EVOLUTION CAPITAL

**NYR | INITIATION OF COVERAGE | HEALTHCARE**

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# First-in-Class Cardioprotection

## Nyrada Inc. Ltd

Nyrada (ASX: NYR) is developing Xolatryp, a first-in-class TRPC3/6/7 channel inhibitor designed to protect heart muscle from the damage caused when blood flow is restored after a heart attack – a condition known as myocardial ischaemia-reperfusion injury (MIRI). There is no approved drug for this. Supported by strong preclinical efficacy (up to 86% cardioprotection) and a clean Phase I safety profile, the company is set to begin dosing patients in a Phase IIa trial in April 2026. At current pricing, the market is applying a steep probability-of-success discount that, in our view, underprices the upside from a first-in-class asset entering clinical proof-of-concept in a large, uncontested therapeutic space.

This report is structured around the three debates that will determine whether Nyrada can deliver on their value proposition:

**Debate #1: Is MIRI a real commercial opportunity?** Every prior pharmacological attempt at cardioprotection has failed in patients. The field's track record is poor, but the failures are explicable: wrong targets, wrong timing, wrong endpoints. Xolatryp's upstream mechanism is fundamentally differentiated. The therapeutic void is not a reflection of absent demand; it reflects absent supply. Over 600,000 PCIs are performed annually in the US with no approved adjunctive pharmacotherapy. At realistic pricing of US$3,000-6,000 per treatment, the US TAM alone exceeds US$1.8bn.

**Debate #2: Can the Phase IIa deliver a strong efficacy signal?** The Phase IIa is randomised, double-blind, and placebo-controlled across ~100 patients, with cardiac MRI infarct sizing as the key secondary endpoint; a gold-standard measure on which an MI treatment (SSO2) secured FDA approval. The trial design directly addresses the methodological failures of prior MIRI studies. A 10-20% relative infarct-size reduction with statistical significance would constitute the first clinical proof-of-concept for pharmacological cardioprotection via TRPC channel inhibition, and a dataset capable of attracting serious partnering interest from large cardiovascular pharma.

**Debate #3: What is the platform worth beyond MIRI?** Xolatryp's mechanism is not organ-specific. The same calcium-overload cascade drives secondary brain injury in ischaemic stroke and traumatic brain injury (TBI), and Nyrada has statistically significant preclinical data in both. They have a collaboration with Walter Reed Army Institute of Research (WRAIR), providing defence-grade TBI validation at minimal cost. Neither indication is priced in today. A parallel Phase II in a neurological indication would transform Nyrada from a single-asset cardiac story into a multi-indication platform, materially expanding partnering leverage and deal economics.

Our valuation framework incorporates only the lead MIRI indication, heavily risked at a 10-15% cumulative probability of success. We assign no value to the stroke or TBI programs. At our base case of US$500M global peak sales, the implied per-share valuation ranges from A$0.87 to A$1.30, with a clear path to a 2-3x re-rating on positive Phase IIa data. The near-term value story is straightforward: each Phase II milestone (safe dosing confirmations, recruitment updates, interim signals, and top-line results) progressively de-risks the asset and narrows the discount the market is applying today.

| | |
|---|---|
| **Recommendation** | **SPEC BUY** |
| **Price Target** | **$1.04** |
| **Share Price** | **$0.485** |
| **TSR** | **114%** |

**Company Profile**

| | |
|---|---|
| Market Cap | $118.8M |
| Enterprise Value | $111.7M |
| SOI (diluted) | 297.6M |
| Free Float | 54.6% |
| ADV (3-month) | $828k |
| 52-Week Range | $0.091-1.435 |

**Price Performance**


| % | 1M | 3M | 12M |
|---|---|---|---|
| Absolute | -27.0% | -40.8% | 400% |
| ASX/S&P200 | -7.1% | -3.1% | 5.4% |

**Company Overview**

Nyrada Inc (ASX: NYR) is a clinical-stage biotechnology company developing Xolatryp, a first-in-class small-molecule TRPC ion channel inhibitor with dual applications in neuroprotection and cardioprotection. The company's lead programme targets myocardial ischaemia-reperfusion injury (MIRI) in STEMI patients, with a Phase IIa clinical trial commencing in Q1 2026 following a successful Phase Ia safety study. Xolatryp's mechanism also has demonstrated preclinical efficacy in stroke and traumatic brain injury, providing platform optionality across multiple high-unmet-need indications.

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# Investment Thesis

Up to half of the total injury to the heart in myocardial infarction is caused not by the original blockage, but by reperfusion injury sustained when blood flow is restored via PCI; and there is no FDA-approved cardioprotective pharmacological product to address this. Xolatryp is a first-in-class small molecule that protects against reperfusion injury by blocking TRPC3/6/7 channels, the gateways through which pathological calcium floods into heart tissue cells at the moment of reperfusion, preventing the downstream cascade of mitochondrial overload, oxidative stress, and cell death that drives infarct expansion. The opportunity: over 600,000 PCIs are performed annually in the US alone with no approved adjunctive pharmacotherapy, representing a large, well-defined addressable market in a therapeutic void.

At the current share price, the implied valuation is below global peak sales of US$350M at a 10% probability of reaching approval – a reasonable baseline for a Phase II-entry cardiovascular drug, but one that leaves substantial room for re-rating as clinical milestones are achieved. Our valuation framework incorporates only the lead MIRI indication, heavily risked and discounted, and assigns no value to the stroke or traumatic brain injury programs, which remain at preclinical stage.

Near-term value is driven by Phase IIa catalysts: first patient dosed, safety review completions, recruitment updates, and top-line results, each progressively de-risking the asset. Positive data demonstrating statistically significant infarct-size reduction would shift cumulative probability of success from ~10% to ~20-25%, implying a 2-3x re-rating from current levels on our base case assumptions alone. Beyond MIRI, the stroke and TBI programs represent embedded optionality; a successful dual-indication data package would materially expand partnering leverage and deal economics.

There is binary risk and the Company will require further capital. The question is whether the market is adequately pricing the upside from a first-in-class asset entering clinical proof-of-concept in a large, uncontested therapeutic space. We believe it is not.

# Financial Summary

| VALUATION DETAILS | |
|---|---|
| Share Price (A$) | $0.485 |
| Market Cap (A$m) | $118.8M |
| Enterprise Value (A$m) | $111.7M |

| STATEMENTS (A$) | FY25 | 1H FY26 |
|---|---|---|
| ***Income Statement*** | | |
| Revenue | 2,558,803 | 846,243 |
| EBITDA | (4,841,894) | (3,185,726) |
| EBIT | (4,845,671) | (3,187,188) |
| **Net Income** | **(4,845,671)** | **(3,187,188)** |
| | | |
| ***Balance Sheet*** | | |
| Cash & Cash Equivalents | 2,930,601 | 7,122,199 |
| Inventory | - | - |
| Receivables | 2,340,496 | 3,243,531 |
| Other Assets | 29,136 | 27,613 |
| **Total Assets** | **5,300,233** | **10,393,343** |
| Total Debt | - | - |
| Other Liabilities | 1,723,222 | 548,968 |
| **Total Liabilities** | **1,723,222** | **548,968** |
| **Shareholders' Equity** | **3,577,011** | **9,844,375** |
| | | |
| ***Cash Flow Statement*** | | |
| Net Income | (4,845,671) | (3,187,188) |
| Add: D&A | 3,777 | 1,462 |
| Add: Share-based payments | 177,218 | 738,218 |
| Less: Change in NWC | (387,271) | (2,020,423) |
| **Cash Flow from Operations** | **(5,051,947)** | **(4,467,931)** |
| **Cash Flow from Investing** | **-** | **(2,224)** |
| Equity Raised (net) | 3,191,520 | 8,674,927 |
| Less: Dividends Paid | - | - |
| **Cash Flow from Financing** | **3,191,520** | **8,674,927** |
| Unlevered Free Cash Flow | (5,051,947) | (4,470,155) |

| PER SHARE DATA | FY25 | 1H FY26 |
|---|---|---|
| Shares Out (dil., m) | 200.1 | 234.4 |
| Normalised EPS (A$) | -0.024 | -0.014 |
| Dividends (A$/share) | - | - |
| Payout | N/A | N/A |

| RATIOS | FY25 | 1H FY26 |
|---|---|---|
| ***Liquidity*** | | |
| Current Ratio | 3.1x | 19.0x |
| Quick Ratio | 3.1x | 19.0x |
| | | |
| ***Solvency*** | | |
| Debt to Equity | 0.0x | 0.0x |
| Equity to Assets | 67.5% | 94.7% |
| | | |
| ***Profitability*** | | |
| ROA | n/m | n/m |
| ROE | n/m | n/m |
| EBITDA Margin | n/m | n/m |
| NPAT Margin | n/m | n/m |
| | | |
| ***Valuation*** | | |
| P/E | n/m | n/m |
| EV/Revenue | n/m | n/m |
| EV/EBITDA | n/m | n/m |
| Dividend Yield | 0.0% | 0.0% |

# The Science Behind Xolatryp

## MIRI: The Key Challenge in STEMI

When a STEMI patient arrives at hospital and the cardiologist opens the blocked artery with primary PCI (Percutaneous Coronary Intervention; the preferred emergency treatment for STEMI), blood flow returns to starving heart muscle. This is lifesaving; however, the act of restoring blood blow itself damages the heart. This phenomenon is called myocardial ischaemia-reperfusion injury (MIRI), and it is estimated to account for up to 50% of the final infarct size in STEMI patients. By the time the patient leaves the cath lab, up to half the damage to the heart may have been caused not by the original blockage, but by the treatment. **There is no approved pharmacological therapy** to address this.

## Calcium Overload Problem

Why does reperfusion damage cells? Under normal conditions, heart muscle cells (cardiomyocytes) maintain a delicate balance of calcium ions ($Ca^{2+}$). Calcium is the essential signalling molecule that triggers each heartbeat. A specialised internal storage compartment within the cell, called the sarcoplasmic reticulum, releases precisely controlled bursts of calcium to make the muscle contract, then rapidly pulls it back in to allow the muscle to relax. At rest, the concentration of free calcium inside the cell is roughly 10,000 times lower than outside it. Maintaining this steep gradient is critical: calcium must be kept low inside the cell so that each release produces a clean, powerful contraction signal. It is the most tightly regulated ionic difference in the cell.

During ischaemia, the heart muscle is starved of oxygen. Without oxygen, the cell can no longer produce energy (ATP) efficiently and switches to a far less effective emergency mode (anaerobic metabolism). ATP levels collapse. This matters because the pumps that maintain the calcium gradient are energy-dependent – they need ATP to keep pushing calcium and other ions in the right direction. Two key pumps, $Na^+/K^+$-ATPase and the SERCA pump, begin to fail. At the same time, lactic acid builds up inside the cell, making the interior increasingly acidic. The cell tries to correct this by activating a different transporter (the $Na^+/H^+$ exchanger) to push acid out, but this floods the cell with sodium. The excess sodium then reverses yet another transporter (the $Na^+/Ca^{2+}$ exchanger), which now starts pulling calcium in rather than pushing it out. The net result: calcium levels inside the cell rise dangerously.

However, there is a paradox. During ischaemia, the very acidity that is damaging the cell also provides a partial brake; it keeps a critical structure called the mitochondrial permeability transition pore (mPTP) firmly shut. The mPTP is essentially a gateway in the cell's mitochondria (its power generators). As long as this gateway stays closed, the cell can survive, even in a damaged state. The acidic environment during ischaemia keeps it closed, preventing immediate cell death.

The real damage begins when oxygenated blood returns at reperfusion. Three things happen almost simultaneously:

i. First, pH rapidly normalises as lactic acid is washed out by the returning blood flow. This removes the protective brake on the mPTP.

