UPDATE ON CLADRIBINE TABLETS FOR THE TREATMENT OF RELAPSING–REMITTING MULTIPLE SCLEROSIS

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Cladribine is a synthetic deoxynucleoside analogue that produces preferential and sustained reductions in specific lymphocyte subtypes implicated in the pathogenesis of multiple sclerosis (MS), providing the rationale for the use of cladribine tablets in a short-course annual dosing regimen. This dosing regimen was used to investigate the efficacy and safety of cladribine tablets in patients with relapsing–remitting MS (RRMS) in the CLARITY study.

In CLARITY, a phase III, randomized, double-blind, placebo-controlled, multicentre, 96-week study, a total of 1,326 patients with RRMS were randomized 1:1:1 to receive placebo or cladribine tablets at cumulative doses of 3.5 or 5.25 mg/kg. Treatment was administered orally in short courses (once daily for 4 or 5 consecutive days) starting in Weeks 1 and 5 (3.5 mg/kg group) or Weeks 1, 5, 9 and 13 (5.25 mg/kg group), followed by two short courses at Weeks 48 and 52 (both groups). Primary and secondary efficacy endpoints were met with high levels of statistical significance. Thus, patients treated with cladribine tablets achieved 55–58% reductions in the annualized relapse rate over the 96-week study ($p<0.001$), together with a 31–33% lower risk of 3-month sustained disability progression ($p<0.05$) and reductions of up to 88% in the number of T1 Gd+ lesions, active T2 lesions and combined unique lesions compared with placebo over 96 weeks ($p<0.001$ for all comparisons). These improvements with cladribine tablets therapy were both rapid (with effects apparent as early as 4 weeks after the first treatment course) and sustained over the course of the 96-week study, and were observed across clinically relevant patient populations defined by different baseline characteristics (including patients stratified by age, disease duration, presence/absence of T1 Gd+ lesions at baseline or number of relapses in the year preceding study entry).

Since remission of disease activity is becoming an increasingly important goal in the treatment of MS, it is also important to note that data from the CLARITY study revealed significantly greater proportions of patients remaining free from disease activity defined by multiple disease parameters (absence of relapse, 3-month sustained disability progression and active lesions on brain MRI), compared with placebo. This disease activity-free status was sustained to study completion ($p<0.001$ at all time points), with two thirds of cladribine-treated patients who were disease activity-free at Week 24 remaining free from disease activity at Week 96.

The frequency of all reported treatment-emergent adverse events (AEs) was comparable across treatment groups. The most common AE was lymphopenia, as expected from the mechanism of action of cladribine. However, patients treated with cladribine tablets demonstrated high levels of both treatment compliance (>99%) and study retention, such that ≤9.5% of patients had AEs leading to treatment delay/interruption, and ≤2% of patients had AEs leading to study discontinuation. Furthermore, AE profiles in the first and second 48-week treatment periods were similar; data did not show a higher frequency of any specific AE in the second treatment period which, if observed, could suggest cumulative toxicity. Malignancies (3 cases reported during the study in the cladribine treatment groups, and 1 in post-study surveillance) were isolated events across different organ systems.

The efficacy, tolerability and safety findings with cladribine tablets therapy in the CLARITY study were associated with significant reductions in health resource utilization relative to placebo therapy. The mean number of clinic visits and emergency room visits were significantly lower in the 3.5 or 5.25 mg/kg cladribine tablets groups than placebo (all $p<0.01$), and hospital stays were reduced by a mean 3.90 and 1.92 days, respectively.

A robust clinical study programme is currently underway that will continue to investigate the potential of cladribine tablets in relapsing forms of MS, including a 96-week extension to the CLARITY study, and studies both in early MS (the ORACLE MS study) and as an add-on treatment in patients with inadequate response to interferon beta therapy (ONWARD study). In addition, PREMIERE, a long-term safety registry, is planned as an active surveillance system that will build on existing knowledge of the safety of cladribine tablets and better characterize the long-

tem safety profile through a long-term evaluation of subjects who have participated in clinical trials of cladribine tablets.
Applications have been submitted to the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the use of cladribine tablets in relapsing forms of MS and relapsing–remitting MS (RRMS), respectively.