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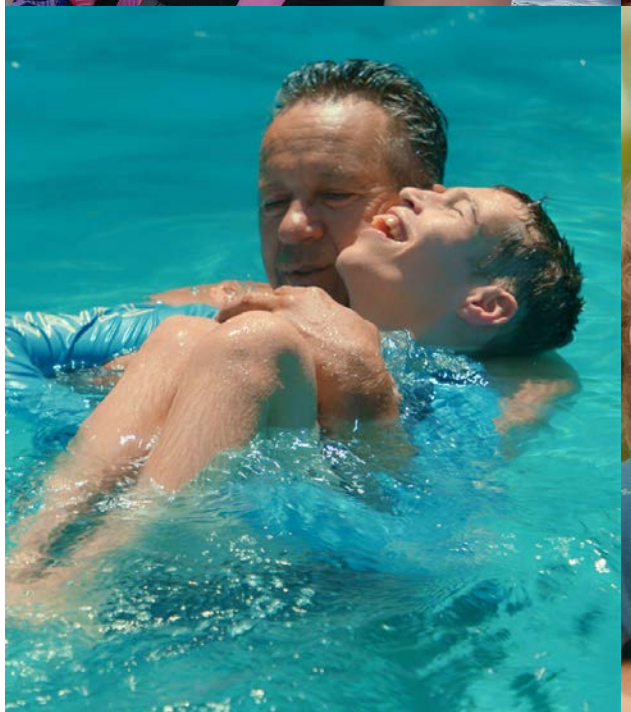
# Bioshares 2025

8 August 2025

IMPROVING THE LIVES OF PEOPLE WITH NEURODEVELOPMENTAL DISABILITIES






# Forward looking statements

This presentation contains forward looking statements that involve risks and uncertainties. Although we believe that the expectations reflected in the forward looking statements are reasonable at this time, Neuren can give no assurance that these expectations will prove to be correct. Actual results could differ materially from those anticipated. Reasons may include risks associated with drug development and manufacture, risks inherent in the regulatory processes, delays in clinical trials, risks associated with patent protection, future capital needs or other general risks or factors.

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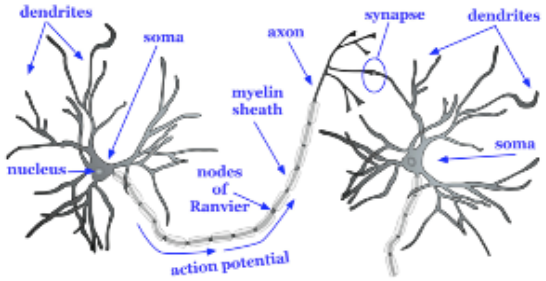
# Ground-breaking impact on pediatric neurological Orphan indications

## Neurodevelopmental disorders

- **Rett** *(MECP2)*
- **Fragile X** *(FMR1)*
- **Phelan-McDermid** *(SHANK3)*
- **Angelman** *(UBE3A)*
- **Pitt Hopkins** *(TCF4)*
- **Prader-Willi** *(15q11-q13)*

## Brain injury

- **Hypoxic-Ischemic Encephalopathy** *(lack of oxygen or blood flow to the brain before, during or shortly after birth)*




*Impaired communication between neurons, abnormal formation/pruning of dendrites & chronic inflammation*

**Neuren's drugs target the critical role of IGF-1 in this upstream process, using analogs of naturally occurring peptides that can be taken orally as liquids**

*Excitotoxicity, mitochondrial dysfunction, and acute & chronic inflammatory processes*

***Severe impact on nearly every aspect of life***

- **Walking and balance issues**
- **Anxiety and hyperactivity**
- **Seizures**
- **Impaired communication**
- **Intellectual disability**
- **Impaired social interaction**
- **Impaired hand use**
- **Sleep disturbance**
- **Gastrointestinal problems**

***Long-term impact on survivors***

- **Developmental delays**
- **Seizures**
- **Cognitive impairment**
- **Cerebral palsy**

