Efficacy and Safety of the Bruton’s Tyrosine Kinase Inhibitor Evobrutinib (M2951) in Patients with Relapsing Multiple Sclerosis over 48 Weeks: a Randomized, Placebo-Controlled, Phase 2 Study

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Objective:
Phase 2 study to compare evobrutinib (M2951) with placebo in relapsing multiple sclerosis (RMS).

Background:
Evobrutinib is a highly-specific oral inhibitor of Bruton’s tyrosine kinase, a key regulator of B cell and macrophage functions implicated in MS.

Design/Methods: In this double-blind study (NCT02975349), adult patients (≤65 years) with RMS were randomized to evobrutinib 25mg QD, 75mg QD, 75mg BID, open-label dimethyl fumarate (240mg BID; reference arm), or placebo for 48 weeks; placebo-treated patients switched to evobrutinib 25mg QD after 24 weeks. The primary endpoint was the total number of T1 gadolinium-enhancing (T1Gd+) lesions at Weeks 12, 16, 20, and 24. Secondary endpoints included annualized relapse rate (ARR), MRI measures at Weeks 24 and 48, and safety.

Results:
Of 267 randomized patients, 227 (85.0%) completed 48 weeks’ treatment. The primary endpoint was met: evobrutinib 75mg QD and BID significantly reduced the total number of T1Gd+ lesions at Week 12, 16, 20 and 24 versus placebo; a significant dose response was observed (p=0.001). There was no evidence of change in effect on T1Gd+ lesions (mean±SD; Wilcoxon signed-rank test) between Weeks 24 and 48 with evobrutinib 75mg BID (0.24±0.88 to 0.49±1.22; p=0.23) or evobrutinib 75mg QD (0.28±0.91 to 0.85±2.87; p=0.57). ARR (unadjusted [95% CI]) was 0.25 (0.12–0.44) for evobrutinib 75mg QD and 0.11 (0.04–0.25) for 75mg BID over 48 weeks, and 0.37 (0.17–0.70) for placebo over 24 weeks. Evobrutinib appeared well-tolerated throughout the study at all doses. Shifts to Grade 3–4 ALT and AST elevations from normal (grade 0) occurred in 8 (5.4%) and 6 (3.9%) evobrutinib-treated patients respectively, largely driven by events with onset within the first 24 weeks.

Conclusions: To our knowledge, evobrutinib is the first BTK inhibitor to demonstrate disease activity reduction in an autoimmune indication. The observed benefit-risk profile of evobrutinib supports further clinical development.