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Original article

Shorter infusion time of ocrelizumab: Results from the randomized, double-blind ENSEMBLE PLUS substudy in patients with relapsing-remitting multiple sclerosis

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Abbreviations: AE, adverse event; CCOD, clinical cut-off date; eCRF, electronic Case Report Form; IRR, infusion-related reaction; ITT, Intent-to-Treat; MedDRA, Medical Dictionary for Regulatory Activities; MS, multiple sclerosis; PK, pharmacokinetics; PT, preferred term; RMS, relapsing multiple sclerosis; RoW, rest of the world; RRMS, relapsing-remitting multiple sclerosis; SAE, serious adverse event; SOC, system organ class; US, United States

Keywords:
Ocrelizumab
shorter infusion
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infusion-related reaction

ABSTRACT

Background: Ocrelizumab is an approved intravenously administered anti-CD20 antibody for multiple sclerosis (MS). Shortening the 600 mg infusion to 2 hours reduces the total site stay from 5.5–6 hours (approved infusion duration including mandatory pre-medication and post-infusion observation) to 4 hours. The safety profile of shorter-duration ocrelizumab infusions was investigated using results from ENSEMBLE PLUS.

Methods: ENSEMBLE PLUS is a randomized, double-blind substudy to the single-arm ENSEMBLE study (NCT03085810). In ENSEMBLE, patients with early-stage relapsing-remitting MS received ocrelizumab 600 mg infusions every 24 weeks for 192 weeks. In ENSEMBLE PLUS, ocrelizumab 600 mg administered over the approved 3.5-hour infusion time (conventional duration) is compared with a 2-hour infusion (shorter duration); the durations of the initial infusions (2 × 300 mg, 14 days apart) were unaffected. The primary endpoint was the proportion of patients with infusion-related reactions (IRRs) following the first Randomized Dose.

Results: From November 1, 2018, to December 13, 2019, 745 patients were randomized 1:1 to the conventional or shorter infusion group. At the first Randomized Dose, 99/373 patients (26.5%) in the conventional and 107/372 patients (28.8%) in the shorter infusion group experienced IRRs. The majority of IRRs were mild or moderate; > 99% of all IRRs resolved without sequelae in both groups (conventional infusion group, 99/99; shorter infusion group, 106/107). No IRRs were serious, life-threatening, or fatal. No IRR-related discontinuations occurred. During the first Randomized Dose, 22/373 (5.9%) and 39/372 (10.5%) patients in the conventional and shorter infusion groups, respectively, had IRRs leading to infusion slowing/interruption. Adverse events were consistent with the known safety profile of ocrelizumab.

Conclusion: The rates and severity of IRRs were similar between conventional and shorter infusions. No new safety signals were detected. Shortening the infusion time to 2 hours reduces the total site stay time (including

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mandatory pre-medication/infusion/observation) from 5.5–6 hours to 4 hours, and may reduce patient and site staff burden. A short video summarizing the key results is provided in supplemental material.

1. Introduction

Ocrelizumab is a humanized anti-CD20 monoclonal antibody approved for the treatment of relapsing multiple sclerosis (RMS) and primary progressive multiple sclerosis [1, 2]. Infusion-related reactions (IRRs) were among the most common adverse events (AEs) reported with ocrelizumab in the controlled treatment periods of the pivotal Phase III trials (OPERA I [NCT01247324], OPERA II [NCT01412333], and ORATORIO [NCT01194570]) [3, 4]. In the pooled OPERA population and the ORATORIO population, IRRs were mostly mild to moderate, were more frequent with the first ocrelizumab infusion, and decreased with subsequent dosing [3-5].

Ocrelizumab is currently administered as an initial dose of two 300 mg intravenous infusions 2 weeks apart, each lasting at least 2.5 hours, with subsequent doses administered every 6 months as single 600 mg infusions lasting at least 3.5 hours [1, 2]. The infusion schedule also includes pre-medication 30–60 minutes prior to each infusion of ocrelizumab, with a 1-hour post-infusion observation period. In general, but now also in light of the COVID-19 pandemic, there is an increasing burden on patients and hospital staff. Reducing the infusion time may minimize the treatment burden for patients and reduce the time required at the infusion site, without compromising on patient safety [6-8].

The ENSEMBLE PLUS study is a randomized, double-blind substudy to the single-arm ENSEMBLE study (NCT03085810) evaluating the safety, including IRRs, of a shorter infusion of ocrelizumab versus conventional infusion in a subgroup of eligible patients with relapsing-remitting multiple sclerosis (RRMS) enrolled in the main ENSEMBLE study. Primary results from ENSEMBLE PLUS in a cohort of 580 patients (interim clinical cut-off date [CCOD] September 27, 2019) demonstrated that the frequency and severity of IRRs were comparable between conventional and shorter ocrelizumab infusion periods [9]. Here, we describe the results from the full cohort of patients randomized into ENSEMBLE PLUS (n = 745).

