

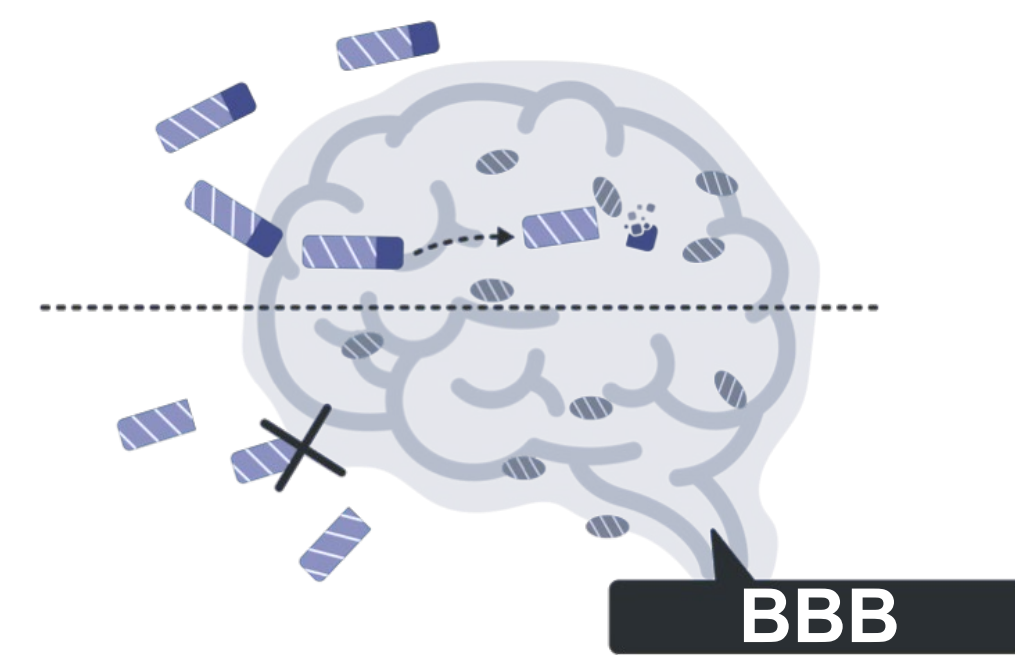
Preliminary evidence of functional improvement and remyelination in a large animal model of MS using the brain-enhanced thymomimetic LL-341070

ID Duncan, J Verhoeve, J Kiland, H Rylander, S Cameron, J Pritchard, D Radecki, M Reilly, B August, E Nunez*, R Gandhi* and JA Vivian*

University of Wisconsin, Madison WI and *Autobahn Therapeutics, San Diego CA

Background & Objective

- Current immunomodulatory treatments of multiple sclerosis (MS) including glatiramer acetate, interferon- β -1 α and fingolimod have limited benefit for the demyelination observed in MS.
- The feeding of an irradiated diet to cats results in a clinical presentation involving motor dysfunction correlated with widespread demyelination of the CNS (Duncan et al. 2009).
- The thyroid hormone receptor (TR) agonist T₃ promotes oligodendrocyte progenitor cell differentiation, resulting in improved remyelination in multiple animal models of demyelination, including models of MS (Franco et al. 2008).
- While T₃ readily crosses the blood brain barrier (BBB), limited TR selectivity and peripheral effects limit its therapeutic utility for CNS indications.
- LL-341070 is a CNS-penetrant fatty-acid amide hydrolase (FAAH) activated prodrug of LL-341070A, a potent and selective small molecule agonist of TR- β .
- Similar to T₃, LL-341070A enhances oligodendrocyte precursor cell differentiation *in vitro*, and LL-341070 demonstrates improvements in the clinical score and demyelination in an experimental autoimmune encephalomyelitis model of MS (Woerner et al. 2021).
- Objective:** To evaluate the clinical benefit and remyelinating effects of the CNS-directed TR- β agonist prodrug LL-341070 in an animal model of MS.



Materials & Methods

Subjects & Diet

- Ten male domestic cats aged 1-2 years were fed an irradiated diet (45 kGrays) for up to ten months.