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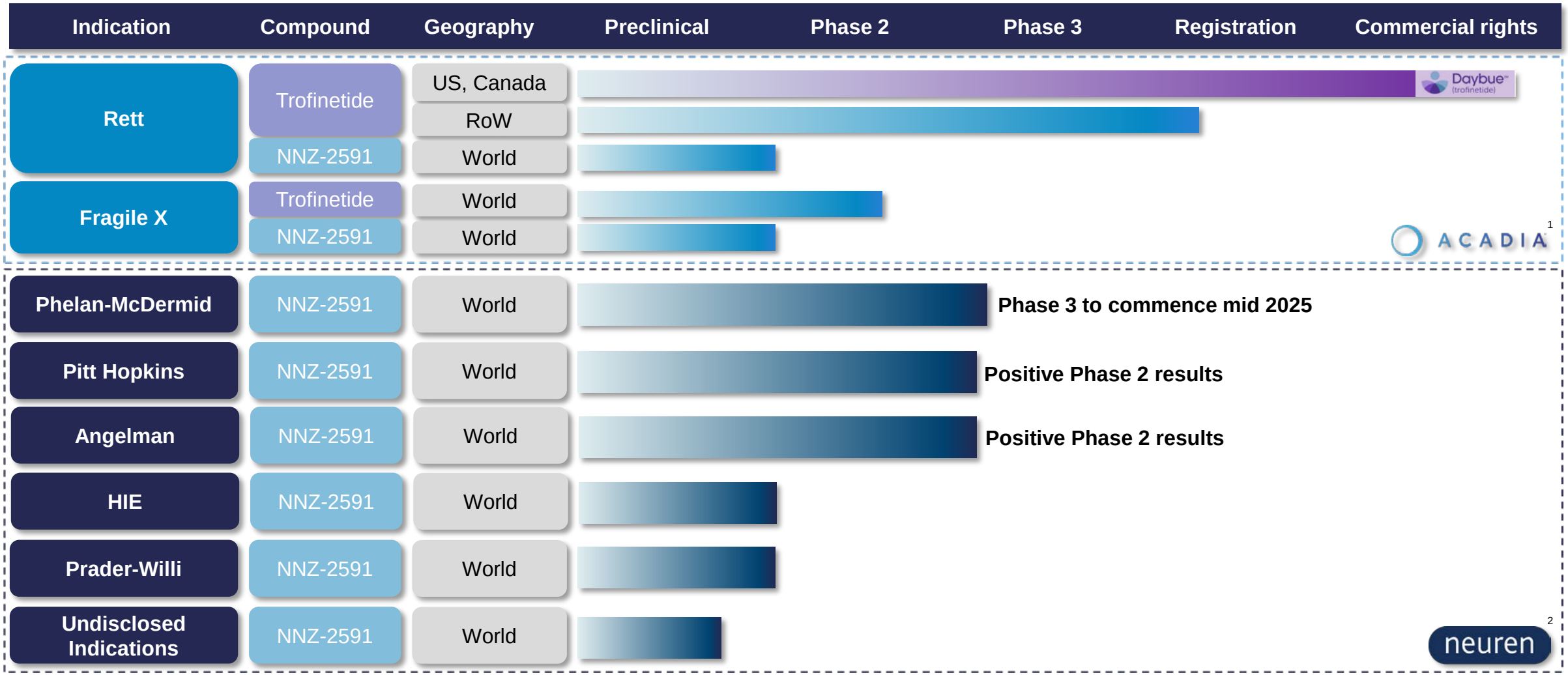
# Strong late-stage pipeline supported by commercial product




[1] Exclusive license for Trofinetide and NNZ-2591 (Rett and Fragile X only) globally [2] Wholly owned by Neuren

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# Large potential upside enabled by financial strength

Maximise value of **NNZ-2591** as a multiple indication platform

- ✓ Positive Phase 2 results in each of **Phelan-McDermid, Pitt Hopkins and Angelman syndromes**
- ✓ Alignment with FDA for Phase 3 program in **Phelan-McDermid syndrome**
- ✓ Advancing **HIE** and potentially other Orphan indications

Long-term income growth from Acadia's successful global commercialization of Daybue™ (trofinetide)

