An Analysis of Malignancy Risk in the Clinical Development Programme of Cladribine Tablets in Patients With Relapsing Multiple Sclerosis

INTRODUCTION

- In patients with relapsing-remitting multiple sclerosis (RMS), treatment with two short annual courses of cladribine tablets (CT, 3.5 mg/kg) cumulative dose produced significant improvements in clinical and neurological measures of disease activity.
- Malignancy is an adverse event (AE) of special interest for immunomodulatory therapies. Although the lymphopenia reductions seen after each annual treatment with cladribine tablets 3.5 mg/kg are transient (despite sustained permanent clinical efficacy benefits),7 it is of interest to assess the effects of treatment on safety.
- In CLARITY, there was a numerically higher incidence of malignancies in the CT group compared with the placebo group. However an independent review showed a similar rate of malignancy with cladribine tablets as with other disease modifying drugs (DMDs) in RMS clinical trials.8
- An integrated analysis based on the entirety of the clinical experience with oral cladribine in RMS (up to 8 years of follow-up) can provide further insights into malignancy risk.

OBJECTIVES

- To assess malignancy risk with cladribine tablets 3.5 mg/kg and placebo in data from 3 Phase III trials and the PREMERE registry, and to compare the incidence rate with a global malignancy database.

METHODS

- Safety data relating to treatment with cladribine tablets 3.5 mg/kg or oral monotherapy were taken from a Phase III trial that involved treatment with cladribine tablets 3.5 mg/kg and a placebo in a 2:1 ratio (active treatment: placebo).
- Malignancy case reports were taken from a monotherapy oral (MO) cohort. Analysis of malignancy used a conservative approach:
  - All cases with a reported preferred term within the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query “Malignant or Unspecified Tumors” (cut-off date 20 February 2015) and the Global Drug Safety database were analyzed using all malignancy events in 4 studies that involved treatment with cladribine tablets 3.5 mg/kg (Table 1).

RESULTS

Patients

- The MO cohort included 923 patients (Table 2) who had been randomized to treatment with cladribine tablets 3.5 mg/kg (423 patient-years of exposure) and 641 patients treated with placebo (2026 patient-years of exposure).
- In patients with relapsing RMS, treatment with two short annual courses of cladribine tablets 3.5 mg/kg and placebo, incidence rates difference (RD) and incidence rate ratios (RR) were calculated (Table 3).

RISK OF MALIGNANCIES OVER TIME

- To further investigate any possible association between malignancies and exposure to cladribine tablets, the occurrence of malignancies over time was assessed.
- The malignancy rate for cladribine tablets 3.5 mg/kg during Years 1–4 was very low (0.10 per 100 person-years) and during Years 5–8+ it was higher than exposure to placebo because the malignancy rate was constant during these periods (Table 5).

CONCLUSIONS

- Analysis of malignancy risk showed that the rate of malignancies with cladribine tablets 3.5 mg/kg was almost identical (97.9, 95% CI 0.44–1.85) to the GLOROCAN malignancy risk rates (Table 1).

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REFERENCES


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