2. Materials and methods

2.1. Trial design and patients

The ENSEMBLE PLUS substudy is a prospective, multicenter, randomized, double-blind Phase IIIb study designed to evaluate the safety of a shorter-duration infusion of ocrelizumab in patients with early-stage RRMS enrolled in the main ENSEMBLE study. In ENSEMBLE, treatment-naive patients (age 18–55 years) with a confirmed diagnosis of RRMS (as per 2010 McDonald criteria) [10], disease duration ≤3 years, one or more relapses/signs of MRI activity in the prior 12 months, and an Expanded Disability Status Scale score of 0–3.5 (inclusive), received ocrelizumab 600 mg infusions every 24 weeks for 192 weeks (up to eight doses) with mandatory pre-medication. The target enrollment was 700 patients in the ENSEMBLE PLUS substudy, which included 150 patients already enrolled in the main ENSEMBLE study plus 550 newly enrolled patients; the number of patients recruited was based on the precision of the confidence intervals expected. Patients with a previous serious ocrelizumab-related IRR were excluded from the substudy.

In all patients, the first dose of ocrelizumab was administered, per label, as an initial dose of two 300 mg infusions, separated by 14 days (Supplemental Fig. 1). Randomization to either the conventional infusion group or the shorter infusion group occurred at Week 24 for newly enrolled patients. For patients already enrolled in the main ENSEMBLE study, randomization occurred at their next scheduled infusion (Week 48, 72, 96, or 120). Patients eligible to take part in this substudy were randomized (1:1) into a conventional infusion group (infusion duration: 3.5 hours) and a shorter infusion group (infusion duration: 2 hours), stratified by region (Australia, Canada, United States [US] versus rest of the world [RoW]) and dose at which the patient is randomized. An independent voice/web response system (IxRS) provider conducted randomization (with use of blocked randomization) and holds the treatment assignment code. In the conventional infusion group, patients received 600 mg ocrelizumab in 500 mL 0.9% sodium chloride infused over approximately 3.5 hours every 24 weeks for the remainder of the study duration. In the shorter infusion group, patients received an infusion of 600 mg ocrelizumab in 500 mL 0.9% sodium chloride infused over 2 hours, followed by 100 mL 0.9% sodium chloride given as a slow infusion over the remaining 1.5 hours, in order to mimic the conventional infusion duration of 3.5 hours, every 24 weeks for the remainder of the study duration (Supplemental Fig. 2a). Patients, site personnel, and the sponsor study management team remained blinded during the study. Infusions were preloaded and placed into standardized infusion cover bags on an infusion rack; the infusion administration pump was covered and operated only by an unblinded infusion nurse (Supplemental Fig. 2b). Blood samples for pharmacokinetics (PK) were only collected at the first ocrelizumab infusion post-randomization, one sample 5–30 minutes before the intravenous methylprednisolone premedication and samples 30 minutes after the completion of the shorter infusion and of the conventional infusion, representing the peak concentration of ocrelizumab. This manuscript reports results from the CCOD of December 13, 2019, when all patients had received the first Randomized Dose.

2.2. Standard protocol approvals, registrations, and patient consent

The relevant institutional review boards/ethics committees approved the trial protocols (NCT03085810). All patients provided written informed consent. The Steering Committee and study investigators gathered the data, and the sponsor performed the data analyses. The authors and Steering Committee agreed to submit the manuscript for publication.

2.3. Study objectives

The primary endpoint was the proportion of patients with IRRs during the infusion or within 24 hours after the infusion of the first Randomized Dose. Secondary endpoints included the severity and symptoms of IRRs, IRRs leading to treatment discontinuation, and the proportion of patients with IRRs overall and by dose after randomization. Additional exploratory endpoints related to IRRs were evaluated, and the overall safety was assessed.

AEs that occurred during or within 24 hours after the infusion and were judged to be related to the infusion were captured as an IRR on the AE electronic Case Report Form (eCRF), and associated IRR symptoms were reported on the dedicated IRR eCRF. In order not to miss any IRRs, investigational sites contacted the patients via phone after 24 hours post-infusion to capture any other IRR that might have occurred during this time period. IRR symptoms were coded by Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT). IRRs were classified as occurring during the infusion or within 24 hours after the end of the infusion. IRR events occurring in a patient at both time points (during and post-infusion) were reported as two separate IRRs per infusion.

The primary summaries of IRRs were performed using the Intent-to-Treat (ITT) Population. All randomized patients were included in the ITT Population; patients were analyzed according to their randomized treatment, regardless of treatment actually received.

2.4. Safety reporting

Safety was assessed through the monitoring and recording of AEs and serious AEs. AEs were defined as all AEs including IRRs and serious MS relapses, but excluding non-serious MS relapses. AEs were reported from the first Randomized Dose onwards until the CCOD. All AEs with an onset date after the date of the first Randomized Dose were included, even if the onset was after the patient discontinued randomized treatment. AEs and serious AEs were coded by MedDRA Version 22.1 and summarized by SOC and PT.

Safety analyses are based on the Safety Population. This included all randomized patients who received any dose or part of a dose of ocrelizumab treatment and were analyzed according to the treatment actually received.

