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Integrated analysis of pooled clinical safety data allows comprehensive characterisation of the safety profile of cladribine tablets (CT) 10mg (3.5mg/kg cumulative dose over 2 years [CT3.5]) in patients with relapsing multiple sclerosis. This analysis aimed to update the previously reported serious treatment emergent adverse event (TEAE) profile of CT3.5 following integration of final data from the PREMIERE registry, and report post-approval safety data from worldwide sources.

The monotherapy oral cohort (CT3.5, N=923, patient-years [PY]=3936.69; placebo [PBO], N=641, PY=2421.47) was derived from the CLARITY, CLARITY Extension, and ORACLE-MS trials, and the PREMIERE registry. Adjusted incidences per 100PY were calculated for AEs, cumulative to the end of PREMIERE (October 2018). Serious and non-serious AEs from post-approval sources are also summarised.

Patient characteristics were balanced between treatment groups (mean age [37.8 years,CT3.5; 37.2 years,PBO], proportion of females [66.3%,CT3.5; 66.1%,PBO] and proportion of patients with prior disease modifying drug experience [19.9%,CT3.5; 20.4%,PBO]). Incidences per 100PY for ≥1 serious TEAE were 3.80 (CT3.5), and 3.05 (PBO). Incidences per 100PY for serious lymphopenia (preferred term [PT]) was 0.10 (CT3.5), 0 (PBO). For serious infections and infestations (system organ class), incidences per 100PY were 0.60 (CT3.5), 0.42 (PBO); for serious herpes zoster (PT): 0.05 (CT3.5), 0 (PBO). Incidences per 100PY for malignant tumours were 0.26 (CT 3.5), 0.12 (PBO). Post-approval sources reported 1622 AEs in the Periodic Benefit-Risk Evaluation Report, of which 275 were serious; none represented a new safety signal.

No new major safety findings were identified in this finalised integrated dataset which includes final data from PREMIERE. This profile is consistent with the previously published integrated safety analysis profile. No new safety signals were identified in the real world post-approval data of cladribine tablets.

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Long-Term Disease Stability Assessed by the Expanded Disability Status Scale in Patients Treated with Cladribine Tablets in the CLARITY and CLARITY Extension Studies

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Treatment with cladribine tablets 10mg (cumulative dose 3.5mg/kg [CT3.5] over 2 years) in CLARITY and CLARITY Extension reduced relapse rate and slowed disability progression versus placebo in patients with relapsing remitting multiple sclerosis (RRMS). This post hoc analysis evaluated long-term disease stability assessed by the Expanded Disability Status Scale (EDSS) after treatment with CT3.5 in patients with RRMS in CLARITY and CLARITY Extension.

Patients randomised to CT3.5 in CLARITY and placebo in CLARITY Extension, with ≥1 post-baseline EDSS measurement, were included (CP3.5; n=98). EDSS score over-time (from CLARITY randomisation to end of follow-up in CLARITY Extension, including the bridging interval between studies) was assessed at 6-monthly intervals, and separately time to 3- and 6-month confirmed EDSS score progression from CLARITY baseline. EDSS score worsening/improvement in each year was defined as any increase/decrease in minimum EDSS score at 6-monthly intervals; all other cases were classified as stable. Increase or decrease was defined as an EDSS score change of 1, 1.5 or 0.5 points at baseline EDSS ≤4.5, 0, ≥5.0 respectively.

Five years post-CLARITY baseline, median EDSS remained stable versus baseline. Median EDSS score (95% confidence interval [CI]) for CP3.5 patients was 2.5(2.0-3.5) versus 3.0(2.5-3.5) at baseline. In each 12-month period, percentage of patients with EDSS score stability was >50%; improvement, 21-30%; worsening, 0-25%. During Year 5, percentage of patients with EDSS stability was 53.9%; improvement, 21.3%; worsening, 24.7%. Less than 30% of patients reached 3- or 6-month confirmed EDSS progression by Year 5.

EDSS score was stable up to 5 years post-CLARITY baseline for the CP3.5 group. Between 20-30% of patients demonstrated improvement in EDSS score versus baseline each year.

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Long Term, Registry-Based, Prospective, Post-Authorization Safety Study Evaluating Adverse Events of Special Interest in Patients with Highly Active Relapsing Multiple Sclerosis Newly Started on Cladribine Tablets – CLARION

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To generate high quality safety data, multiple Sclerosis (MS) registries have begun to collect safety data more systematically, and use MedDRA coding of serious adverse events (SAE) to harmonise data collection across registries. Major MS registries and seven pharmaceutical companies all agreed on a common safety protocol, which is informing a standardised approach to the use of MS registries for SAE collection. CLARION is a prospective, multi-country, observational cohort study involving nine MS registries covering 14 countries. CLARION will evaluate the safety profile, in terms of adverse events of special interest (AESI), of patients initiating cladribine tablets (CT, n=4,000) versus those initiating fingolimod (n=4,000).

CLARION combines primary (Germany) and secondary data (other countries) and is projected to last up to 15 years with 10 years of follow-up for each included patient. Enrolled patients are those newly initiating CT or fingolimod according to the local label for MS after the date of CT launch in the relevant country or, in countries with primary data collection, after providing signed informed consent (<24 weeks after initiation of CT or fingolimod treatment). Patients are excluded if they received fingolimod prior to CT or if they received CT prior to fingolimod. Analysis of merged data from the different registries will be performed. Adjusted incidence rate and adjusted incidence rate ratios of each AESI

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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