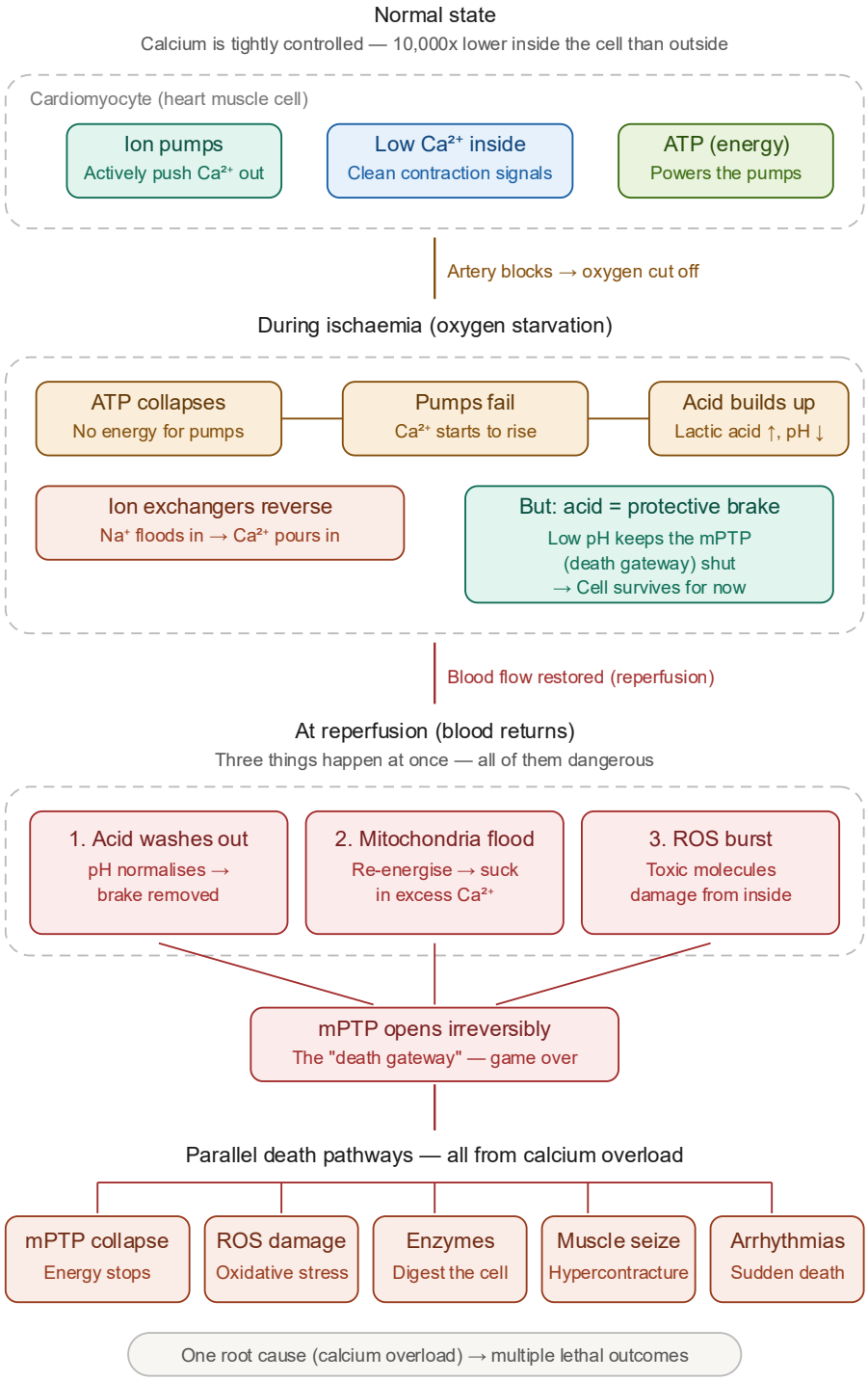
ii. Second, the mitochondria re-energise and restore their electrical charge (membrane potential), which actively drives calcium from the cell's interior into the mitochondria themselves. The mitochondria, now flooded with calcium, become overloaded.

iii. Third, a metabolic byproduct called succinate, which accumulated during the period of oxygen starvation, is rapidly burned off. This process generates a burst of toxic molecules called reactive oxygen species (ROS), which are chemical agents that damage cell structures from the inside.

This combination of calcium overload, oxidative stress from ROS, and the removal of the acid brake converges on the mPTP, triggering its irreversible opening. Once the mPTP opens, it is essentially game over for the cell. The mitochondria lose their electrical charge, energy production stops, the mitochondria swell and rupture, and the cell is committed to death.

Critically, this is not a single-pathway event. The excess calcium simultaneously triggers multiple destructive processes: it opens the mPTP, activates enzymes that break down cell structures (proteases called calpains, and phospholipases), generates further ROS through an enzyme system called NADPH oxidase 2 (Nox2), causes the heart muscle fibres to violently and irreversibly shorten (hypercontracture), and triggers dangerous heart rhythm disturbances (ventricular arrhythmias) that can cause sudden cardiac death. These are parallel, redundant lethal mechanisms, all branching from the same root: pathological calcium entry.

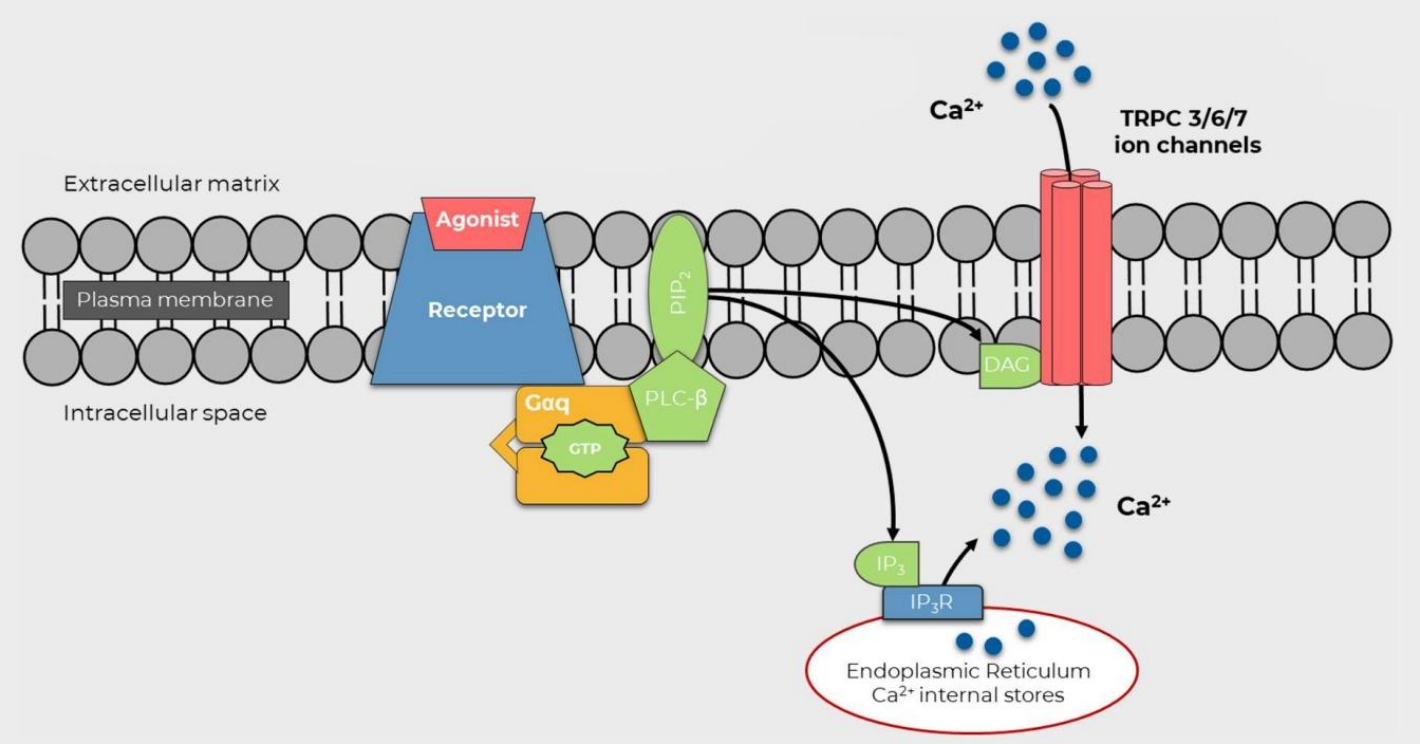
**Figure 1: The calcium overload cascade in myocardial ischaemia-reperfusion injury. Source: Evolution Capital.**



## TRPC Channels

Transient Receptor Potential Canonical (TRPC) channels are a subfamily of 7 members (TRPC1-7), which group into functional clusters by sequence and activation mechanism. TRPC1/4/5 (activated by store depletion) and TRPC3/6/7 (activated by diacylglycerol, or DAG, a lipid signalling molecule). The TRPC3/6/7 subfamily is activated by receptor-driven biochemical signals. Under normal conditions, TRPC channels are expressed at very low levels in adult cardiomyocytes. But under pathological stress, including the conditions created by ischaemia and reperfusion, their expression and activity increase dramatically.

**Figure 2: TRPC3/6/7 channel activation pathway: receptor-driven Gαq signalling activates PLC-β, generating DAG which opens TRPC3/6/7 channels and allows pathological calcium influx into the cardiomyocyte. Xolatryp blocks the channel itself, preventing calcium entry at source. Source: Nyrada Inc.**




A critical breakthrough was a 2017 study published in *Proceedings of the National Academy of Sciences* (PNAS) using triple-knockout mice lacking TRPC3, TRPC6, and TRPC7 (TRPC3/6/7). These mice showed markedly reduced ischaemia-reperfusion injury compared to wild-type controls, directly demonstrating that the TRPC3/6/7 channel subfamily is a major conduit for the pathological calcium entry that drives reperfusion injury. Blocking TRPC activity or genetically ablating these channels protected cardiac tissue and cells from ischaemic reperfusion injury.

**Figure 3: Genetic ablation of TRPC3/6/7 channels reduces infarct size by 45% in a murine I/R model (30 min ischaemia / 24 hr reperfusion). White = infarct; red = area at risk; blue = perfused tissue. Source: He et al., PNAS 2017.**

