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.
Neuren snapshot

- Stock code ASX: NEU – market cap approximately A$130 million
- Developing new treatments for neurological conditions
  - Significant unmet needs and commercial opportunities with no approved drugs
  - Regulatory advantages – candidates for Fast Track, Orphan Drug, Breakthrough Therapy
  - Strong support from advocacy groups and other stakeholders
- Lead drug candidate trofinetide
  - Clinical improvement observed in Rett syndrome and Fragile X syndrome Phase 2 trials
  - Broad range of clinical effects consistent with known normalising actions on brain function
  - Excellent safety and tolerability profile to date
  - Utility in neurodevelopmental disorders, neurodegenerative diseases and brain Injury
- Strategy to realise value
  - Generate clinical data in Phase 2 trials
  - Define optimum pathway towards New Drug Applications
  - Optimise manufacturing processes for commercial product supply
  - Engage with commercial partners
Scientific foundation

- **IGF-1** is a naturally occurring growth factor in the brain
- Glypromate (**GPE**) separates from IGF-1 in the brain
- IGF-1 and GPE maintain and restore equilibrium in the brain
- **Trofinetide** is a synthetic analogue of GPE with a longer half-life, better stability and suitability as an oral medication
- **Trofinetide** influences the processes in impaired development and injury of the brain, but has virtually no effects in normal cells and animals:
  - Inhibits neuroinflammation
  - Normalises function of microglia
  - Normalises inter-neuronal communication
- **NNZ-2591** is in the same class of peptides, with higher bioavailability and potential for a solid oral dosage form
- **Trofinetide** and **NNZ-2591** both potentially treat a wide range of neurological conditions
## Multiple disorders have common causes and effects

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Neuro-inflammation</th>
<th>Microglial Activation</th>
<th>Neuronal Signaling</th>
<th>Apoptosis</th>
<th>Impaired Neurogenesis</th>
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Trofinetide development strategy

**Common foundation:**
- Acute and chronic toxicity studies
- Commercial manufacturing
- Phase 1 clinical studies

**Neurodevelopmental disorders**
- **Rett syndrome:**
  - Two phase 2 trials completed
  - Fast Track designation
  - Orphan drug designation
- **Fragile X syndrome:**
  - Phase 2 trial completed
  - Fast Track designation
  - Orphan drug designation
- **Other autism spectrum disorders**

**Neurodegenerative diseases**

**Acute brain injury**
- **Severe and moderate TBI:**
  - Partnership with US Army
  - Phase 2 trial completed
  - Fast Track designation
- **Mild TBI (Concussion):**
  - Partnership with US Army
Trofinetide commercial exclusivity

- Issued composition of matter patents owned by Neuren
  - US and Europe – expire 2022, potential to extend to 2027

- Exclusivity periods from orphan drug designation in Rett syndrome and Fragile X syndrome
  - US – 7 years from marketing authorization, potentially plus 6 months if approved for pediatric use
  - European Union – 10 years from marketing authorization, potentially plus 2 years if approved for pediatric use

- Method of treatment applications in autism spectrum disorders (ASDs)
  - Issued US patent for Rett syndrome – expires 2032
  - Issued Australian patent for ASDs – expires 2032
  - Other applications pending in US, Europe and other territories
Trofinetide in Rett syndrome

- Non-inherited mutation on the X chromosome – estimated 1/10,000 females

- Most physically disabling of the autism spectrum disorders - symptoms include:
  - Intellectual disability, loss of speech and motor control
  - Compulsive hand movements
  - Disorders of breathing and cardiovascular function
  - Muscle rigidity
  - Seizures

- Profound disability and financial burden for patients and families

- No approved treatments available

- Trofinetide in Rett syndrome:
  - Statistically significant clinical improvement in Phase 2 trial in ages 5 to 15
  - Trends of clinical improvement in smaller initial Phase 2 trial in ages 16 to 45
  - Commence Phase 3 trial in children, adolescents and adults in 2018
  - Potential disease modification rather than treating isolated symptoms
Recently completed Phase 2 trial in girls aged 5 to 15

- Double-blind, placebo-controlled Phase 2 trial in girls aged 5 to 15 years
  - Conducted at 12 US hospitals, led by world-leading clinicians in Rett syndrome, supported by rettsyndrome.org
  - 62 subjects randomised to 4 groups (50 mg/kg, 100 mg/kg, 200 mg/kg or placebo), 20 further subjects randomised to 200 mg/kg or placebo

- 200mg/kg dose group achieved statistically significant clinical improvement compared with placebo in 3 syndrome-specific measures completed by clinicians and caregivers:
  - Rett Syndrome Behavior Questionnaire (RSBQ), Clinical Global Impression of Improvement (CGI-I), Rett Syndrome Domain Specific Concerns (RTT DSC)

- Improvement considered clinically meaningful by leading physicians
  - ~15% improvement from treatment baseline in a short duration trial
  - Improvement continued increasing through to end of treatment, indicating longer dosing may achieve further improvement
  - Evidence of biological activity across multiple symptom areas

- Trofinetide was well tolerated with no safety concerns identified
The RSBQ is a well-validated instrument that has been used in other Rett syndrome clinical trials, has been correlated with quality of life outcomes and has been characterized and validated in peer-reviewed publications.

