Neuren (NEU) - ASX Announcement **6 March 2020**

Compelling results for NNZ-2591 dose-ranging study in Phelan-McDermid syndrome model

Highlights:

- **Study in *shank3* knockout mouse model of 6 weeks treatment with 4 dose levels of NNZ-2591 or placebo**
- **Builds on previous positive study of 3 weeks treatment with NNZ-2591 or placebo**
- **Compelling results inform planned clinical trials in patients:**
  - **Clear dose response demonstrated with 4 escalating dose levels**
  - **Optimum dose identified, informing dose selection for planned Phase 2 clinical trials**
  - **Better efficacy after 6 weeks treatment compared with 3 weeks at the same dose level**
  - **Consistent results achieved across all 8 behavioral tests and seizure incidence**
- **Neuren has Orphan Drug designation from FDA for NNZ-2591 in each of Phelan-McDermid syndrome, Angelman syndrome and Pitt Hopkins syndrome**

Melbourne, Australia, 6 March 2020: Neuren Pharmaceuticals (ASX: NEU) today reported compelling results from a dose ranging study of NNZ-2591 in a model of Phelan-McDermid syndrome (PMS), which will be used to inform dose selection for Neuren's planned clinical trials in patients. PMS is a rare genetic condition in which the most common characteristics are intellectual disability, delayed or absent speech, symptoms of autism, low muscle tone, motor delays, and epilepsy. There is currently no treatment specifically for PMS.

The study was conducted in the *shank3* knockout mouse model in which the *shank3* gene is deleted to mimic Phelan-McDermid syndrome in humans. As well as causing PMS, disruption of the *SHANK3* gene is thought to be associated with a large number of cases of autism spectrum disorder. Wild type mice and knockout mice were treated with either placebo or one of 4 escalating doses of NNZ-2591 for 6 weeks. The study builds on the positive results previously reported by Neuren in a study of 3 weeks' treatment with NNZ-2591 compared with placebo, which formed the basis for the Orphan Drug designation granted by the US Food and Drug Administration (FDA).

The knockout mice exhibit deficits that can be measured by behavioral tests of anxiety, repetitive behaviors, memory, learning, sensory motor function, sociability and daily living skills. The results, which were consistent across all 8 behavioral tests and the incidence of seizures, showed that the lowest dose ("x" mg/kg) was not effective, the 2x mg/kg dose was partially effective, the 4x mg/kg dose was fully effective and indistinguishable from the highest dose of 8x mg/kg . This clearly demonstrates that the 4x mg/kg dose was the optimum dose level in the mouse model. Comparison with pk data from Neuren's planned Phase 1 clinical trial will inform the equivalent human dose for the planned Phase 2 trials in patients.

A further observation was that the 4x mg/kg dose in the 6 weeks study showed better efficacy than the same dose in the 3 weeks study, indicating that efficacy increases with treatment duration. Neuren plans to test treatment with NNZ-2591 for 12 weeks in the Phase 2 trials.

The 4x mg/kg dose level was also shown to be effective in Neuren's previously reported positive studies of 6 weeks treatment duration in models of Angelman syndrome and Pitt Hopkins syndrome. This data formed the basis for the Orphan Drug designations granted by the FDA in each of these indications.

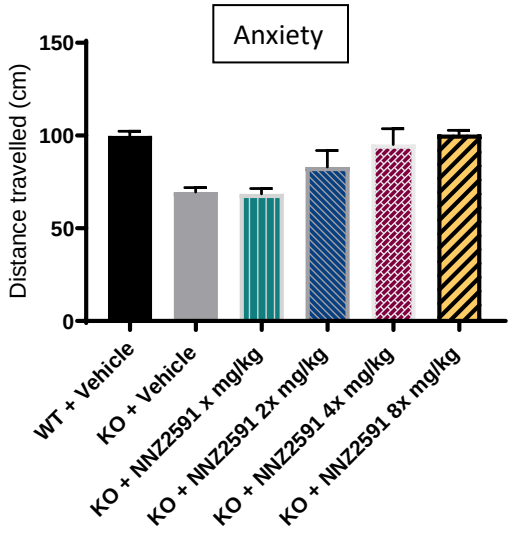
The following table and charts present the results in the incidence of seizures and the 8 behavioral tests for:

