BACKGROUND AND AIMS

• Ocrelizumab is a recombinant human 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
• Frequent use 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 higher number of female breast cancer events in the ocrelizumab group
• The rate of malignancies, and specifically female breast cancers, in ocrelizumab-treated patients with multiple sclerosis (MS) under routine clinical care needs further data to characterise and confirm the risk
• Follow-up is planned regardless of whether patients discontinued treatment with ocrelizumab (or alternative MS DMT)

METHODS

• The incidence rates of SAEs, including malignancies and infections, will be compared between patients with MS newly initiated ocrelizumab treatment and those newly initiating IFN-β 1a or 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

Inclusion criteria:
- Patients with multiple sclerosis (MS)
- Age ≥ 18 years
- No previous exposure to ocrelizumab
- New treatment with ocrelizumab during the study observational period

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

Data Sources

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

Data Analysis

• Results will be monitored through regular 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, and 8 and at completion of the study (see Figure 4 for key study milestones)

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

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR expected to be ruled out</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy</td>
<td>Malignancy (excl. NMSC)</td>
</tr>
<tr>
<td></td>
<td>1.43</td>
</tr>
<tr>
<td></td>
<td>Breast cancer (female)</td>
</tr>
<tr>
<td></td>
<td>1.79</td>
</tr>
<tr>
<td>Infections</td>
<td>PML</td>
</tr>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Herpes-related infections</td>
</tr>
<tr>
<td></td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>Candida-related infections</td>
</tr>
<tr>
<td></td>
<td>1.59</td>
</tr>
<tr>
<td></td>
<td>Respiratory infections</td>
</tr>
<tr>
<td></td>
<td>1.20</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infections</td>
</tr>
<tr>
<td></td>
<td>1.16</td>
</tr>
</tbody>
</table>

Assumptions underlying these calculations: (i) No difference in risk between the exposed and unexposed (i.e., HR = 1); (ii) Proportion of female = 69%; (iii) Female breast cancer rates: NMSC, nomenclature according to WHO, PML, progressive multifocal leukoencephalopathy.

REFERENCES