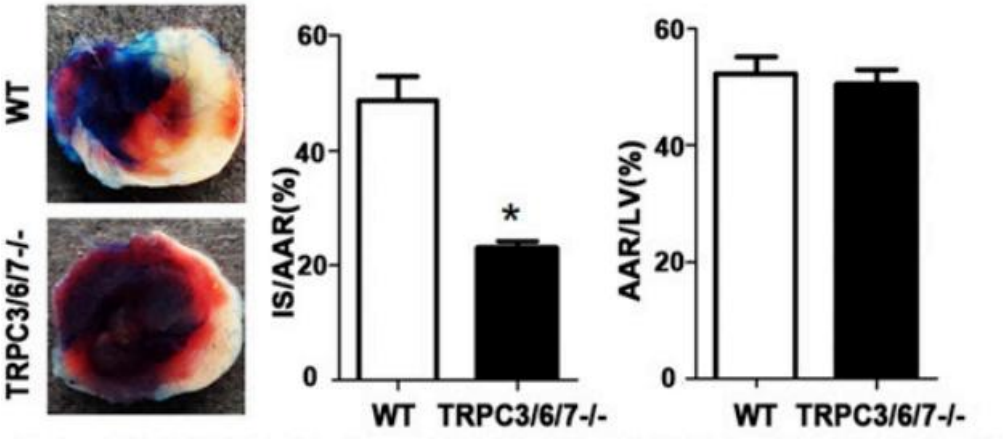
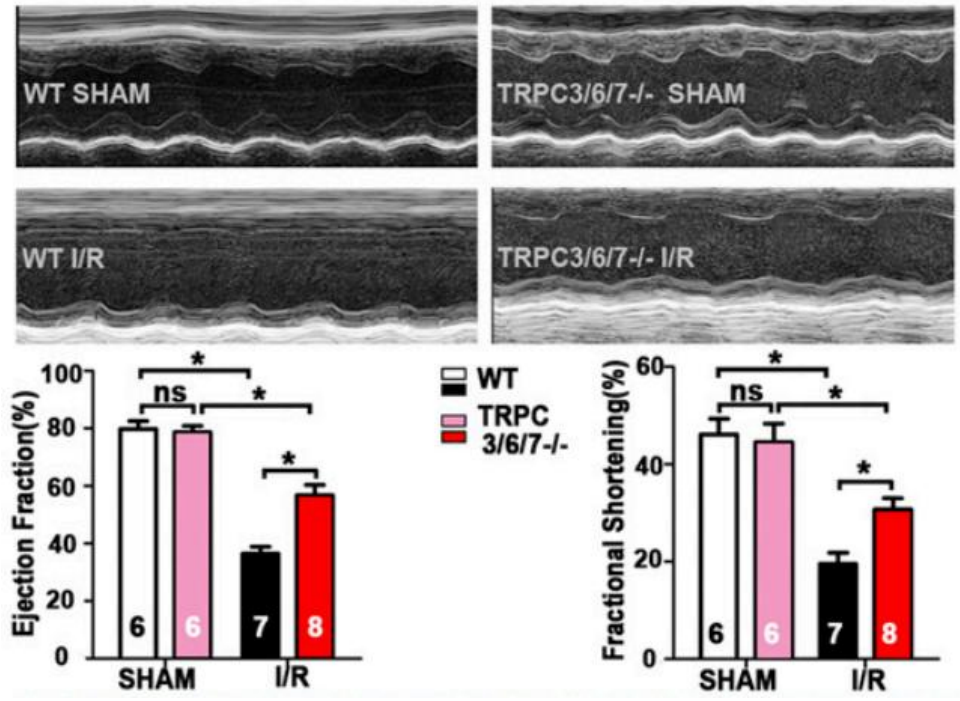



**Figure 4: TRPC3/6/7 knockout mice preserve ejection fraction and fractional shortening after I/R versus wild-type controls, confirming that TRPC channel blockade protects cardiac function, not just tissue viability. Source: He et al., PNAS 2017.**




Re Figure 4 above, ejection fraction and fractional shortening are the two primary clinical measures of the heart's pumping capacity: they are routinely assessed in every STEMI patient and are the strongest predictors of long-term outcomes including heart failure progression, rehospitalisation, and mortality. The fact that TRPC3/6/7 knockout mice preserved both measures after I/R is significant because it demonstrates that the benefit of TRPC channel blockade extends beyond limiting acute tissue death to preserving the functional performance of the heart, which is ultimately what determines whether a patient develops chronic heart failure or recovers.

## Xolatryp: Mechanism of Action

Xolatryp is a first-in-class small molecule that blocks TRPC3/6/7 channels: the gateways through which pathological calcium enters cardiomyocytes at reperfusion. It is administered as an intravenous infusion around the time of PCI, ensuring it is circulating before, during, and after the moment the blocked artery is reopened. Rather than targeting any single downstream pathway, it blocks the one upstream event – calcium entry – that feeds them all. The analogy is a river system: rather than building dams on every tributary downstream, Xolatryp blocks the source at its headwaters.

Critically, this mechanism is not organ-specific. TRPC3/6/7 channels are expressed in neurons as well as cardiomyocytes, and the same calcium-overload cascade drives secondary brain injury following ischaemic stroke and traumatic brain injury. Collaborative studies with the Walter Reed Army Institute of Research (WRAIR) confirmed in September 2025 that Xolatryp reduces mitochondrial calcium ion loading in brain tissue. This is direct mechanistic validation that the drug operates through the same pathway across organ systems, establishing Xolatryp as a platform compound.

A drug's potency is measured by how little of it is needed to block its target. While Nyrada has not yet disclosed Xolatryp's specific potency data, the Phase II dose was selected based on Phase I data to ensure the drug reaches blood levels sufficient for near-complete channel blockade throughout the critical reperfusion window.

# Debate #1: Is MIRI a Real Commercial Opportunity?

For more than half a century, the cardioprotection field has pursued a simple and intuitive idea: if reperfusion itself damages the heart, intervening at the moment of reperfusion should save muscle. Hundreds of agents have worked in animal models. Almost none have worked in patients. The question for investors is whether Xolatryp is entering a field defined by durable unmet need, or one that is simply intractable.

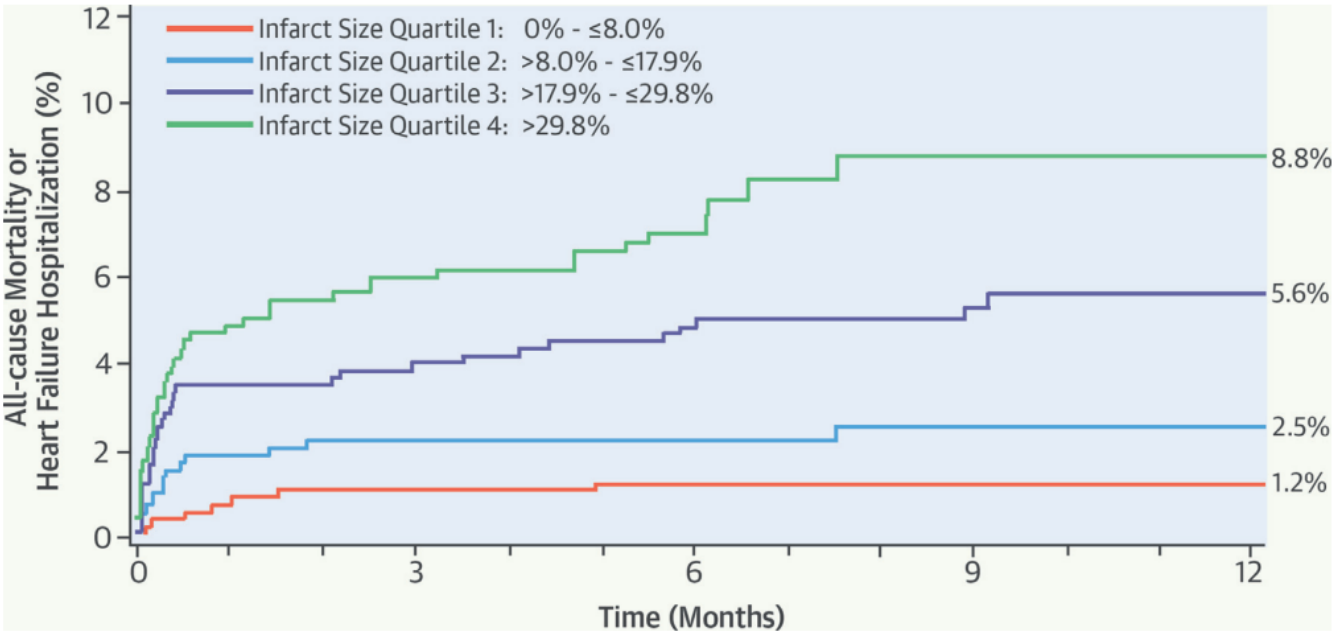
## The Problem: Reperfusion Injury Accounts for Up to Half of Final Infarct Size

When a STEMI patient arrives at hospital and undergoes primary PCI, the restoration of blood flow is lifesaving. But reperfusion is a double-edged sword. The sudden reintroduction of oxygenated blood to ischaemic tissue triggers a cascade of pathological events – calcium overload, oxidative stress, mitochondrial permeability transition pore opening, and inflammatory cell infiltration – that can destroy cardiomyocytes which survived the initial ischaemia. This phenomenon, myocardial ischaemia-reperfusion injury (MIRI), is estimated to account for up to 50% of the final infarct size in STEMI patients.

The clinical consequences are significant. Despite improvements in door-to-balloon times, mortality and heart failure rates in STEMI patients have plateaued. Approximately 20-30% of STEMI patients develop heart failure within one year of their event. Each 5% absolute increase in infarct size is associated with a ~20% relative increase in the hazard of death or heart failure hospitalisation at one year. There is a clear and quantifiable imperative to reduce infarct size beyond what PCI alone achieves.

A landmark pooled analysis of 2,632 STEMI patients across 10 randomised primary PCI trials demonstrated a strong, graded relationship between infarct size measured within one month of reperfusion and subsequent death or heart failure hospitalisation: patients in the largest infarct quartile experiencing a greater than seven-fold higher event rate than those in the smallest (see Figure 3 below).

**Figure 5: One-year rate of all-cause mortality or heart failure hospitalisation by infarct size quartile following primary PCI. Every 5% increase in infarct size is independently associated with a 19% increase in mortality and a 20% increase in HF hospitalisation. Source: Stone et al., JACC 2016; n=2,632.**




## Scale of Opportunity: A Large, Well-Defined Addressable Market

STEMI represents approximately 38% of all acute coronary syndrome presentations. In the United States alone, the annual incidence of myocardial infarction is approximately 750,000 events (550,000 new, 200,000 recurrent), with STEMI accounting for an estimated 200,000-300,000 of these. Over 600,000 PCIs are performed annually across more than 1,600 centres in the US. Globally, over 3 million STEMI cases are estimated annually. In Europe, approximately 5.8 million new ischaemic heart disease cases were reported across ESC member states in 2019.

The initial addressable population for Xolatryp is well-defined: STEMI patients presenting within six hours of symptom onset who undergo primary PCI. This is a procedure-adjacent use case: the drug is administered intravenously around the time of PCI in the coronary care unit, meaning the target patient is already in a controlled clinical setting with clear diagnosis. Unlike chronic disease indications that require patient identification and ongoing compliance, the MIRI treatment window is a single, acute intervention tied to an existing procedure.

## The Bear Case: Hindrance of Previous Failures

The history of cardioprotection research is littered with therapies that looked transformative in rodent models and failed spectacularly in humans. Why should this time be different? This is the strongest version of the bear case.

**Figure 6: Every major pharmacological and procedural approach to cardioprotection has failed to demonstrate clinical benefit in adequately powered STEMI trials, despite robust preclinical data. Source: Evolution Capital; trial data from referenced publications.**

| Intervention | Mechanism | Key Trial(s) | Outcome |
|---|---|---|---|
| **Cyclosporine A** | mPTP inhibitor which prevents mitochondrial permeability transition pore opening | CIRCUS (n=970); CYCLE (n=410) | No benefit on infarct size, LV remodelling, or clinical outcomes vs. placebo |
| **Ischaemic postconditioning** | Brief coronary re-occlusion cycles post-PCI to activate salvage pathways | DANAMI-3-iPOST (n=1,234); POST (n=700) | No reduction in composite of death + HF hospitalisation; mixed infarct size results |
| **Remote ischaemic conditioning (RIC)** | Limb ischaemia/reperfusion cycles to trigger systemic protective signals | CONDI-2/ERIC-PPCI (n=5,401) | No benefit on cardiac death or HF hospitalisation at 12 months (largest RIC trial to date) |
| **TRO40303** | Mitochondrial-targeted compound (oxidative stress pathway) | MITOCARE (n=163) | No reduction in infarct size |
| **Delcasertib** | PKC-delta inhibitor | PROTECTION AMI (n=1,010) | No reduction in infarct size or CK-MB AUC |
| **IV Metoprolol** | Beta-blocker — reduces $O_2$ demand, modulates reperfusion signalling | METOCARD-CNIC (n=270); EARLY-BAMI (n=683) | Mixed: METOCARD showed benefit in anterior STEMI; EARLY-BAMI neutral overall (underpowered) |

Many of these agents showed robust preclinical efficacy, sometimes across multiple animal models, yet failed to translate. The field's leading researchers have attributed these failures to several recurring problems:

- **Inappropriate animal models:** Most preclinical MIRI studies use young, healthy animals without the comorbidities (diabetes, hypertension, dyslipidaemia, ageing) and concomitant medications (statins, antiplatelets, ACE inhibitors) that characterise real STEMI patients. These co-factors can interfere with cardioprotective signalling pathways.

