Title: An analysis of malignancy risk in the clinical development programme of cladribine tablets in patients with relapsing multiple sclerosis

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Background: An independent meta-analysis (Pakpoor et al. Neurol Neuroimmunol Neuroinflamm 2015;2:e158) in Phase III trials (with a 2-year duration) of disease modifying drugs (DMDs) in patients with relapsing MS found no increased rate of malignancy with cladribine tablets (CT) versus other DMD treatments. Data from additional trials involving CT 3.5 mg/kg (CT3.5) and a safety registry (up to 8 years' follow-up) allow further insights into malignancy risk.

Objective: To assess malignancy risk with CT3.5 monotherapy and placebo (PBO) in data from 3 Phase III trials and a registry, and compare the incidence rate with a global database.

Methods: The CT 3.5 population comprised 923 patients (3433 patient-years' [PY] total exposure time) and the PBO group comprised 641 patients (2026 PY). Individual case reports of malignancies were reviewed by independent, blinded adjudication committee. Standardized incidence ratios (SIR) were calculated using the GLOBOCAN reference population (excluding non-melanoma skin cancers [NMSCs]) and a Danish reference population for NMSC rates.

Results: The incidence per 100 PY of confirmed malignancy was CT3.5 0.293 (95%CI 0.158–0.544) and PBO 0.148 (95%CI 0.048–0.460); the risk difference 95% CI included 0 (-0.166–0.414). The CT 3.5 malignancy SIR was almost identical (0.97, 95%CI 0.44–1.85) to the GLOBOCAN matched reference population. The PBO group SIR was numerically lower (0.48, 95% CI 0.14–1.53). There were no cases of haematological, lymphoproliferative or virus-induced cancers. There was no clustering of specific tumour types, and the incidence of skin cancer was not increased after treatment with CT3.5 versus PBO. The incidence of malignancies with CT3.5 was constant and did not increase over time.

Conclusions: Analysis of malignancy rates in a cohort that includes patients with up to 8 years' follow-up confirms the conclusions of the earlier meta-analysis; the incidence of malignancies with CT3.5 is similar to a matched reference population.

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