Progressive multifocal leukoencephalopathy (PML) is the major limitation to the use of natalizumab in multiple sclerosis (MS). Since 2012, three factors allow to identify patients in whom the risk of PML might outweigh treatment benefits: exposure to natalizumab for more than 24 months, previous use of immunosuppressants and a positive JC virus serology. So far, the impact of risk stratification on PML incidence has not been evaluated.

The objective of this study was to describe the temporal evolution of the incidence of natalizumab-associated PML in France between 2007 and 2016 and to evaluate the impact of risk minimization procedures on PML incidence before and after 2013.

Methods
Retrospective, observational, multicentric, epidemiological study on data collected in OFSEP (Observatoire francophone de la Sclérose en Plaques).

Population of interest
Patients with both MS and PML related to a treatment with natalizumab, since April 15th 2007.

Results
Baseline characteristics of the study population (Flow-chart in Figure 1)
6318 patients were included in the at-risk population. Age at MS onset was 28.5±9.1 years (range 1.1–72.4), with 74.1% females. Mean exposure to natalizumab was 39.6±30.2 months (range 0.01–164.8). 1372 (21.7%) were exposed to at least one immunosuppressive treatment before natalizumab. 61 PML were registered originally in the database and 9 additional cases were reported during the validation period. Twenty-five cases were excluded from the analysis: 2 cases were only suspected but not confirmed by CSF PCR for JC virus or brain biopsy, 6 cases occurred after 2016 (in 2017, 1 in 2018) and 17 cases were not followed by OFSEP participants before the diagnosis of PML. 45 definite PML were finally analyzed. Thirty-one (68.9%) were females, mean age was 28.7±6.7 years (range 17.4–42.6) at MS onset and 43.5±7.0 years (range 27.1–58.8) at PML onset. Eight cases (17.7%) started after natalizumab was stopped (mainly because of a positive JCV serology), 5 in the first 3 months, 3 between 3 and 6 months. Mean exposure to natalizumab was 52.0±24.2 months (range 4.7–117.1). One case (2.2%) occurred in the first 12 months of treatment, 3 (6.7%) between 12 and 24 months, 5 (11.1%) between 24 and 36 months, 18 (40.0%) between 36 and 48 months, and 19 (43.5%) between 48 and more than 60 months.

Flow-chart and Crude incidence rates between 2007 and 2016
The univariate Poisson regression model was considered by integrating the year as a linear covariate and patient-year’s exposures to natalizumab were considered in the offset term.

Stratification by period (before and after 2013)
This model allowed to estimate the annual variation in incidence rate ratio (IRR) and the number of expected cases. A multivariate analysis was performed by adjusting for sex and age at treatment initiation and a stratified analysis by period before and after 2013 to evaluate the impact of risk stratification. Analyses were performed with SAS 9.4 software and R 3.4.3. P <0.05 was considered statistically significant.

Risk stratification model
The questionnaire was completed by 33 of the 34 participating centers (97.1%). All declared using JCV results in the management of their patients, 97% at natalizumab initiation and 3% after 18 months. Two centers do not consider previous use of immunosuppressants and 3 duration of treatment in the risk/benefit discussion.

Initiation of natalizumab is considered by up to 90.9% in JCV+ patients, whereas 9.1% do not use natalizumab at all in this situation; 86.7% use JCV index, with variable high-risk thresholds: 0.7 in 2 centers, 0.8 in 22 and 1.5 in 4 (96.6%) limit the duration of exposure to natalizumab to 12, 18 or 24 months (4, 9 and 13 centers respectively). In JCV− patients, restesting is done every 6 months in 30/33 centers, more frequently in 2 and only annually in 1. MRI follow-up is done annually in 27 centers and every 6 months in 6. In JCV− patients with a low index (according to the local threshold), restesting is done every 6 months in 24/32 centers, more frequently in 7 (3–4 months) and only annually in 1. MRI follow-up is done more than once in 28 centers (quarterly in 11, bi-annually in 17) after 12, 18 or 24 months of exposure (respectively 8, 9 and 8 centers) and once in 3; it remains annual in 4.

Conclusion
The study was designed to define the first baseline country, a significant decrease in the incidence of natalizumab-associated PML in France in 2013, in a temporal concordance with the introduction of risk stratification guidelines based on JCV serology and index, treatment duration and prior immunosuppressant use. If the overall risk recently decreased, PML did not disappear so far. It is likely that natalizumab was maintained despite the detection of risk factors in patients for whom the fear of a poor control of MS activity exceeded the perception of the risk of PML. Although a causal relationship cannot be established, this encourages continuing and reinforcing all educational activities to prevent the risk of PML.

The Observatoire Français de la Sclérose en Plaques (OFSEP) is supported by a grant provided by the French State and handled by the "Agence Nationale de la Recherche." within the framework of the "Investissements pour l’Avenir" program, under the reference ANR-10-COSH-002, by the Euginie Dévic EDMUS Foundation against multiple sclerosis and by the ARSEP Foundation.