LETTER OF SUPPORT

DDT BMQ000116

May 25, 2021

International Progressive Multiple Sclerosis Alliance
Fluid Biomarkers Implementation Team
C/O Kathryn E. Smith
Scientific Steering Committee Member/Co-Chair Fluid Biomarkers Team
154 Hamburg Road
Lyme, CT 06371

And

Robert J. Fox, M.D.
Scientific Steering Committee Chair Elect/Co-Chair Fluid Biomarkers Team
Mellen Center for Muscular Sclerosis
Cleveland Clinic Main Campus
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9500 Euclid Avenue
Cleveland, OH 44195

Dear Kathryn E. Smith and Dr. Robert J. Fox:

We are issuing this Letter of Support to the International Progressive Multiple Sclerosis Alliance (the Alliance) to encourage the further study and use of neurofilament light (NfL) chain measured in plasma or serum as an exploratory pharmacodynamic/response biomarker for early clinical trials in progressive multiple sclerosis (MS).

There is an unmet need for additional effective therapies for the treatment of progressive MS. The development of such treatments may be accelerated if novel biomarkers are developed to overcome the limitations of traditional imaging outcomes in early phase trials. For example, brain atrophy, as assessed by MRI, has a number of limitations as a treatment response biomarker. Loss of volume is not pathologically specific, depends upon many factors such as tissue hydration, and thus follows a complicated trajectory after starting treatment. Neurofilament light, a neuroaxonal cytoskeletal protein released upon neuronal damage, may have the potential to reflect ongoing pathology over the entire CNS, and thus may be more responsive to the effects of treatment.

We support the International Progressive MS Alliance's proposal for the further study of NfL to

determine its full utility in measuring treatment response in progressive MS trials. Current evidence, including data from several large clinical trials, summarized in Kapoor et al., 2020, suggests that NfL may be correlated with other measures of progressive MS disease activity, and may reflect response to treatment.

Correlations between NfL and measures of progressive MS disease activity and disease progression such as imaging and disability measures are of interest. The literature summary that you submitted to FDA suggests that in many of the studies reported, NfL decreases in progressive MS patients in response to treatment; however, instances were observed where NfL levels decreased in the absence of clinical outcomes being met, and also where NfL levels did not significantly change despite clinical outcomes being met. Further understanding of these apparently discordant trial results is necessary.

Additional supportive evidence for NfL in relapsing MS patients may be potentially relevant for progressive MS. Further studies of NfL using legacy trial biobanks and ongoing trials may help to clarify the relationship of changes in NfL concentrations with disability measures, including the time course of NfL changes and their clinical meaningfulness.

Significant gaps remain in our understanding of NfL and must be addressed before NfL can be suitable as a pharmacodynamic/response biomarker in early progressive MS clinical trials, including:

- Sample collection and assay methods should be standardized in order to align results across current (and future) assay platforms, which will support analytical validity.
- A normative database of NfL concentrations in healthy volunteers and patients with MS is required. This database should include the effects of age and comorbidities, which may facilitate the development of disease models to support trial design and clinical validation.
- Additional analyses of legacy clinical trial datasets may help clarify the predictive value of baseline concentrations of NfL, define how NfL responds to different types of therapies, and clarify the relationship between NfL levels and clinical and imaging outcomes. An important consideration is the relative extent to which inflammatory activity and other disease processes contribute to changes in NfL.

Standard protocols and reference materials are needed to ensure data comparability across different systems. Strong emphasis on applying good scientific, laboratory, and software development practices for quality control and validation of NfL measured in serum or plasma is imperative.

We encourage exploration of serum or plasma NfL as a pharmacodynamic/response biomarker in early progressive MS clinical trials. We will consider data collection on this biomarker to be exploratory in nature. We believe data sharing and integrating data across trials can foster an accelerated path for progressive MS drug development programs. If sponsors intend to include analyses of this biomarker to support regulatory decision making for a given IND drug development program, they should prospectively discuss the approach to these analyses with the Division of Neurology 2 in CDER.

Any groups (academia, industry, government) that would like to join in this effort or have information or data that may be useful can contact Kathryn Smith (Kathryn.ellen.smith@gmail.com) or view www.progressivemsalliance.org.

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