Transposon Announces Final Results from a Phase 2 Study of TPN-101 for the Treatment of C9orf72-Related Amyotrophic Lateral Sclerosis and/or Frontotemporal Dementia

TPN-101 treatment reduced the rate of decline of Vital Capacity by 50% compared to placebo after 24 weeks, an objective respiratory measure that correlates with mortality in patients with ALS

Treatment with TPN-101 also showed a slowing of ALS disease progression as measured by the ALSFRS-R global clinical scale

TPN-101 had lowering effects on key biomarkers of neurodegeneration and neuroinflammation, including NfL, NfH, and IL-6

Meta-analysis of the combined patient populations from the company's Phase 2 studies in C9orf72-related ALS/FTD and PSP showed a statistically significant NfL-lowering effect of TPN-101

Transposon plans to advance TPN-101 into a Phase 3 registration study for C9orf72-related-ALS

SAN DIEGO, California, July 24, 2024 – Transposon Therapeutics, a biotechnology company developing a platform of novel, orally administered therapies for the treatment of neurodegenerative and aging-related diseases, including Alzheimer's disease, today announced final results from its Phase 2 study of TPN-101 in patients with amyotrophic lateral sclerosis (ALS) and/or frontotemporal dementia (FTD) related to hexanucleotide repeat expansion in the C9orf72 gene (C9orf72-related ALS/FTD). Final results from this study confirmed the excellent safety profile of TPN-101 and showed clinical signs of disease-modifying effects in patients with these disorders, which align with previously reported safety and therapeutic activity in patients with Progressive Supranuclear Palsy (PSP). These findings are consistent with TPN-101's reduction of neuroinflammation and neurodegeneration through blocking the activity of LINE-1, a human-specific retrotransposon that is no longer adequately suppressed in many neurodegenerative disorders and aging.

ALS is a progressive and uniformly fatal neurodegenerative disease with a mean survival of two-to-three years. Respiratory failure is the most common cause of death for people with ALS. Vital Capacity (VC) is an objective measure of respiratory function that correlates with mortality in these patients. After 24 weeks, C9-ALS participants treated with TPN-101 experienced approximately 50% less decline in VC compared to those treated with placebo (LS mean change -8.4% *vs* -16.5%). When the participants in the placebo group were switched to TPN-101 during the open-label period, the decline in VC over the following 24 weeks (-7.2%) was less than half that while on placebo and comparable to that in the original TPN-101 group during the double-blind period. Overall, the 48-week changes in both groups were lower than expected based on natural history in similar study populations.

The decline on the Revised ALS Functional Rating Scale (ALSFRS-R) was comparable between the TPN-101 and placebo groups during the 24-week double-blind period (LS mean -7.2 points *vs* -6.7). However, during the 24-week open-label extension period, the decline on the ALSFRS-R in the original TPN-101 group was less than half that during the initial 24-week period and less than half that of the placebo group during both study periods. The decline in ALSFRS-R in the original TPN-101 group over the entire 48 weeks was approximately 40% less than expected based on natural history data, indicating a global clinical benefit with longer treatment.

"The effects of TPN-101 across multiple key endpoints in this study are encouraging and represent an important step forward in finding a potential treatment for this serious illness," said Merit Cudkowicz, M.D., Chair of the Massachusetts General Hospital Department of Neurology, Julieanne Dorn Professor of Neurology at Harvard Medical School, and principal investigator in the Phase 2 study of TPN-101 for C9orf72-related ALS/FTD. "I look forward to advancing the development of TPN-101 and what that could mean for people living with C9-ALS."

In participants with C9-ALS, those treated with TPN-101 had lower levels of neurofilament light chain (NfL) compared with placebo at the end of the double-blind period. NfL is the primary biomarker of neurodegeneration, and the NfL results at both Weeks 24 and 48 are consistent with findings from the company's Phase 2 study of TPN-101 for the treatment of PSP. TPN-101 also had lowering effects on additional biomarkers of neurodegeneration and neuroinflammation, including neurofilament heavy chain (NfH), interleukin 6 (IL-6), neopterin, and osteopontin.

A meta-analysis of the combined C9-ALS and PSP populations from the two Phase 2 studies of TPN-101 showed a statistically significant NfL-lowering effect of TPN-101 versus placebo at Week 24 ($p = 0.034$). The consistency of biomarker improvements in these two studies evaluating patients with different clinical conditions supports the treatment hypothesis that these diseases share a common LINE-1-related pathophysiology.

"Today there are very limited treatment options for ALS patients and based on these results that show patients treated with TPN-101 experience impactful benefits across multiple functional and biomarker measures, we plan to rapidly advance TPN-101 into a Phase 3 registration study for the treatment of C9-ALS," said Dennis Podlesak, Chairman and Chief Executive Officer of Transposon. "In addition to ALS, we are committed to advancing TPN-101 for the treatment of PSP, Alzheimer's disease and other neurodegenerative and autoimmune disorders with the goal of providing new and innovative therapies that can significantly improve the lives of those battling these devastating diseases."

Transposon intends to present detailed data from this study at upcoming scientific meetings.

About the Phase 2 Study in C9orf72-related ALS/FTD

The Phase 2 study in C9orf72-related ALS/FTD is multi-center, randomized, double-blind, placebo-controlled parallel-group, two-arm study with an open-label treatment phase in patients with C9orf72-related ALS and/or FTD. Participants (n=42) were randomized to receive daily doses of 400 mg of TPN-101 or placebo. The study includes a six-week screening period, a 24-week double-blind treatment period, a 24-week open label treatment period, and a follow-up visit four weeks post-treatment. All phases of the study, including the 24-week open label treatment

period, have been completed. Further information on the study can be accessed at ClinicalTrials.gov.

About TPN-101

TPN-101 specifically inhibits the LINE-1 reverse transcriptase that promotes LINE-1 replication. LINE-1 elements are a class of retrotransposable elements that in humans are uniquely capable of replicating and moving to new locations within the genome. When this process becomes dysregulated, LINE-1 reverse transcriptase drives overproduction of LINE-1 DNA, triggering innate immune responses that contribute to neurodegenerative, autoimmune and aging-related disease pathology.

About ALS and FTD

ALS is a neurodegenerative disease characterized by progressive muscle weakness, loss of ability to speak, eat, move or breathe. FTD is a progressive frontal / temporal cortex disease associated with behavior and personality changes, emotional problems, and difficulty walking, communicating or working. With onset commonly in middle age or earlier, patients with ALS have a mean survival of two-to-three years. Patients with FTD have a mean survival of nine years.

About Transposon

Transposon Therapeutics, Inc. is a clinical-stage biopharmaceutical company developing a platform of novel therapies for the treatment of neurodegenerative and aging-related diseases, including Alzheimer's disease. The company's lead clinical compound, TPN-101, is first-in-class to address LINE-1 reverse transcriptase for treating neurodegenerative and autoimmune diseases. The company also has a discovery platform supporting a deep pipeline of novel therapies to address additional indications.

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