ENSENSE PLUS Study Design: An Investigation of Shortened Ocrelizumab Infusion Time on Infusion-Related Reactions in Patients With Relapsing Multiple Sclerosis From the Phase IIIb ENENSE PLUS Study

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BACKGROUND AND OBJECTIVE

Ocrelizumab is an intravenously administered, humanised anti-CD20 monoclonal antibody approved for the treatment of relapsing forms of multiple sclerosis (MS) and primary progressive MS

- The current approved total infusion time of ocrelizumab (600 mg dose) is 3.5–6 hours, and includes:
  - Premedication/infusion preparation: 1 hour
  - Infusion: 3.5–4 hours
  - Post-infusion observation: 1 hour
- A reduction in infusion time may reduce the burden of administration on the patient, nursing staff and hospital facilities

- Infusion-related reactions (IRRs) are the most common ocrelizumab treatment-related adverse events (AEs)2
- IRR frequency is greatest during the first infusion and severity is generally not related to mild-to-moderate

- The frequency and grade of IRRs in patients with relapsing MS who received ocrelizumab in the pivotal Phase III study is presented in Figure 1
- IRR frequency/severity can be minimised by following the guidelines for the management of specific AEs (Table 1)

Figure 1. IRRs by infusion and grade in relapsing multiple sclerosis patients receiving ocrelizumab 600 mg IV in pivotal Phase III OPERA I and OPERA II (pooled data) studies

Table 1. Infusion pretreatment and guidelines for management of specific adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Action to be taken</th>
</tr>
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<tbody>
<tr>
<td>Mild-to-moderate IRR (e.g. headache)</td>
<td>Infusion should be reduced to half the rate at the time of onset of the event and the patient should receive symptomatic treatment. The infusion should be restarted only after all symptoms have resolved. The initial infusion rate may be increased according to the patient’s infusion schedule</td>
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<tr>
<td>Severe IRR (e.g. flushing, fever and throat pain)</td>
<td>If the patient experiences a severe IRR or a complex of flushing, fever, and throat pain symptoms, the infusion should be interrupted immediately and the patient should receive symptomatic treatment. The infusion should be restarted only after all symptoms have resolved. The initial infusion rate may be increased according to the patient’s infusion schedule</td>
</tr>
<tr>
<td>Life-threatening or disabling IRR (e.g. anaphylaxis)</td>
<td>Immediately stop ocrelizumab if there are signs of life-threatening or disabling/recovering IRR and if an infusion such as an acute hypotension or anaphylaxis requires emergency medical treatment. The patient should receive appropriate treatment. Permanently discontinue ocrelizumab in these patients</td>
</tr>
</tbody>
</table>

- The impact of reducing infusion time on ocrelizumab-related IRRs will be investigated in ENENSE PLUS
- ENENSE PLUS is a substudy of an ongoing Phase IIb, open-label, single-arm investigation of the effectiveness and safety of ocrelizumab in patients with early-stage relapsing-remitting MS (RRMS) (ENSEMBLE [NCT03568810]).
- The objective of this presentation is to describe the design of the ENENSE PLUS substudy

METHODS

Study Design

- In the ENENSE PLUS substudy, a subgroup of eligible patients from the main ENENSE PLUS study will be randomised with equal allocation into a conventional infusion group (infusion duration: 3.5 hours) and a short infusion group (infusion duration: 2 hours) at the next scheduled infusion under a double-blind setting
- In addition to the optional randomisation of patients from ENENSE PLUS, ENENSE PLUS will recruit an additional 300 patients (first enrolled within ENENSE PLUS) for the evaluation of IRRs starting at the Week 24 infusion

- ENENSE PLUS inclusion criteria:
  - Diagnosis of early-stage RRMS (per revised McDonald 2010 criteria)2
  - Age 18–55 years (inclusive) and disease duration ≤3 years
  - Expanded Disability Status Scale score 0–5.5 (inclusive) and treatment naïve
  - ≥1 relapse or 1 gadolinium-enhancing lesion in prior 12 months
  - Inclusion in double-blind randomisation
  - Disease-modifying therapy treatment naïve
  - Patients with prior serious ocrelizumab-related IRRs will be excluded from ENENSE PLUS
  - IRR frequency and severity will be examined after each infusion administration
  - The design of ENENSE PLUS is presented in Figure 2
  - The location of ENENSE PLUS study sites is presented in Figure 3

DISCLOSURES

*Disclosure form is not available but can be requested.**grant(s) or support(s) received from (e.g.,paracetamol) approximately 30–60 minutes prior to each infusion. Additional antipyretics (e.g. paracetamol) may also be considered; **study was a human trial approved by the Rector of Heinrich-Heine University Düsseldorf from Bayer, Biogen, F. Hoffmann-La Roche Ltd, GeNeuro SA, Genzyme, MedImmune, Merck Serono, Novartis,

Figure 2. ENENSE PLUS study design

Figure 3. ENENSE PLUS study sites locations

Study Treatments

- Patients in ENENSE receive ocrelizumab 300 mg infusions on Day 1 and on Weeks 2 and 300 mg infusions on week 24, 48, 72, 96, 120, 144 and 186. Patients already included in ENENSE can be randomised directly to the ENENSE PLUS conventional and short infusion protocols at any upcoming infusion.
- Patients entering ENENSE who were already enrolled in ENENSE will enter ENENSE PLUS at any visit after the Week 24 visit and receive ocrelizumab per the schedule above:
  - The first dose will be administered as 2 x 300 mg infusions 14 days apart
  - Ocrelizumab 300 mg infusions are administered as:
    - Conventional infusion group: 500 mL infusions over 3.5 hours
    - Short infusion group: 500 mL infusions over 2 hours with an additional saline 100 mL infusion administered over 15 hours to maintain blinded conditions
  - The saline switch in the short infusion group will be mimicked in the conventional infusion group
  - IRRs will be administered by unblinded infusion staff
- ENENSE PLUS infusion schedule is presented in Figure 4

Figure 4. Infusion schedule

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LITERATURE