**A$445m income from Daybue™ across 2023/24**

**A$341** million cash at 31 Mar 2025


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# Achieving the organisational capability to maximise NNZ-2591 value

**2018 – at original Acadia deal**

10 people
A$10 million

**2025 – executing Phase 3**

- ✓ 30 people
- ✓ Clin/reg execution capability
- ✓ CMC and Clin/reg centres of excellence
- ✓ Elevated quality systems
- ✓ A$300 million

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# DAYBUE / Trofinetide

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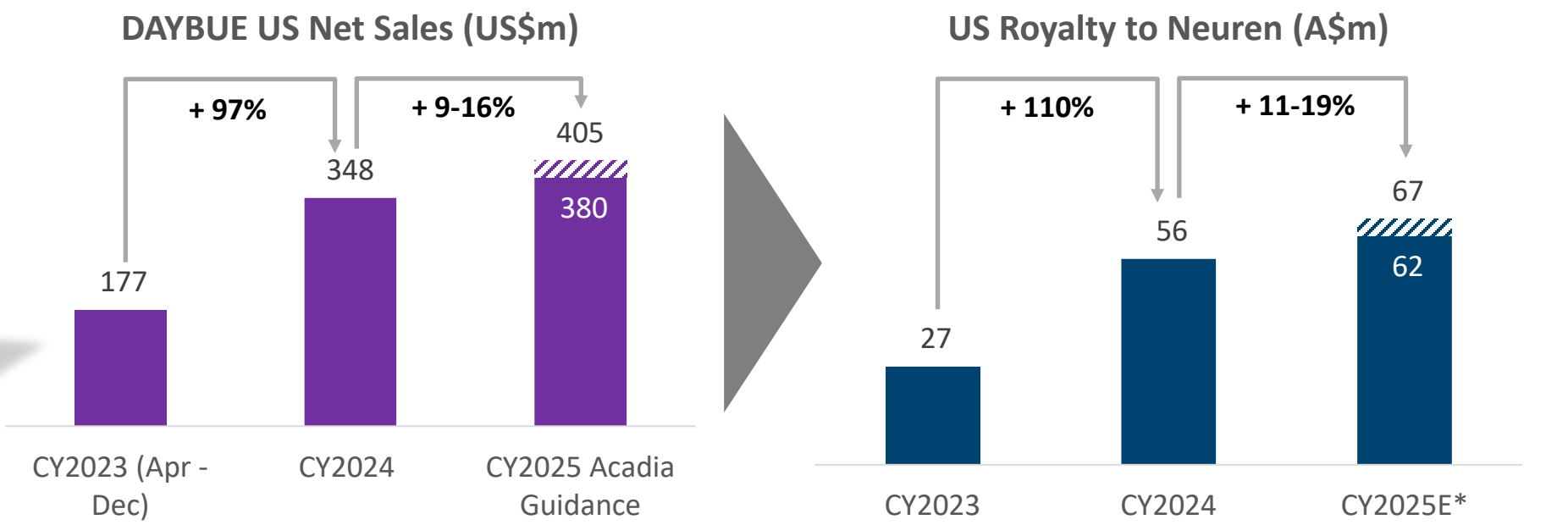
# Growing sustainable income from DAYBUE™ (trofinetide)

| Potential Rett patients | US | Canada | Europe | Japan |
|---|---|---|---|---|
| | 6,000 - 9,000[1] | 600 - 900[1] | 9,000 - 12,000[1] | 1,000 - 2,000[1] |


[1] Acadia estimates

* Based on CY25 Acadia DAYBUE US Net Sales Guidance of US$380-405m, 10% of DAYBUE net sales up to US$250m and 12% of DAYBUE net sales between US$250m and US$500m, and AUDUSD of 0.65

