MANUSCRIPT: Long-Term Surveillance of Ocrelizumab-Treated Patients with Multiple Sclerosis

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BACKGROUND AND AIMS

- Ocrelizumab is a recombinant humanised monoclonal antibody that selectively targets CD20$^+$ B cells[1]
- Ocrelizumab has demonstrated superior efficacy to interferon (IFN) β-1a in patients with relapsing multiple sclerosis (RMS),[2] and to placebo in patients with primary progressive multiple sclerosis (PPMS)[3] in double-blind, randomised Phase III trials
- Frequencies of adverse events (AEs) and serious adverse events (SAEs) in the ocrelizumab group were similar to IFN β-1a or placebo[2,3]
- Pooled Phase III trial data in patients with RMS and PPMS indicated an imbalance in malignancies in the ocrelizumab treatment group versus pooled IFN β-1a and placebo, which was driven by a higher number of female breast cancer events in the ocrelizumab group
- The rate of malignancies, and specifically female breast cancer, in ocrelizumab-treated patients remained within the range of epidemiological background rates in the general population[4]
- However, no firm conclusion could be made concerning malignancy risk, due to the low number of events and limited follow-up
  - Therefore, further data are needed to characterise the long-term safety of ocrelizumab in the real-world setting
- The post-marketing safety study MANUSCRIPT (EUPAS28619) has been approved by the European Medicines Agency, in order to characterise the long-term safety profile of ocrelizumab in patients with multiple sclerosis (MS)
  - MANUSCRIPT is one of several post-marketing safety studies, e.g. the VERISMO[5] and CONFIDENCE[6] studies
- The aim of MANUSCRIPT is to assess and characterise the long-term safety data, including the rates of malignancies and serious infections, among patients with MS treated with ocrelizumab under routine clinical care

METHODS

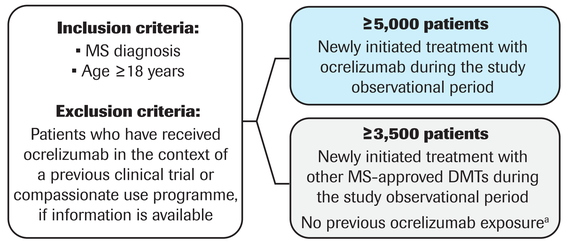
Study Design

- MANUSCRIPT is a multi-source, multi-country, non-interventional, longitudinal post-marketing safety study based on secondary use of data captured for patients with MS who have newly initiated treatment with ocrelizumab or another MS disease-modifying therapy (DMT)
  - The study population and objectives of MANUSCRIPT are provided in **Figures 1 and 2**

METHODS

- The incidence rates of SAEs, including malignancies and infections, will be compared between patients with MS newly initiating ocrelizumab treatment and those newly initiating treatment with other approved MS DMTs
- The overall study duration will be 10 years
- Patients will be followed from the first treatment with ocrelizumab or alternative approved MS DMT until the end of the follow-up period, death, or loss to follow-up, whichever comes first
  - Follow-up is planned regardless of whether patients discontinue treatment with ocrelizumab (or alternative MS DMT)

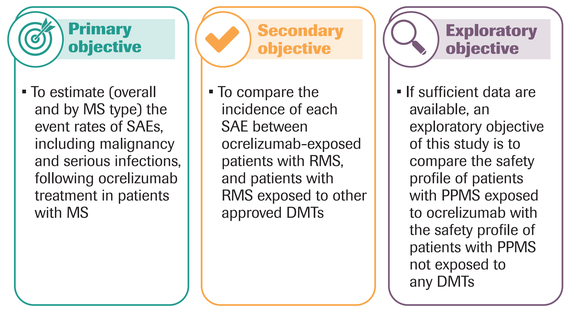
Figure 1. MANUSCRIPT patient population



[a]Patient who has never received treatment with ocrelizumab (complete available history).
DMT, disease-modifying therapy; MS, multiple sclerosis.

- In addition, there will also be a non-DMT comparator group of PPMS patients who have never received ocrelizumab or any other DMT within the complete history recorded within available medical records and during individual follow-up in the study observational period

Figure 2. MANUSCRIPT study objectives

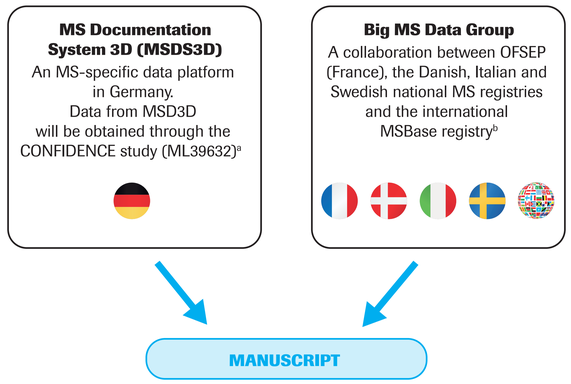


DMT, disease-modifying therapy; MS, multiple sclerosis; PPMS, primary progressive MS; RMS, relapsing MS; SAE, serious adverse event.

Data Sources

- MANUSCRIPT will use existing data from routine healthcare, recorded in MS-specific registry sources (**Figure 3**)

Figure 3. MANUSCRIPT data sources



[a]CONFIDENCE is a prospective, multicentre, non-interventional long-term study, which collects primary data from patients with RMS or PPMS newly treated with ocrelizumab, and other MS DMTs, in routine clinical practice; [b]The international MSBase registry includes several European and Middle Eastern countries, Egypt, Australia and Canada.
MS, Multiple Sclerosis; OFSEP, Observatoire Français de la Sclérose en Plaques.

Data Analysis

- Results will be monitored through regular descriptive interim reports of incidence rates for all safety endpoints, including 95% confidence intervals (CIs)
- Comparative analyses will be performed, reporting on Cox regression hazard ratios, using propensity score-based methods to ensure cohort comparability
  - Comparative analysis will be performed at Years 4, 6, 8 and at completion of the study (see **Figure 4** for key study milestones)
- Risk for malignancy will be assessed through an *ever-treated* exposure model (for as long as the study follow-up, regardless of treatment shift)
- Meta-analyses of results across the data sources will be conducted using aggregated results from each source
- Semi-annual regulatory safety reports are also scheduled

Figure 4. MANUSCRIPT key study milestones

RESULTS

- The sample size and study duration will provide sufficient precision to address the primary objective
  - See **Table 1** for hazard ratios expected to be ruled out with 80% power

Table 1. Hazard ratios expected to be ruled out with 80% power

Outcome	HR expected to be ruled out
Malignancy	
Malignancy (excl. NMSC)	1.43
Breast cancer (female)	1.79
Infections	
PML	10
Herpes-related infections	2.6
Candida-related infections	1.59
Respiratory infections	1.20
Urinary tract infections	1.16

Assumptions underlying these calculations: (i) No difference in risk between the exposed and unexposed (i.e. HR=1); (ii) Proportion of females = 60%.
HR, hazard ratio; NMSC, nonmelanoma skin cancer;
PML, progressive multifocal leukoencephalopathy.

CONCLUSIONS

The MANUSCRIPT post-marketing safety study will advance the understanding of the long-term safety profile of ocrelizumab, through the assessment of the potential risk of malignancies and serious infections in patients with MS newly exposed to ocrelizumab

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