and corresponding 95% confidence intervals, will be estimated. Quality assurance, focusing on registry processes and practices as well as data quality will be tracked using pre-specified metrics and analysis plans.

CLARION will provide safety evidence for neurologists and patients to assist the treatment decision process for patients with highly active relapsing MS.

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Reduction of Risk of Secondary Progressive Multiple Sclerosis Within Two Years of Treatment with Cladribine Tablets: An Analysis of the CLARITY Study

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Cladribine tablets 10mg (cumulative dose 3.5mg/kg [CT3.5];N=433) over 2 years showed efficacy vs placebo (PBO;N=437) in patients with relapsing multiple sclerosis (CLARITY). This post hoc analysis explored the relationship between baseline expanded disability status scale (EDSS) and risk of progression to secondary progressive multiple sclerosis (SPMS) or to EDSS ≥6.0, in CLARITY.

Progression to SPMS was not recorded during the trial, a proxy composite definition was used: confirmed disability progression (CDP), CDP within the leading functional score (FS), EDSS post-baseline ≥4.0, pyramidal FS ≥2, all conditions met for ≥3 months in the absence of a relapse. Progression to EDSS≥6.0 was defined by having ≥1 post-baseline EDSS≥6.0 with 3- or 6-month CDP. Odds ratios (OR) and corresponding confidence intervals (CI) were estimated by a logistic regression model with treatment and baseline EDSS (≤3.0 or ≥3.5) as fixed effects.

Proxy SPMS progression occurred in 6.7% CT3.5 patients vs 13.5% PBO (OR 0.46[95%CI:0.28,0.76]; p=0.0024). For baseline EDSS≤3.0 patients, proxy SPMS progression was 3.5%(CT3.5,n=257) vs 7.7%(PBO,n=235); OR 0.44(95%CI:0.19,0.99); p=0.0471. Baseline EDSS≥3.5, proxy SPMS progression was 12.2%(CT3.5,n=148) vs 22.4%(PBO,n=157); OR 0.48(95%CI:0.26,0.9); p=0.0212. Proportions of patients with ≥1 EDSS value ≥6.0 post-baseline were 6.4%(CT3.5) vs 14.5%(PBO); OR 0.4(95%CI:0.24,0.66); p=0.0004. Patients with 3-month CDP with EDSS≥6.0 were 3.5%(CT3.5) vs 8.0%(PBO); OR 0.42(95%CI:0.22,0.82); p=0.0114, patients with 6-month CDP with EDSS≥6.0, were 2.8%(CT3.5) vs 5.8%(PBO); OR 0.48(95%CI:0.22,1.02); p=0.0566. Patients with baseline EDSS≤3.0 that had ≥1 EDSS≥6.0, 0.8%(CT3.5) vs 4.3%(PBO); OR 0.18(95%CI:0.04,0.81); p=0.0262. Baseline EDSS≥3.5, 16.2%(CT3.5) vs 29.9%(PBO); OR 0.45(95%CI:0.26,0.79); p=0.0051.

The risks of progressing to SPMS (proxy) within 2 years of treatment, or experiencing EDSS≥6.0, were significantly reduced with CT3.5 vs PBO, regardless of baseline EDSS (≤3.0 or ≥3.5).

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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

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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).

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.

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.

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.

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Osteoporosis in Multiple Sclerosis: The Bystander Effect

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