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
- Ocrelizumab has demonstrated superior efficacy to interferon (IFN) β-1a in patients with relapsing-remitting multiple sclerosis (RRMS) and to placebo in patients with primary progressive multiple sclerosis (PPMS) 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
- 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 high number of female breast cancer events in the ocrelizumab group
- The rate of malignancies, and specifically female breast cancers, in ocrelizumab-treated patients was within the range of epidemiological background rates in the general population
- 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 (EUPAS26019) 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 VERSIMO and CONFIDENCE 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-center, 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

Data Sources

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

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

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>HR expected to be ruled out</th>
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</thead>
<tbody>
<tr>
<td>Malignancy (excl. NMSC)</td>
<td>1.42</td>
</tr>
<tr>
<td>Breast cancer (female)</td>
<td>1.79</td>
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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 interferon β-1a or placebo with PPMS 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 study population

Inclusion criteria:
- MS diagnosis
- Age ≥ 18 years

Exclusion criteria:
- Patients who have received ocrelizumab in the context of a previous clinical trial or compassionate use programme if information is available

Figure 2. MANUSCRIPT study objectives

- 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 with available medical records and during individual follow-up in the study observational period

Figure 3. MANUSCRIPT data sources

REFERENCES

5. Wormser D, et al. AAN 2019;Poster P4-2-043.

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

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
- Risk for malignancy will be assessed through an over-treated exposure model (for as long as the study follow-up, regardless of treatment status)
- 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

Table 2. Hazard rates expected to be ruled out with 80% power

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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

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Figure 4. MANUSCRIPT key study milestones

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