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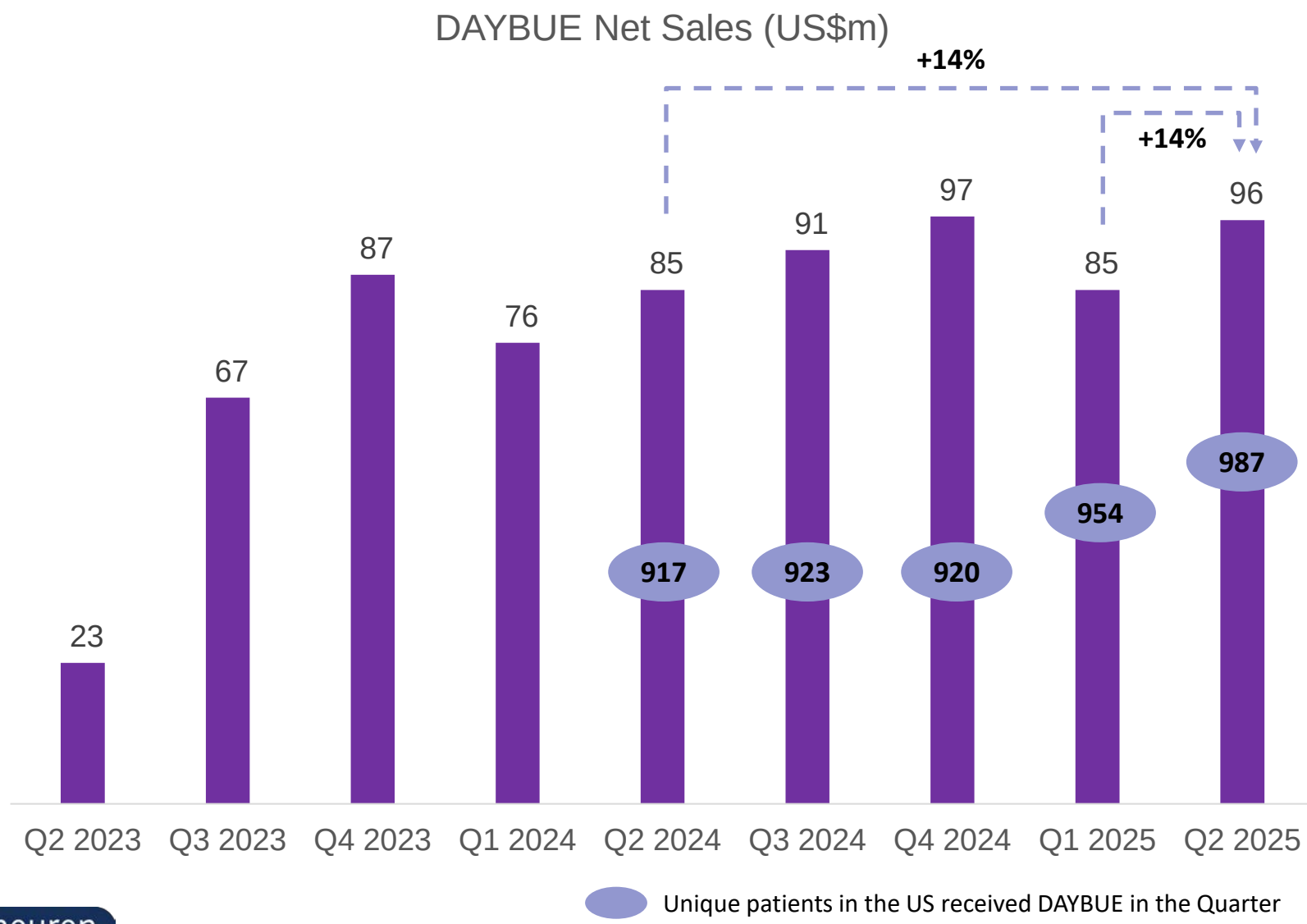
# A new phase of expansion and acceleration




- 2/3 of US patients yet to try DAYBUE
- Completed expansion of DAYBUE field force by ~30% to accelerate future growth in the US
- Early signs of successful penetration outside the CoEs with 3/4 of Q2 patient referrals from the community
- Stable persistency with 70% of Q2 active patients on treatment >12 months
- Global expansion in progress and on track