- **Single-target approaches to a multi-pathway injury:** Reperfusion injury involves parallel, redundant cell-death pathways. Blocking one downstream mediator (e.g. the mPTP alone) may be insufficient if other pathways (calcium overload, oxidative stress, inflammation) continue to drive cardiomyocyte death.

- **Poor trial design:** Many trials enrolled heterogeneous patient populations (anterior + inferior STEMI, variable ischaemic times, patients with and without collateral flow), diluting the treatment signal. Biomarker-only endpoints (CK-MB, troponin AUC) proved unreliable surrogates for true infarct size. Dose-finding and timing optimisation were often inadequate or absent.

- **Timing of intervention:** Several agents were administered too late – after significant necrosis had already occurred – or were unable to reach the ischaemic myocardium through an occluded artery.

**The Exception That Proves the Rule: SS02 Therapy**

It is worth noting that the therapeutic void is not quite absolute. In April 2019, the FDA approved SuperSaturated Oxygen (SSO2) Therapy (TherOx/ZOLL), a catheter-based device that delivers hyperbaric oxygen directly to ischaemic myocardium immediately after PCI. SSO2 demonstrated a 26% relative reduction in infarct size in the AMIHOT-II trial and favourable one-year outcomes in the IC-HOT propensity-matched analysis (0% death or new-onset heart failure vs. 12.3% in controls).

However, SSO2's approval is narrowly scoped: it is indicated only for left anterior descending (LAD) STEMI treated within six hours – a subset of total STEMI volume. It is a device-based therapy requiring capital equipment, a catheter-based delivery system, and 60 minutes of post-PCI infusion in the cath lab, creating workflow and capacity

constraints. Adoption has been modest. SSO2 demonstrates that the FDA will approve therapies that reduce MIRI-related infarct size, and that the regulatory pathway exists, but it also illustrates the commercial limitations of a device-centric approach in an acute procedural setting.

Xolatryp, as a simple IV infusion that can be administered outside the cath lab (in the coronary care unit, before, during, and after PCI), would represent a fundamentally different delivery paradigm, one more likely to integrate into existing STEMI workflows without cath-lab throughput constraints.

## The Bull Case: NYR's Differentiation

As detailed in the science section, reperfusion injury involves multiple downstream pathways that converge on a common upstream trigger: pathological calcium entry through TRPC3/6/7 channels. By blocking these channels, Xolatryp addresses the root cause rather than any single downstream effector – a fundamentally different approach from prior failed strategies:

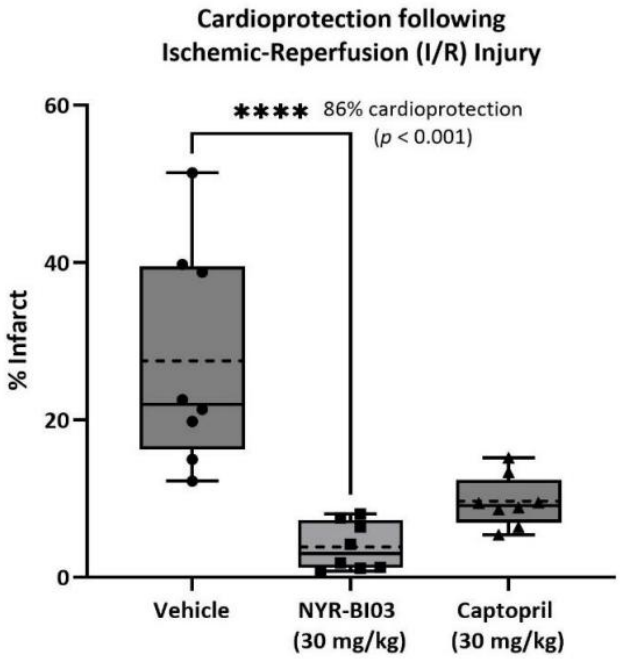
**Figure 7: Mechanistic comparison of cardioprotective approaches showing why prior agents failed: each targeted a single downstream pathway or indirect mechanism, leaving the root-cause calcium overload intact. Xolatryp is the first to intervene at the channel level. Source: Nyrada Inc.; Evolution Capital analysis.**

| Approach | Target Level | Limitation |
|---|---|---|
| Cyclosporine (mPTP inhibitor) | Downstream: blocks one specific pore after mitochondrial damage has begun | Does not prevent $Ca^{2+}$ overload or oxidative stress upstream |
| Ischaemic conditioning | Downstream: activates endogenous salvage kinase pathways | Pathways may be impaired by comorbidities and concomitant medications |
| Beta-blockers (metoprolol) | Indirect: reduces $O_2$ demand, some reperfusion signalling | Does not directly address calcium entry or mitochondrial overload |
| **Xolatryp (TRPC3/6/7 inhibitor)** | **Upstream: blocks pathological $Ca^{2+}$ entry at the channel level, before downstream cascades activate** | **First-in-class; no clinical efficacy data yet (Phase IIa commencing March 2026)** |

The preclinical evidence supporting this mechanism is substantial. In validated rodent models of MIRI, Xolatryp delivered:

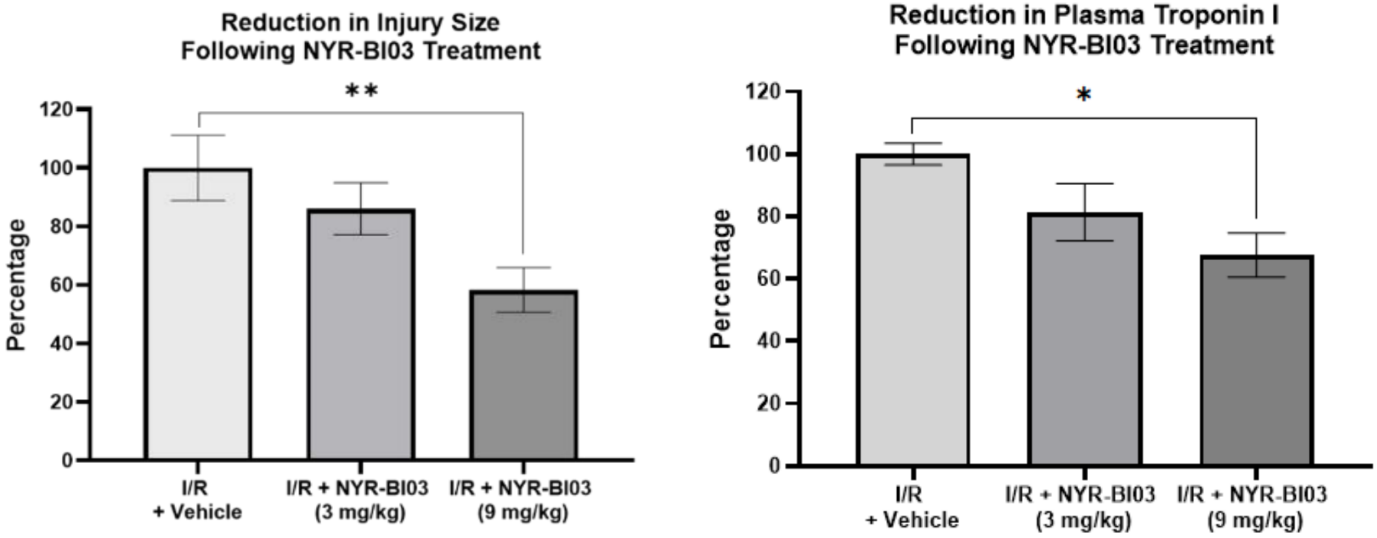
- **42% reduction in cardiac injury with a 3-hour** continuous infusion.
- **86% cardioprotection** with a 24-hour infusion protocol ($p < 0.001$, n=8 per group). Captopril, an FDA-approved ACE inhibitor used as the positive control, produced a substantially lower cardioprotective effect – directly illustrating the distinction between indirect haemodynamic support and direct channel-level cardioprotection.

**Figure 8: Infarct size (% of left ventricle) in a rodent model of acute myocardial ischaemia-reperfusion injury. Source: Nyrada Inc. ASX announcement, 1 October 2024.**




- **88% reduction in ventricular arrhythmias (VF/VT)**, a clinically meaningful secondary benefit given that arrhythmia is a leading cause of early mortality in STEMI.

**Figure 9: Dose-dependent reductions in infarct size (left; 42%, p = 0.008) and plasma Troponin I (right; 32%, p = 0.014) at 9 mg/kg following a 3-hour IV infusion in a rodent MIRI model (n=10). Source: Nyrada Inc. ASX announcement, 8 May 2025.**




- **Improved cardiac structure and function** with reduced biomarkers of injury.

The arrhythmia reduction data are particularly notable. Ventricular fibrillation and tachycardia are major contributors to sudden cardiac death in the peri-reperfusion period. No prior cardioprotective agent has demonstrated this degree of anti-arrhythmic effect in MIRI models alongside infarct-size reduction.

Further mechanistic validation comes from the TBI program, where WRAIR studies confirmed that Xolatryp reduces mitochondrial calcium loading in brain tissue – demonstrating cross-organ mechanistic consistency that strengthens the biological rationale for the cardiac application.

**Procedure-adjacent Dosing: The Timing Advantage**

A critical lesson from prior failures is that timing matters enormously. Many agents were administered after significant irreversible damage had already occurred, or could not reach the ischaemic zone through an occluded artery. Xolatryp's IV infusion model is designed to be procedure-adjacent: administration begins in the coronary care unit around the time of PCI, ensuring the drug is ideally present in the circulation before, during, and after reperfusion. This creates a clean intervention window that aligns with the biology: the drug is on board precisely when the calcium-overload cascade is triggered by restored blood flow.

This contrasts with ischaemic conditioning (which must be initiated at exact time-points relative to reperfusion and may be impractical in emergency settings) and with agents that required sub-selective intracoronary delivery (adding procedural complexity and cath-lab time).

## Competitive Landscape: A Therapeutic Void

The competitive dynamics in MIRI are unusual for a large-market indication. There is no approved pharmacological therapy that directly protects cardiomyocytes from reperfusion injury. The only approved adjunctive therapy is SSO2 (ZOLL/TherOx), a device limited to LAD STEMI with modest commercial adoption, discussed earlier in this section. The standard of care for STEMI remains timely PCI plus guideline-directed pharmacotherapy (antiplatelets, anticoagulants, statins, beta-blockers, ACE inhibitors), none of which specifically target reperfusion injury.

**Captopril: Pharmacological Precedent**

The closest pharmacological precedent is captopril, an ACE inhibitor with a historical FDA indication for post-MI survival. Captopril is sometimes used off-label in the peri-PCI setting, but its mechanism is fundamentally indirect: it reduces cardiac workload through afterload reduction and neurohormonal attenuation, rather than directly protecting cardiomyocytes from acute calcium overload at reperfusion. In Nyrada's pivotal rodent MIRI study, captopril (as positive control) produced a substantially lower cardioprotective effect than Xolatryp's 86%. The two drugs are complementary, not substitutional: ACE inhibitors manage haemodynamics and long-term remodelling, while Xolatryp would be administered acutely around PCI to limit reperfusion-mediated tissue death. The commercial opportunity is therefore additive to existing ACE inhibitor use in STEMI care.

## Pricing & Commercial Framework: Guiding the TAM

An IV-administered adjunct to PCI in the acute STEMI setting would be analogous to other high-value hospital-administered therapies in acute cardiovascular care. Unlike outpatient drugs, an IV therapy administered during a PCI hospitalisation is bundled into the fixed Medicare DRG payment, meaning the cost of any new drug must be absorbed within this payment unless a supplemental mechanism applies.

