VERISMO: A Post–Marketing Safety Study to Determine the Incidence of All Malignancies and Breast Cancer in Patients With Multiple Sclerosis Treated With Ocrelizumab

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BACKGROUND

- Ocrelizumab is a recombinant, humanized, 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 Phase III trials
  - The proportions of patients with adverse events (AEs) or serious AEs (SAEs) were similar across the ocrelizumab, IFN β-1a, and placebo groups
  - Pooled Phase III trial data in patients with RMS and PPMS indicated an imbalance in malignancies between the ocrelizumab and control arms, which was driven by a higher number of female breast cancer events in the ocrelizumab group
- Further data are needed to characterize the long-term safety of ocrelizumab in the real-world setting
- The post-marketing safety study VERISMO (BA39731) has been developed in line with regulatory requirements (U.S. Food and Drug Administration), to assess long-term safety data of ocrelizumab in the real-world setting and further characterize the safety profile in patients with multiple sclerosis (MS) newly exposed to ocrelizumab

OBJECTIVE

- The primary objective of VERISMO is to determine and characterize the incidence and mortality rates of all malignancies, including breast cancer, among patients with MS treated with ocrelizumab under routine clinical care

METHODS

Study Design

- VERISMO is a multi-source, multi-country, noninterventional, longitudinal post-marketing safety study on patients with MS who have newly initiated treatment with ocrelizumab or other MS disease-modifying therapies (DMTs)
  - The study population and objectives of VERISMO are provided in **Tables 1** and **2**
- The cohort study is based on a *new user* design of ocrelizumab or other approved MS DMTs
- The incidence rates of all malignancies and breast cancer will be compared between ocrelizumab-exposed patients with MS and those newly treated with alternative approved MS DMTs, as well as general populations
  - Data from Germany will be obtained through CONFIDENCE (ML39632),[4] a prospective, multicentre, noninterventional 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
  - These will be pooled with data collected in the United States to build the study database for VERISMO
- The VERISMO study will include an internal comparator cohort of 2,360 patients newly treated with approved MS DMTs other than ocrelizumab

Table 1. VERISMO patient population

	VERISMO
Patient population	▪ Expected to enroll 6,360 patients (aged ≥18 years) with MS who have newly initiated treatment with ocrelizumab (≤30 days prior to study entry) or with another MS-approved DMT in the US and Germany — 4,000 ocrelizumab-exposed patients — 2,360 patients exposed to other MS-approved DMTs (alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, or teriflunomide)
	▪ Enrollment of patients will ensure at least 70% of the population is female in order to adequately power breast cancer event rates
	▪ Patients who received previous rituximab or ocrelizumab treatment, or who are actively participating in other MS clinical trials will be excluded

DMT, disease-modifying therapy; MS, multiple sclerosis.

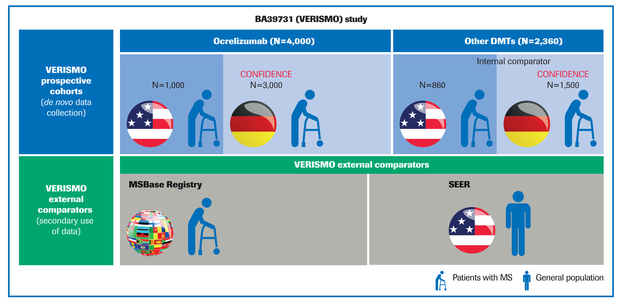
Table 2. VERISMO study objectives

	VERISMO
Primary objective	▪ To determine the incidence rate of all malignancies and breast cancer following the first ocrelizumab treatment among patients with MS
Secondary objectives	▪ To determine the mortality rate of breast cancer and all malignancies following the first ocrelizumab treatment among patients with MS ▪ To compare the observed incidence and mortality rates of breast cancer and all malignancies between ocrelizumab-exposed patients with MS and patients newly treated with approved MS DMTs other than ocrelizumab, as well as general populations ▪ To determine the event rate of all SAEs in the ocrelizumab-treated patients with MS

DMT, disease-modifying therapy; MS, multiple sclerosis; SAE, serious adverse event.

- VERISMO will also include comparison with external populations:
  - The MSBase Registry (global), which collects treatment and outcome information from routine clinical practice for patients with MS
  - The Surveillance, Epidemiology, and End Results (SEER) Program, which publishes malignancy incidence and survival data for general populations using malignancy registries in the United States
  - VERISMO data sources are described in **Figure 1** and data collection summarized in **Table 3**

Figure 1. VERISMO study population



DMT, disease-modifying therapy; MS, multiple sclerosis; SEER, Surveillance, Epidemiology, and End Results.