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# Key growth drivers in the US

| | Current | Illustrative Upside |
|---|---|---|
| **1** Diagnosed population expanding towards prevalence of 6,000-9,000<br>• Already grown significant from 4,500 at launch | 5,500–5,800 | 6,000 - 9,000 |
| **2** Continue growing penetration beyond ~1/3 of diagnosed patients treated to date<br>• 987 active patients in Q2 2025, up 3% on Q1 2025<br>• Acadia recently expanded size of field force by ~30%<br>• Launched branded direct-to-consumer campaigns<br>• Bringing positive experience to life, using growing body of real-world evidence, including LOTUS study, HCP peer-to-peer program, caregiver program series<br>• Acadia surveyed HCPs state over next 24 months they expect to increase total RXs of DAYBUE to >70% of their eligible patients | Low 30% | 70% |
| Patients treated | ~1,800 | 4,000 - 6,000 |
| **3** Maintaining stabilized persistency rate<br>• >50% after 12 months, >45% after 18 months<br>• 70% of active patients have been on treatment >12 months | | 45 - 50% |
| Active patients | 987 | 1,800 – 3,000 |

Latest stats based on Acadia 2Q 2025 financial results presentation 6 August 2025, R&D Day presentation 25 Jun 2025, 1Q 2025 financial results presentation 7 May 2025, 4Q and full year 2024 Earnings Presentation 26 February 2025, 43rd Annual JP Morgan Healthcare Conference Presentation 14 January 2025, 2Q Second Quarter 2024 Earnings Presentation 6 Aug 2024

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# Long term growth opportunity for trofinetide through global expansion

**Canada**

600 - 900 Rett patients[1]

Approved in Oct 2024

**US**

6,000 - 9,000 Rett patients[1]

Launched in Apr 2023

**Europe**

9,000 - 12,000 Rett patients[1]

MAA filed with potential approval Q1 2026

Active named patient supply programs CLINIGEN

Acadia building commercialisation team

**Japan**

1,000 - 2,000 Rett patients[1]

Orphan Drug Designation status granted

Clinical study start in Q3 2025 to support marketing application

**RoW**

Active named patient supply programs in Israel and select rest of the world countries

Rafa.

FarmaMondo

[1] Acadia estimates

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# NNZ-2591

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# NNZ-2591 is a multi-indication platform

## Most advanced program in PMS and PTHS, oral therapy for AS, new treatment paradigm for HIE

NNZ-2591

| Indications | Usage | Orphan | Rare Pediatric | Fast Track | Positive Phase 2 | Phase 3 agreed | Competitive position |
|---|---|---|---|---|---|---|---|
| **Phelan-McDermid syndrome (PMS)** | **Chronic** | ✓ | ✓ | | ✓ | ✓ | **Most advanced clinical program** |
| Pitt Hopkins syndrome (PTHS) | Chronic | ✓ | ✓ | ✓ | ✓ | | Most advanced clinical program |
| Angelman syndrome (AS) | Chronic | ✓ | ✓ | | ✓ | | Two RNA therapies (spinal injections) in Phase 3 |
| **Hypoxic-Ischemic Encephalopathy (HIE)** | **Acute + chronic** | | | | | | **Only program for treatment beyond initial injury** |
| Other pending | | | | | | | |

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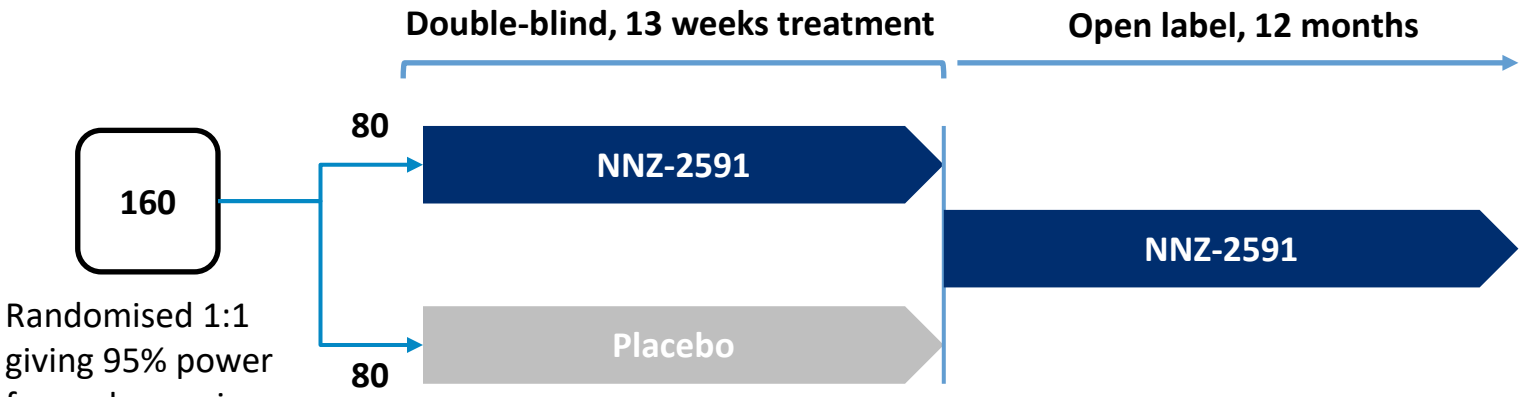
# Preparing to commence first ever Phase 3 trial in PMS