**New Technology Add-On Payment (NTAP)**

The NTAP pathway is critical. CMS's New Technology Add-On Payment program provides supplemental payments on top of the base DRG rate for up to three years for new technologies that offer substantial clinical improvement. Median NTAP payments have ranged from approximately US$3,650 to US$22,750 per discharge in recent years, with cardiovascular technologies comprising the single largest category of approvals. A first-in-class cardioprotective agent that demonstrably reduces infarct size in STEMI would have a compelling case for NTAP eligibility, particularly if granted FDA Breakthrough Therapy designation, which would allow it to bypass the "substantial clinical improvement" criterion entirely.

**Pricing Precedents: the GPIIb/IIIa Inhibitor Analogy**

The closest historical pricing analogy for Xolatryp is the GPIIb/IIIa inhibitor class: abciximab (ReoPro), eptifibatide (Integrilin), and tirofiban (Aggrastat). These IV-administered antiplatelet agents were introduced in the mid-to-late 1990s as adjuncts to PCI in acute coronary syndromes, essentially the same clinical settings to Xolatryp. At launch, abciximab was priced at approximately US$1,350 per treatment course (bolus plus 12 to 24-hour infusion), while eptifibatide was positioned slightly lower at approximately £455–553 (roughly US$600–750 at contemporary exchange rates) per course in the UK. In US hospital practice, comparative economic studies found total in-hospital drug costs of approximately US$1,000-1,500 per treatment for the GPIIb/IIIa class, with abciximab consistently at the premium end. These agents generated multi-billion-dollar peak revenues: ReoPro alone achieved approximately US$600 million in annual sales at its peak. However, the GPIIb/IIIa inhibitors did not reduce infarct size or prevent heart failure. They reduced acute thrombotic complications. An agent with a demonstrably larger clinical impact (reducing infarct size and downstream heart failure) would command a meaningfully higher price than the GPIIb/IIIa precedent.

**Pharmacoeconomic Justification: The Downstream Cost Offset**

The pharmacoeconomic case is potentially very strong. Heart failure is the second most common inpatient diagnosis billed to Medicare, with direct annual US costs estimated at US$39-60 billion. Approximately 20-30% of STEMI patients develop heart failure within one year, with average annual direct costs per patient of ~US$31,500 rising to ~US$46,000 in the first year post-diagnosis. A therapy that meaningfully reduces infarct size would directly reduce the incidence of post-STEMI heart failure, generating cumulative downstream savings potentially exceeding US$50,000-100,000 per case avoided over a patient's lifetime through reduced hospitalisations, readmission penalties, and chronic management costs.

**A Too Early Pricing Range Estimate for Xolatryp**

The above considered, we believe a realistic per-treatment price for Xolatryp in the US market falls in the range of US$3,000-6,000. The low end reflects a modest premium to the GPIIb/IIIa class. The upper end reflects the value-based pricing that a first-in-class agent with demonstrable infarct-size reduction and heart failure prevention would support, anchored by the downstream cost offsets.

**TAM Estimate**

Over 600,000 PCIs are performed annually in the US across more than 1,600 centres. Approximately 200,000-300,000 are primary PCIs for STEMI. Globally, over 3 million STEMIs are estimated annually. At the low end of the pricing and volume ranges, the US TAM comes to approximately $600 million p.a. The global TAM is around US$9 billion.

Worth noting that these numbers do not account for potential use in all PCI patients, and they assume no premium pricing above our low-of-the-range estimate. On a risk-adjusted basis, accounting for clinical, regulatory, and commercial execution risk, we believe the US TAM alone supports a multi-hundred-million-dollar annual revenue opportunity at realistic pricing, reinforcing the attractiveness of this asset to a large-pharma partner with cardiovascular commercial infrastructure.

## Our View

Prior failures in cardioprotection are explicable: wrong targets, wrong timing, wrong endpoints, wrong populations. Xolatryp's design incorporates those lessons – upstream mechanism, procedure-adjacent dosing, gold-standard MRI endpoint, well-defined STEMI population – giving it the strongest mechanistic and methodological foundation of any MIRI candidate to date.

# Debate #2: Can the Phase IIa Deliver a Strong Efficacy Signal?

Can Nyrada's Phase IIa trial, in approximately 100 STEMI patients across up to 10 Australian hospitals, generate data persuasive enough to validate Xolatryp's mechanism and attract a development or commercial partner?

## Trial Design

The Phase IIa is a randomised, double-blind, placebo-controlled, multicentre study in STEMI patients presenting within six hours of symptom onset who are undergoing primary PCI. Patients will be randomised 1:1 to Xolatryp or placebo, with treatment administered as an intravenous infusion around the time of PCI. The trial is being coordinated by Professor William Chan at Western Health, Melbourne, a respected interventional cardiologist and clinical trialist, with Accelagen serving as CRO.

**Figure 10: Phase IIa trial design summary. Source: Nyrada Inc.**

| Parameter | Detail |
|---|---|
| Design | Randomised, double-blind, placebo-controlled, multicentre |
| Population | ~100 STEMI patients presenting within 6 hours of symptom onset, undergoing primary PCI |
| Enrichment | Primarily TIMI flow 0-1 patients (no/minimal collateral flow to ischaemic territory); approximately 50% of STEMI presentations. TIMI grade assessed immediately prior to PCI. |
| Randomisation | 1:1 (Xolatryp : placebo) |
| Intervention | IV infusion of Xolatryp, procedure-adjacent dosing around PCI. Dosing begins as soon as practicable after consent, with dosing permitted to start post-PCI if required. |
| Primary endpoints | Safety, tolerability, pharmacokinetics, pharmacodynamics |
| Key secondary endpoint | Infarct size measured by cardiac MRI (late gadolinium enhancement) |
| Exploratory endpoints | Arrhythmia incidence over 24 hours; troponin I kinetics; Day 30 patient questionnaire |
| Sites | Up to 10 Australian hospitals (coronary care units); potential expansion to NZ, Singapore, Canada, US |
| Coordinating PI | Professor William Chan, Western Health, Melbourne |
| CRO | Accelagen |
| Timeline | First patient dosing: March 2026. Completion: 9–18 months post-first dose (recruitment-dependent) |
| Regulatory | HREC approved; IND application to FDA planned for potential US expansion |

Several design choices are worth highlighting, as they directly address the structural reasons prior MIRI trials failed:

- **Well-defined patient population:** By restricting enrolment to STEMI patients presenting within six hours of symptom onset, the trial selects for a population where reperfusion injury is most clinically relevant and where the treatment signal is least likely to be diluted by extensive irreversible necrosis. This directly addresses the criticism of prior trials that enrolled heterogeneous populations with variable ischaemic times.

- **Procedure-adjacent dosing:** The IV infusion is timed around PCI, ensuring Xolatryp is circulating before, during, and after the moment of reperfusion. Prior

agents that were administered too late (after significant necrosis) or via impractical delivery routes lost the intervention window. Importantly, the protocol permits dosing to commence post-PCI if pre-procedural administration is not feasible, providing operational flexibility without protocol deviation.

- **Gold-standard efficacy endpoint:** Cardiac MRI with late gadolinium enhancement (LGE) is the consensus reference standard for in vivo infarct size quantification. This is the endpoint on which TherOx's SSO2 secured FDA approval. Biomarker-only surrogates (CK-MB, troponin AUC) were a major weakness in earlier trials: they are influenced by reperfusion timing, sampling protocols, and patient variability. MRI infarct sizing provides a direct, reproducible, and prognostically validated measurement.

- **Adequate sample size for signal detection:** With approximately 50 patients per arm, the trial is sized to detect a clinically meaningful difference in infarct size. The AMIHOT-II trial (n=222) demonstrated a 26% relative infarct-size reduction with SSO2, establishing the benchmark for what is achievable in this patient population. Xolatryp's preclinical effect sizes (42-86% cardioprotection) suggest ample headroom, though translation loss is expected.

## Why Cardiac MRI Changes the Equation

The evolution of cardiac MRI (CMR) as a clinical trial endpoint is one of the most important developments for MIRI. LGE-CMR has been clearly established as the best in vivo surrogate for infarct size, with a JACC Scientific Expert Panel consensus confirming its role as the reference standard. Crucially, CMR-measured infarct size is independently and incrementally prognostic: each 1% increase in infarct size (as a proportion of LV mass) is associated with a 13% increase in the hazard of death or heart failure hospitalisation.

This matters for two reasons. First, it provides a biologically meaningful and clinically validated endpoint that directly correlates with patient outcomes, addressing the criticism that prior trials relied on surrogate biomarkers with tenuous links to clinical benefit. Second, it provides the regulatory foundation for an approval pathway. The FDA accepted MRI infarct-size reduction as the basis for SSO2's premarket approval in 2019. A Phase IIa demonstrating statistically significant infarct-size reduction by CMR would therefore generate a data package with direct regulatory precedent.

Additional CMR-derived measures such as microvascular obstruction (MVO), myocardial salvage index, LV ejection fraction (LVEF), and LV volumes provide secondary readouts that further characterise the treatment effect and its clinical significance. MVO in particular is an independent predictor of adverse cardiac events and would strengthen the mechanistic narrative if reduced by Xolatryp.

## The Bear Case: Execution Risk in the Acute Setting

STEMI trials are difficult to recruit. Patients present as emergencies, consent windows are narrow, and enrolment at Australian hospitals may be slow (though we saw faster-than-expected recruitment in Argenica's (ASX: AGN) recruitment of acute ischaemic stroke patients in their phase II trial completed in 2025).

Clinical research in the acute STEMI setting presents genuine logistical challenges:

- **Consent complexity:** STEMI patients present in emergency conditions where clinical priority dominates, and approximately 40% of eligible patients consent when approached in the emergency department. Nyrada has designed the consent process to begin in the ambulance, with provision for legally authorised representatives – a pre-hospital workflow that maximises the treatment window and addresses the timing constraint that has historically limited enrolment in acute cardiac trials.

- **Recruitment pace:** STEMI presentations are unpredictable, and even high-volume PCI centres may only see a handful of eligible patients per month. The protocol allows for international expansion to New Zealand, Singapore, Canada, and the US (pending IND approval), providing recruitment flexibility without protocol amendment.

- **Signal dilution:** Heterogeneity in ischaemic time, collateral circulation, and comorbidity burden can dilute the treatment signal. The company's enrichment strategy – primarily targeting TIMI flow grade 0-1 patients (~50% of STEMI presentations), using MRI rather than biomarkers – should concentrate the signal, but a 100-patient trial cannot fully eliminate biological noise.

- **Translation risk:** The most fundamental concern remains: can any agent translate preclinical MIRI efficacy into human benefit? Until the Phase IIa reads out, this remains the dominant binary risk.

## Defining Trial Success

The phase IIa is not registrational. It is mechanism-validating and partner-attracting. We see a spectrum of possible outcomes and implications:

**Figure 11: Spectrum of Phase IIa outcomes and their implications for partnering and valuation. Source: Evolution Capital.**

| Scenario | Data Outcome | Implications |
|---|---|---|
| **Bull case** | Statistically significant infarct-size reduction ($p<0.05$) on CMR, clean safety profile, consistent PK, supportive secondary endpoints (MVO, LVEF) | First-in-class clinical proof-of-concept. Opens partnering discussions with large pharma. Supports IND filing and potential registrational trial design. Substantial re-rating catalyst. |
| **Base case** | Trend toward infarct-size reduction (not statistically significant), good safety, clear PK signal. Positive subgroup effects (e.g. anterior STEMI, shorter ischaemic times). | Suggestive but not definitive. May support a larger, adequately powered Phase IIb/III. Partnering possible but on less favourable terms. Modest re-rating. |
| **Bear case** | No signal on infarct size, no meaningful secondary endpoint trends, or safety concerns emerge. | Mechanism not yet validated in humans. Asset de-risked to downside. Partnering unlikely. Material downside to share price. |

The critical question is what effect size is realistic. SSO2's AMIHOT-II trial demonstrated a 26% relative infarct-size reduction, which the FDA accepted for approval. In absolute terms, the median infarct size in control patients was approximately 25% of LV mass, with SSO2-treated patients showing approximately 18.5%. A 5% absolute reduction in infarct size is associated with a ~20% relative reduction in the hazard of death or heart failure hospitalisation at one year; a clinically meaningful threshold.

