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Efficacy and Safety of Tolebrutinib Versus Placebo in Non-Relapsing Secondary Progressive Multiple Sclerosis: Results from the Phase 3 HERCULES Trial

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Introduction:

Tolebrutinib is a potent, brain-penetrant and bioactive Bruton's tyrosine kinase (BTK) inhibitor that targets B cells and microglia and has the potential to modulate both peripheral and central pathologic processes in multiple sclerosis (MS) that lead to disability accumulation. Tolebrutinib is being investigated in four phase 3 trials across the spectrum of MS,** including non-relapsing secondary progressive MS (nrSPMS)** for which there are no approved treatments.

Objectives/Aims:

To report the results of the phase 3 HERCULES trial, which evaluated the efficacy and safety of tolebrutinib in participants with nrSPMS.

Methods:

HERCULES (NCT04411641) was a phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group, event-driven trial. Participants were 18–60 years of age with SPMS and had an Expanded Disability Status Scale (EDSS) score of 3.0–6.5, inclusive, documented evidence of disability progression during the prior 12 months, and no clinical relapses during the prior 24 months before screening. Participants were randomised 2:1 to receive oral tolebrutinib (60 mg once daily) or matching placebo. Stratification factors were age (<40 vs ≥40 years) and region (US vs non-US). The primary endpoint was time to onset of 6-month confirmed disability progression (CDP) as measured by EDSS. Secondary endpoints included additional measures of disability, magnetic resonance imaging outcomes and safety.

Results:

A total of 1131 participants were randomised across 31 countries between October 23, 2020, and January 12, 2023. At baseline, the overall mean age was 48.9 years, and 62% were female. Mean time since relapsing-remitting MS symptom onset was 17.3 years, and mean time since most recent relapse was 7.5 years. Most participants (77%) had previously received ≥1 disease-modifying therapies. At baseline, mean EDSS score was 5.53 (median 6.0; interquartile range 5.0–6.3), 12.8% of participants had gadolinium-enhancing T1 lesions, and mean (standard deviation) T2 lesion volume was 18.9 (14.6) cm3. The last participant visit is expected to occur in July 2024. Efficacy and safety results will be presented at ECTRIMS.

Conclusion:

The presented HERCULES trial results will provide a comprehensive assessment of tolebrutinib efficacy and safety in participants with nrSPMS.

Disclosures:

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