#018 Safety, Biomarker Responses, and Preliminary Efficacy Following a Single Intrathecal Dose of RAG-17, a Novel siRNA Therapeutic for SOD1-ALS: Results from an Ongoing Phase I/II Study

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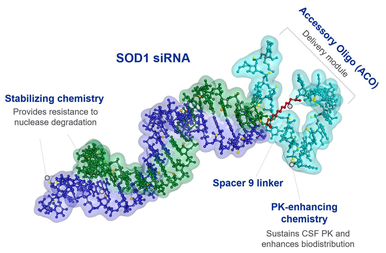
Introduction

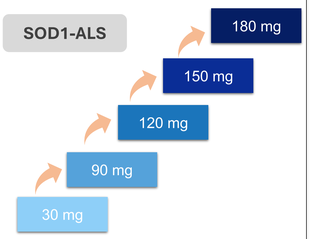
- Superoxide dismutase 1 (SOD1) mutations are a well-validated driver of amyotrophic lateral sclerosis (ALS). Current molecular therapies often require frequent intrathecal (IT) dosing, highlighting the need for longer-acting alternatives.
- RAG-17: A novel, highly potent small interfering RNA (siRNA) designed to silence SOD1 mRNA.
- RAG-17 utilizes proprietary Smart Chemistry-Aided Delivery (**SCAD**™) technology. SCAD conjugates the siRNA to an accessory oligonucleotide (**ACO**), enabling widespread central nervous system (CNS) distribution and durable target engagement via IT administration.
- In SOD1^{G93A} ALS mouse models, RAG-17 demonstrated a significantly prolonged duration of action and extended survival compared to standard antisense oligonucleotide (ASO) therapy [1, 2].

RAG-17: A SCAD-siRNA



Study Design

- **Trial Structure**: A randomized, double-blind, placebo-controlled, single ascending dose (SAD) phase of an ongoing Phase I/II clinical trial (**NCT06556394**).
- **Dosing & Randomization**: Participants with SOD1-ALS (N=20) were enrolled across 5 sequential dose cohorts (30, 90, 120, 150, and 180 mg). Within each cohort (n=4), patients were randomized 3:1 to receive a single IT administration of RAG-17 or placebo.
- **Key Endpoints**:
  - Primary: Safety and tolerability.
  - Secondary & Exploratory: Pharmacokinetics (PK), target engagement biomarkers (CSF SOD1 and plasma NfL), and clinical function (ALSFRS-R).



Protocol Amendment Note: *ALSFRS-R monitoring was added to the trial protocol after the 30 mg, 90 mg, 120 mg, and 150 mg cohorts had already completed treatment. Therefore, functional clinical data is exclusively available for the 180 mg cohort.*

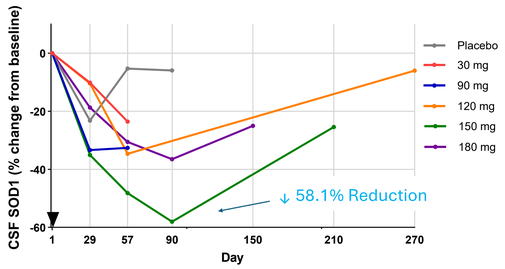
Baseline Characteristics (N=20)

- **Demographics**: Mean age 49.0 years (SD: 11.2); 55% Male.
- **Disease Status**: Mean time from symptom onset was 26.3 months. Mean baseline ALSFRS-R total score was 35.0 (SD: 7.1).
- **Standard of Care**: Riluzole use (55%); Edaravone use (10%).
- **Baseline Biomarkers**: Plasma NfL geometric mean was 121.1 pg/mL (Range: 24.1–636).

Results

A single IT dose of RAG-17 reduces plasma NfL by 81% at 150 days and halts ALSFRS-R decline at 90 days with a favorable safety profile.