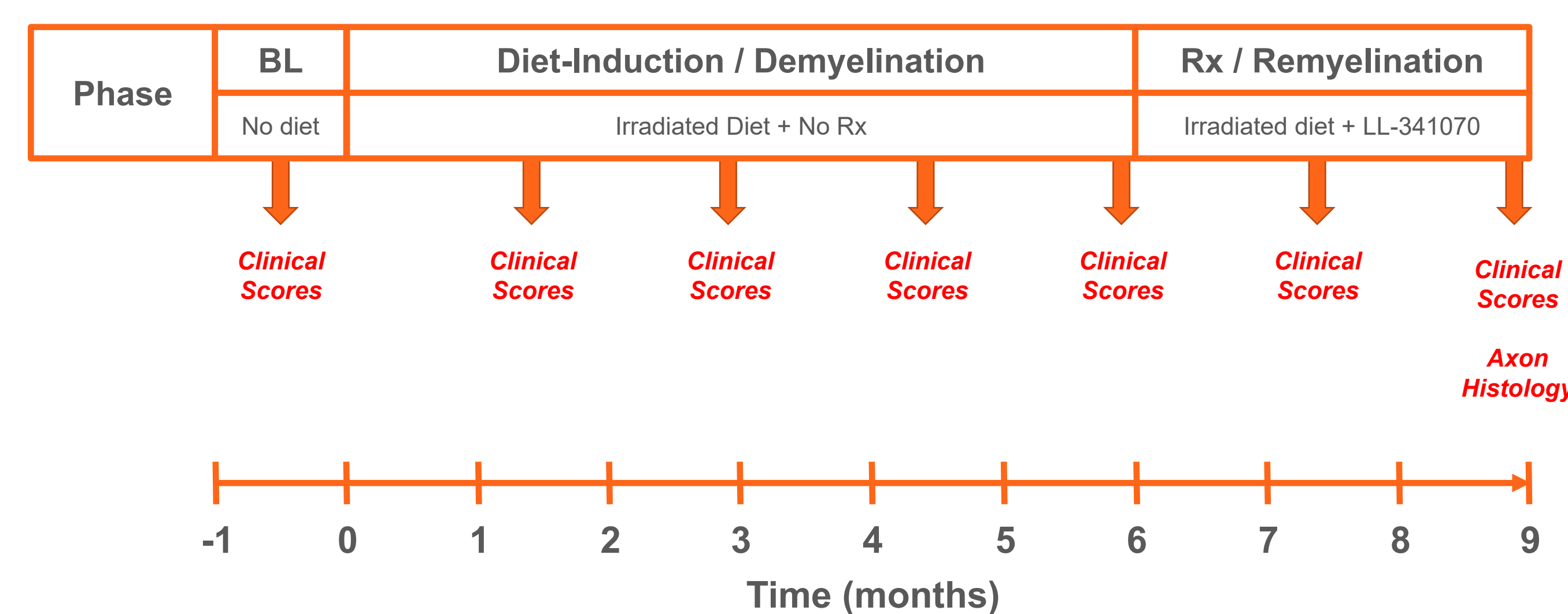
Clinical scoring

- A behavioral scoring system (0-4, with higher values representing greater impairment) was used to grade the presence and progression of ataxia and paresis, which largely affected the hind limbs (Duncan et al. 2009). Clinical scores were obtained throughout the course of the study.
 - Of the ten cats, five demonstrated no or only mild symptoms. The remaining five cats developed notable and progressive disease; when a minimum score of 2 was reached, treatment with LL-341070 (100 μ g/kg q.d. s.c.) was initiated.

