PRESSRELEASE

SHIONOGI

**Zatolmilast, an Investigational Treatment for Fragile X Syndrome, Receives Rare Pediatric Disease Designation from the U.S. FDA**

**OSAKA, Japan, September 27, 2023 -** Shionogi & Co., Ltd. (Head Office: Osaka, Japan; Chief Executive Officer: Isao Teshirogi, Ph.D.; hereafter "Shionogi") announced the U.S. Food and Drug Administration (FDA) has granted Tetra Therapeutics Inc. (hereafter "Tetra"), a Shionogi Group Company, Rare Pediatric Disease Designation for zatolmilast (BPN14770), an investigational treatment being studied for Fragile X syndrome (FXS), a leading cause of inherited intellectual disability and autism.

FDA grants Rare Pediatric Disease Designation (RPD) for serious and life-threatening diseases that primarily affect children ages 18 years or younger and fewer than 200,000 people in the United States. The RPD designation allows Tetra to request a priority review voucher from FDA which, if granted, may be used for a subsequent human drug application. Zatolmilast was also awarded Orphan Drug Designation by the FDA in 2018.

“We are committed to advancing a potential medicine for people with Fragile X syndrome, a rare genetic disorder which affects all aspects of life for individuals and families. While symptoms vary among individuals, intellectual disability is one of the most prevalent neuropsychiatric hallmarks of the disorder,” said Chad Coberly, JD, Chief Executive Officer, Tetra Therapeutics. “A treatment that has the potential to improve cognition could lead to enhanced memory formation as well as improved vocabulary and reading skills. Overall gains in these domains may help people with Fragile X syndrome, their families and caregivers.”

Shionogi acquired Tetra in 2020 as part of its mission to develop medications for unmet medical needs and thereby contribute meaningfully to society. Tetra’s clinical programs, which focus on addressing cognitive function in FXS and other disorders, align strategically with Shionogi’s global vision. Shionogi is advancing the zatolmilast development program with the intent, if it is approved, to offer people living with FXS the first cognitive treatment developed specifically for this rare genetic disorder.

**Zatolmilast Clinical Program**

Zatolmilast is an investigational drug that is believed to work by modulating a signaling molecule called cyclic AMP (cAMP), which may promote the maturation of connections between neurons that are impaired in individuals with FXS.

In a randomized, double-blind, placebo-controlled two-way crossover Phase 2 trial that included 30 adult males with FXS, the primary endpoint of this study was safety. An exploratory analysis of the efficacy of zatolmilast showed improvement in cognition, specifically in language domains including picture vocabulary and oral reading recognition.[1] Clinically meaningful improvements in daily functioning were also observed.[1] The most commonly reported adverse events were vomiting and upper respiratory tract

infections, however rates were similar between the active and placebo arms. No participants discontinued the study due to adverse events.

Zatolmilast is currently being evaluated in a pivotal Phase 2b/3 program, which includes two randomized, double-blind, placebo-controlled studies of 150 participants each. The first, Study 204 (NCT05163808), includes adolescent males ages 9-17. The second, Study 301 (NCT05358886), includes adult males ages 18-45. The zatolmilast clinical program also includes Study 302 (NCT05367960), an open-label extension study available to participants after completing Study 204 or Study 301.

Primary endpoints for the studies include a cognitive assessment of the efficacy of zatolmilast, as measured by the cognition crystallized composite score of the National Institutes of Health Toolbox Cognitive Battery (NIH-TCB), a calculated score from a series of tests to assess the subjects' change from baseline of the Picture Vocabulary and Oral Reading domains of the NIH-TCB, as well as determinations of the drug's safety and tolerability. Secondary endpoints include assessments of daily living, caregiver and clinician improvement scales and other domains from the NIH-TCB.

**About Fragile X Syndrome (FXS)**

FXS is a leading genetic cause of inherited intellectual disability and the most common known cause of autism in the U.S.[2] FXS is known to have a greater effect on males than females because the mutation of the *FMR1* gene is carried on the X chromosome.[3] The most important clinical abnormality associated with FXS is global developmental delay and intellectual disability.[4] The IQ of males with full mutation varies, with a mean value of 40–51.[4] Other common symptoms of FXS include aggressiveness, attention problems and anxiety.[2] FXS can cause challenges across many aspects of daily life, such as impacting individuals' ability to care for themselves and communicate with others.[3]

**About Tetra Therapeutics**

Tetra Therapeutics, a Shionogi Group Company, is a clinical stage biotechnology company focused on developing a portfolio of therapeutic products to address unmet needs in central nervous system diseases and disorders. In addition to advancing the zatolmilast clinical program, Tetra also has a PDE4B Inhibitor in pre-clinical development. Tetra Therapeutics is headquartered in Grand Rapids, Michigan. For more information, visit tetratherapeutics.com.

**About Shionogi**

Shionogi & Co., Ltd. is a leading global research-driven pharmaceutical company dedicated to bringing benefits to patients based on its corporate philosophy of "supplying the best possible medicine to protect the health and well-being of the patients we serve." Shionogi has discovered and developed novel antibiotics, medicines for HIV and influenza and currently markets medicines for infectious diseases and central nervous system disorders. Shionogi's global pipeline includes research programs in infectious disease, pain/CNS, metabolic disorders, oncology and stroke. For more information, 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, lack of availability 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.*

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[2] Cleveland Clinic. (2021, May 18). Fragile X Syndrome: Diagnosis, Symptoms & Treatment. Cleveland Clinic. https://my.clevelandclinic.org/health/diseases/5476-fragile-x-syndrome
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[4] Ciaccio, C., Fontana, L., Milani, D., et al. Fragile X syndrome: A review of clinical and molecular diagnoses. *Italian Journal of Pediatrics*. (2017, April 19). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5395755/