COVER PAGE

Official Title:	An Observational Study Utilising Data From the US Tysabri TOUCH Programme and Select EU MS Registries to Estimate the Risk of Progressive Multifocal Leukoencephalopathy (PML) and Other Serious Opportunistic Infections Among Patients Who Were Exposed to an MS Disease Modifying Treatment Prior to Treatment With Tysabri
NCT Number: **EU PAS Number:**	NCT03399981 EUPAS19800
Document Date:	04 March 2025
Name of Sponsor/Company:	Biogen MA Inc./Biogen Idec Research Limited
Name of Finish Product:	Natalizumab
Name of Active Ingredient:	Natalizumab (BG00002; Tysabri)
Study Indication:	Relapsing-Remitting Multiple Sclerosis

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1. ABSTRACT

Title

An observational study utilising data from the US Tysabri TOUCH programme and select EU MS registries to estimate the risk of progressive multifocal leukoencephalopathy (PML) and other serious opportunistic infections among patients who were exposed to an MS disease modifying treatment prior to treatment with Tysabri

Keywords

Progressive multifocal leukoencephalopathy, serious opportunistic infections, multiple sclerosis, Tysabri, natalizumab

Rationale and background

In 2015, the marketing authorisation holder (MAH) sought to extend the approved indication for Tysabri to include patients who were nonresponders to other first-line disease-modifying therapies (DMTs). As a condition of the approval of the variation, the European Union (EU) Pharmacovigilance Risk Assessment Committee required the MAH to conduct a noninterventional postauthorisation safety study aimed at determining the risk of PML and other serious opportunistic infections (SOIs) in patients who were previously treated with at least 1 DMT. This study was designed to assess the risk of PML and other SOIs in patients who switched to Tysabri from newer DMTs (fingolimod, dimethyl fumarate [DMF], and teriflunomide) compared with those who switched from established DMTs (interferon-beta and glatiramer acetate).

Study objectives

To estimate the incidence of PML and other SOIs in patients switching to Tysabri from established and newer DMTs.

Study design

This observational study included cumulative data from patients who switched to Tysabri from an established or newer DMT through 31 December 2020 and followed up until 31 December 2023.

Setting

Data from the United States Tysabri TOUCH programme, select EU multiple sclerosis (MS) registries (NTD, were used to estimate the risk of PML and other SOIs.

Patients and study size, including dropouts

The study included Tysabri-naive patients who switched from the established or newer DMTs and then received ≥1 Tysabri infusions. It included 81,564 patients (newer DMTs: 5712 from fingolimod, 8427 from DMF, and 2975 from teriflunomide; established DMTs: 65,169).

Variables and data sources

This study extracted descriptive data (baseline characteristics; Tysabri exposure) and outcome data (PML and other SOIs).

Results/Discussion

PML Risk Estimates

While the incidence rate (95% confidence interval [CI]) of PML was lower for patients switching from newer DMTs (0.200 [0.100-0.357]) when compared with patients switching from established DMTs (0.697 [0.607-0.796]), after adjustment for covariates using patient-level data from TOUCH, a logistic regression analysis demonstrated that there was no association between the type of DMT a patient switched from (established or newer) and the odds of developing PML in patients with known anti-John Cunningham virus antibody status (odds ratio [OR] 1.3, 95%CI: 0.5-3.3, p-value=0.6431).

Incidence of SOIs (Excluding PML)

The incidence rate (95% CI) of SOIs per 1000 patient-years was 8.684 (7.878-9.549) in the newer DMTs group (11.740 [10.210-13.433], 7.419 [6.410-8.541], and 9.264 [7.406-1.442] in the fingolimod, DMF, and teriflunomide groups, respectively) and 9.182 (8.828-9.546) in the established DMTs group. Although the unadjusted incidence rate was slightly higher in the fingolimod group and slightly lower in the DMF group compared with the established DMTs group, after adjustment for covariates using patient-level data from TOUCH, a logistic regression analysis demonstrated that there was no association between the type of DMT a patient switched from (established or newer) and the odds of developing an SOI (fingolimod, OR 0.9, 95%CI: 0.7-1.3, p-value=0.4318; DMF, OR 0.8, 95%CI: 0.6-1.1, p-value=0.6863; teriflunomide, OR 0.7, 95%CI: 0.4-1.1, p-value=0.2516).

Conclusions

The study demonstrates that there is no increased risk of PML or other SOIs (excluding PML) for patients switching to Tysabri from newer versus established DMTs.

Marketing authorisation holder

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Date of Abstract: 04 March 2025