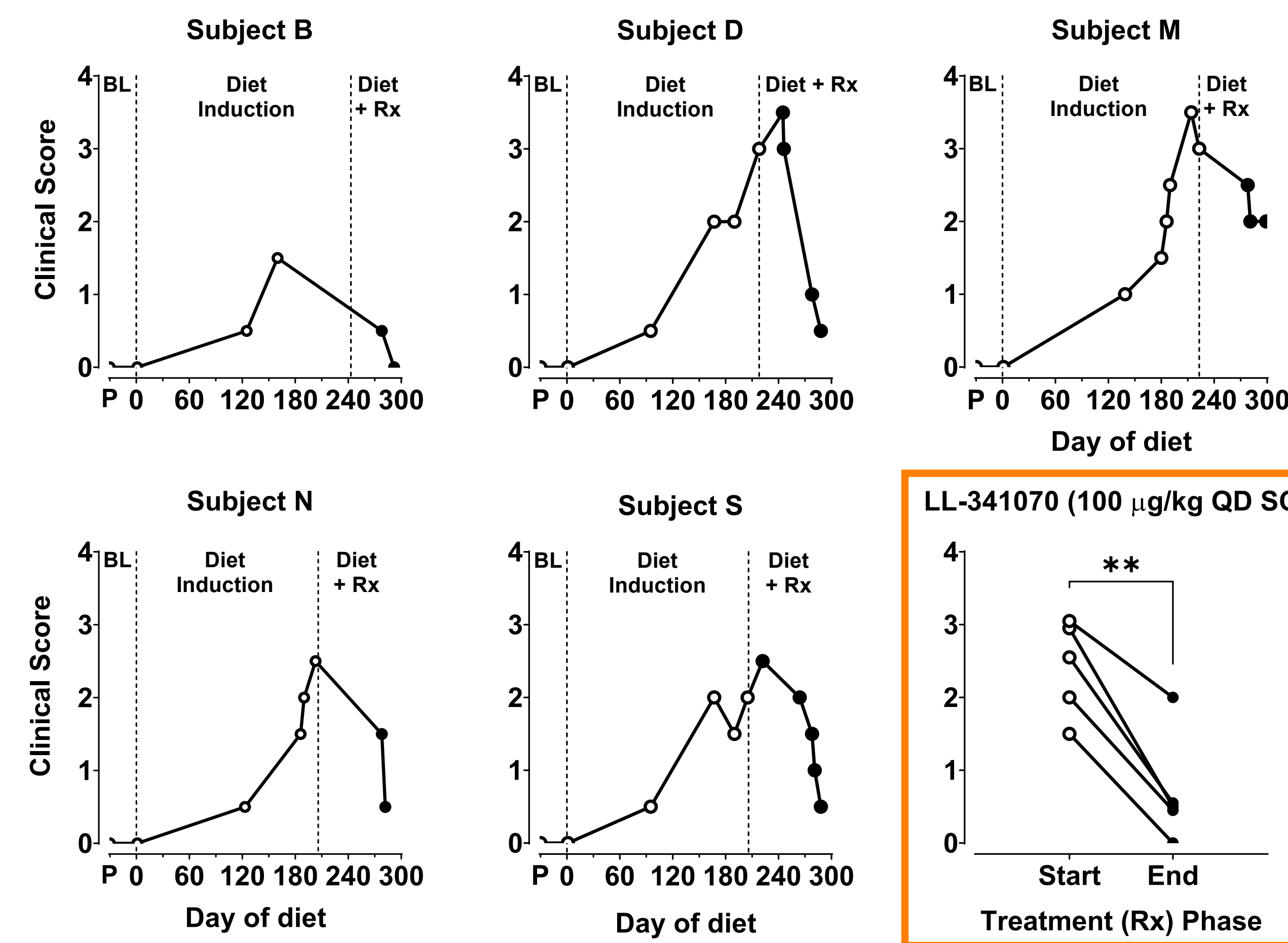
Axon histology

- Light microscopy: Axons were categorized into remyelinated, demyelinated and unchanged based on myelin thickness in the CNS (optic nerve, cerebellum, subcortical white matter) and spinal cord (cervical, thoracic and lumbar segments). A minimum of 150 axons were categorized for each image in a blinded fashion.
- Electron microscopy: G-ratio measurements were determined on thin sections from the corpus callosum.