## Same population and dose as positive Phase 2 trial, similar design to successful Rett Phase 3

Single Phase 3 trial:

- Randomised, double-blind, placebo-controlled
- 160 children aged 3-12 with Phelan-McDermid syndrome
- Target dose equivalent to dose tested in Phase 2
- Expected total cost US$80m – 90m, funded from existing cash




| Co-primary Endpoints | Positive Phase 2 Results |
|---|---|
| **Phelan-McDermid Syndrome Assessment of Change (PMSA-C), *previously referred to as CGI-I in Phase 2*** | 16/18 subjects showed improvement<br>Mean score: 2.4<br>P < 0.0001 |
| **Receptive Communication sub-domain of the Vineland Adaptive Behavior Scales, 3rd Edition (VABS-3 Receptive-Raw Score)** | 16/18 subjects showed improvement<br>Mean improvement: 7.5 (from baseline of 29.0)<br>P = 0.0001 |

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# NNZ-2591 in HIE – targeting a new paradigm of treatment

HIE program retains all the advantages of the other NNZ-2591 programs:

- Orphan Drug
- Pediatric
- Urgent unmet need
- Limited competition
- Leverages the non-clinical and manufacturing platform that has been built

**Clinical & Regulatory**

- Exploring potential for **Phase 2/3 trial**
- **Pre-IND** meeting with FDA planned for **Q4 2025**
- Concentration of clinical sites at large hospitals available

**Scientific Foundation**

- **IGF-1** promotes cell survival, modulates inflammation, and regulates synaptic transmission
- **IGF-1** levels are reduced in infants with HIE, correlating with HIE severity and outcome
- Supporting data from a range of in-vitro and in-vivo models

**Commercial**

- Standard of care is therapeutic hypothermia (TH), which reduces mortality and morbidity
- Critical unmet need to **improve long-term outcomes** with a treatment that enhances neuroplasticity post TH
- **Repeating pool of patients**
- Addressable in ICUs - a **new in-hospital channel** for Neuren
- Eligible for **Orphan and Rare Pediatric Disease** designations

