Title: A pooled analysis of the efficacy of cladribine tablets 3.5 mg/kg in RMS patients with EDSS ≥3.5 or ≤3.0 at baseline in the CLARITY and ONWARD studies.

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Background: In the CLARITY and ONWARD studies, cladribine tablets demonstrated efficacy across a spectrum of patients with relapsing multiple sclerosis (RMS). Patients with EDSS ≥3.5 are at higher risk of conversion from relapsing-remitting multiple sclerosis (RRMS) to secondary progressive multiple sclerosis (SPMS) with relapses. Combining data from the double-blind study periods enables the effects of 2 years' treatment with cladribine tablets (3.5mg/kg cumulative dose) to be assessed in patients with higher EDSS at study entry.

Objective: To assess efficacy of cladribine tablets 3.5mg/kg in subgroups of patients with EDSS ≥3.5 vs. ≤3.0 at baseline.

Methods: Data from the 2-year, double-blind periods of CLARITY and ONWARD (n=1,067) were used to analyse the effect of cladribine tablets 3.5mg/kg on annualised relapse rate (ARR) by comparing patients who entered the study with a baseline EDSS ≥3.5 (n=414) and the complementary subgroup with baseline EDSS ≤3.0 (n=653). ONWARD compared cladribine+interferon-β and placebo+interferon-β.

Results: The observed ARR (95% CI) in the EDSS ≥3.5 subgroup was 0.17 (0.13–0.21) for cladribine tablets (n=212) vs 0.36 (0.30–0.43) for placebo (n=202). In the EDSS ≤3.0 subgroup, ARR (95% CI) was 0.13 (0.11–0.16) for cladribine tablets (n=361) vs 0.33 (0.28– 0.38) for placebo (n=292). The treatment effect of cladribine 3.5 mg/kg versus placebo was similar between EDSS subgroups, with an ARR risk ratio of 0.47 (0.34–0.64) in the EDSS ≥ 3.5 subgroup compared to 0.40 (0.31–0.53) in the EDSS ≤ 3.0 subgroup (subgroup by treatment interaction, p>0.5). The treatment effect in both subgroups was nominally significant (p<0.0001).

Conclusions: There was no meaningful difference in the observed treatment effect on ARR between EDSS subgroups supporting the concept that cladribine tablets 3.5 mg/kg is effective for patients with RMS, including those with higher EDSS and at increased risk of conversion to SPMS with relapses.

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