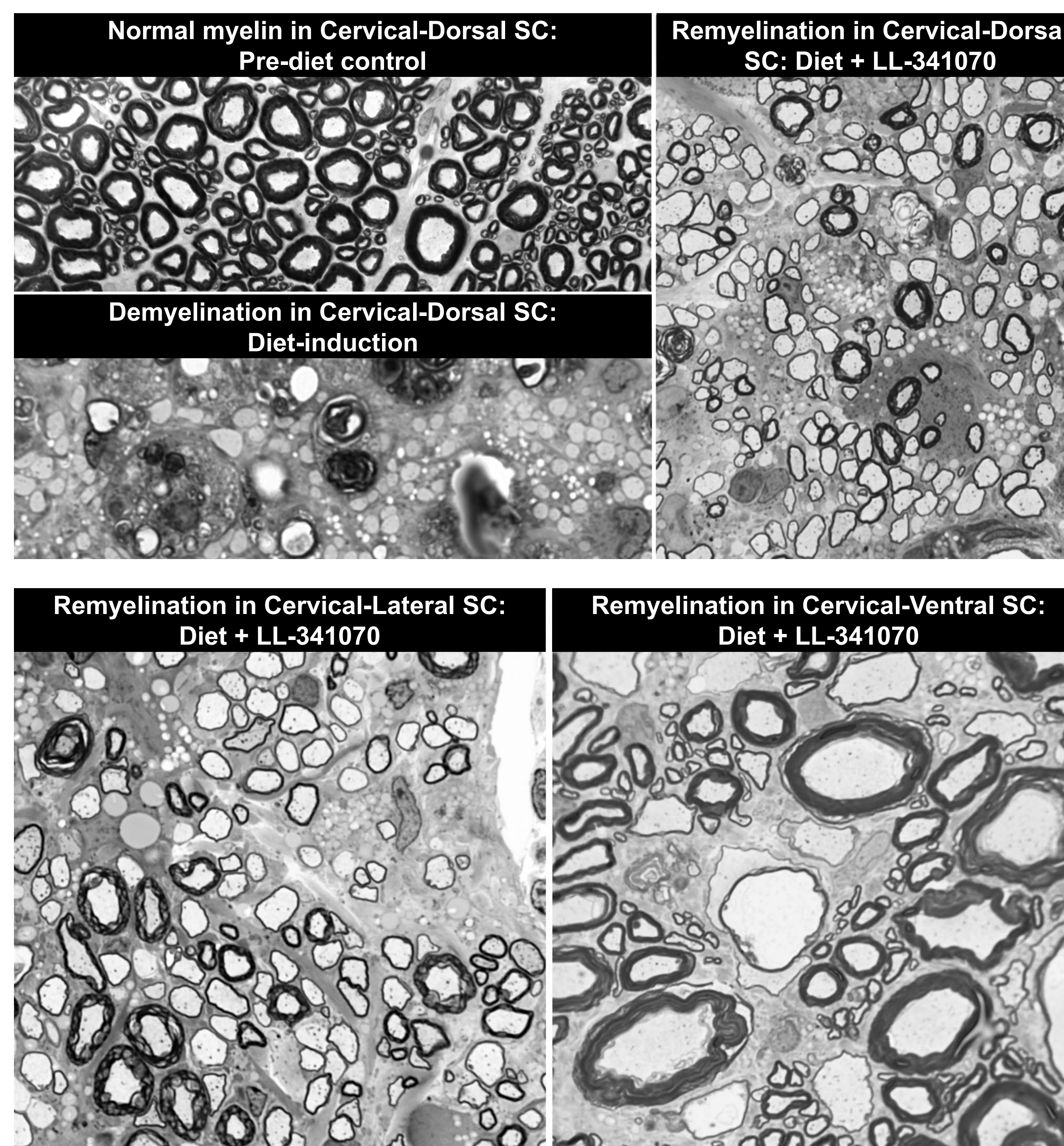
Experimental Design / Timeline



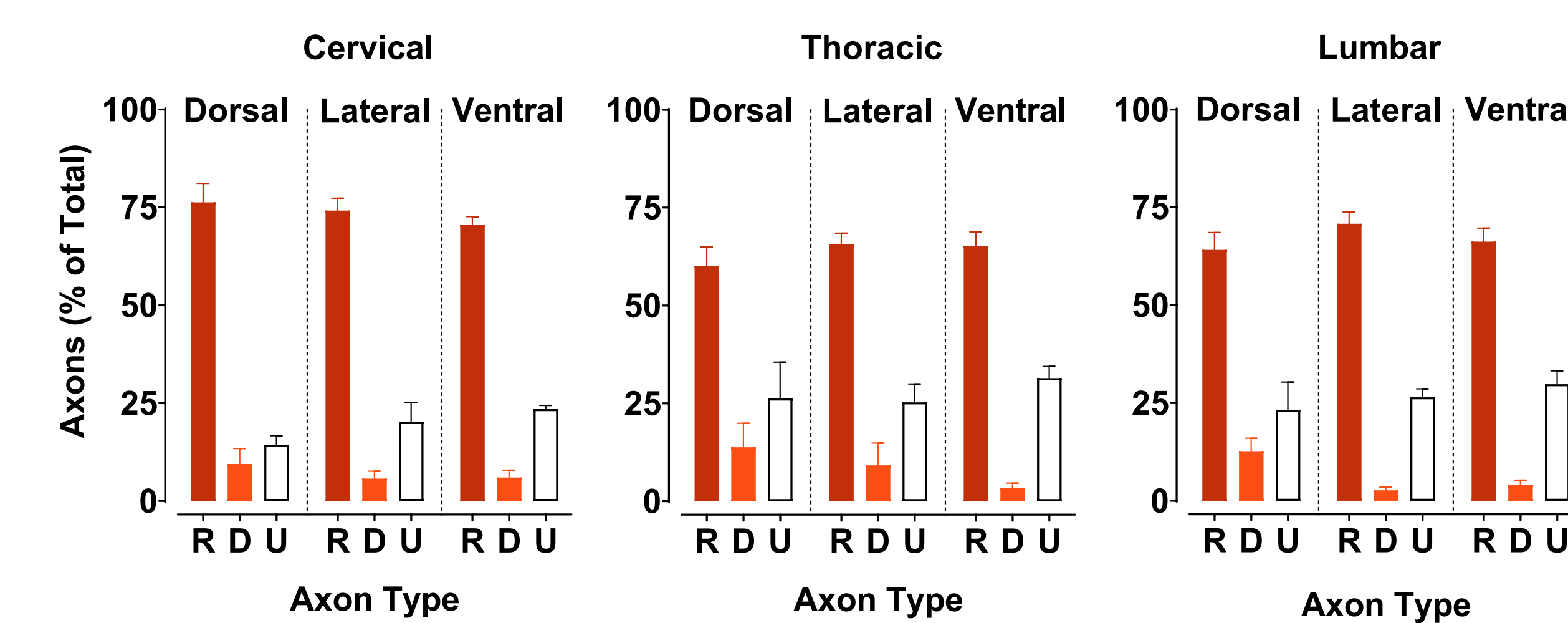
Clinical improvement with LL-341070



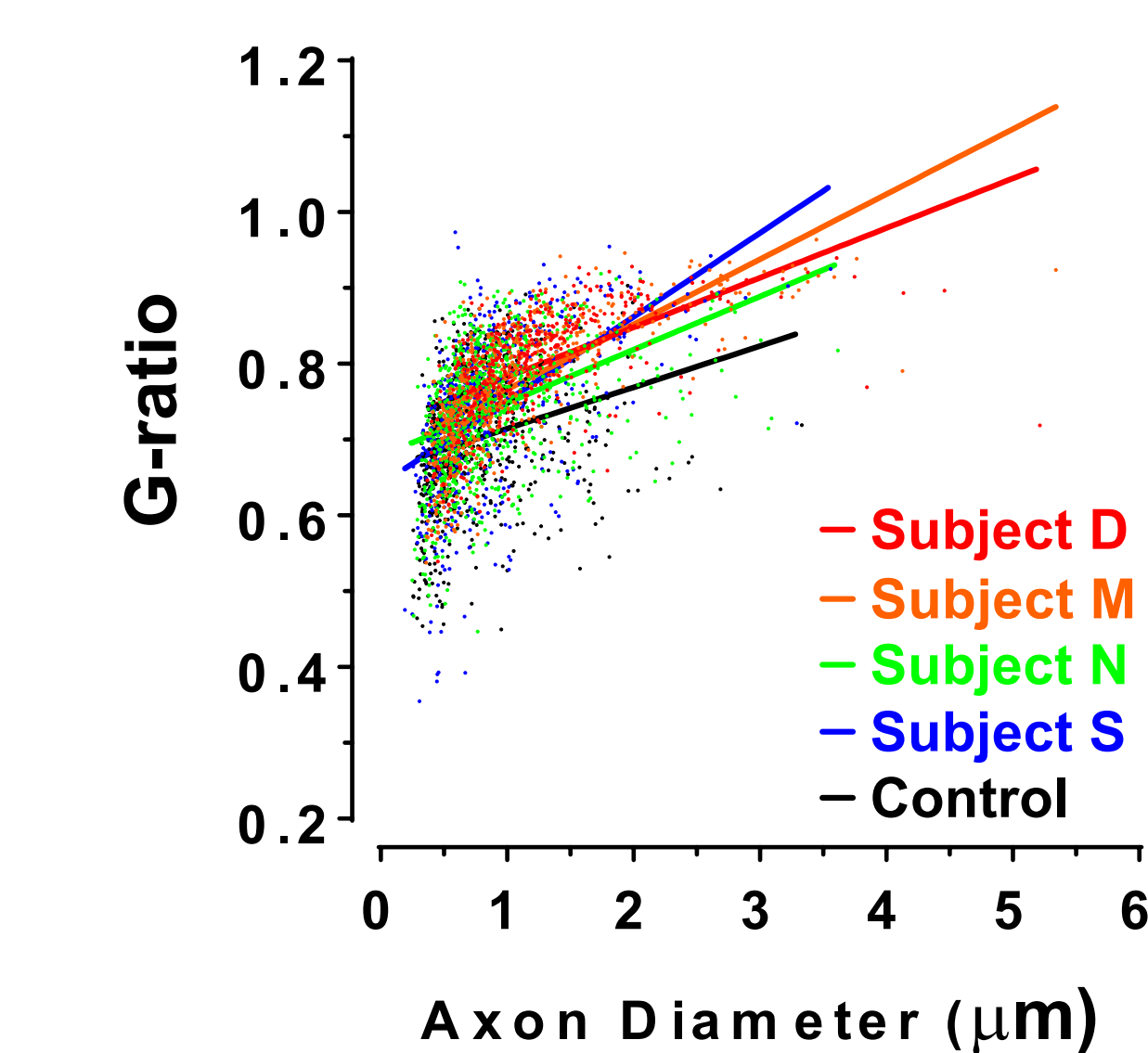
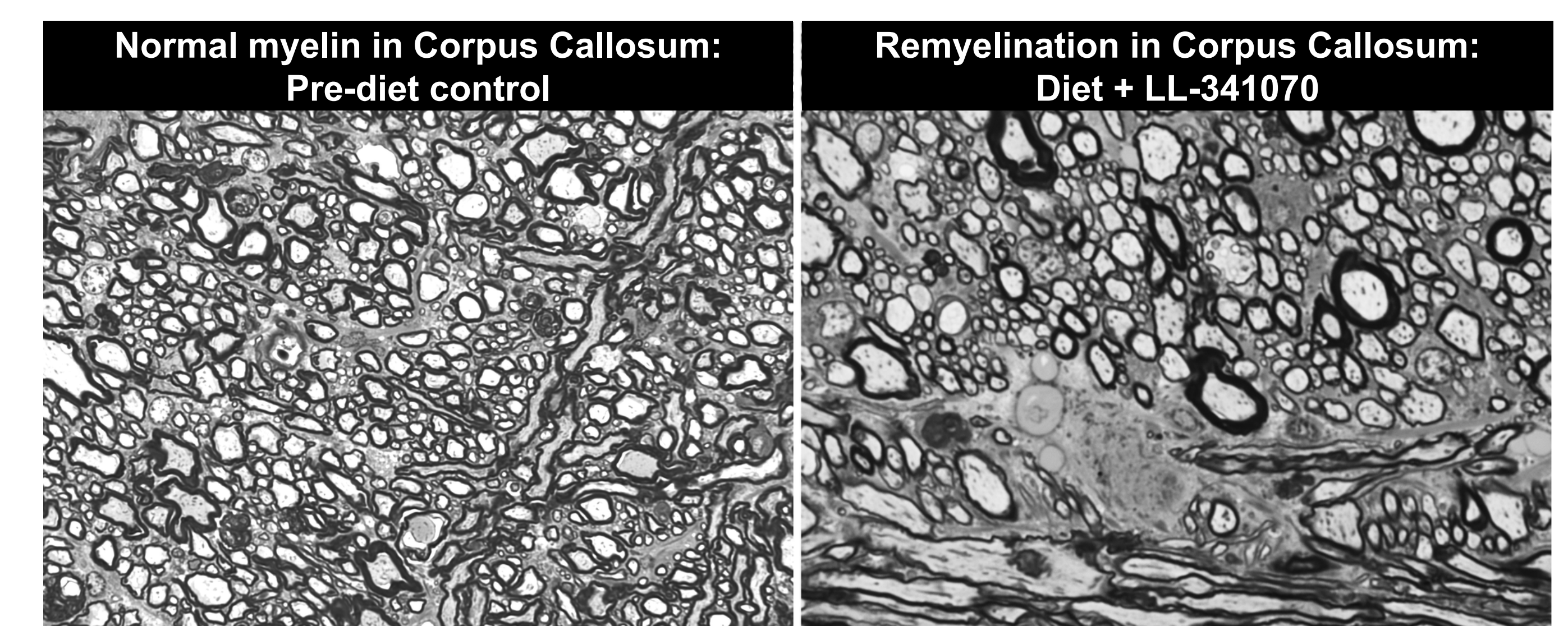