Xolatryp's preclinical data (42% cardioprotection at 3-hour infusion, 86% at 24-hour infusion) suggest substantially larger effect sizes in animal models. However, the well-documented translation loss between preclinical and clinical settings means investors should expect a more modest clinical effect. If Xolatryp achieves even just **a 10-20% relative infarct-size reduction** with statistical significance, we believe this would represent a compelling proof-of-concept and a dataset that would attract serious partnering interest from large cardiovascular pharma.

## Timeline: Catalysts & Expected Readout Windows

The first patient dosing, expected in April 2026, is itself a meaningful catalyst. It confirms regulatory readiness, site activation, and operational execution. From first patient dosed, the company has guided to a 9-18-month window for trial completion, implying a potential data readout in Q4 2026 to H2 2027. The wide range reflects recruitment uncertainty inherent in acute-setting trials.

**Figure 12: Near-term catalyst timeline from first patient dosed through top-line data readout. Source: Nyrada Inc.; Evolution Capital estimates.**

| Milestone | Expected Timing | Significance |
|---|---|---|
| First patient dosed (Phase IIa) | April 2026 | Confirms trial activation; de-risks operational/regulatory readiness. |
| PK/safety review (first 8 patients) | H1 2026 | PK sampling and formal safety review on the first 8 dosed patients. Not a futility analysis, but confirms PK exposure at target levels (i.e. sustained plasma concentrations at or above the IC90) and validates the safety profile in the STEMI population. A clean readout would be a meaningful early de-risking signal. |
| IND submission to FDA | 2026 (timing TBC) | Opens US clinical pathway; enables international site expansion. |
| 50% enrolment | H2 2026 (estimate) | De-risks recruitment timeline; provides early read on site performance. |
| Phase IIa completion / top-line data | Q4 2026 – H2 2027 | Primary value inflection point. Mechanism validation or failure. |

An IND submission to the FDA, planned during 2026, is an important parallel workstream. Even if the Phase IIa is conducted primarily in Australia, an active IND would signal regulatory engagement with the world's most important market and enable potential US site expansion if Australian recruitment requires supplementation.

## The Partnering Question: What Makes This Asset Licensable?

Large pharmaceutical companies with cardiovascular franchises have demonstrated renewed appetite for licensing and acquiring cardiovascular assets. Novartis alone executed multiple cardiovascular partnerships in 2024-25, including a pair of deals with Shanghai Argo Biopharmaceutical worth up to US$4.2 billion in total value, and a US$3.1 billion acquisition of Anthos Therapeutics for a Factor XI inhibitor. Novo Nordisk acquired Cardior Pharmaceuticals and its heart failure microRNA platform. Eli Lilly acquired Verve Therapeutics for gene-editing-based cardiovascular therapies. The sector is active.

However, MIRI/cardioprotection specifically remains an untested partnering category. There are no recent licensing precedents for acute infarct-size-reduction agents, precisely because none have generated compelling Phase II data. This is both a risk and an opportunity: there is no comp set to anchor valuation expectations, but a positive Phase IIa readout would be uniquely differentiated in the partnering landscape. No other company would hold first-in-class clinical data demonstrating pharmacological cardioprotection in STEMI patients.

We believe the characteristics that make Xolatryp licensable upon a successful Phase IIa are:

- First-in-class mechanism with no approved pharmacological competition
- Clinical proof-of-concept in a large, well-defined patient population (STEMI)
- Established regulatory pathway (MRI infarct-size endpoint, SSO2 precedent)
- Simple IV dosing model that integrates into existing PCI workflows
- Platform potential across additional ischaemia-reperfusion indications (stroke, TBI)

- Clean IP position as a novel small molecule with composition-of-matter protection. The composition-of-matter patent, filed in September 2024 with 20 years of protection, covers a broad portfolio of active compounds under a Markush structure (i.e. a family of related molecules, not just Xolatryp itself), providing the highest level of IP protection available for a small-molecule drug. The patent is wholly owned by Nyrada with no royalties payable to third parties. Publication is imminent.

The typical structure for an acute cardiovascular asset licensed on Phase II data would involve an upfront payment, development milestones tied to regulatory filings and Phase III completion, and commercial milestones plus royalties on net sales. For a first-in-class asset in a large unmet-need indication, upfront payments in the range of US$20-80 million with total deal values of US$200–500 million+ (inclusive of milestones) would be consistent with comparable-stage licensing transactions in specialty pharma, though we caution that direct comps are limited.

## Our View

The Phase IIa is well-designed by modern cardioprotection standards, directly addressing the methodological failures of prior trials. Execution risks – consent complexity, recruitment pace, and preclinical-to-clinical translation – are real but known and manageable, not structural flaws. The STEMI setting is logistically challenging but not uncharted: hundreds of STEMI trials have been successfully recruited, including SSO2's IC-HOT study (100 patients across multiple US sites).

The asymmetry for investors lies in the read-through from the data. A positive Phase IIa result would be the first clinical demonstration of pharmacological cardioprotection via TRPC channel inhibition – a genuine first-in-class proof-of-concept. It would validate not only the STEMI indication but also the broader mechanism applicable to stroke and TBI (Debate #3). A negative result would be binary and damaging, but the preclinical effect sizes, the mechanistic rationale, and the improved trial design give us reason to believe the probability of a clinically meaningful signal is meaningfully above the base rate for MIRI trials.

**That said, we do not expect Nyrada to pursue a licensing transaction on the back of Phase IIa data alone.** Given the greenfield competitive landscape across three large indications and the scarcity value of a first-in-class clinical dataset in MIRI, we believe the rational strategy is to retain optionality. A positive Phase IIa would validate the TRPC3/6/7 mechanism in humans for the first time, dramatically shifting the risk profile of the entire platform. In that scenario, we expect management to expand the Phase II-level data package – potentially initiating exploratory studies in stroke or broadening the cardiac dataset – rather than licensing at a point of minimum leverage. The clinical de-risking inflection from a successful Phase IIa is substantial, but it is the beginning of the value-creation curve, not its peak; taking on further development risk, while demanding additional capital, would preserve significantly more upside for existing shareholders.

# Debate #3: What Is the Platform Worth Beyond MIRI, and Can Nyrada Fund the Journey?

MIRI is only one expression of the underlying pathology that Xolatryp targets. Calcium-driven mitochondrial damage occurs wherever ischaemia-reperfusion injury or acute trauma disrupts tissue, and that includes the brain. Does Nyrada's TRPC inhibition platform carry embedded optionality that the market is not pricing?

## Xolatryp as a Platform Asset

TRPC3/6/7 channels are not cardiac-specific. They are expressed in neurons, and the same calcium-overload cascade that drives reperfusion injury in cardiomyocytes drives secondary injury in the brain following ischaemic stroke and traumatic brain injury (TBI). This is not a theoretical extrapolation. Nyrada has generated statistically significant preclinical efficacy data across all three indications using the same compound.

**Figure 13: Preclinical efficacy data across three indications using the same compound and mechanism. Source: Nyrada Inc.**

| Indication | Model / Collaborator | Key Result | Statistical Significance |
|---|---|---|---|
| **MIRI (cardiac)** | Rodent ischaemia-reperfusion; IV infusion around reperfusion | 86% cardioprotection (24h infusion); 42% (3h infusion); 88% arrhythmia reduction | Significant across endpoints; dose-response demonstrated |
| **Ischaemic stroke** | Photothrombotic stroke model; UNSW Sydney | 42% preservation of brain tissue in the penumbra region | p = 0.0213 |
| **Traumatic brain injury** | Penetrating TBI model; WRAIR / UNSW Sydney collaboration | Statistically significant neuroprotection; preserved tissue integrity (MRI-confirmed); reduced mitochondrial $Ca^{2+}$ loading | p = 0.043 (ANOVA); blinded MRI analysis |

The mechanistic coherence across these results is critical. In all three models, Xolatryp's mechanism of action is consistent: it blocks TRPC3/6/7 channels, limiting pathological calcium influx, preventing mitochondrial overload, and preserving tissue integrity. The September 2025 mitochondrial data from the WRAIR TBI study explicitly confirmed this. Xolatryp reduced mitochondrial calcium ion loading in the brain, the first time mitochondrial function has been evaluated following drug intervention in WRAIR's penetrating TBI model. This was not merely supportive of the cardiac thesis; it constitutes direct mechanistic validation that the drug works through the same pathway in the brain as it does in the heart.

## Ischaemic Stroke

Ischaemic stroke accounts for approximately 87% of all strokes and affects an estimated 12.2 million people annually worldwide. In the United States, approximately 700,000 ischaemic strokes occur each year. Despite the scale of the problem, the pharmacological treatment landscape is remarkably limited. Intravenous thrombolysis (alteplase/tenecteplase) remains the only approved drug class, and it addresses clot dissolution but not the secondary tissue damage that occurs during and after reperfusion. Mechanical thrombectomy has improved outcomes for large-vessel occlusion strokes, but as with PCI in STEMI, the act of restoring blood flow itself triggers reperfusion injury in the brain.

There is **no FDA-approved neuroprotective therapy** for ischaemic stroke. The history of failed neuroprotection trials in stroke mirrors the MIRI field almost exactly: over 1,000 agents tested preclinically, more than 250 clinical trials conducted, and zero approved therapies. Nerinetide (NoNO Inc.) was an advanced recent candidate but failed to show benefit in its pivotal ESCAPE-NA1 trial in 2020. ARG-007 (Argenica) was found to be safe and well-tolerated in a phase II trial (completed 2025) in acute ischemic stroke patients and didn't interfere with standard clot-dissolving treatments. the study showed no significant benefit across the total participant group, however a detailed sub-analysis revealed a strong efficacy signal in high-risk patients, specifically those with severe strokes and poor collateral blood flow, who demonstrated reduced brain tissue death and improved functional recovery. Regardless, by no means was this the 'knockout' result the market hoped for.

Xolatryp's 42% penumbral tissue preservation in the preclinical stroke model is therefore scientifically meaningful. Clinical translation is not guaranteed, but nonetheless, Nyrada is strongly positioned to enter this field, which has a massive unmet need, zero approved competition, a history of failure that has driven other developers away, and an upstream

mechanism that addresses the root-cause calcium pathology that prior approaches missed.

## Traumatic Brain Injury (TBI): Strategic Optionality Via the WRAIR Collaboration

Preclinical work was conducted in collaboration with the **Walter Reed Army Institute of Research (WRAIR)** – the US Department of Defense's premier biomedical research facility – and UNSW Sydney. The penetrating TBI model used in the study simulates the type of brain injuries commonly sustained by military personnel, a population of acute strategic interest to the US DoD.

Approximately 69 million individuals suffer from TBI annually worldwide, with an estimated 2.8 million TBI-related emergency department visits in the US alone each year. In military populations, TBI is described as the "signature wound" of modern combat. There are currently **no FDA-approved pharmacological treatments that directly prevent secondary brain damage after TBI**. Existing interventions manage symptoms (anti-seizure medications, analgesics, rehabilitation) rather than addressing the underlying pathology.

The strategic value of the WRAIR collaboration lies in several dimensions. First, it provides Nyrada with access to a validated, defence-grade TBI model and world-class neuroscience expertise at minimal direct cost to the company. Second, positive results from this collaboration carry signalling value: a US government research partner validating your drug's neuroprotective efficacy carries credibility with pharma partners and regulators that is difficult to replicate through company-sponsored studies alone. Third, military TBI programs have historically attracted dedicated US government funding streams (including BARDA and the Congressionally Directed Medical Research Programs), which could provide a non-dilutive pathway to clinical development in this indication.

