# Integration of Ocrelizumab Safety Data From the German Study CONFIDENCE Into the Global Post-Marketing Safety Studies MANUSCRIPT and VERISMO

T Ziemssen,[1] H Berthold,[2] P Dirks,[2] J Evershed,[3] K Gunzenhauser,[3] J Leemhuis,[2] D Stokmaier,[3] Q Wang,[3] G Ferreira,[3] D Wormser[3]

[1]Center of Clinical Neuroscience, Neurological Clinic, Carl Gustav Carus University Clinic, Dresden University of Technology, Dresden, Germany; [2]Roche Pharma AG, Grenzach-Wyhlen, Germany; [3]F. Hoffmann-La Roche Ltd, Basel, Switzerland

## INTRODUCTION AND PURPOSE

- Ocrelizumab (OCR) is a recombinant, humanised, monoclonal antibody that selectively targets $CD20^+$ B cells[1]
- OCR has demonstrated superior efficacy to interferon (IFN) β-1a in patients with relapsing multiple sclerosis,[2] and to placebo in patients with primary progressive multiple sclerosis,[3] in Phase III trials
  - The proportions of patients with adverse events (AEs) or serious AEs were similar across the OCR, IFN β-1a and placebo groups
  - Pooled trial data indicated an imbalance in malignancies between the OCR and control arms, which was driven by a higher number of female breast cancer events in the OCR group
- Further data are needed to characterise the long-term safety of OCR in the post-marketing setting, and a programme comprising two observational studies – MANUSCRIPT and VERISMO – has been developed to fulfil regulatory requirements (U.S. Food and Drug Administration and European Medicines Agency)
- The CONFIDENCE study will collect data to be included in the global post-authorisation safety (PAS) studies MANUSCRIPT and VERISMO
- CONFIDENCE will assess long-term safety data (e.g. incidence of malignancies and serious infections) of OCR in the real-world setting and further characterise the safety and benefit–risk profile in patients with multiple sclerosis (MS) newly exposed to OCR in Germany

## OVERALL AIM

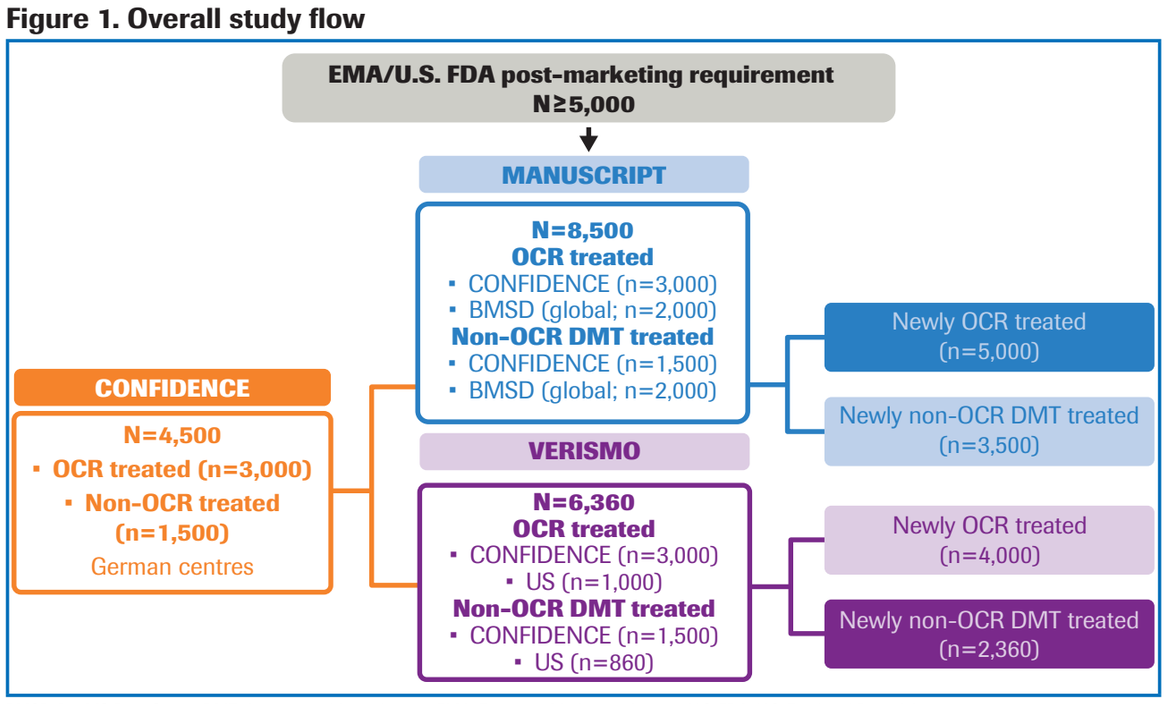
- To further assess and characterise the long-term safety profile of OCR, including malignancy, in patients with MS in a real-world setting

