Development of a Bayesian Progression Model to assess the impact of an intervention on the progression of multiple system atrophy

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SUBMISSION DETAILS

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Methodological Issue Being Addressed Multiple system atrophy (MSA) is a rare, rapidly progressive movement disorder with a steep rate of decline on the Unified MSA Rating Scale (UMSARS, the gold-standard rating scale) and without any effective treatment. Typical trials assessing potential disease modification in movement disorders are relatively long and evaluate the treatment effect at a fixed timepoint using a categorical time mixed model for repeated measures to evaluate effect post-treatment, missing the opportunity to assess treatment effect from long-term individual progression trajectories. Additionally, within categorical time repeated measures models of function, one must carefully consider how to handle missing data due to intercurrent events such as withdraws due to disease progression and death to avoid bias in estimates of change in function at individual timepoints. Given the rarity of the disease and lack of information from prior trials, efficient use of all available data is crucial to detect clinically meaningful effects on slowing clinical progression within feasible trials in MSA.

Introduction To develop a MSA disease progression model that optimizes the long-term information retrieved from each individual, offers a clinically interpretable, slope-based primary outcome, and takes advantage of the robustness of the Bayesian methodology and use of posterior probabilities for decision-making; with the intent of enriching with natural history data.

Methods First, published MSA progression data were used to build a Bayesian Progression Model (BPM) that reflected up to 2 years of clinical progression (UMSARS) and incorporated: repeated measures for the change from baseline in the UMSARS-total score over a recurring visit schedule; piece-wise linear rate of progression per 12-week time interval; time as continuous to reflect actual time of assessments; a patient-level random effect in rate of progression; treatment effect expressed as a proportional slowing of clinical progression vs. placebo; and conservative/non-informative model priors. Next, the BPM was used as the primary analysis of a phase 2, proof-of-concept trial which incorporated a variable double-blind treatment period (48-72 weeks), where natural history data was used for enrichment. Observations from the phase 2 trial were then used to extend the BPM framework to account for other disease aspects and evaluate the appropriateness of the model framework for future use.

Results Although the results were non-significant in the intent-to-treat phase 2 population, prespecified and post-hoc analyses of patients with MSA-C or less impairment at baseline showed separation of the active-treated group from placebo in relation to slowing in clinical progression

with sufficient probability (>97.5%) of being a true effect as evaluated with posterior distributions. Following enrichment of the phase 2 placebo group using individualized natural history MSA data from European and Chinese cohorts, the results were further substantiated – confirming the appropriateness of the model and highlighting the absence of a strong placebo effect in this trial context.

Conclusion Bayesian modelling provides an appropriate framework for assessing disease progression in a rare disease such as MSA that currently has no effective treatment. Moving forward, the BPM will be further extended to account for other disease milestones assessed by a time-to-event approach.

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Keywords

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Guidelines I have read and understand the Poster Guidelines

Disclosures JW, CE, and SZ are employed by H Lundbeck A/S. TJ, MQ, and BW are employed by Berry Consultants, which was provides consultancy to H Lundbeck A/S. FK has no conflict to disclose.

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