Neuren (NEU) – ASX Announcement **16 February 2021**

Neuren adds Prader-Willi syndrome to pipeline with compelling results for NNZ-2591 in pre-clinical model

Highlights:

- **Prader-Willi syndrome is a neurodevelopmental disorder with urgent unmet need that severely impacts the lives of patients and their families**
- **Incidence of 1 in 10,000 to 30,000 people worldwide; characterised by insatiable hunger, obesity, diabetes, weak muscles, intellectual disabilities and behavioural problems**
- **Key symptoms were eliminated after treatment with NNZ-2591 in *Magel2*-null mouse model of Prader-Willi syndrome:**
  - **Both dose levels normalised all behavioral deficits**
  - **Obesity eliminated by high dose**
  - **Abnormally high insulin levels reduced to normal by high dose**
  - **Abnormally low levels of circulating IGF-1 increased to normal by high dose**
  - **Low dose partially improved obesity, insulin levels and circulating IGF-1 levels**
  - **NNZ-2591 had no impact on normal mice - the consistent ability to treat impaired animals successfully, but have no effects on normal animals ("state-dependent" effects) is a valuable attribute of NNZ-2591**
- **Orphan drug designation applications to be submitted in US and Europe**
- **Foundational development already completed for NNZ-2591 should enable Phase 2 trial in Prader-Willi syndrome**
- **Preparing for Phase 2 trials in Phelan-McDermid, Angelman and Pitt Hopkins syndromes**

Melbourne, Australia: Neuren Pharmaceuticals (ASX: NEU) today announced that Prader-Willi syndrome has been added to its development pipeline for NNZ-2591 following a study in a pre-clinical model that showed compelling effects of treatment on key symptoms of Prader-Willi syndrome. All behavioral deficits were eliminated and the important problems of obesity and excessive insulin were also reduced to normal.

Neuren CEO Jon Pilcher commented: "These excellent results have once again reinforced the potential for NNZ-2591 to make a difference across multiple neurodevelopmental disorders in which signaling between brain cells and IGF-1 metabolism are impaired. We look forward to working with Prader-Willi families and clinicians, as we are already doing with Phelan-McDermid, Angelman and Pitt Hopkins, to bring this potential treatment to fruition."

Neuren intends to submit applications for Orphan drug designation in the US and Europe. NNZ-2591 has already received Orphan drug designation for Phelan-McDermid, Angelman and Pitt Hopkins syndromes in both territories following similarly compelling pre-clinical model results. Neuren is preparing to commence Phase 2 clinical trials in each of those three syndromes in 2021. The foundational data for NNZ-2591 from manufacturing, non-clinical studies and the Phase 1 trial should also enable an Investigational New Drug application (IND) and Phase 2 development for Prader-Willi syndrome.

Study details

The blinded, controlled study was conducted in normal ("Wild type") mice and *Magel2*-null mice, which mimic the behavior and metabolic profile of Prader-Willi syndrome in humans. The following six groups of ten mice each were dosed orally each day for six weeks with vehicle (placebo) or NNZ-2591:

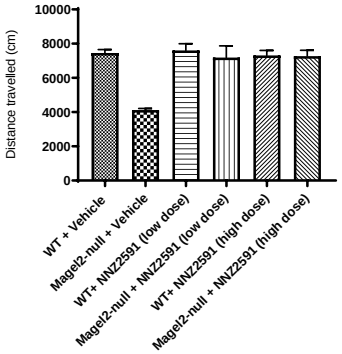
Treatment Group
Wild type (WT) + Vehicle
Magel2-null + Vehicle
WT + NNZ-2591 (low dose)
Magel2-null + NNZ-2591 (low dose)
WT + NNZ-2591 (high dose)
Magel2-null + NNZ-2591 (high dose)

Behavioral tests examined hypoactivity, daily living, social interaction, cognition and anxiety. Obesity was examined by measuring fat mass; blood levels of insulin and circulating IGF-1 were also measured. The results (mean for each group) are shown in the charts and table below. In summary:

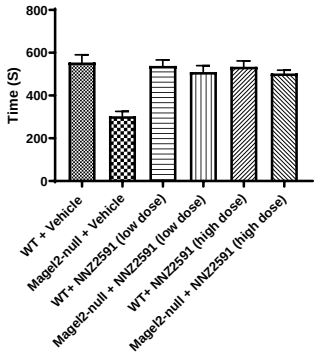
- In each of these tests the *Magel2*-null mice treated with vehicle were significantly impaired compared with Wild type mice treated with vehicle ($p<0.0001$).
- In all behavioral tests after treatment with both high and low doses of NNZ-2591 the *Magel2*-null mice were indistinguishable from Wild type mice ($p>0.05$).
- After treatment with the high dose of NNZ-2591 the fat mass, insulin levels and circulating IGF-1 levels of the *Magel2*-null mice were all indistinguishable from Wild type mice ($p>0.05$). The *Magel2*-null mice treated with the low dose of NNZ-2591 showed partial reversion to normal levels.
- Treatment with NNZ-2591 showed no effects on Wild type mice.

neuren pharmaceuticals

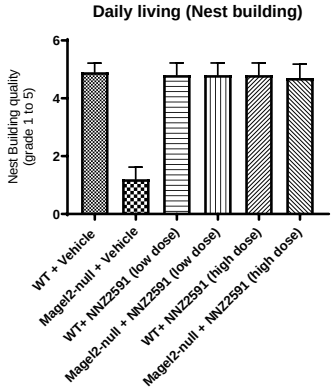
Hypoactivity (Open Field distance travelled)