**Anthracycline-Induced Cardiotoxicity: Oncology-Supportive Care Optionality**

A further, less discussed application of Xolatryp's TRPC inhibition mechanism lies in oncology-supportive care. Anthracyclines (doxorubicin, epirubicin, daunorubicin) remain a backbone of treatment for breast cancer, lymphoma, leukaemia, and sarcoma, but their clinical utility is constrained by cumulative, dose-dependent cardiotoxicity that can cause irreversible cardiomyopathy and heart failure. Emerging research has identified TRPC channels as mediators of anthracycline-induced cardiac injury: doxorubicin activates TRPC3/6 channels in cardiomyocytes, driving pathological calcium entry and mitochondrial dysfunction through the same upstream mechanism that Xolatryp targets in ischaemia-reperfusion injury. This mechanistic overlap raises the possibility that TRPC3/6/7 inhibition could protect the heart during chemotherapy without interfering with the drug's anti-tumour activity, which operates through distinct DNA-intercalation and topoisomerase II pathways in cancer cells.

The commercial significance is substantial. Dexrazoxane is currently the only FDA-approved cardioprotective agent for anthracycline therapy, and its use is narrowly restricted to patients who have already received a cumulative doxorubicin dose of ≥300 mg/m². There is no approved prophylactic cardioprotectant available from the first dose. The unmet need is large: anthracycline-based regimens are administered to hundreds of thousands of patients annually worldwide, and cardiotoxicity monitoring and management represent a significant cost burden for oncology practices. We do not incorporate this indication into our valuation, but we note it as meaningful embedded optionality that could materially broaden Xolatryp's platform story and appeal to a wider set of potential licensing partners, including oncology-focused pharmaceutical companies that would not otherwise engage with a cardiovascular asset.

## Funding Considerations

We believe the optimal capital allocation strategy for Nyrada involves horizontal expansion of the platform, as opposed to vertical progression into a Phase III STEMI trial. Vertical progression on the back of strong Phase IIa data would require significant dilutive equity capital and increases the binary clinical development risk.

**The Neuren Playbook: Valuing the Platform, Not Just the Indication**

The playbook is illustrated by Neuren Pharmaceuticals (ASX: NEU), which validated trofinetide across multiple neurological indications (TBI, Rett syndrome, Fragile X) rather than rushing a single indication to Phase III. This multi-indication de-risking created the scarcity value that drove Neuren's transformational Acadia partnership. Nyrada is at an incomparably earlier stage, but the architectural elements are present: a first-in-class mechanism with data across multiple indications, capital-efficient development anchored by Australian R&D incentives, and a licensing-ready model. A partner acquiring rights to Xolatryp would place a significantly higher premium on an asset with clinical proof-of-concept in both cardiac and neurological indications.

**Expected Strategy**

We anticipate Nyrada will seek to strengthen its balance sheet to fund a parallel Phase IIa program in either Ischaemic Stroke or Traumatic Brain Injury (TBI). Beyond the clinical value of validating the platform, this strategy addresses a critical capital markets dynamic: the recruitment "lull." Large cardiovascular trials, such as the upcoming STEMI study, naturally involve extended periods of quiet accumulation while patient enrolment completes. By launching a concurrent Phase IIa in a neurological indication – which often entails shorter follow-up times or different recruitment dynamics – Nyrada can generate high-impact news flow during the STEMI trial's silent periods. This dual-track approach serves to maintain investor engagement and liquidity, preventing the share price drift often seen in single-asset biotech stories during long data-readout wait times.

# Valuation

With revenues at least five to six years away and binary clinical risk ahead, we anchor our valuation on three complementary frameworks: a precedent transaction analysis grounded in real-world deal pricing for early-stage cardiovascular assets, a peak sales sensitivity matrix across a range of commercial scenarios and probability-of-success assumptions, and a milestone-based valuation waterfall illustrating how each clinical de-risking event expands the implied per-share value.

## Precedent Transactions Analysis

**TRPC Channel Inhibitor Deals**

Direct comparables are scarce, but broader analogues are instructive. No TRPC inhibitor has yet reached market approval, but Boehringer Ingelheim's apecotrep, a selective TRPC6 inhibitor, achieved positive Phase II results in Focal Segmental Glomerulosclerosis (FSGS) in January this year. This marks the first clinical proof that TRPC channel inhibition works in human disease. Boehringer is also advancing apecotrep into chronic kidney disease more broadly.

Apecotrep is an oral formulation (Xolatryp: IV), but the underlying pharmacological principle is shared: TRPC channels mediate pathological calcium entry that drives tissue injury across multiple organ systems. Boehringer's clinical validation of TRPC6 inhibition in the kidney therefore carries broader read-through significance. It confirms that the target class is druggable in humans, that selective TRPC channel blockade is tolerable in a chronic dosing setting, and that the mechanism translates from preclinical models into clinical benefit – each of which de-risks the biological rationale underpinning Xolatryp's development in cardiac and neurological indications. The fact that a top-20

global pharmaceutical company has committed substantial clinical-stage resources to TRPC channel pharmacology validates the target class at an industry level and signals that Nyrada's mechanism is being taken seriously well beyond the company's own preclinical work.

**Cardioprotection & IRI Deals**

Bristol-Myers Squibb's acquisition of Cardioxyl (2015) is the single most relevant transaction. BMS paid up to US$300M upfront and near-term milestones for CXL-1427, a Phase 2 IV nitroxyl donor for acute decompensated heart failure, with total deal value reaching US$2.075 billion. The drug was never advanced to Phase 3, yet BMS paid a substantial premium for a novel acute cardiac mechanism. This deal demonstrates that big pharma will pay significant sums for differentiated acute cardiovascular mechanisms even at Phase 2.

Roche's acquisition of Trophos (2015) included TRO40303, a mitochondrial translocator protein ligand designed to prevent cardiac IRI, alongside lead asset olesoxime for SMA. Roche paid €120M upfront with up to €470M total. TRO40303's MITOCARE Phase 2 trial failed to reduce infarct size in AMI patients. Olesoxime also failed.

TherOx's SSO2 Therapy stands as the only FDA-approved treatment proven to reduce cardiac muscle damage in LAD-STEMI patients after PCI. ZOLL Medical acquired TherOx in June 2019, shortly after FDA approval, for undisclosed terms.

The key takeaway: the BMS/Cardioxyl deal (US$300M upfront / US$2.1B total at Phase 2 for a novel acute cardiac mechanism) represents the best comparable for what Xolatryp could achieve in a licensing or acquisition scenario, while the graveyard of failed IRI drugs explains why investors will demand robust Phase IIa data before assigning premium valuations.

**Figure 14: Precedent transactions in cardioprotection and acute cardiovascular therapeutics. The BMS/Cardioxyl deal (US$300M upfront / US$2.1B total for a Phase 2 acute cardiac mechanism) represents the most relevant comparable for Xolatryp. Source: Company filings; Evolution Capital.**

| Deal | Year | Drug & mechanism | Stage | Upfront | Total value | Outcome |
|---|---|---|---|---|---|---|
| BMS / Cardioxyl | 2015 | CXL-1427, nitroxyl donor for acute HF | Phase 2 | ~US$300M (incl. near-term) | US$2.1B | Shelved |
| Chiesi / Medicines Co. | 2016 | Cangrelor (IV P2Y12 inhibitor) + 2 drugs | Approved | US$260M | US$792M | Marketed |
| Roche / Trophos | 2015 | Olesoxime + TRO40303 (mPTP/TSPO) | Ph II-III + Ph I | €120M | €470M (~US$543M) | Both failed |
| ZOLL / TherOx | 2019 | SSO2 supersaturated oxygen (device) | FDA approved | Undisclosed | Undisclosed (US$159M raised) | Marketed — only FDA-approved IRI therapy |
| Schering-Plough / PeriCor | 2007 | Acadesine, adenosine regulator for CABG IRI | Phase 3-ready | US$20M | Undisclosed | Failed futility 2010 |
| Stealth BioTherapeutics | 2019 IPO | Elamipretide, cardiolipin peptide for STEMI IRI | Phase 2 | US$78M IPO | US$324M total raised | EMBRACE trial failed; pivoted |

**Early-Stage Cardiovascular Drug Deals**

Cardiovascular has become a premium deal area in 2024-2025, driven by impending patent cliffs (Eliquis, Entresto) and novel mechanisms. This creates a favourable backdrop for Nyrada, even without a deal-seeking strategy.

- **Sanofi & MyoKardia partnership (September 2014):** At the preclinical/early Phase I stage for mavacamten (cardiac myosin inhibitor for HCM), Sanofi paid US$45M upfront plus US$200M in milestones, investing ~US$230M over four years. Sanofi later walked away from the deal. BMS ultimately acquired MyoKardia post-Phase 3 for US$13.1 billion in October 2020. This trajectory from

US$45M preclinical upfront to US$13.1B acquisition demonstrates the enormous value creation possible for novel cardiac mechanisms that deliver on efficacy.

- **AstraZeneca & CinCor Pharma (January 2023):** AZ acquired CinCor and its Phase 2 aldosterone synthase inhibitor baxdrostat for US$1.3B upfront plus US$500M CVR, totaling US$1.8B. The deal was struck opportunistically after a Phase 2 failure in one indication (uncontrolled HTN) cratered CinCor's stock, while positive Phase 2 data in resistant HTN remained. Phase 3 subsequently succeeded.

- **Novartis & Tourmaline Bio (September 2025):** Novartis acquired this post-Phase 2 anti-IL-6 antibody company targeting ASCVD for **US$1.4 billion** (59% premium). Tourmaline had licensed pacibekitug from Pfizer for just US$5M cash plus equity in 2022. Phase 2 TRANQUILITY data showed 85-86% reduction in hs-CRP. This is a near-perfect stage and indication analogue: a post-Phase 2 company with a novel mechanism for cardiovascular protection acquired for over a billion dollars.

- **Novartis & Argo Biopharma (January 2024 + September 2025):** Across two deals for siRNA cardiovascular programs at Phase I-IIa stage, Novartis committed US$345M in upfront payments with total potential value exceeding US$9.4 billion.

## Peak Sales Sensitivity Analysis

The methodology is straightforward: we estimate global peak sales across a range of scenarios derived from our pricing and TAM analysis, apply a cumulative probability of success (PoS) from Phase II entry to FDA approval, and discount the resulting risk-adjusted peak revenue using a 3x revenue multiple – a figure that implicitly captures an assumed ~50-60% peak operating margin, a ~10-year commercial window from launch to loss of exclusivity, and a ~12-15% WACC discount back to present value.