The RSBQ is designed to measure the frequency of 45 neurobehavioral items, reflecting the severity of the syndrome. The items are rated from 0 to 2 by the caregiver:

- 0: the item is not true for an individual
- 1: the item is somewhat or sometimes true in the individual
- 2: the item is often or very true in the individual

The items are organized into eight subscales: General Mood, Breathing Problems, Hand Behaviors, Repetitive Face Movements, Body Rocking and Expressionless Face, Night-time Behaviors, Fear/Anxiety, and Walking/Standing.
RSBQ – 200mg/kg versus placebo

Mean improvement after 6 weeks of treatment

- A decrease on the y-axis indicates clinical improvement
- Mean improvements for 200mg/kg and placebo were, respectively, 16% and 6% of the treatment baseline
- Caregiver rates the frequency of 45 neurobehavioral items, reflecting the severity of the syndrome
- Neuren plans to use RSBQ as a primary efficacy measure in pivotal trial
RSBQ subscales – Cohen’s D effect sizes

RSBQ Subscales

- Repetitive Face Movements SS - vs. Placebo
- Night-time Behaviors SS - vs. Placebo
- General Mood SS - vs. Placebo
- Breathing Problems SS - vs. Placebo
- Hand Behaviors SS - vs. Placebo
- Fear/Anxiety SS - vs. Placebo
- Body Rocking and Expressionless Face SS - vs. Placebo
- Walking/Standing SS - vs. Placebo

<-- In Favor of Active  In Favor of Placebo -->

-2 -1.5 -1 -0.5 0 0.5 1 1.5 2
RSBQ items – Cohen’s D effect sizes

RSBQ items with largest effect size in favour of active

13 – Spells of screaming for no apparent reason during the night
30 – Spells of inconsolable crying for no apparent reason during the day
22 – Screams hysterically for long periods of time and cannot be consoled
34 – Makes grimacing expressions with the face
16 – There are times when she appears miserable for no apparent reason
28 – Makes mouth grimaces
5 – There are times when the breath is held
18 – Does not use hands for purposeful grasping
4 – Makes repetitive movements involving fingers around the tongue
7 – Spells of apparent anxiety/fear in unfamiliar situations
42 – Spells of inconsolable crying for no apparent reason during the night
6 – Air or saliva is expelled from the mouth with force
14 – Abrupt changes in mood
25 – Abdomen fills with air and sometimes feels hard

<-- In Favor of Active  In Favor of Placebo -->
CGI-I – 200mg/kg versus placebo

Mean improvement after 6 weeks of treatment

- A decrease on the y-axis indicates greater clinical improvement
- Clinician rates how much the subject’s overall illness has improved or worsened, relative to baseline, with ratings anchored to Rett syndrome symptom descriptions
- 22% of subjects in the 200mg/kg dose group received a CGI-I score of 2 (“much improved”) compared with 4% of subjects in the placebo group
- CGI-I expected to be a key secondary efficacy measure in pivotal trial
Median improvement after 6 weeks of treatment

- **Exact Median Test was used** - Statistical Analysis Plan prespecified use of a non-parametric method if data did not meet assumptions of a general linear model.
- **A decrease on the y-axis indicates clinical improvement**
- **Median improvements for 200mg/kg and placebo were, respectively, 15% and 5% of the treatment baseline**
- **Clinician assesses on a visual analog scale the severity of concerns identified for each subject on an individual basis**
Initial Phase 2 trial in ages 16 to 45

- Double-blind, placebo-controlled Phase 2 trial of 4 weeks of treatment with two dose levels (35 mg/kg and 70 mg/kg of body weight twice daily)

- 56 subjects aged 16 to 45 years randomized, with 53 subjects completing the trial

- Both dose levels were well tolerated and no safety concerns were identified

- Higher dose exceeded the pre-specified criteria for improvement in core efficacy measures compared with placebo

- Both doses showed trends of increasing effect with duration of treatment

- The clinical improvement in the trial encompassed core symptoms of Rett syndrome
  - Observed in both clinician and caregiver assessments
  - Included communication/speech, alertness and social interaction, anxiety, breathing abnormalities, hand movements/function, motor/muscular dysfunction, seizures and GI dysfunction
Core efficacy measures

**Motor Behavior Assessment Change Index**

- Analysis of group mean values
- Solid line is 70mg/kg, dotted line is placebo
- The two different shaded areas indicate the treatment period and the period post-cessation of treatment
- A negative value on the y-axis indicates clinical improvement

**Clinical Global Impression of Improvement**
Rett syndrome development plan

- Discuss Phase 2 clinical data and Phase 3 trial plans with FDA (Division of Neurology) in H1 2017

