New Preclinical Research Suggests Utility of Tetra Discovery Partners' BPN14770 to Provide Therapeutic Benefit in Fragile X Syndrome

- **Daily treatment with BPN14770 in a mouse Fragile X model showed reduced hyperarousal, improved social interactions, and improved natural behaviors, as well as changes in neuronal dendrite structure**
- **Benefit persisted two weeks after washout of the drug**
- **BPN14770 has demonstrated human safety and tolerability in Phase 1 clinical safety study**
- **Research results published online this week in *Scientific Reports***

Grand Rapids, MI (November 7, 2017) – New preclinical research suggests the potential utility of BPN14770, a selective PDE4D inhibitor currently under development by Tetra Discovery Partners as a prospective treatment for memory and cognitive problems associated with Alzheimer's disease, in the treatment of Fragile X Syndrome (FXS) and possibly other autism spectrum disorders.

Daily treatment of adult male *fmr1* C57B16 knockout mice (a standard FXS animal model) for 14 days reduced hyperarousal, and improved social interactions and increased natural behaviors such as nesting and marble burying compared to control FXS mice that received a placebo. At the same time, there was no deleterious effect on behavioral scores in normal wild-type mice treated with BPN14770. The behavioral benefits of BPN14770 in the FXS mice endured for two weeks after drug washout. Microscopic analysis of neurons in the prefrontal cortex from the treated FXS mice showed an improvement in dendritic spine morphology; this finding, combined with the 11 hour half-life of BPN14770 in mice, suggests that the enduring treatment benefits of BPN14770 were not due to slow washout of the drug.

The new research was published online today in *Scientific Reports*, an online, open-access primary research publication from the publishers of *Nature* by Tetra Discovery Partners and the company's research collaborators.

"This preclinical study strongly supports PDE4D as a therapeutic target for the treatment of FXS," said Mark E. Gurney, Ph.D., Chairman and Chief Executive Officer of Tetra Discovery Partners. "We have already demonstrated evidence of human safety and tolerability for BPN14770 in a Phase 1 study in healthy young and elderly volunteers. This research suggests BPN14770 may also have utility in the treatment of FXS, which is associated with a spectrum of neuropsychiatric symptoms, mild to severe cognitive impairment and intellectual disability, and potentially also find use in the treatment of other conditions on the autism spectrum."

“The results from these studies are very promising,” commented Michael Tranfaglia, M.D., Medical Director and Chief Scientific Officer of the FRAXA Research Foundation. “Inhibition of PDE4 has been validated as a treatment strategy by many research groups in the Fragile X field. However, the current study demonstrates the enhanced therapeutic potential of PDE4D inhibition with BPN14770, which shows the ability to rescue major Fragile X phenotypes not only in acute dosing, but in chronic dosing as well.

“Furthermore, the significant carryover of BPN14770 effects, even two weeks after treatment suggests this drug candidate has genuine long-term beneficial effects on Fragile X pathology,” Dr. Tranfaglia continued. “Additionally, tolerance has been a major problem with other drug classes studied as potential treatments for Fragile X syndrome, such as mGluR5 NAMs and GABA-B agonists, but no tolerance was seen in studies with BPN14770. The selective nature of this compound, which targets only PDE4D, also greatly improves the tolerability of the drug over past-studied, general PDE4 inhibitors, which should facilitate clinical trials in this difficult-to-treat population.”

About Fragile X Syndrome

Fragile X syndrome is a genetic condition that results from the silencing of the X-linked, fragile X mental retardation-1 (*FMR1*) gene. FXS patients display a range of behavior and other symptoms, including seizures, sleep disorders, anxiety, irritability, hyperactivity, autism, mild-to-severe cognitive impairment and intellectual disability. While FXS occurs in both genders, the condition is more common and generally more severe in males. There is no cure for FXS, and medications may be used to treat seizures, mood problems or other neuropsychiatric symptoms. FXS occurs in approximately 1 in 4,000 males and 1 in 8,000 females.

About BPN14770

BPN14770 is a novel therapeutic agent that selectively inhibits phosphodiesterase-4D (PDE4D) to enhance early and late stages of memory formation. This unique mechanism of action has the potential to improve cognitive and memory function in devastating disorders including Alzheimer’s disease, schizophrenia, and learning/ developmental disabilities such as Fragile X syndrome. BPN14770 has completed three human Phase 1 clinical trials enrolling 147 subjects and has shown excellent safety, oral bioavailability, and preliminary cognitive benefit in elderly subjects. Preparations are under way to initiate a Phase 2 trial of BPN14770 in patients with Alzheimer’s disease in the first half of 2018.

About the FRAXA Research Foundation

FRAXA's mission is to find effective treatments and ultimately a cure for fragile X syndrome - the most common inherited cause of autism worldwide. FRAXA funds research and clinical trials at universities all over the world. For more information please visit our website at http://www.fraxa.org.

About Tetra Discovery Partners

Tetra Discovery Partners is a clinical stage biotechnology company developing a portfolio of therapeutic products that will bring clarity of thought to people suffering from Alzheimer's disease and other brain disorders. Tetra uses structure-guided drug design to discover mechanistically novel, allosteric inhibitors of phosphodiesterase 4 (PDE4), an enzyme family that plays key roles in memory formation, learning, neuroinflammation, and traumatic brain injury. Tetra was a recipient of an NIH Blueprint Neurotherapeutics Program cooperative research agreement, and also receives major funding from the National Institute on Aging, the Alzheimer’s Drug Discovery Foundation, the National Institute of Neurological Disorders and Stroke,

and the National Institute of Mental Health through the Small Business Innovation Research (SBIR) program. Tetra Discovery Partners is headquartered in Grand Rapids, Michigan. For more information, please visit the company's website at http://www.tetradiscovery.com.

Forward-Looking Statements

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