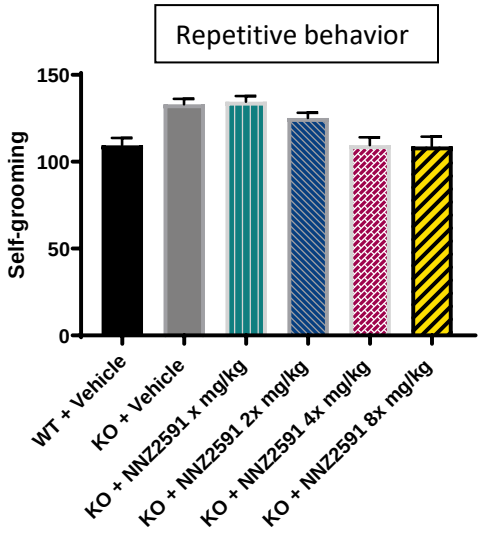
- Wild type mice with placebo ("vehicle")
- Knockout mice with placebo
- Knockout mice with dose x mg/kg
- Knockout mice with dose 2x mg/kg
- Knockout mice with dose 4x mg/kg
- Knockout mice with dose 8x mg/kg

Each dose level was also tested in wild type mice and was indistinguishable from wild type with placebo (i.e. NNZ-2591 had no effect on wild type mice, consistent with previous studies).

Incidence of seizures:

WT + vehicle	KO + vehicle	KO + x mg/kg	KO + 2x mg/kg	KO + 4x mg/kg	KO + 8x mg/kg
0%	60%	50%	30%	10%	10%





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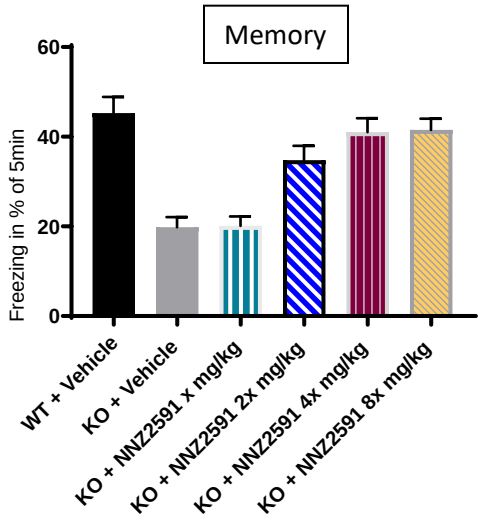