2.5. Statistical methods

Safety assessments were summarized using descriptive statistics with no formal hypothesis testing. The proportion of patients with IRRs that occurred during the infusion or within 24 hours after the infusion of the first Randomized Dose of ocrelizumab was compared between the shorter and conventional infusion groups, and point estimates of the between-treatment difference and associated symmetric 95% CIs were estimated; these estimates are presented, both unstratified and stratified, by dose at which the patient was randomized and by region (Australia/Canada/US versus RoW). The weighted average of the proportion difference across strata based on Cochran-Mantel-Haenszel weights was estimated. This approach resulted in a stratified estimated difference between the proportions in the two randomized groups, which was presented along with an associated 95% CI.

All summaries of IRRs are based on the ITT Population (all randomized patients), safety analyses are based on the Safety Population (all randomized patients who received any dose or part of a dose of ocrelizumab treatment), and the PK data are based on the PK population (randomized patients receiving any ocrelizumab treatment who had ≥1 measurable concentration value).

Table 1
Baseline patient demographics and disease characteristics.

	Conventional infusion (N = 373)	Shorter infusion (N = 372)
Age at first Randomized Dose,[a] years, mean (SD)	**34.2 (8.6)**	**34.2 (9.0)**
Sex, n (%)		
Male	138 (37.0)	133 (35.8)
Female	235 (63.0)	239 (64.2)
Race, n (%)		
African Indian or Alaska native	2 (0.5)	4 (1.1)
Asian	4 (1.1)	5 (1.3)
Black or African American	15 (4.0)	11 (3.0)
Native Hawaiian or other Pacific Islander	0	1 (0.3)
White	312 (83.6)	308 (82.8)
Multiple	16 (4.3)	20 (5.4)
Unknown	24 (6.4)	23 (6.2)
Weight, kg, mean (SD)	**76.7 (20.1)**	**75.5 (21.1)**
BMI, kg/m^2, mean (SD)	**26.3 (6.2)**	**26.1 (6.7)**
Time since first symptom,[a] years, mean (SD)	**1.8 (1.0)**	**1.8 (1.2)**
Randomization assignment by stratification, n		
US/Canada/Australia	112	112
ROW	261	260

All patients, ITT Population.
With the exception of age and duration since RMS diagnosis, all other demographic characteristics were recorded at the screening visit of the ENSEMBLE study.
BMI, body mass index; ITT, Intent-to-Treat; MS, multiple sclerosis; RMS, relapsing multiple sclerosis; ROW, rest of the world; US, United States.
[a] Calculated as the date of first Randomized Dose minus date of birth (for age) or date of first MS symptom (for time since first symptom), divided by 365.25.

3. Results

3.1. Patient disposition and analysis population

A total of 754 patients were enrolled in the ENSEMBLE PLUS study (207 from the main ENSEMBLE study and 547 newly enrolled patients) across 96 investigational sites across 22 countries. Of the 754 patients enrolled, 745 patients were randomized (1:1), stratified by region and dose at which the patient was randomized, to the conventional infusion group (N = 373) or shorter infusion group (N = 372) (Fig. 1). At the

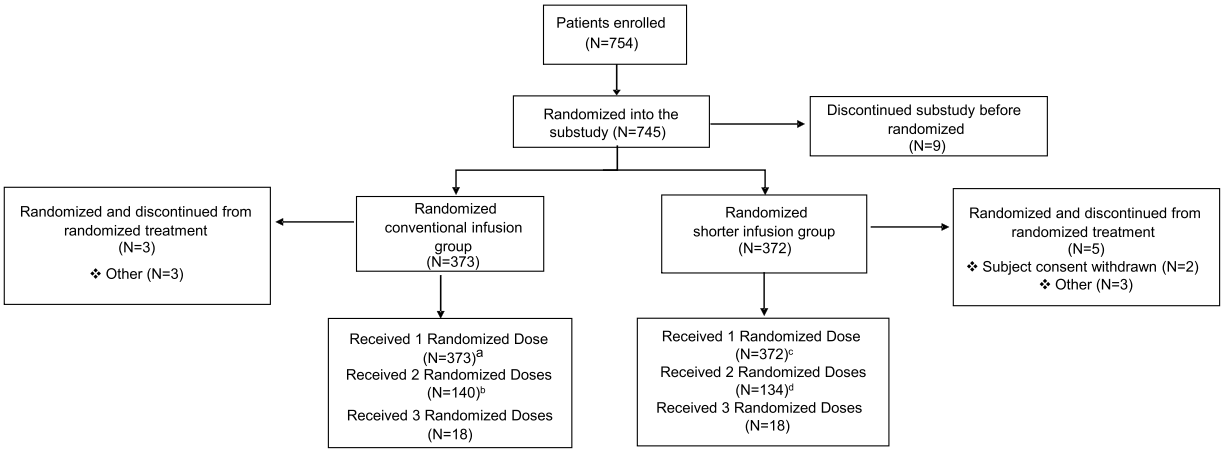

Fig. 1. Patient disposition and analysis population.
[a] Patients in the conventional infusion arm who received the first Randomized Dose only, n = 233.
[b] Patients in the conventional infusion group who received the first and second Randomized Doses only, n = 122. [c] Patients in the shorter infusion arm who received the first Randomized Dose only, n = 238. [d] Patients in the shorter infusion group who received the first and second Randomized Doses only, n = 116. CCOD: December 13, 2019. CCOD, clinical cut-off date.