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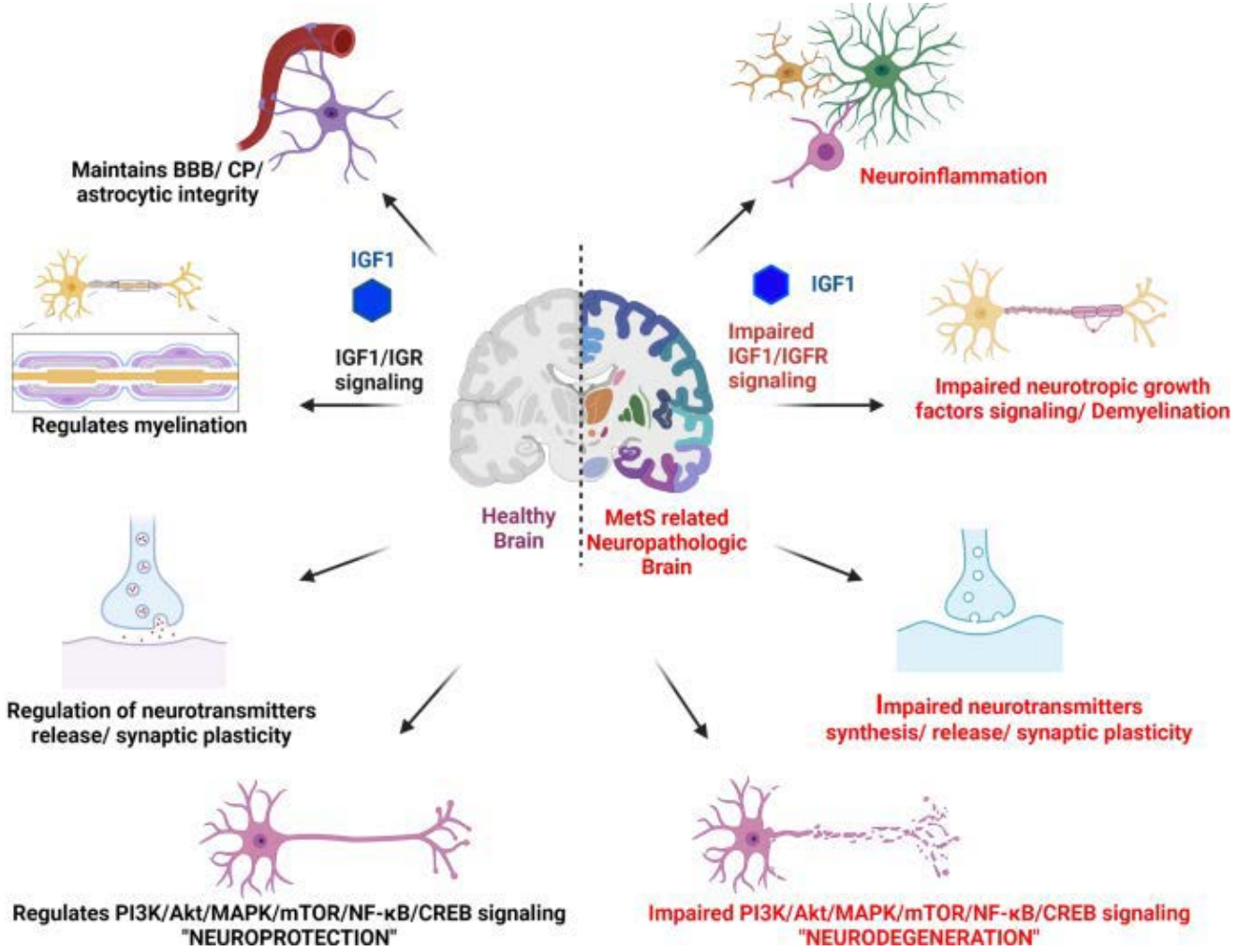
# IGF-1 signaling promotes cell survival, modulates inflammation, and regulates synaptic transmission, all of which are impaired in HIE




Arjunan et al. Cell Biosci. 2023; 13:1:16.