- Finalise manufacturing process for pivotal trial, New Drug Application (NDA) and commercial supply
  - Optimization and scale-up of API synthesis and isolation continuing
  - To-be-marketed drug product stability testing in progress
  - Plans well advanced to enable initiation in H2 2017 of manufacture using commercial process in preparation for supplying a Phase 3 trial

- Complete chronic toxicity studies required for NDA and pivotal trial
  - First species will conclude in H1 2017, complete second species in H1 2018

- Commence Phase 3 trial in 2018
Trofinetide in Fragile X syndrome

- Inherited X chromosome mutation – full mutation causes Fragile X syndrome
  - 1 / 4,000 males and 1 / 6,000 females estimated to have full mutation
  - More severe in males, ~50% of females have some features of the syndrome

- The most common inherited cause of intellectual disabilities and the most common known cause of autism - symptoms include:
  - Intellectual disabilities
  - Anxiety and unstable mood
  - Seizures (approximately 1 in 4)
  - Attention deficit, hyperactivity and autistic behavior

- No approved treatments available

- Trofinetide in Fragile X syndrome:
  - Clinical improvement observed in Phase 2 trial in adolescents and adults
  - Validation of rating scale for use in pivotal clinical trials is in progress
  - Next trial in children aged 3 to 12 in 2018, followed by Phase 3 trial in children, adolescents and adults
Completed Phase 2 trial in adolescents and adults

- Double-blind, placebo-controlled Phase 2 trial of 28 days of treatment with two dose levels (35 mg/kg and 70 mg/kg of body weight twice daily)
- 70 subjects aged 12 to 45 years received treatment, with 68 subjects completing the trial
- Both dose levels were well tolerated and no safety concerns were identified
- Higher dose exceeded pre-specified targets and demonstrated a consistent pattern of clinical improvement, observed in both clinician and caregiver assessments
- Improvements across a range of core symptoms of Fragile X syndrome
  - Captured by new Fragile X-specific measures as well as by the Aberrant Behavior Checklist
  - Included higher sensory tolerance, reduced anxiety, better self-regulation, more social engagement
- Improvements observed with the low dose were less consistent and did not meet pre-specified targets, but there was evidence of a dose response
Core efficacy measures that met target

- Analysis of mean clinical responses at end of treatment for each treatment group
- A negative value on the y-axis indicates clinical improvement
Trofinetide in Traumatic Brain Injury (TBI)

- >1.5 million head injuries annually in the US alone
- Leading cause of death and disability, especially in young and elderly
- No approved treatments available
- Partnership funding of ~US$25 million has been contributed by US Army
- Results of Phase 2 trial ("INTREPID") in moderate to severe TBI
  - Favourable safety profile confirmed
  - Statistically significant ($p=0.008$) and clinically relevant benefit of active over placebo in patients with severe TBI who completed RBANS
    - series of tests completed by the patient for assessing cognitive impairment
    - validated for use in TBI and extensively used to diagnose and track dementia
  - No difference between active and placebo in patients with severe TBI and moderate TBI, assessed by the primary efficacy measures that were used in past TBI trials:
    - GOS-E (measure of global function)
    - MPAI-4 (measure of daily living activities)
Next steps in TBI

- Neuren and US Army discussing feasibility of a second trial in severe TBI, or moderate to severe TBI, optimised by including:
  - RBANS as primary efficacy endpoint
  - More targeted definition of trial population
  - Randomisation stratified by injury severity
  - Substantially higher doses and longer treatment, enabled by safety profile

- Development in mild TBI (Concussion) being conducted by Neuren and US Army is on hold while future strategy is considered
Second drug candidate: NNZ-2591

- Cyclic dipeptide with higher oral bioavailability, improved stability and potential for oral solid dosage form
- Demonstrated efficacy in pre-clinical models of Parkinson’s disease, stroke, traumatic brain injury, peripheral neuropathy, Fragile X syndrome, memory impairment and multiple sclerosis
- Issued composition of matter patents in US, Europe and Japan, expiring in 2024, with potential to extend to 2029
- Issued US patents for methods of treating Parkinson’s disease, peripheral neuropathy and cognitive impairment; international applications pending for methods of treating autism spectrum disorders
Share information

Issued shares: 1.84 billion

Closing price 31 March 2017: 7.0 cents

52 week range: 4.1 cents – 12.0 cents

1 Includes 90 million loan funded shares, which will provide additional funds of $6 million when loans are repaid.
# Key milestones

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Estimated timing</th>
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<tbody>
<tr>
<td>Discuss Rett syndrome Phase 2 clinical data and Phase 3 trial plans with FDA</td>
<td>H1 2017</td>
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<tr>
<td>Complete chronic toxicity studies for NDA and Phase 3 trial:</td>
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<td>• First species</td>
<td>H1 2017</td>
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<td>• Second species</td>
<td>H1 2018</td>
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<tr>
<td>Finalise commercial manufacturing process for Phase 3 trial</td>
<td>H2 2017</td>
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<tr>
<td>Commence Rett syndrome Phase 3 trial</td>
<td>2018</td>
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<tr>
<td>Commence Fragile X syndrome pediatric trial</td>
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