RAG-17, a Novel siRNA Therapy for SOD1-ALS: Safety and Preliminary Efficacy from a First-in-human Trial

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Objective:

To evaluate the safety, pharmacokinetics, and preliminary efficacy of RAG-17 in SOD1-ALS patients.

Background:

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that typically results in survival of less than five years post-diagnosis. Superoxide Dismutase 1 (SOD1), the most frequently observed gene mutation in Asian ALS patients, has been targeted in past therapies with limited success. RAG-17 is a novel siRNA therapy targeting SOD1, conjugated to a smart chemistry aided delivery (SCAD) system for enhanced CNS delivery via intrathecal injection.

Design/Methods:

This first-in-human, open-label, single-center, dose-escalation study (CREATION, NCT05903690) enrolled six SOD1-ALS patients to receive intrathecal injections of RAG-17 over a 240-day period.

Results:

Six participants received 6 to 7 doses, with dose escalations up to 150 mg, and one participant reaching 180 mg per dose. No dose-limiting toxicities (DLTs) or serious adverse events (SAEs) were reported. Adverse events were mild and included muscle tremors (2/6) and headaches (2/6). Plasma concentration of RAG-17 peaked at 6-12 hours post-administration and cleared within 48 hours. CSF SOD1 protein levels decreased by over 50% in five subjects. Plasma neurofilament light chain (NfL) levels also showed significant reductions. Notably, all subjects experienced an average decrease of 2.17 points in the ALS Functional Rating Scale-Revised (ALSFRS-R) score, equivalent to a 0.29-point decline per month. Forced vital capacity (FVC) remained stable in most patients, with two showing a significant increase from baseline.

Conclusions:

The CREATION study demonstrates that RAG-17 is safe and exhibits potential efficacy in treating ALS patients. The results from this study highlight the therapeutic promise of RAG-17, offering new avenues for the management of ALS.

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