CCOD, three patients (0.8%, n = 3/373) had discontinued from the conventional infusion group and five patients (1.5%, n = 5/372) had discontinued from the shorter infusion group. Reasons for withdrawal in the conventional infusion group were 'other' (n = 3), and in the shorter infusion group were 'other' (n = 3) and 'subject consent withdrawn' (n = 2). Baseline demographics and disease characteristics were well balanced across both infusion groups (Table 1). The majority of patients were female (63.0–64.2%) and white (82.8–83.6%), with mean age of 34.2 years and a mean time since first MS symptom of 1.8 years. The proportion of patients with IRRs prior to the first Randomized Dose was n = 107 (28.7%) in the conventional and n = 114 (30.6%) in the shorter infusion group.

3.2. Shorter infusion time summary

All randomized patients received at least one Randomized Dose of ocrelizumab. In total, 140/373 patients (37.5%) and 134/372 patients (36.0%) in the conventional and shorter infusion group, respectively, received the second Randomized Dose of ocrelizumab. Eighteen patients (4.8%) in both the conventional and shorter infusion groups received the third Randomized Dose. The median (IQR) infusion times across all Randomized Doses in the conventional and shorter infusion groups were 215 (193–350) minutes and 120 (100–300) minutes, respectively, resulting in a reduction in median infusion time of approximately 95 minutes.

3.3. Infusion-related reactions

A summary of IRRs that occurred at the first Randomized Dose is presented in Table 2. The number of patients who experienced an IRR (during or within 24 hours post-infusion) following the first Randomized Dose (primary endpoint) was 99/373 patients (26.5%) in the conventional infusion group and 107/372 patients (28.8%) in the shorter infusion group (difference in proportions, stratified estimates [95% CI]: 2.44% [–3.83%, 8.71%]; Fig. 2). The number of patients who experienced an IRR following the second Randomized Dose was 26/140 patients (18.6%) in the conventional infusion group and 36/134 patients (26.9%) in the shorter infusion group. Of those who had received the third Randomized Dose at the CCOD, 1/18 patients (5.6%) and 4/18 patients (22.2%) in the conventional and shorter infusion group, respectively, experienced an IRR. The majority of IRRs reported at each Randomized Dose were mild (Grade 1) or moderate (Grade 2) in severity (Table 3). Across all Randomized Doses, there were four severe (Grade 3) IRRs in total, in separate patients; one in the conventional infusion group (laryngeal inflammation) and three in the shorter infusion group (headache, oropharyngeal pain/pharyngeal swelling, and fatigue). No IRRs were serious, life-threatening or fatal, and no IRR-related discontinuations occurred. The majority of all IRRs (conventional infusion group, n = 99/99 [100%]; shorter infusion group, n = 106/107 [99.1%]) resolved without sequelae in both groups (Table 3). One patient in the shorter infusion group was still recovering from Grade 2 back pain/fatigue/nausea at the CCOD.

In patients receiving the first Randomized Dose at Dose 4, the rate of IRRs at first Randomized Dose was lower in the conventional infusion arm (n = 8/61; 13.1%) compared with the shorter infusion arm (n = 17/59; 28.8%) (Fig. 2). It is thought that IRRs prior to randomization increase the probability of an IRR at a later dose; the rate of patients with IRRs prior to randomization and who received their first Randomized Dose at Dose 4 was 4.8% (n = 18/373) in the conventional infusion group (versus 7.3% [n = 27/372] in the shorter infusion group). Overall, in the conventional infusion group, 19.5% of patients (n = 52/266) with no pre-randomization IRR experienced an IRR, and in the shorter infusion group, 19.0% of patients (n = 49/258) with no pre-randomization IRR experienced an IRR at the first Randomized Dose (Table 4).

During the infusion of the first Randomized Dose, IRRs were experienced by 44/373 patients (11.8%) in the conventional group and 65/372 patients (17.5%) in the shorter infusion group overall (Table 3). The most common symptoms during the infusion, occurring in ≥5% of patients in each group, were throat irritation, dysphagia, and ear pruritus. Within the 24 hours post-infusion, IRRs were reported by 66/373 patients (17.7%) in the conventional infusion group and 53/372 patients (14.2%) in the shorter infusion group, respectively. Most common symptoms within 24 hours post-infusion were fatigue, headache, and nausea (Table 3).

At the first Randomized Dose, 42/99 patients (42.4%) in the conventional and 45/107 patients (42.1%) in the shorter infusion group received symptomatic treatment for any IRR. Most common symptomatic treatments in both groups included antihistamines, antiemetics, and analgesics.

In total, 22/373 patients (5.9%) and 39/372 patients (10.5%) had an IRR at the first Randomized Dose that led to intervention (i.e. slowing down or temporary interruption of the infusion) in the conventional and shorter infusion group, respectively (Table 3). The most common symptom that led to intervention of the infusion was throat irritation.

There was no correlation between peak serum ocrelizumab concentration and observed IRRs. Vital signs (pulse rate, systolic blood pressure, and diastolic blood pressure) were similar between both arms.

Table 2
Overall rates and severity of IRRs at all randomized doses.