## METHODS

### *Study Design*

- MANUSCRIPT and VERISMO are multi-source, multi-country, noninterventional, longitudinal cohort PAS studies on patients with MS who have newly initiated treatment with OCR (and other MS disease-modifying therapies [DMTs]) (see **Figure 1** for data sources and overview of study flow)
  - The objectives and populations of the studies are provided in **Table 1** and **Figure 2**
  - Participants will be followed up for as long as possible, and up to 10 years, or until censoring, loss to follow-up or death
  - The VERISMO study will include an internal comparator cohort as well as external comparators, including data from the international MSBase Registry and the US Surveillance, Epidemiology, and End Results (SEER) Program (**Figure 2**)
  - MANUSCRIPT and VERISMO data sources are described in **Figure 2** and data collection/analyses for both studies are summarised in **Tables 2** and **3**

**Figure 1. Overall study flow**




BMSD, Big MS Data Group; DMT, disease-modifying therapy; EMA, European Medicines Agency; U.S. FDA, U.S. Food and Drug Administration; MS, multiple sclerosis; OCR, ocrelizumab.

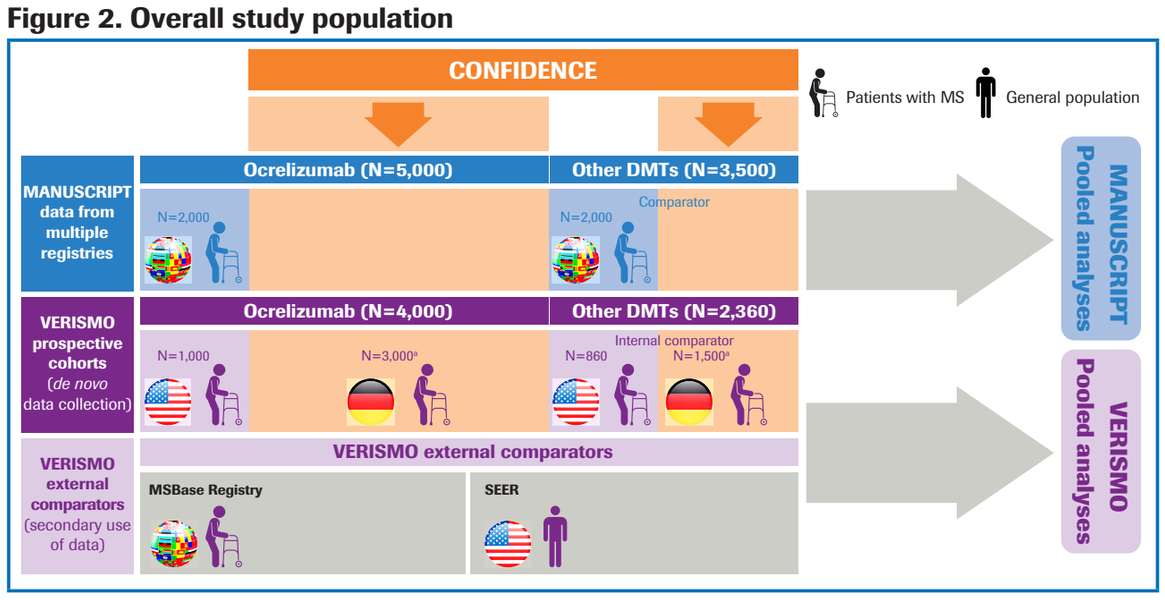
**Table 1. MANUSCRIPT and VERISMO study objectives and patient populations**

| | MANUSCRIPT | VERISMO |
|---|---|---|
| **Patient population** | ▪ Expected to acquire data from ~8,500 patients (aged ≥18 years) with MS who have newly initiated treatment with OCR or another DMT during the study period, or patients with MS not on DMT in routine clinical practice | ▪ Expected to enrol 6,360 patients (aged ≥18 years) with MS who have newly initiated treatment with OCR or with another DMT in the US and Germany |
| **Primary objective** | ▪ To estimate the rates of serious adverse events, including malignancies and serious infections, following OCR treatment | ▪ To determine the incidence rate of breast cancer and all malignancies following the first OCR treatment |
| **Secondary objective(s)** | ▪ To compare the incidence of each serious adverse event between OCR-exposed patients and patients exposed to other approved DMTs, within the same data source and by MS type (RMS and PPMS) | ▪ To determine the event rate of all serious adverse events in OCR-treated patients<br>▪ To determine the mortality rate of breast cancer and all malignancies following the first OCR treatment among patients with MS<br>▪ To compare the observed incidence and mortality rates of breast cancer and all malignancies between OCR-exposed patients and patients newly treated with approved MS DMTs other than OCR, as well as general populations |
| **Data sources** | ▪ Primarily based on data from existing MS and population registries (BMSD) | ▪ Based on *de novo* prospective data collection |

BMSD, Big MS Data Group; DMT, disease-modifying therapy; MS, multiple sclerosis; OCR, ocrelizumab; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis.

