Title: Use of a Prediction Algorithm for Randomized Stratification in an Amyotrophic Lateral Sclerosis Study

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The Methodological Question Being Addressed: A prediction algorithm for disease progression in amyotrophic lateral sclerosis (ALS) was developed using a random forests method. This algorithm is being adopted with screening and baseline data as input to predict disease progression, with results informing randomization stratification for a study assessing the effect of an investigational medical product (IMP) on ALS progression.

Introduction (Aims): The neurodegenerative disorder ALS affects central nervous system motor neurons and often leads to death within 5 years of symptom onset. Although ≥30 agents have shown promise in preclinical models of ALS, only one has been approved to slow functional decline in humans. The aim of the current study is to evaluate an IMP that may have anti-inflammatory, neuroprotective, and neuroregenerative effects that could delay ALS progression. Variability in the progression of ALS presents challenges for trial design. Some trials use a ≥12-week observational lead-in phase to stratify patients by baseline rate of disease progression. An algorithm to predict ALS progression, which has outperformed ALS clinicians, was developed and has the potential to change ALS therapeutic trial design. This phase 2 trial integrates one of the prediction algorithms to stratify patients according to rate of predicted disease progression, thus obviating the traditional lead-in phase.

Methods: This multicenter, double-blind, placebo-controlled study will begin with a ≤28-day screening period. Eligible subjects will be randomly assigned (2:1 ratio) to receive the IMP or volume-matched

placebo once daily from baseline to 36 weeks. Randomization will be stratified on the basis of riluzole use and the predicted 36-week decline in the ALS Functional Rating Scale-Revised (ALSFRS-R) score using the algorithm. Subjects will either taper and discontinue study drug or continue the daily IMP during a 48-week open-label extension phase. Endpoints include change from baseline in ALSFRS-R score, slope of decline in pulmonary function test scores, survival, and occurrence of adverse events.

Results: As of December 7, 2017, 25 subjects have been screened and 17 randomized. Of the 17 randomized, 15 have a predicted rate of decline ≤1, and 2 have a predicted rate of decline >1.

Conclusions: This study will be the first to incorporate a prediction algorithm for rate of disease progression rather than a traditional lead-in phase to stratify randomization of patients with ALS. This modification to the trial design minimizes the time of subject enrollment prior to administration of an IMP and shortens the length of the trial. These are key benefits because of the high morbidity and mortality associated with ALS. The accuracy of the algorithm will be investigated by comparing the prediction with the actual rate of disease progression during the trial. If successful in accurately stratifying subjects with rapid versus slow disease progression, this approach has potential for use in future protocols evaluating therapeutic efficacy in ALS.

Disclosures: Susan VanMeter, MD, is an employee and stockholder of Mallinckrodt, ARD Inc., and a stockholder of GlaxoSmithKline. Patrice Becker, MD, and Enxu Zhao, MS, are employees and stockholders of Mallinckrodt, ARD Inc. Todd Levine, MD, has nothing to disclose.