Table 3. VERISMO data collection at different study time points

Key data collected	Baseline	Follow-up (approx. every 6 months)	End of study
Exposure			
Ocrelizumab and other MS DMTs Prior Current	• •	 •	 •
Outcome/observation			
SAEs		•	•
Malignancies		•	•
NMSC		•	•
Covariates			
Patient demographics and medical history	•		
Malignancy risk factors	•		
MS disease and treatment history	•		
Height, weight, and safety laboratory values	•	•	•
EDSS score	•	•	•
Prior and concomitant medication	•	•	•
MS relapses	•	•	•
Pregnancy status	•	•	•

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; NMSC, non-melanoma skin cancer; SAE, serious adverse event.

- Patients will be followed for at least 5 years or until death, whichever occurs first
- Follow-up is planned regardless of whether patients discontinue treatment with ocrelizumab (or other approved MS DMTs)

VERISMO Data Analysis

- Interim safety analyses will be performed on a regular basis
- Comparative analysis will be performed at completion of the study (see **Table 4** for key study milestones)
- Total patient-time-at-risk will be calculated from the first ocrelizumab (or other DMT) dose until the event, death, loss to follow-up, or end of study, whichever occurs first, irrespective of the duration of treatment exposure
- The incidence rate of all malignancies and breast cancer among patients exposed to ocrelizumab will be calculated as the number of incidence events and episodes (repeated events) divided by the total patient-years at risk
- All safety endpoints will be reported using incidence rates, adjusted and unadjusted, and 95% CIs
- Incidence rates of malignancies will be presented for the following subgroups:
  - Sex
  - Age group
  - MS type
  - Duration of treatment and cumulative exposure to ocrelizumab and other DMTs
- Similar analyses will be performed to determine the cause-specific mortality rates for all malignancies and breast cancer
- Comparisons of AE risk between ocrelizumab and other DMTs will use inverse probability of treatment weights (IPTW) to control for important confounders, including age, sex, MS disease severity (as measured by Expanded Disability Status Scale, MRI results, and relapses), and malignancy risk factors
- Comparison with external comparators will compare incidence and mortality rates in patients exposed to ocrelizumab with data from MSBase and the SEER Program using direct and indirect methods of incidence rates standardization

Table 4. VERISMO key study milestones

Milestone	Planned date
Study start	Q2 2019
End of data collection	Nov 2029 (at the latest)
Final report of study results	Nov 2030 (at the latest)

RESULTS

- Planned enrollment in VERISMO includes 6,360 adult patients from the US and Germany: 4,000 ocrelizumab-treated and 2,360 treated with other MS DMTs
- The sample size and study duration will provide sufficient precision around the incidence rates to address the primary objective
  - The minimum detectable hazard ratio with 80% power will be 1.46 for the rate of all malignancies and 2.00 for the rate of female breast cancer
- VERISMO will integrate the results of CONFIDENCE in regular interim safety analyses and comparative long-term safety analyses
- Comparative analyses will compare the risk of AEs in patients receiving ocrelizumab versus other DMTs, accounting for confounders
  - Based on survival (time-to-event) Cox-regression methods adjusted for IPTW
- Comparison with external comparators will be based on standardized incidence rates

CONCLUSION

- The VERISMO post-marketing safety study will advance the understanding of the safety profile of ocrelizumab through the assessment of the potential risk of breast cancer and all malignancies in patients with MS newly exposed to ocrelizumab

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REFERENCES

1. Klein C, *et al. MAbs* 2013;5:22–33.
2. Hauser SL, *et al. N Engl J Med* 2017;376:221–234.
3. Montalban X, *et al. N Engl J Med* 2017;376:209–220.
4. Ziemssen T, *et al. ECTRIMS* 2018;ePoster EP1627.

DISCLOSURES

D Wormser is an employee and shareholder of F. Hoffmann-La Roche Ltd. J Evershed is an employee of Roche Products Ltd. G Ferreira has received grants and personal fees from F. Hoffmann-La Roche Ltd. D Stokmaier and Q Wang are employees of F. Hoffmann-La Roche Ltd. T Ziemssen has received grants and personal fees from Biogen, Novartis, Sanofi, and Teva, and personal fees from Almirall, Bayer, F. Hoffmann-La Roche Ltd, and Merck.

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