Randomized Dose		Conventional infusion (N = 373)	Shorter infusion (N = 372)
First	**Number (%) of patients with an infusion**	**373 (100.0)**	**372 (100.0)**
	Number (%) of patients with any IRR (primary endpoint)	**99 (26.5)**	**107 (28.8)**
	Mild (Grade 1)	69 (69.7)[a]	67 (62.6)[a]
	Moderate (Grade 2)	30 (30.3)[a]	37 (34.6)[a]
	Severe (Grade 3)	0	3 (2.8)[a]
Second	**Number (%) of patients with an infusion**	**140 (37.5)**	**134 (36.0)**
	Number (%) of patients with any IRR	**26 (18.6)**	**36 (26.9)**
	Mild (Grade 1)	19 (73.1)[a]	24 (66.7)[a]
	Moderate (Grade 2)	6 (23.1)[a]	12 (33.3)[a]
	Severe (Grade 3)	1 (3.8)[a]	0
Third	**Number (%) of patients with an infusion**	**18 (4.8)**	**18 (4.8)**
	Number (%) of patients with any IRR	**1 (5.6)**	**4 (22.2)**
	Mild (Grade 1)	1 (100.0)[a]	3 (75.0)[a]
	Moderate (Grade 2)	0	1 (25.0)[a]
	Severe (Grade 3)	0	0

IRR, infusion-related reaction.
[a] Percentages based on the total number of patients with any IRR.

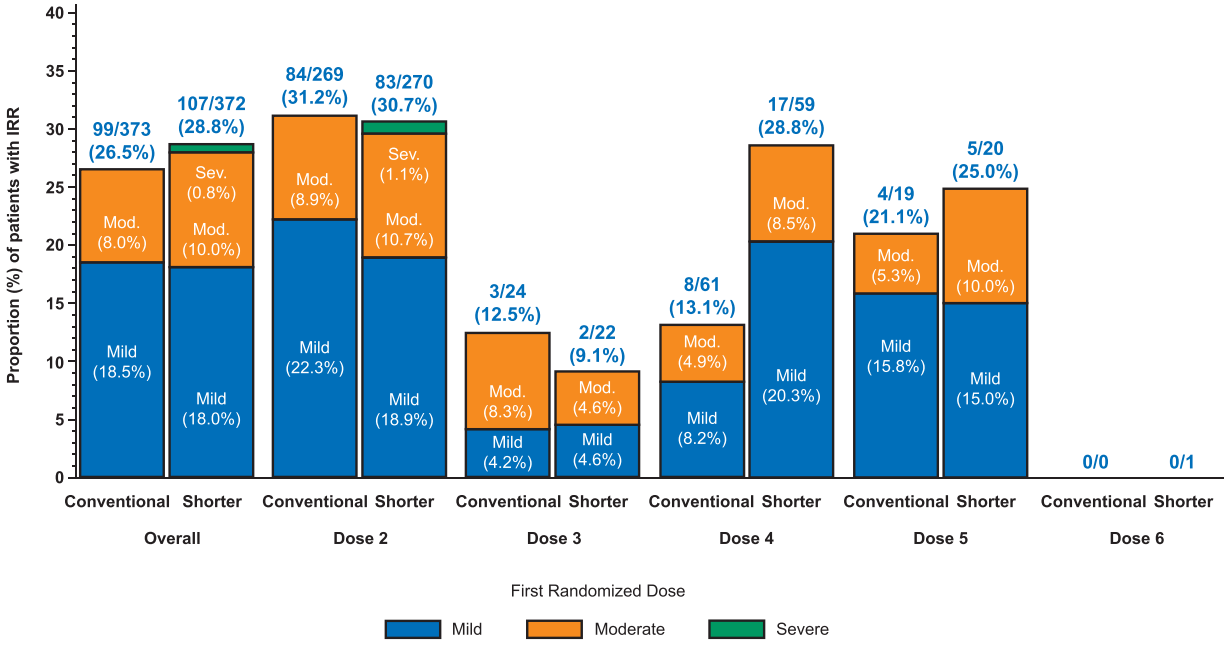

Fig. 2. Patients with at least one IRR at the first Randomized Dose.
Difference in proportions of patients with an IRR overall (first two columns): unstratified estimates (95% CI): 2.22% (–4.20%, 8.64%); stratified estimates (95% CI): 2.44% (–3.83%, 8.71%). IRR, infusion-related reaction.

3.4. Adverse events

Overall, 58.8% of patients (n = 218/371) in the conventional infusion group and 54.8% of patients (n = 205/374) in the shorter infusion group experienced AEs (Table 5). The most common AEs, reported in ≥5% of patients in each treatment arm, were IRRs, nasopharyngitis, and headache. Most AEs were mild or moderate; eight severe (Grade 3) AEs were reported in the conventional infusion arm and six in the shorter infusion arm. There was one life-threatening (Grade 4) AE, which occurred in the conventional infusion arm; this was a case of typhoid fever which recovered and the patient did not discontinue from ocrelizumab. One patient in the conventional infusion group discontinued from ocrelizumab treatment due to an AE (depressive symptom; not considered to be related to ocrelizumab); no patients in the shorter infusion group discontinued due to an AE. Serious AEs were reported by nine patients in total: four in the conventional infusion group and five in the shorter infusion group. One patient in the conventional group withdrew from ocrelizumab treatment due to a serious AE (depressive symptom; not considered to be related to ocrelizumab). There were no fatal AEs.