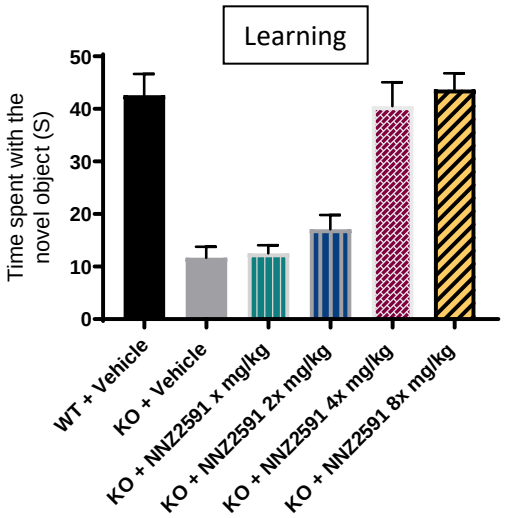

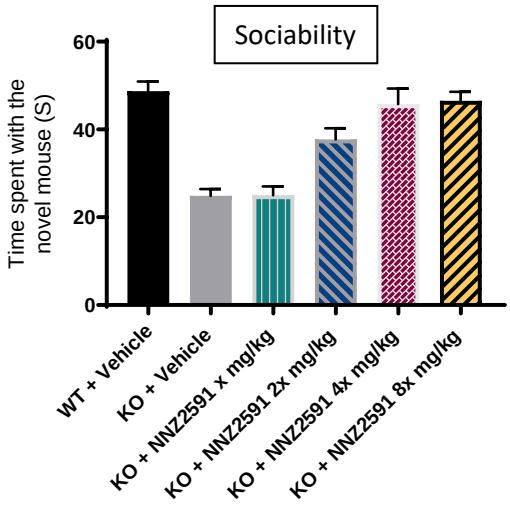

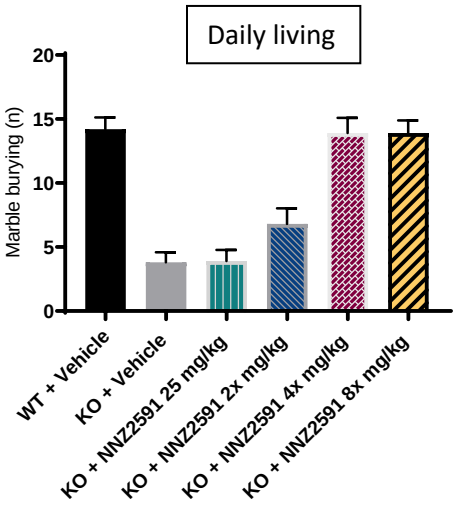

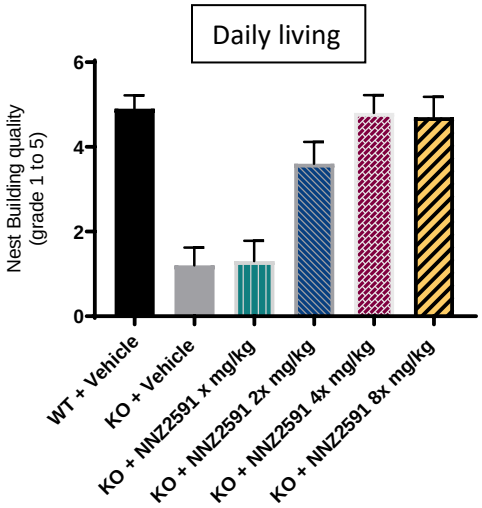

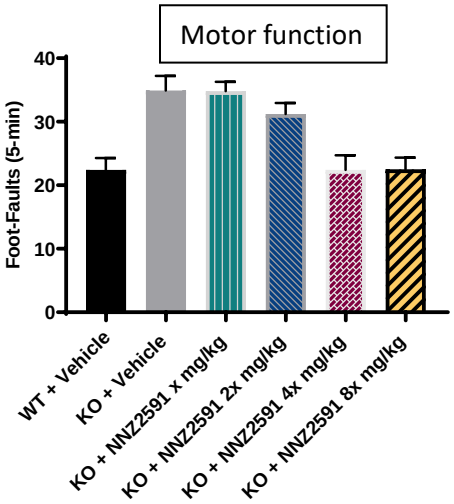

About Neuren

Neuren is developing new therapies for neurodevelopmental disorders with high unmet need, utilizing synthetic analogs of neurotrophic peptides that occur naturally in the brain. Neuren's lead drug candidate trofinetide is currently in a Phase 3 clinical trial for Rett syndrome and has completed a Phase 2 clinical trial in Fragile X syndrome. The programs in Rett syndrome and Fragile X syndrome have each received Fast Track designation by the US Food and Drug Administration and Orphan Drug designation in both the United States and the European Union. Neuren has granted an exclusive license to ACADIA Pharmaceuticals Inc. for the development and commercialization of trofinetide in North America, whilst retaining all rights outside North America. Neuren is advancing the development of its second drug candidate NNZ-2591 for Phelan-McDermid syndrome, Angelman syndrome and Pitt Hopkins syndrome, each of which has received Orphan Drug designation in the United States.

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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
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