- MANUSCRIPT: CONFIDENCE data will be combined with data from the BMSD (Big MS Data Group) which combines clinical data from multiple registries (MSBase; France OFSEP [Observatoire Français de la Sclérose en Plaques]; Denmark, Sweden and Italy)
- VERISMO: CONFIDENCE patient-level data will be pooled with US-based patient-level data collected *de novo* from VERISMO study sites
- CONFIDENCE will enrol 4,500 patients with MS; 3,000 new OCR users and 1,500 new users of other MS DMTs from at least 250 neurological centres in Germany

**Figure 2. Overall study population**




[a]CONFIDENCE study population is included in both MANUSCRIPT and VERISMO.
DMT, disease-modifying therapy; MS, multiple sclerosis; SEER, Surveillance, Epidemiology, and End Results.

**Table 2. MANUSCRIPT and VERISMO data collection**

| Key data collected | MANUSCRIPT | VERISMO |
|---|---|---|
| **Exposure** | | |
| OCR and other MS DMTs | | |
| Prior | • | • |
| Current | • | • |
| **Outcome/observation** | | |
| Safety | | |
| SAEs | • | • |
| AESIs | | • |
| Malignancies | • | • |
| Nonmelanoma skin cancer | • | • |
| **Covariates** | | |
| Patient demographics and medical history | • | • |
| Malignancy risk factors[a] | • | • |
| MS disease and treatment history | • | • |
| Vital signs and measurements[b] | • | • |
| EDSS score | • | • |
| Concomitant medication | • | • |
| MS relapses | • | • |
| Pregnancy status | • | • |

[a]MANUSCRIPT data limited – as available in data source; [b]VERISMO data limited to height, weight, and safety laboratory values.
AESI, adverse event of special interest; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; OCR, ocrelizumab; SAE, serious adverse event.

**Table 3. MANUSCRIPT and VERISMO data analysis**

| MANUSCRIPT | VERISMO |
|---|---|
| ▪ All safety endpoints will be presented using incidence rates and 95% CIs<br>▪ Comparative analyses will be performed using a Cox regression model (for incident event) or a Poisson regression model (for recurrent event), and adjusted for measured confounders using propensity score weighting, within each data source<br>▪ Meta-analyses of results across the data sources will be conducted using aggregated data from each source | ▪ All safety endpoints will be presented using incidence rates and 95% CIs<br>▪ Comparison with internal comparators will be performed using a Cox regression model (for incident event) or a Poisson regression model (for recurrent event), and adjusted for measured confounders using propensity score weighting<br>▪ Comparison with external comparators will compare incidence or mortality rates exposed to OCR with data from MSBase Registry and SEER using direct and indirect methods of standardisation |

CI, confidence interval; OCR, ocrelizumab; SEER, Surveillance, Epidemiology, and End Results.

## RESULTS

- The MANUSCRIPT and VERISMO studies are expected to run for approximately 7 to 10 years
- Patient recruitment for the CONFIDENCE study started in April 2018
- MANUSCRIPT and 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 safety events in patients receiving OCR vs other DMTs, accounting for confounders
  - Comparative analyses will be based on incidence rate ratios and survival (time-to-event) Cox regression methods

## CONCLUSIONS

- The post-marketing studies MANUSCRIPT and VERISMO will further characterise the safety profile of ocrelizumab in patients with MS newly exposed to the drug, with a focus on malignancy
- VERISMO is focused on the risk of malignancies, and MANUSCRIPT evaluates long-term safety follow-up, including the risk of malignancies and serious infections
- CONFIDENCE data collected *de novo* will be integrated with existing data from MS registries, providing large-scale data sets for long-term safety assessment studies

## DISCLOSURES

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. H Berthold and P Dirks are employees of Roche Pharma AG. H Berthold is a shareholder of F. Hoffman-La Roche Ltd. J Evershed is an employee of Roche Products Ltd. K Gunzenhauser and D Wormser are employees and shareholders of F. Hoffmann-La Roche Ltd. J Leemhuis is an employee of Roche Pharma AG and shareholder of F. Hoffmann-La Roche Ltd. D Stokmaier and Q Wang are employees of F. Hoffmann-La Roche Ltd. G Ferreira is a contractor providing services to F. Hoffmann-La Roche Ltd.

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