4. Discussion

Results from the ENSEMBLE PLUS study show that the frequency, severity, and symptoms of IRRs were similar between conventional and shorter ocrelizumab infusions at the first Randomized Dose.

The majority of IRRs experienced in the shorter infusion group were mild to moderate in severity, which demonstrates good tolerability of shorter ocrelizumab infusions. Overall, in ENSEMBLE PLUS, 1 out of the 126 IRRs (0.8%) in the conventional group were severe (Grade 3) and 3 out of the 147 IRRs (2.0%) in the shorter infusion group were severe; there were no Grade 4 or Grade 5 IRRs reported and no IRRs resulted in discontinuation of the infusions up to the CCOD. No IRRs were serious, life-threatening, or fatal.

Interestingly, the most common IRR symptoms that occurred during the infusion of the first Randomized Dose were different from those observed within 24 hours post-infusion. The most common symptoms during the infusion were pruritus, dysphagia, and throat irritation. This was similar to the symptoms observed in pivotal trials [3-5]. The most common symptoms which occurred within 24 hours post-infusion in ENSEMBLE PLUS were fatigue, headache, and nausea.

Overall, <10% of IRRs led to intervention (slowing down or temporary interruption of the infusion). At the first Randomized Dose, there was a lower incidence of IRRs leading to infusion slowing/interruption in the conventional (22 of 373 patients; 5.9%) versus shorter (39 of 372 patients; 10.5%) infusion group. However, these interventions were mild and did not lead to discontinuation of the infusion, nor to a higher rate of IRRs requiring medical treatment in the shorter infusion group. Furthermore, despite interventions, the median infusion time in the shorter infusion group remained at 120 minutes.

In patients receiving the first Randomized Dose at Dose 4, the rate of IRRs at first Randomized Dose was higher in the shorter infusion arm compared with the conventional arm. This was likely due to an imbalance in the number of patients with prior IRRs before the first Randomized Dose. When looking only at patients without any prior IRR, the rate of IRR at first Randomized Dose was similar in both arms. This suggests that having an IRR before the first Randomized Dose was an important identified predictor for experiencing another IRR, and that the speed of the infusion did not appear to affect the rates or severity of IRRs.

Whilst the rates of IRRs at the second and third Randomized Dose at the CCOD appear to be slightly higher in the shorter infusion group compared with the conventional infusion group, the low number of patients precludes drawing meaningful conclusions. As the ENSEMBLE PLUS substudy is ongoing, rates of IRRs over Randomized Doses will be continued to be monitored closely.

Overall, the AEs observed in ENSEMBLE PLUS were consistent with the known safety profile of ocrelizumab [3-5], and no new safety signals were observed. The safety profile of ocrelizumab remains unchanged.

The ENSEMBLE PLUS study was carried out in a very specific RRMS population, with patients who had early disease. In-depth analyses have not been carried out, but overall, there is not expected to be a difference in IRRs based on MS phenotype (RRMS, RMS or primary progressive MS [PPMS]). The CHORDS study (NCT02637856) assessed ocrelizumab in US patients with RRMS who had a suboptimal response to previous

Table 3
Summary of IRRs at first Randomized Dose by: **(i)** Symptoms of IRRs during the infusion; **(ii)** Symptoms of IRRs within 24 hours post-infusion; **(iii)** Symptomatic treatment of IRRs; **(iv)** IRRs leading to intervention in ocrelizumab infusion; **(v)** Outcomes of IRRs.