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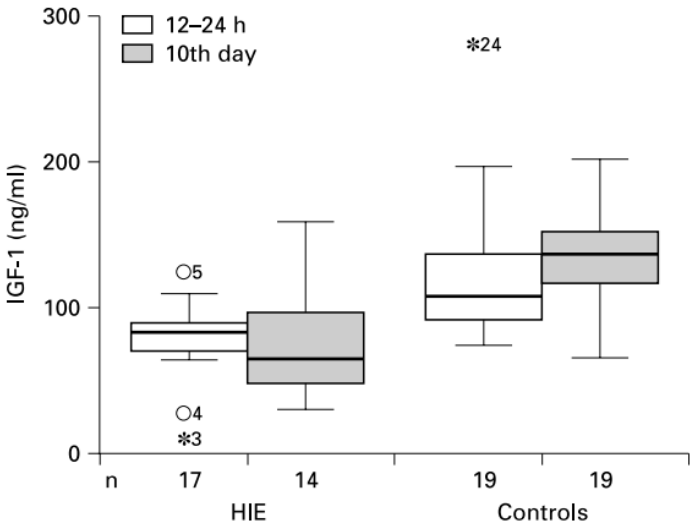
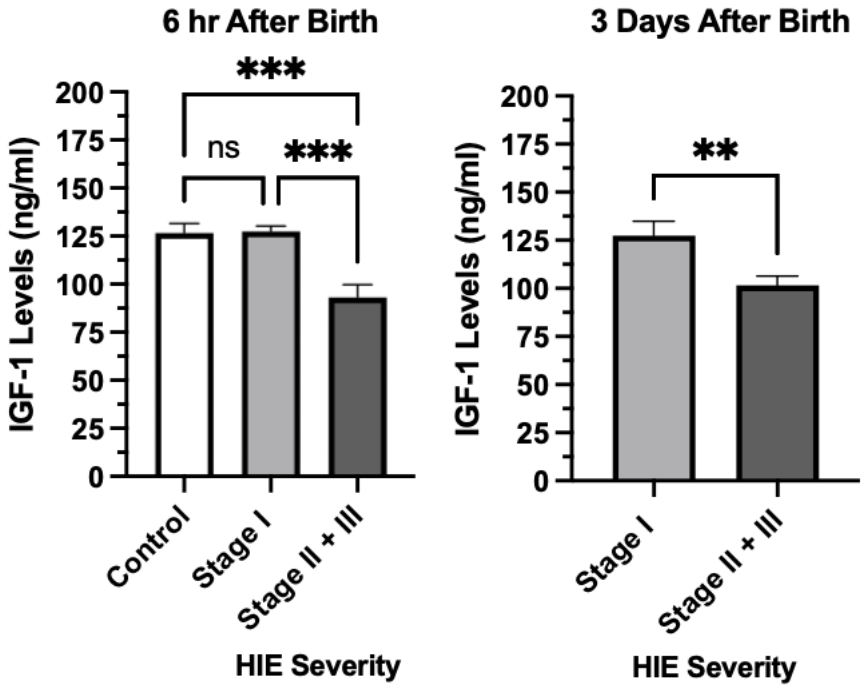
# Multiple studies have shown that IGF-1 levels are reduced in term newborns with HIE




Mean +/- SEM of IGF-1 levels in blood plasma. Satar et al. *Biol Neonate*. 2004;85(1):15-20.




Mean +/- SEM of IGF-1 levels in blood plasma. ** p<0.01; *** p < 0.001. Modified from Umran et al. *Am J Perinatol.* 2016;33(7):640-5.

| Group | Cases | IGF-1 level | |
|---|---|---|---|
| | | Acute phase | Recovery phase |
| Control group | 18 | 53.36±6.51 | 60.142±5.82 |
| Mild HIE | 35 | 36.12±2.49 | 58.26±6.4 |
| Moderate HIE | 19 | 29.22±3.68 | 41.39±7.0 |
| Severe HIE | 6 | 18.73±3.01 | 24.15±4.56 |
| $F/\chi^2$ | | 8.53 | 7.26 |
| *p* | | <0.05 | <0.05 |

Note: $p<0.05$, the difference had statistical significance.

Comparison of serum IGF-1 levels of all HIE groups within 1 day (acute phase) and 14 days (recovery phase) after birth. Liu et al. *Eur Rev Med Pharmacol Sci.* 2018;22(10):3173-3181.

**Negative correlation between IGF-1 levels and HIE severity was observed in Umran et al. and Liu et al.**

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# Broad body of in-vivo and in-vitro pre-clinical evidence for NNZ-2591

NNZ-2591 limits microglial activation and reduces the area of infarct in rat models of hypoxic brain injury

NNZ-2591 reverses the induction of inflammatory cytokines and activating transcription factor 3 (ATF3) in a model of traumatic brain injury

NNZ-2591 reduces cell death caused by excitotoxic damage, a key outcome of hypoxic-ischemic injury

NNZ-2591 inhibits cytotoxicity and reduced neuronal firing - features of oxygen/glucose deprivation

NNZ-2591 boosts IGF-1 levels in microglia

NNZ-2591 has a long heritage in brain injury…….

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# CONTACT

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