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

D Wormser,¹ J Evershed,² G Ferreira,¹ D Stokmaier,¹ Q Wang,¹ T Ziemssen³

BACKGROUND

- Ocrelizumab is a recombinant, humanized, monoclonal antibody that selectively targets CD20⁺ B cells¹
- 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

DISCLOSURES

E Wormser is an employee of F. Hoffmann-La Roche Ltd. J Evershed is an employee of Roche Ltd. J Evershed is an employees of F. Hoffmann-La Roche Ltd. J Evershed is an employees of F. Hoffmann-La Roche Ltd. J Evershed is an employee of Roche Ltd. J Evershed is an employees of F. Hoffmann-La Roche Ltd. J Evershed is an employees of F. Hoffmann-La Roche Ltd. J Evershed is an employee of Roche Ltd. J Evershed is an employee of Roche Ltd. J Evershed is an employees of F. Hoffmann-La Roche Ltd. J Evershed is an employees of F. Hoffmann-La Roche Ltd. J Evershed is an employee of Roche Ltd. J Evershed is an employees of F. Hoffmann-La Roche Ltd. J Evershed is an employee of Roche Ltd. J

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Table 1. VERISMO patient population

	VERISMO		Decelling	Follow-up		rates for all malignancies and bre	east cancer		
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 	Key data collected	Baseline	(approx. every 6 months)	End of study	 Comparisons of AE risk between or 	crelizumab and other DMTs will use inverse		
		Exposure				probability of treatment weights (IPTW) to control for important confounders, including age, sex, MS disease severity (as measured by Expanded Disability Status Scale, MBI results, and relapses), and malignancy risk factors			
		Ocrelizumab and other MS DMTs Prior							
	 — 4,000 ocrenzumablexposed patients — 2,360 patients exposed to other MS-approved DMTs (alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, or teriflunomide) 	Current	•	•	•	Status Scale, Mini results, and relapses), and many hancy lisk factors			
		Outcome/observation				Comparison with external comparators will compare incidence and mortality rates in patients exposed to corolize mab with data from MSRass and the SEEP			
	 Enrollment of patients will ensure at least 70% of the population is female in order to adequately power breast cancer event rates 	SAEs		•	•	Program using direct and indirect methods of incidence rates standardizatio			
	 Patients who received previous rituximab or ocrelizumab treatment, or who are actively participating in other MS clinical trials will be excluded 	Malignancies		•	•	Table 4. VERISMO key study milestones			
		NMSC		•	•				
DMT, disease-modifying therapy; MS, multiple sclerosis.		Covariates				Milestone	Planned date		
Table 2. VERISMO study objectives		Patient demographics and medical history	•			Study start	Q2 2019		
	VERISMO	Malignancy risk factors	•			End of data collection	Nov 2029 (at the latest)		
Primary objective	 To determine the incidence rate of all malignancies and breast cancer 	MS disease and treatment history	•			Final report of study results	Nov 2030 (at the latest)		
	To determine the meetal's material have to be a first or anong patients with IVIS	Height, weight, and safety laboratory values	•	•	•				
Secondary objectives	 To determine the mortality rate of breast cancer and all malignancies following the first ocrelizumab treatment among patients with MS 	EDSS score	•	•	•	 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 			
	 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 	Prior and concomitant medication	•	•	•				
		MS relapses	•	•	•				
	 To determine the event rate of all SAEs in the ocrelizumab-treated patients with MS 	Pregnancy status	•	•	•				

	VERISMO		Decelling	Follow-up		rates for all malignancies and broken	east cancer		
		Key data collected	Baseline	(approx. every 6 months)	End of study	 Comparisons of AE risk between o 	crelizumab and other DMTs will use inverse		
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 	Exposure				robability of treatment weights (IPTW) to control for important confounder			
		Ocrelizumab and other MS DMTs				 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 			
	 — 4,000 ocrelizumab-exposed patients 	Prior	•						
	 — 2,360 patients exposed to other MS-approved DMTs (alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, or teriflunomide) 	Outcome/observation							
	 Enrollment of patients will ensure at least 70% of the population is female in order to adequately power breast cancer event rates 	SAEs		•	•				
	 Patients who received previous rituximab or ocrelizumab treatment, or who are actively participating in other MS clinical trials will be excluded 	Malignancies		•	•	Table 4. VERISMO key study milestones			
		NMSC		•	•				
DMT, disease-modifying therapy; MS, multiple sclerosis.		Covariates				Milestone	Planned date		
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		Height, weight, and safety laboratory values	•	•	•				
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 DIMTs other than ocrelizumab, as well as general populations 	EDSS score	•	•	•				
		Prior and concomitant medication	•	•	•	Planned enrollment in VERISIVIO includes 6,360 adult patients from the US and Germany: 4,000 ocrelizumab-treated and 2,360 treated with other MS DMTs			
		MS relapses	•	•	•	 The sample size and study duration will provide sufficient precision around the incidence rates to address the primary objective 			
	 To determine the event rate of all SAEs in the ocrelizumab-treated patients with MS 	Pregnancy status	•	•	•				

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

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% Cls
- 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

- 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

- 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.