	Conventional infusion (N = 373)	Shorter infusion (N = 372)
Number (%) of patients with an infusion	**373 (100.0)**	**372 (100.0)**
Number (%) of patients with any IRR	**99 (26.5)**	**107 (28.8)**
Number (%) of patients with any IRR during the infusion[a]	**44 (11.8)**	**65 (17.5)**
Number (%) of patients with any IRR within 24h post-infusion[a]	**66 (17.7)**	**53 (14.2)**
(i) Symptoms of IRRs during the infusion[b]		
Respiratory, thoracic and mediastinal disorders	**24 (24.2)**	**40 (37.4)**
Throat irritation	19 (19.2)	32 (29.9)
Oropharyngeal	4 (4.0)	6 (5.6)
Throat tightness	2 (2.0)	1 (0.9)
Dyspnea	1 (1.0)	1 (0.9)
Pharyngeal swelling	0	2 (1.9)
Dry throat	1 (1.0)	0
Increased upper airway secretion	0	1 (0.9)
Laryngeal inflammation	1 (1.0)	0
Nasal congestion	0	1 (0.9)
Oropharyngeal edema	0	1 (0.9)
Gastrointestinal disorders	**9 (9.1)**	**11 (10.3)**
Dysphagia	7 (7.1)	8 (7.5)
Nausea	0	2 (1.9)
Dyspepsia	1 (1.0)	0
Glossodynia	0	1 (0.9)
Lip pruritus	1 (1.0)	0
Odynophagia	0	1 (0.9)
Oral pain	0	1 (0.9)
Skin and subcutaneous tissue disorders	**7 (7.1)**	**10 (9.3)**
Rash	1 (1.0)	7 (6.5)
Pruritus	3 (3.0)	3 (2.8)
Erythema	2 (2.0)	0
Rash pruritic	1 (1.0)	0
Ear and labyrinth disorders	**6 (6.1)**	**7 (6.5)**
Ear pruritus	6 (6.1)	6 (5.6)
Ear discomfort	0	1 (0.9)
Nervous system disorders	**4 (4.0)**	**5 (4.7)**
Headache	3 (3.0)	3 (2.8)
Burning sensation	0	1 (0.9)
Sensory disturbance	0	1 (0.9)
Somnolence	1 (1.0)	0
General disorders and administration site conditions	**6 (6.1)**	**2 (1.9)**
Chest discomfort	4 (4.0)	0
Fatigue	1 (1.0)	1 (0.9)
Feeling hot	0	1 (0.9)
Influenza-like illness	1 (1.0)	0
Vascular disorders	**0**	**4 (3.7)**
Hypertension	0	2 (1.9)
Hypotension	0	1 (0.9)
Pallor	0	1 (0.9)
Eye disorders	**1 (1.0)**	**1 (0.9)**
Eye pruritus	1 (1.0)	0
Lacrimation increased	0	1 (0.9)
Investigations	**1 (1.0)**	**1 (0.9)**
Blood pressure diastolic decreased	1 (1.0)	0
Blood pressure increased	0	1 (0.9)
Cardiac disorders	**0**	**1 (0.9)**
Bradycardia	0	1 (0.9)
Musculoskeletal and connective tissue disorders	**1 (1.0)**	**0**
Back pain	1 (1.0)	0
(ii) Symptoms of IRRs within 24 hours post-infusion[b]		
General disorders and administration site conditions	**31 (31.3)**	**22 (20.6)**
Fatigue	23 (23.2)	20 (18.7)
Pyrexia	4 (4.0)	1 (0.9)
Chest discomfort	1 (1.0)	0
Chest pain	1 (1.0)	0
Feeling hot	1 (1.0)	0
Feeling jittery	1 (1.0)	0
Injection site bruising	1 (1.0)	0
Pain	1 (1.0)	0
Peripheral swelling	0	1 (0.9)
Swelling face	0	1 (0.9)
Thirst	1 (1.0)	0
Nervous system disorders	**32 (32.3)**	**21 (19.6)**
Headache	24 (24.2)	18 (16.8)
Dizziness	4 (4.0)	1 (0.9)
Tremor	2 (2.0)	1 (0.9)
Paresthesia	2 (2.0)	0
Tension headache	1 (1.0)	1 (0.9)
Disturbance in attention	1 (1.0)	0
Migraine	1 (1.0)	0
Gastrointestinal disorders	**9 (9.1)**	**11 (10.3)**
Nausea	8 (8.1)	7 (6.5)
Diarrhea	0	2 (1.9)
Abdominal discomfort	0	1 (0.9)
Feces soft	0	1 (0.9)
Flatulence	1 (1.0)	0
Respiratory, thoracic and mediastinal disorders	**11 (11.1)**	**5 (4.7)**
Oropharyngeal pain	3 (3.0)	2 (1.9)
Throat irritation	4 (4.0)	1 (0.9)
Dyspnea	3 (3.0)	0
Dry throat	1 (1.0)	0
Dyspnea exertional	0	1 (0.9)
Nasal congestion	0	1 (0.9)
Sneezing	0	1 (0.9)
Vascular disorders	**13 (13.1)**	**3 (2.8)**
Flushing	9 (9.1)	3 (2.8)
Hot flush	3 (3.0)	0
Pallor	1 (1.0)	0
Musculoskeletal and connective tissue disorders	**7 (7.1)**	**4 (3.7)**
Pain in extremity	3 (3.0)	1 (0.9)
Arthralgia	1 (1.0)	1 (0.9)
Back pain	0	2 (1.9)
Myalgia	2 (2.0)	0
Limb discomfort	0	1 (0.9)
Muscle fatigue	1 (1.0)	0
Skin and subcutaneous tissue disorders	**5 (5.1)**	**3 (2.8)**
Pruritus	3 (3.0)	1 (0.9)
Rash	3 (3.0)	0
Erythema	0	2 (1.9)
Cardiac disorders	**2 (2.0)**	**4 (3.7)**
Tachycardia	1 (1.0)	3 (2.8)
Palpitations	2 (2.0)	1 (0.9)
Ear and labyrinth disorders	**0**	**1 (0.9)**
Vertigo	0	1 (0.9)
Infections and infestations	1 (1.0)	0
Oral herpes	1 (1.0)	0
(iii) Number (%) of patients with any symptomatic treatment for any IRR	**42 (42.4)**[b]	**45 (42.1)**[b]
Paracetamol	8 (19.0)[c]	5 (11.1)[c]
Diphenhydramine hydrochloride	9 (21.4)[c]	13 (28.9)[c]
Chlorphenamine	8 (19.0)[c]	9 (20.0)[c]
(iv) Number (%) of patients with any IRR leading to intervention in ocrelizumab infusion	**22 (5.9)**	**39 (10.5)**
Infusion discontinued	0	0

