P628

Efficacy and Safety of the Bruton's Tyrosine Kinase Inhibitor Evobrutinib in Patients with Relapsing Multiple Sclerosis Over 48 Weeks: A Randomized, Placebo-Controlled, Phase 2 Study

Xavier Montalban[1], Douglas L Arnold[3], Martin S Weber[5], Ivan Staikov[7], Karolina Piasecka-Stryczynska[7], Emily C Martin[9], Sana Syed[9], Fernando Dangond[9], Jerry S Wolinsky[10]

[1]Vall d'Hebron University Hospital, Barcelona, Spain, [2]University of Toronto, Toronto, Canada, [3]Montreal Neurological Institute and Hospital, Montreal, Canada, [4]NeuroRx Research, Montreal, Canada, [5]Institute of Neuropathology, Universitätsmedizin Göttingen, Göttingen, Germany, [6]Department of Neurology, Universitätsmedizin Göttingen, Göttingen, Germany, [7]Department of Neurology, Acibadem City Clinic Tokuda Hospital, Sofia, Bulgaria, [8]Outpatient Neurology Clinic, Hanka Hertmanowska MS Care Center, Plewiska, Poland, [9]Global Clinical Development Center, EMD Serono Research & Development Institute, Inc., Billerica, United States, [10]McGovern Medical School, University of Texas Health Science Center at Houston (UTHealth),Houston,United States

Background: Evobrutinib (M2951) is a highly selective oral inhibitor of Bruton's tyrosine kinase, a key regulator of B cell and myeloid cell functions implicated in multiple sclerosis (MS). This was a Phase 2 study to compare evobrutinib with placebo in relapsing MS (RMS).

Method(s): In this double-blind study (NCT02975349), adults with RMS were randomized to evobrutinib 25 mg once-daily (QD), 75 mg QD, 75 mg twice-daily (BID), open-label dimethyl fumarate (240 mg BID; reference), or placebo for 48 weeks. Placebo-treated patients were switched to evobrutinib 25 mg QD after 24 weeks. Primary endpoint: total number of T1 gadolinium enhancing (T1 Gd+) lesions over Weeks 12–24. Secondary endpoints included annualized relapse rate (ARR), magnetic resonance imaging measures, and safety. The study received full patient and Institutional Review Board approval.

Result(s): Of 267 randomized patients, 227 (85.0%) completed 48 weeks. Evobrutinib 75 mg QD and BID significantly reduced the total number of T1 Gd+ lesions over Weeks 12–24 versus placebo (primary endpoint; Table). There was no evidence of change in effect on T1 Gd+ lesions (mean±SD; Wilcoxon signed-rank test) between Weeks 24 and 48 with evobrutinib 75 mg BID (0.24±0.88 to 0.49±1.22; p=0.23) or evobrutinib 75 mg QD (0.28±0.91 to 0.85±2.87; p=0.57). ARR (unadjusted [95% confidence interval]) over 48 weeks was 0.25 (0.12–0.44) for evobrutinib 75 mg QD, 0.11 (0.04–0.25) for 75 mg BID, and 0.37 (0.21–0.59) for placebo (Table). All evobrutinib doses appeared well-tolerated. Transaminase elevations were predominantly mild; some Grade 3–4 events were observed; all had their onset within the first 24 weeks; transaminase elevations were asymptomatic and reversible on evobrutinib withdrawal.

Conclusion: To our knowledge, evobrutinib is the first BTK inhibitor to demonstrate disease activity reduction in MS. The observed benefit-risk profile of evobrutinib in this Phase 2 study supports further clinical development in RMS.