradigm Shift* (2021), Lyden P, et al. (2021). Stroke. 52(9):3063–3071.

[8] Funahashi Y, et al. (2024). Sci Signal. 17(853):eado9852.

New findings identify two additional channels involved in brain injury

Argenica is reporting for the first time that xaranetide inhibits CaV2.2 and ASIC1a, two additional channels involved in brain injury. Testing by specialist laboratory ApconiX in the United Kingdom measured electrical currents through these channels and an NMDA receptor subtype. Xaranetide inhibited all three channel types tested.

CaV2.2 helps control calcium entry and the release of chemical signals, including glutamate, between brain cells. Inhibiting it could limit another contributor to injury. ASIC1a responds to acidity; when oxygen and blood flow are reduced, tissue can become acidic, and this channel contributes to the resulting damage. Both extend the rationale beyond NMDA inhibition.

These findings build on previously published research by Professor Bruno Meloni and colleagues[9], which demonstrated that R18D (xaranetide) reduces glutamate-induced calcium accumulation in cultured neurons and protects them against excitotoxic injury. The new electrophysiological studies provide more specific evidence of how xaranetide may achieve this effect, demonstrating inhibition of NMDA receptor currents and identifying additional activity at CaV2.2 and ASIC1a channels. Together, these results strengthen the biological rationale for xaranetide's neuroprotective activity by linking earlier observations of reduced calcium overload and improved neuronal survival with inhibition of specific channels involved in brain injury.

By targeting multiple interconnected pathways responsible for secondary brain injury, xaranetide has the potential to preserve brain tissue, reduce neurological disability and improve functional recovery, offering a promising new approach to neuroprotection in patients experiencing acute neurological injury.

This announcement has been approved for release by the Board of Argenica.

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ABOUT ARGENICA

Argenica Therapeutics Limited (ASX: AGN) is a clinical-stage biotechnology company developing innovative neuroprotective therapeutics to improve outcomes for patients following stroke and other acute neurological injuries. The Company's lead drug candidate, xaranetide, is designed to protect vulnerable brain tissue by reducing cell death and limiting secondary damage after an ischaemic event. With a strong scientific foundation and a clear clinical development pathway, Argenica is focused on advancing novel treatments that have the potential to significantly improve patient recovery and transform the standard of care in acute neurology.

[9] Edwards et al. (2018), *Molecular Brain*, 11:8