Poster

PSTR158: ALS and Motor Neuron Diseases

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR158.06/C85

Topic: C.06. Neuromuscular Diseases

Support: the Capital's Funds for Health Improvement and Research（2022-2-2045）
Beijing Nova Program（20230484245）
National Key R&D Program of China（2022YFF1501500, 2022YFF1501501, 2022YFF1501502, 2022YFF1501503, 2022YFF1501504, 2022YFF1501505）
Beijing Laboratory of Oral Health (PXM2021_014226_000041）
Beijing Municipal Science & Technology Commission（No.Z231100004823036）
Ractigen Therapeutics (HX-A-2023004).

Title: Rag-17: a promising new gene silencing therapy for sod1-als- early safety and efficacy data from a first-in-human trial

Authors: *J. YE[1], L. JIANG[1,2], L. WANG[1], Y. PAN[1,2], X. WANG[1,2], H. QU[1], X. LIAO[1], X. ZHOU[1], S. ZHANG[3], M. KANG[3], L.-C. LI[3], W. CHEN[1], Y. WANG[1,2,4,5,6,7,8,9];
[1]Beijing Tiantan Hospital, Capital Med. Univ., Beijing, China; [2]China Natl. Clin. Res. Ctr. for Neurolog. Dis., Beijing, China; [3]Ractigen Therapeut., Suzhou, China; [4]Chinese Inst. for Brain Res., Beijing, China; [5]Natl. Ctr. for Neurolog. Disorders, Beijing, China; [6]Advanced Innovation Ctr. for Human Brain Protection, Capital Med. Univ., Beijing, China; [7]Beijing Lab. of Oral Health, Capital Med. Univ., Beijing, China; [8]Beijing Municipal Key Lab. of Clin. Epidemiology, Beijing, China; [9]Lab. for Clin. Medicine, Capital Med. Univ., Beijing, China

Abstract: Abstract for Neuroscience 2024Title: RAG-17: A Promising New Gene Silencing Therapy for SOD1-ALS - Early Safety and Efficacy Data from a First-in-Human Trial **Abstract:** Amyotrophic lateral sclerosis (ALS) is a chronic progressive neurodegenerative disease and the treatment options remain limited. Amyotrophic lateral sclerosis (ALS) patients with mutations in the superoxide dismutase 1(SOD1)gene are a growing target for targeted therapies. While an antisense oligonucleotide (ASO) recently received approval for this specific population, small interfering RNA (siRNA) offers another powerful approach for gene silencing. However, siRNA delivery to the central nervous system (CNS) has hampered its therapeutic potential. RAG-17 is a novel siRNA therapy targeting SOD1, conjugated to the SCAD delivery system for enhanced CNS delivery via intrathecal injection. Preclinical studies demonstrated significant efficacy in delaying disease onset, improving motor function, and extending survival in ALS models.In June 2023, a pioneering open-label, dose-escalation human study (NCT05903690) began to explore RAG-17’s safety, tolerability, pharmacokinetics, and initial efficacy in adults with SOD1

mutation-related ALS. As of December 10, 2023, six participants have been enrolled, receiving between 2 to 6 doses. The doses have been escalated up to 120-150 mg for most, with one participant reaching 180 mg per dose. The study has so far reported no dose-limiting toxicities (DLTs) or serious adverse events (SAEs). The adverse events noted were mild, including muscle tremors and headaches, predominantly after the first dose, resolving on their own without intervention. The plasma concentration of RAG-17 peaked at 12 hours post-administration and gradually declined, clearing within 48 hours. CSF SOD1 protein levels started to decrease immediately after the first dose and continued to drop with additional doses, achieving over a 50% reduction by the 5^{th} dose. Plasma neurofilament light chain (NFL) levels also showed a trend of reduction, exceeding 50% after just five doses.Encouragingly, preliminary efficacy data suggests potential clinical benefit. Among the first three participants receiving at least four doses, two showed stabilization of ALSFRS-R scores, and one even demonstrated improvement in ALSFRS-R and forced vital capacity (FVC) compared to baseline. The final analysis is expected in July 2024.