**Key Assumptions**

| Assumption | Value |
|---|---|
| US addressable patients (STEMI, <6hr, PCI) | 150,000-200,000 p.a. |
| Ex-US developed market patients | 250,000-400,000 p.a. |
| Price per treatment (mid-range) | US$3,500 |
| Peak penetration (GPIIb/IIIa analogy) | 25-40% |
| US peak revenue range | US$130-280M |
| Global peak revenue range | US$350-750M |
| Revenue multiple applied | 3.0x risk-adjusted peak sales |
| Shares outstanding | 244.62M |
| AUD/USD | 0.706 |

**Implied Valuation Per Share (A$) at 3x Revenue**

Our base case of US$500M global peak sales at 10-15% PoS (reflecting a Phase II-entry cardiovascular drug with first-in-class risk) is highlighted.

| Global Peak Sales | Probability of Success | | | | |
|---|---|---|---|---|---|
| | 5% | 10% | 15% | 20% | 25% |
| US$200M | $0.17 | $0.35 | $0.52 | $0.69 | $0.87 |
| US$350M | $0.30 | $0.61 | $0.91 | $1.22 | $1.52 |
| US$500M | $0.43 | $0.87 | **$1.30** | $1.74 | $2.17 |
| US$750M | $0.65 | $1.30 | $1.95 | $2.61 | $3.26 |
| US$1bn | $0.87 | $1.74 | $2.61 | $3.47 | $4.34 |

**Revenue Multiple Sensitivity (at US$500M Global Peak Sales)**

Our 3.0x base case is conservative relative to the 4-7x EV/Revenue multiples observed for commercial-stage biotech, but appropriate given the distant commercialisation timeline. A 4-5x multiple would be justified if Xolatryp demonstrates label expansion potential beyond STEMI (e.g. NSTEMI-ACS, cardiac surgery) or if the drug secures Breakthrough Therapy designation.

| Revenue Multiple | 2.0x | 3.0x | 4.0x | 5.0x |
|---|---|---|---|---|
| **At $500M / 10% PoS** | $0.58 | **$0.87** | $1.16 | $1.45 |
| **At $500M / 15% PoS** | $0.87 | **$1.30** | $1.74 | $2.17 |
| **At $500M / 20% PoS** | $1.16 | **$1.74** | $2.32 | $2.90 |

**Milestone-Based Valuation Waterfall**

The table below illustrates how Nyrada's implied per-share valuation evolves as clinical milestones progressively de-risk Xolatryp's probability of reaching market approval. We use US$500M global peak sales as the base scenario. BIO/Informa data indicates that cardiovascular drugs transitioning from Phase II to approval have a cumulative success rate of approximately 10%, with Phase II-to-III transition rates of ~24%, Phase III-to-NDA rates of ~45%, and NDA-to-approval rates of ~90%. We apply a modest downward adjustment to reflect the historically high failure rate of cardioprotective agents in the IRI field specifically.

| Milestone | Cumul. PoS | Implied A$/sh (3x) | Implied A$/sh (4.5x) |
|---|---|---|---|
| **Phase IIa entry (current)** | **8-12%** | **$0.70-$1.04** | **$1.04-$1.56** |
| Positive Phase IIa data | 20-25% | $1.74-$2.17 | $2.60-$3.26 |
| Phase III initiation | 28-32% | $2.43-$2.78 | $3.65-$4.17 |
| Positive Phase III data | 60-70% | $5.21-$6.08 | $7.82-$9.12 |
| NDA/BLA submission | 80-85% | $6.95-$7.39 | $10.42-$11.08 |
| FDA approval | 100% | $8.68 | $13.03 |

**Key Takeaways**

At Nyrada's current share price of approximately A$0.485, the market is implying a risk-adjusted valuation below global peak sales of US$350M at a 10% probability of success: a conservative, baseline for a Phase II-entry cardiovascular drug with first-in-class preclinical data but no clinical efficacy signal in patients. The critical near-term catalyst is Phase IIa data, expected in 2027. Positive results demonstrating statistically significant infarct-size reduction would shift the cumulative PoS from ~10% to ~20-25%, implying a 2-3x re-rating from current levels even before any change to peak sales assumptions.

The upside case is substantial. If Xolatryp proves efficacious and secures a licensing or acquisition deal, the comparable transaction benchmarks discussed earlier in this report suggest deal values of US$150-300M upfront with US$1-2B in total potential value. At those levels, even accounting for dilution from future capital raises, the implied per-share valuations are multiples of the current price. The downside, however, is equally binary.

We assign a Price Target of $1.04/sh, reflecting $500m peak sales p.a. at a 12% PoS.

# Appendix

## Key Risks

**Clinical Development Risk**
The Phase IIa trial represents a binary event for the company. Every prior pharmacological attempt to reduce reperfusion injury in STEMI patients has failed in clinical trials, despite strong preclinical data. There is no guarantee that Xolatryp's upstream mechanism will translate from animal models to meaningful infarct-size reduction in humans, and a negative readout would materially impair the value of the company's sole clinical asset.

**Preclinical-to-Clinical Translation Risk**
Xolatryp's preclinical effect sizes (42–86% cardioprotection in rodent models) were achieved in young, healthy animals without the comorbidities or concomitant medications present in real STEMI patients. Translation loss between preclinical and clinical settings is well-documented across drug development and has been particularly pronounced in the cardioprotection field. Investors should expect a substantially smaller clinical effect than the animal data suggest.

**Recruitment & Execution Risk**
STEMI trials are inherently difficult to recruit. Patients present as emergencies with narrow consent windows, and even high-volume PCI centres may only see a handful of eligible patients per month. Slower-than-expected enrolment across the up to 10 Australian sites could delay the trial timeline and data readout beyond the guided 9–18-month window, increasing cash burn and potentially requiring protocol amendments or international site expansion.

**Funding & Dilution Risk**
Nyrada is a pre-revenue company with ongoing cash burn from clinical development activities. Completing the Phase IIa and funding parallel development in neurological indications will likely require additional equity capital raises, which would dilute existing shareholders. The timing and terms of future raises will depend on share price performance, clinical progress, and broader market conditions, all of which are uncertain. An inability to raise capital on acceptable terms could force the company to scale back or delay its development programs.

**Single-Asset Risk**
Nyrada's entire near-term value proposition rests on a single compound, Xolatryp, targeting a single near-term indication. While the platform has potential across stroke and TBI, these remain at preclinical stage with no clinical validation. Any safety signal, manufacturing issue, or intellectual property challenge specific to Xolatryp would affect the entire company, with no diversified pipeline to offset the impact.

**Regulatory Risk**
Even if the Phase IIa produces positive data, Xolatryp faces a long and uncertain regulatory path through Phase III and FDA review. The FDA's expectations for a registrational MIRI trial – including endpoint selection, trial size, and patient population – have not yet been established through formal interaction. Regulatory requirements may be more onerous or costly than currently anticipated, particularly given the field's history of clinical failures.

**Partnering & Commercialisation Risk**
Nyrada is a pre-revenue company with no internal commercialisation infrastructure. Realising value from Xolatryp requires securing a licensing or acquisition partner with cardiovascular commercial capabilities. There is no guarantee that a suitable partner will emerge on acceptable terms, or at all. MIRI/cardioprotection is an untested partnering category with no recent licensing precedents, meaning there is limited visibility on deal structures and valuations. If partnering does not materialise, Nyrada would need to fund late-stage development and commercialisation independently, requiring capital well beyond its current resources.

**IP Risk**
Nyrada's competitive position depends on the strength and enforceability of its composition-of-matter patents covering Xolatryp. Patent challenges, invalidation proceedings, or the emergence of competing TRPC channel inhibitors (such as Boehringer Ingelheim's apecotrep, a selective TRPC6 inhibitor currently in Phase II for FSGS) could erode the company's first-mover advantage. The commercial exclusivity window may also prove shorter than anticipated if generic or biosimilar pathways are established before Nyrada can fully monetise the asset. That said, the IP position carries meaningful structural strengths. The composition-of-matter patent was filed in September 2024 with a 20-year protection window, employing a Markush structure that covers a broad family of related active compounds rather than Xolatryp alone. This is the strongest form of pharmaceutical patent protection available, creating barriers to design-around strategies by competitors. The IP is wholly owned by Nyrada with no third-party royalty obligations, which simplifies future licensing negotiations and preserves the full economic value of the asset. The patent is pending publication, at which point the scope of the claims will become publicly assessable. Importantly, Boehringer Ingelheim's apecotrep is a selective TRPC6 inhibitor with an oral formulation targeting renal indications – a meaningfully different molecule, selectivity profile, route of administration, and clinical application to Xolatryp's TRPC3/6/7 IV inhibitor in acute cardiac and neurological settings. The risk of direct competitive overlap is therefore limited, though the broader validation of the TRPC target class by a major pharmaceutical company is a double-edged dynamic: it de-risks the biology but may attract further entrants over time.

**Key Personnel Risk**
Nyrada is a small company with a lean management team. The loss of key personnel, including CEO James Bonnar or the coordinating principal investigator Professor William Chan, could disrupt clinical execution and delay development timelines. The company's ability to attract and retain experienced clinical, regulatory, and business development talent is critical to advancing Xolatryp through the development pathway and securing a commercial partner.

**Foreign Exchange & Jurisdictional Risk**
Nyrada is an ASX-listed, AUD-denominated company, but its target commercial market is predominantly the United States and other USD/EUR-denominated jurisdictions. Foreign exchange fluctuations between AUD and USD will affect the translation of any future milestone payments, licensing revenues, or deal valuations into Australian dollar terms. Additionally, clinical development across multiple jurisdictions (Australia, potentially NZ, Singapore, Canada, and the US) introduces regulatory and operational complexity, and any changes to R&D tax incentive programs (such as the Australian R&D Tax Incentive) could materially affect the company's effective development costs.

## Board & Management

**John Moore (Non-Executive Chair)**
John Moore serves on the boards of multiple public and private life sciences companies, including Scientific Industries (SCND-OTCQB) and clinical trial informatics company Trialogics. Previously, as CEO of Edson Moore Healthcare Ventures, he managed the US$148 million acquisition of 16 drug delivery investments from Elan Pharmaceuticals. He holds a degree from Rutgers University.

**James Bonnar (MD & CEO)**
James joined Nyrada in February 2018, bringing over 20 years of life sciences experience spanning preclinical research, CMC, regulatory affairs, and clinical operations. Prior to Nyrada, he spent eleven years at Neuren Pharmaceuticals as Director of CMC and Regulatory Affairs, then Director of Clinical Operations, overseeing clinical development in traumatic brain injury and neurodevelopmental disorders – directly relevant experience for Xolatryp's development pathway.

**Christopher Cox (Non-Executive Director)**
Christopher Cox is Co-Founder and General Partner of Population Health Partners, L.P., a global healthcare-focused investment firm. Previously, he served as EVP and Chief Corporate Development Officer of The Medicines Company (2016–2019), a global biopharmaceutical company, where he was responsible for business development and strategy.

**Marcus Frampton (Non-Executive Director)**
Marcus Frampton is Chief Investment Officer of the Alaska Permanent Fund Corporation (APFC), the US$85 billion sovereign wealth fund for the State of Alaska. He has held the role since 2012, with prior experience in investment banking at Lehman Brothers and private equity at PCG Capital Partners.

**Rudiger Weseloh (Ph.D.) (Non-Executive Director)**
Rüdiger Weseloh is Executive Director of Business Development at EMD Serono (Merck KGaA), where over 19 years he has led more than 80 transactions across the drug development value chain in oncology, neurodegenerative diseases, rheumatology, and fertility. He holds a PhD and completed postdoctoral research at the Max-Planck-Institute for Experimental Medicine.

**Ian Dixon (Non-Executive Director)**
Dr Dixon co-founded Cardio Therapeutics Pty Ltd in 2014 and managed its PCSK9 cardiovascular discovery program until the company was acquired by Nyrada in advance of its 2019 IPO. He also co-founded Cynata Therapeutics (ASX:CYP) and Exopharm (ASX:EX1), and holds a PhD in biomedical engineering from Monash University and an MBA from Swinburne University.

**Evolution Capital Ratings System**

| | |
|---|---|
| **Recommendation Structure** | • **Buy:** The stock is expected to generate a total return of >10% over a 12-month horizon. For stocks classified as 'Speculative', a total return of >30% is expected.<br>• **Hold:** The stock is expected to generate a total return between -10% and +10% over a 12-month horizon.<br>• **Sell:** The stock is expected to generate a total return of <-10% over a 12-month horizon. |
| **Risk Qualifier** | • **Speculative ('Spec'):** This qualifier is applied to stocks that bear significantly above-average risk. These can be pre-cash flow companies with nil or prospective operations, companies with only forecast cash flows, and/or those with a stressed balance sheet. Investments in these stocks may carry a high level of capital risk and the potential for material loss. |
| **Other Ratings:** | • **Under Review (UR):** The rating and price target have been temporarily suppressed due to market events or other short-term reasons to allow the analyst to more fully consider their view.<br>• **Suspended (S):** Coverage of the stock has been suspended due to market events or other reasons that make coverage impracticable. The previous rating and price target should no longer be relied upon.<br>• **Not Covered (NC):** Evolution Capital does not cover this company and provides no investment view. |

*Expected total return represents the upside or downside differential between the current share price and the price target, plus the expected next 12-month dividend yield for the company. Price targets are based on a 12-month time frame*.

## Disclaimer & Disclosures



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