CSF SOD1 protein (n=3/dose group)

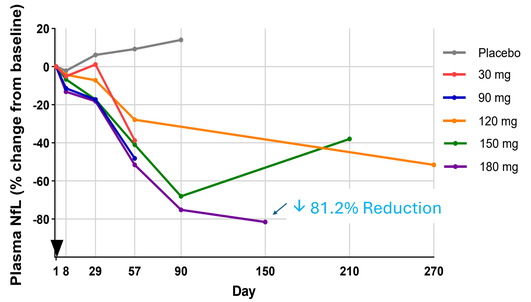


CSF Sampling Protocol:

- ***Cohorts 1–3:*** *Day 57 (Original protocol).*
- ***Cohorts 4–5:*** *Day 90 added.*
- ***Extended Follow-up:*** *Protocol later amended to allow voluntary CSF sampling at various extended timepoints across all cohorts.*

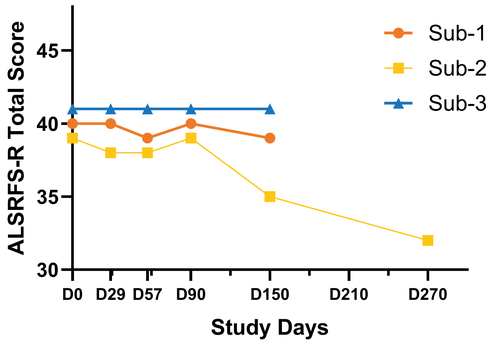
A single IT dose yielded rapid and durable target engagement. In the 150 mg cohort, maximum CSF SOD1 reduction reached **58.1% by Day 90**, with a clinically meaningful 25.4% reduction maintained out to Day 210.

Plasma NfL (n=3/dose group)



RAG-17 induced a progressive and deep reduction in plasma NfL. In the highest dose cohort (180 mg), reduction trajectories from baseline were: 18.3% at Day 29 → 51.5% at Day 57 → 75.2% at Day 90 → 81.2% by Day 150.

Preliminary Clinical Efficacy (ALSFRS-R)



Encouraging Stabilization (180mg♯): Blinded preliminary data shows zero functional decline (ALSFRS-R) at Day 90 across all evaluable subjects (n=3). Minimal decline was maintained at Day 150 (0–4 pts) and extended to 9 months in one subject (-7 pts). *(Note: 1 subject discontinued prior to assessment for administrative reasons).*

♯ **Protocol Context:** Functional assessment via ALSFRS-R was introduced as a protocol amendment following the completion of Cohorts 1 through 4. Consequently, this data is currently only available for the 180 mg cohort.

Pharmacokinetics (PK) and Safety

- **PK**: Systemic plasma exposure increased dose-proportionally from 30 mg up to 150 mg (median T_{max}: 8.0–11.9 h), plateauing at 180 mg. The mean elimination half-life ($t_{1/2}$) ranged from 6.7 to 10.1 hours.
- **Favorable Safety Profile**: RAG-17 was well-tolerated across all evaluated doses.

Metric	Result (Across all doses)
SAEs	0
Grade ≥ 3 TEAEs	0
Common TRAEs	Mild hypoesthesia, transient CSF WBC increase

Conclusions

A single intrathecal dose of RAG-17 demonstrated highly promising early results in patients with SOD1-ALS:

1. **Favorable Safety**: Well-tolerated with no SAEs and only mild-to-moderate TEAEs across all ascending dose cohorts.
2. **Profound Target Engagement**: Unprecedented, durable reductions in both disease-driving protein (CSF SOD1) and neurodegenerative biomarkers (plasma NfL), supporting the potential for an extended dosing interval.
3. **Encouraging Clinical Trends**: Preliminary functional data (ALSFRS-R) suggests a robust stabilization of disease progression in the highest dose cohort, warranting further clinical investigation.

ALSRFS-R: ALS Functional Rating Scale – Revised; AUC: Area Under the Curve; CSF: Cerebrospinal Fluid; D: Day; DL: Dose Level; IT: intrathecal; NfL: Neurofilament Light Chain; SAE: Serious Adverse Event; SD: Standard Deviation; SOD1: Superoxide Dismutase 1; TEAE: Treatment-Emergent Adverse Event; TRAE: Treatment-Related Adverse Event.

References: *1. Duan et al. Local administration of a novel siRNA modality into the CNS extends survival and improves motor function in the SOD1^{G93A} mouse model for ALS. Mol Thera – Nucleic Acids 2024. | 2. Duan et al. RAG-17: A Novel siRNA Conjugate Demonstrating Efficacy in Late-Stage Treatment of SOD1^{G93A} ALS mice. bioRxiv 2023.11.23.568255*

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