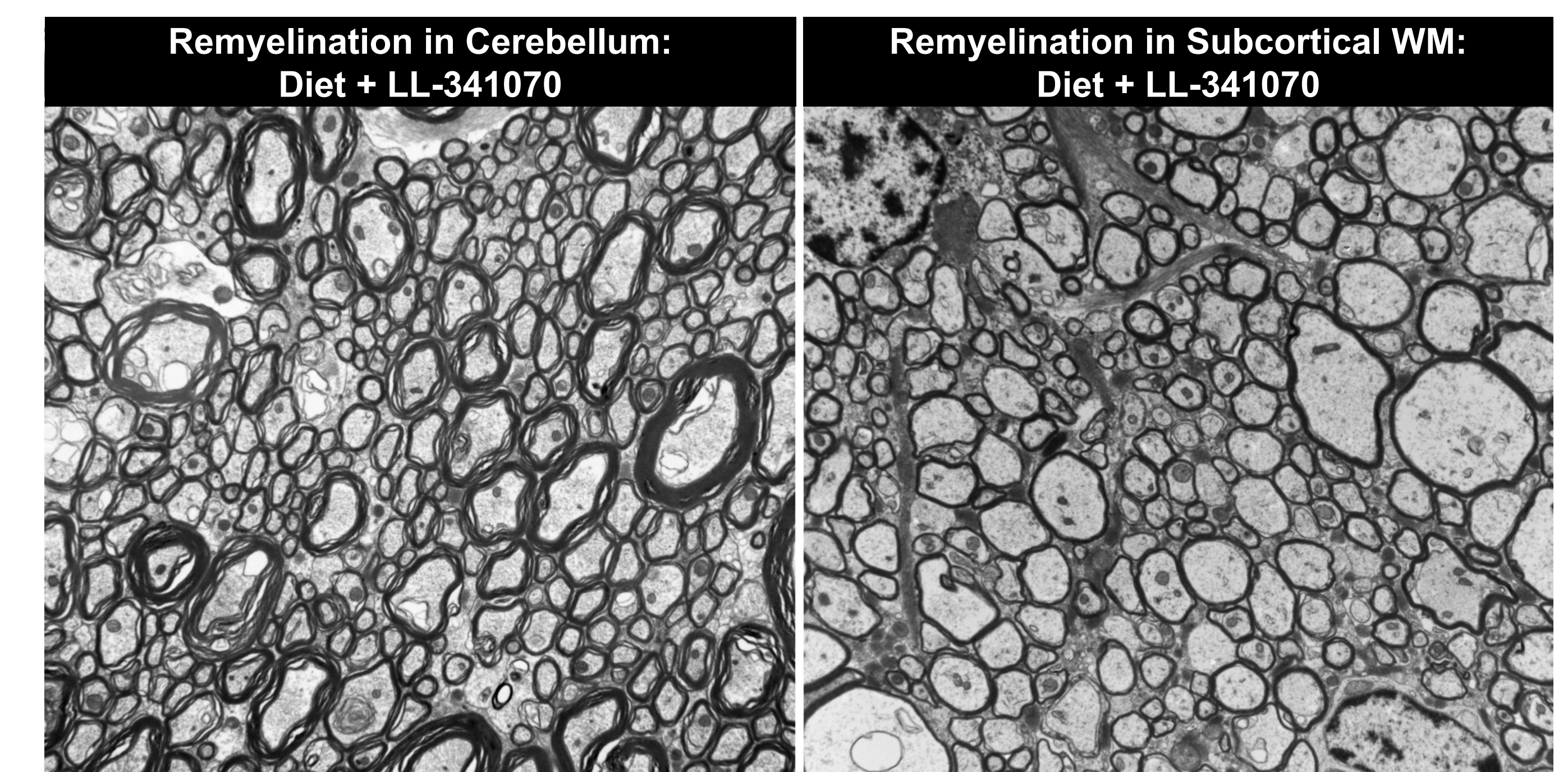
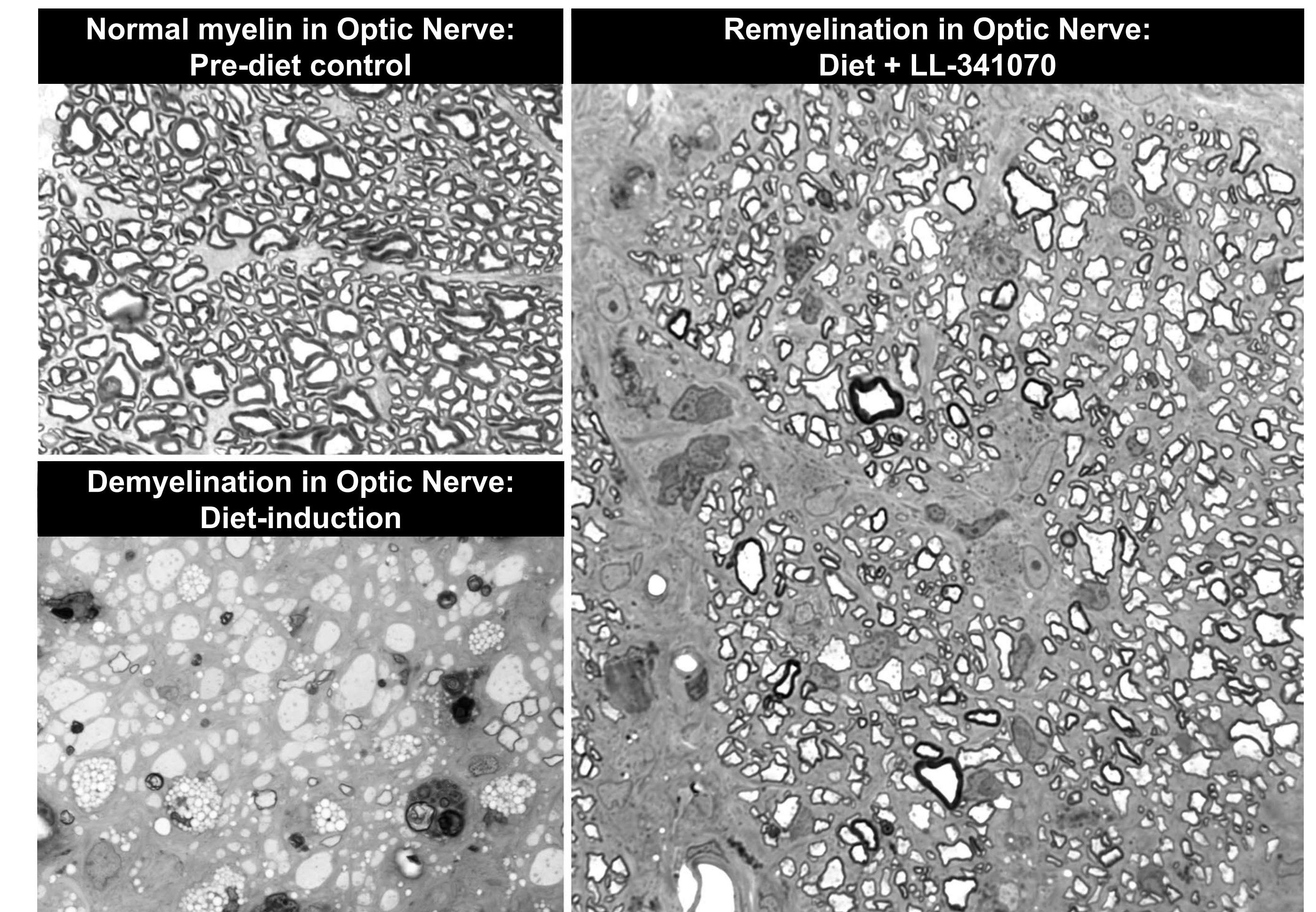
Remyelination in spinal cord with LL-341070



- Robust remyelination was evident throughout all segments and columns of the spinal cord. R: remyelinated, D: demyelinated, U: unchanged.



Remyelination in CNS with LL-341070



- G-ratios from the corpus callosum. Higher g-ratios are demonstrated in the treated cats where remyelination predominates.

Conclusions

- Consumption of an irradiated diet resulted in a clinical presentation involving significant motor dysfunction, previously demonstrated to be correlated with widespread demyelination throughout the CNS, in cats.
- The TR- β prodrug LL-341070 produced dramatic recovery of function with robust and generalized remyelination throughout the CNS and spinal cord when compared with a control, untreated animal with similar levels of demyelination.
- These data demonstrate the potential of CNS-directed TR- β agonists such as LL-341070 as remyelinating therapies in MS and other demyelinating conditions.