SEI-Moleculogic Preclinical Study Design Overview: DNL343v2

1. Objective

This document outlines the proposed preclinical experiments to validate the scientific hypotheses underpinning the SEI-Moleculogic rescue blueprint for DNL343v2. The focus is on ISR modulation timing, glial NRF2 pathway activation, ROS buffering synergy, and the technical feasibility of oscillatory delivery formulations.

2. Preclinical Experiments

[EXPERIMENT 1] ISR Modulation Timing and Efficacy Mapping

- Model: SOD1^G93A ALS mouse
- Arms: Original DNL343 | SEI rescue (low-dose sustained-release) | Placebo
- Endpoints: p-eIF2a, ATF4, CHOP (spinal cord & cortex) over time
- Timepoints: 1h, 6h, 24h, 72h, 7d, 14d
- Readouts: Immunoblot, qPCR, rotarod, grip strength

[EXPERIMENT 2] Glial NRF2 Pathway Activation

- Model: NRF2::Luciferase reporter mice (crossed with SOD1-G93A)
- Arms: DNL343v2 | DNL343v2 + NRF2 inhibitor | Placebo
- Endpoints: HO1, NQO1, GCLC expression; NRF2 nuclear translocation
- Readouts: IHC, qPCR, bioluminescence tracking

[EXPERIMENT 3] Peripheral ROS Buffering via Edaravone

- Model: SOD1-G93A treated with Edaravone or DNL343v2 + Edaravone
- Biomarkers: CNS 8-OHdG, MDA, glutathione ratio (GSH to GSSG ratio)
- Readouts: ELISA, LC-MS, correlation with motor neuron viability

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[EXPERIMENT 4] Oscillatory Delivery Profile Feasibility

- Formulations: Matrix-PLGA | Nanoparticle-pulsatile | Conventional oral

- Outputs: 24-hour release profile, peak-trough ratio, glial bioavailability

- Tools: PKSim, GastroPlus, SEI custom simulator

3. Next Steps

- Finalize in vivo protocols and select CRO/academic partners

- Begin synthesis of SEI-DNL343v2 prototype formulations

- Integrate SEI simulation overlays with PK/PD readouts

- Prepare Type C FDA meeting briefing once preliminary data is generated