Press Release

Shionogi Announces Positive Topline Results from Phase 2 Study of BPN14770, a Drug Candidate for the Treatment of Brain Disorders Associated with Cognitive and Memory Deficits, in Patients with Fragile X Syndrome

- Phase 2 Study conducted by Tetra Therapeutics, a consolidated subsidiary, shows significant cognitive improvement in domains related to language and caregivers reported improved language and daily functioning
- Lead drug candidate continues to be safe and well-tolerated

---

OSAKA, Japan,November 2, 2020 - Shionogi & Co., Ltd. (Head Office: Osaka, Japan; President and CEO: Isao Teshirogi, Ph.D.; hereafter "Shionogi") today announced that BPN14770, a drug candidate for the treatment of brain disorders associated with cognitive and memory deficits, has shown positive topline results from Phase 2 exploratory study in adult patients with Fragile X Syndrome (FXS) conducted by Tetra Therapeutics (hereafter “Tetra”), a consolidated subsidiary.

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 CNS disorders, including FXS, Alzheimer disease (AD) and other dementias, learning/developmental disabilities and schizophrenia. In the Phase 2 study in AD patients, BPN14770 showed a trend toward improvement in cognitive function [1]. In preclinical studies, BPN14770 promoted the maturation of connections between neurons, which is impaired in patients with FXS.

The Phase 2 clinical trial was a randomized, double-blind, placebo-controlled, two-way crossover study in patients with FXS. Each period was 12 weeks in duration with no washout between periods. The study enrolled 30 adult male subjects age 18-41 years with FXS. Subjects received twice a day of BPN14770 or placebo. Parents/caregivers and physician raters were blinded to treatment. All subjects completed both treatment periods, although carryover effects limited the primary statistical analysis of efficacy to Period 1.

Regarding the primary endpoints of safety and tolerability, all subjects (30 patients) completed both treatment periods and BPN14770 demonstrated excellent safety and tolerability. The incidence of adverse events was 36.7% (11 of 30 subjects) and 26.7% (8 of 30 subjects) for BPN14770 and placebo-treated subjects, respectively. The most common adverse event, vomiting, was 10.0% (3 patients) and 6.7% (2 patients) for BPN14770 and placebo-treated subjects, respectively. As a result of exploratory evaluation of efficacy, cognitive assessments using the NIH-Toolbox revealed significant benefit in Oral Reading Recognition (LSMean Difference +2.80, p=0.0157), Picture Vocabulary (+5.79, p=0.0342), and Cognition Crystallized Composite Score (+5.29, p=0.0018). Parent/Caregiver ratings using 100 point Visual Analog Scales revealed benefit that was judged to be clinically significant in Language (LSMean Difference +14.04, p=0.0051) and Daily Functioning (+14.53, p=0.0017). The benefit of BPN14770 was maintained up to 12 weeks after the crossover from drug to placebo.

About the Phase 2 Trial

The Phase 2 clinical trial was a randomized, double-blind, placebo-controlled, two-way crossover study in 30 adult male patients with FXS, ages 18-45, to assess the safety and efficacy of BPN14770. The study was conducted at Rush University Medical Center, Chicago, Illinois by principal investigator Elizabeth M. Berry-Kravis, M.D., Ph.D. with financial support from the FRAXA Research Foundation. Additional information is available through clinicaltrials.gov (Identifier: NCT03569631 [2]).

About BPN14770

BPN14770 is a novel therapeutic agent that selectively inhibits PDE4D to increase the levels of cAMP, a key signaling molecule, in brain. In preclinical models, BPN14770 promotes the maturation of connections between neurons, which is impaired in patients with FXS, the most common genetic form of Autism, an indication for which BPN14770 has received Orphan Drug Designation from the U.S. Food and Drug Administration (FDA). This unique mechanism of action has the potential to improve cognitive and memory function in devastating CNS disorders, including FXS, AD and other dementias, learning/developmental disabilities and schizophrenia.

About Tetra Therapeutics

Tetra Therapeutics, a wholly owned subsidiary of Shionogi & Co., Ltd., is a clinical stage biotechnology company developing a portfolio of therapeutic products that will bring clarity of thought to people suffering from FXS, AD, traumatic brain injury, and other brain disorders. Tetra uses structure-guided drug design to discover mechanistically novel, allosteric inhibitors of the phosphodiesterase 4 (PDE4) enzymes, a family of enzymes that play key roles in memory formation, learning, neuroinflammation, and traumatic brain injury. Tetra Therapeutics is headquartered in Grand Rapids, Michigan. For more information, please visit the company's website at http://www.tetratherapeutics.com.

About Shionogi

Shionogi & Co., Ltd. is a 142-year-old global, research driven pharmaceutical company headquartered in Osaka, Japan, that is dedicated to bringing benefits to patients based on its corporate philosophy of "supplying the best possible medicine to protect the health and wellbeing of the patients we serve." The company currently markets products in several therapeutic areas including anti-infectives, pain, CNS disorders, cardiovascular diseases and gastroenterology. Shionogi's research and development currently target two therapeutic areas: infectious diseases, and pain/CNS disorders.
For more information on Shionogi & Co., Ltd., please visit https://www.shionogi.com/global/en/

Forward-Looking Statements

This announcement contains forward-looking statements. These statements are based on expectations in light of the information currently available, assumptions that are subject to risks and uncertainties which could cause actual results to differ materially from these statements. Risks and uncertainties include general domestic and international economic conditions such as general industry and market

conditions, and changes of interest rate and currency exchange rate. These risks and uncertainties particularly apply with respect to product-related forward-looking statements. Product risks and uncertainties include, but are not limited to, completion and discontinuation of clinical trials; obtaining regulatory approvals; claims and concerns about product safety and efficacy; technological advances; adverse outcome of important litigation; domestic and foreign healthcare reforms and changes of laws and regulations. Also for existing products, there are manufacturing and marketing risks, which include, but are not limited to, inability to build production capacity to meet demand, unavailability of raw materials and entry of competitive products. The company disclaims any intention or obligation to update or revise any forward-looking statements whether as a result of new information, future events or otherwise.

For Further Information, Contact:
Corporate Communications Department
Shionogi & Co., Ltd.
Telephone: +81-6-6209-7885

References

1. Press release on May 26, 2020
   Tetra Discovery Partners and Shionogi & Co., Ltd. Collaborate on BPN14770 Development and Commercialization
2. https://clinicaltrials.gov/ct2/show/NCT03569631