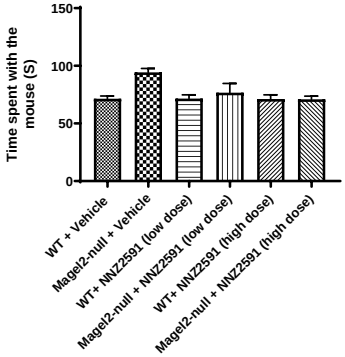
Hypoactivity (Open Field time spent active)



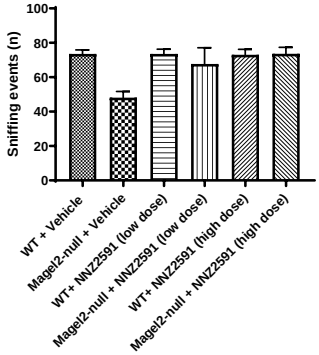
Daily living (Nest building)



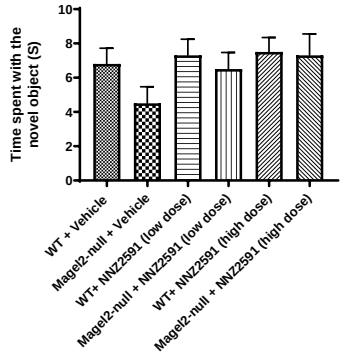
Social preference (novel mouse)



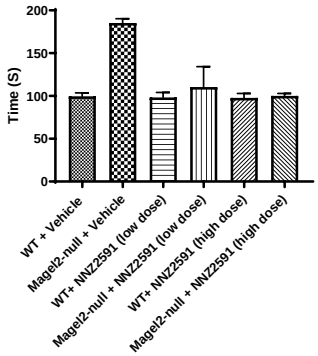
Social Interaction (Sniffing events)



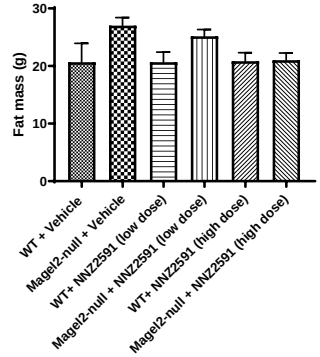
Cognition (Novel Object Recognition)



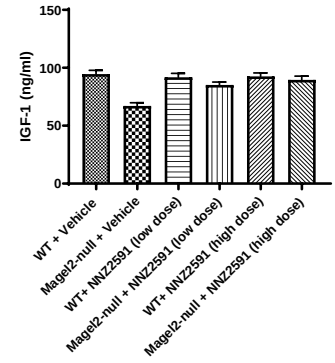
Anxiety (Elevated Plus maze, time spent in open arm)



Obesity (Fat mass)



Circulating IGF-1 levels



Insulin levels (pM)					
WT plus vehicle	*Magel2* -null plus vehicle	WT plus NNZ-2591 low dose	*Magel2* -null plus NNZ-2591 low dose	WT plus NNZ-2591 high dose	*Magel2* -null plus NNZ-2591 high dose
110	173	112	143	115	119

About Prader-Willi syndrome

Prader-Willi syndrome (PWS) is a rare genetic condition caused by loss of function in the 15q11-q13 region on the paternal copy of chromosome 15. Approximately 70% of cases are caused by deletion of a segment of the paternal copy of chromosome 15 and approximately 25% by duplication of the maternal copy of chromosome 15. PWS affects both males and females and can affect individuals of any ethnic or racial background, with an estimated incidence of between 1:10,000 and 1:30,000. PWS is associated with a constellation of symptoms that significantly negatively impact upon quality of life for affected individuals and their families.

PWS is characterised by early failure to thrive followed by the onset of insatiable hunger, which frequently results in obesity, type 2 diabetes, and metabolic syndrome. Additional characteristics include multiple endocrine abnormalities, hypotonia, hypogonadism, sleep disturbances, a challenging neurobehavioral phenotype, self-injurious behavior, mild to moderate intellectual and learning disabilities, and distinctive facial features. Growth hormone deficiency is reported to occur in 40-100% of patients and dysregulation of the growth hormone-IGF-1 axis is considered to be universal, with sub-normal serum IGF-1 levels.

About Neuren

Neuren is developing two new drug therapies to treat multiple serious neurological disorders that emerge in early childhood, none of which have any approved medicines.

The lead drug compound, trofinetide, is currently in a Phase 3 clinical trial for Rett syndrome and has completed a Phase 2 clinical trial in Fragile X syndrome. Both programs have been granted Fast Track designation by the US Food and Drug Administration (FDA). Neuren has granted an exclusive licence to ACADIA Pharmaceuticals Inc. for the development and commercialisation of trofinetide in North America, while retaining all rights outside North America.

Neuren plans to initiate Phase 2 trials of its second drug candidate, NNZ-2591, for each of Phelan-McDermid syndrome, Angelman syndrome and Pitt Hopkins syndrome in 2021.

Because of the urgent unmet need, all five programs have been granted “orphan drug” designation in both the United States and the European Union, a designation that provides incentives to encourage therapies for rare and serious diseases.

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ASX Listing Rules information
This announcement was authorized to be given to the ASX by the board of directors of Neuren Pharmaceuticals Limited, Suite 201, 697 Burke Road, Camberwell, VIC 3124

Forward-looking Statements

This announcement contains forward-looking statements that are subject to risks and uncertainties. Such statements involve known and unknown risks and important factors that may cause the actual results, performance or achievements of Neuren to be materially different from the statements in this announcement.