(*continued on next page*)

Table 3 (*continued*)

	Conventional infusion (N = 373)	Shorter infusion (N = 372)
Infusion interrupted	14 (63.6)[d]	22 (56.4)[d]
Infusion slowed down	8 (36.4)[d]	17 (43.6)[d]
(v) IRR outcome, n (%)[b]		
Recovered/resolved	99 (100)	106 (99.1)
Recovered/resolved with sequelae	0	0
Recovering/resolving	0	1 (0.9)

IRR symptoms are displayed in descending order of frequency of SOC and by preferred term within SOC. If a patient experienced more than one episode of an IRR symptom, then the patient was counted only once for that symptom. If a patient had more than one symptom in an SOC, then the patient was counted only once in that SOC. SOC and preferred terms were defined using MedDRA Version 22.1 thesaurus terms.

IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; SOC, system organ class.

[a] The combined number of patients with IRRs during the infusion and within 24h post-infusion add up to more than the total number of patients with any IRR, as IRR events occurring in a patient at both time points (during and post-infusion) were reported as two separate IRRs per infusion.

[b] Percentages based on the total number of patients with any IRR.

[c] Percentages based on number of patients with any symptomatic treatment for any IRR.

[d] Percentages based on the total number of patients with any IRR leading to intervention of ocrelizumab infusion.

disease-modifying treatments. This study also examined the shorter ocrelizumab infusion rate in these patients and noted very comparable results to ENSEMBLE PLUS, with no new safety signals [11]. The SaROD shorter infusion study in the US (NCT03606460) looked at a population which included some patients with PPMS (in line with the ocrelizumab label). Although it was hard to draw meaningful conclusions due to the small sample size, there were no signals to indicate that MS phenotype could impact the rate or severity of IRRs [12]. Similarly, when looking at data from the ORATORIO or OPERA trials, there was no difference in the rate of IRRs with ocrelizumab according to patient age.

In light of the COVID-19 pandemic, there is an increasing burden on patients and hospital staff. Administering ocrelizumab treatment over a shorter infusion time of 2 hours reduces the total site stay time, which may minimize this burden. Furthermore, shorter infusions may help improve convenience and adherence without changing the overall safety profile of ocrelizumab. The convenience of shorter infusions may have a beneficial impact on patients, and a positive impact on healthcare resources due to time and cost savings [6-8].

5. Conclusions

Overall, results from the ENSEMBLE PLUS substudy provide evidence that ocrelizumab may be infused over a shorter infusion time, without altering the safety profile. Reducing the ocrelizumab infusion time can substantially reduce the administration burden for both patients and site staff, which is of particular importance in light of the current COVID-19 pandemic.

6. Data sharing statement

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here: https://vivli.org/members/ourmembers/. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

Table 4
IRRs by pre-randomization IRR at the first Randomized Dose (by dose at randomization).

Dose at randomization		Pre-randomization IRR		No pre-randomization IRR	
		Conventional infusion (N = 107)	Shorter infusion (N = 114)	Conventional infusion (N = 266)	Shorter infusion (N = 258)
Overall	**Number of patients with an infusion, n (%)**	**107 (100.0)**	**114 (100.0)**	**266 (100.0)**	**258 (100.0)**
	Number of patients with any IRR, n (%)[a]	47 (43.9)	58 (50.9)	52 (19.5)	49 (19.0)
Dose 2	**Number of patients with an infusion, n (%)**	**82 (76.6)**	**76 (66.7)**	**187 (70.3)**	**194 (75.2)**
	Number of patients with any IRR, n (%)[a]	42 (51.2)	43 (56.6)	42 (22.5)	40 (20.6)
Dose 3	**Number of patients with an infusion, n (%)**	**2 (1.9)**	**4 (3.5)**	**22 (8.3)**	**18 (7.0)**
	Number of patients with any IRR, n (%)[a]	1 (50.0)	2 (50.0)	2 (9.1)	0
Dose 4	**Number of patients with an infusion, n (%)**	**18 (16.8)**	**27 (23.7)**	**43 (16.2)**	**32 (12.4)**
	Number of patients with any IRR, n (%)[a]	3 (16.7)	11 (40.7)	5 (11.6)	6 (18.8)
Dose 5	**Number of patients with an infusion, n (%)**	**5 (4.7)**	**6 (5.3)**	**14 (5.3)**	**14 (5.4)**
	Number of patients with any IRR, n (%)[a]	1 (20.0)	2 (33.3)	3 (21.4)	3 (21.4)
Dose 6	**Number of patients with an infusion, n (%)**	**0**	**1 (0.9)**	**0**	**0**
	Number of patients with any IRR, n (%)[a]	0	0	0	0

A pre-randomization IRR is any IRR which occurred prior to randomization into the ENSEMBLE PLUS substudy; for newly enrolled patients, randomization occurred at Dose 2, and for patients already enrolled in the main ENSEMBLE study, randomization could occur at any infusion after the Week 24 visit. Percentages for number of patients with an infusion are based on N.

IRR, infusion-related reaction.

[a] Percentages for number of patients with any IRR are based on number of patients with an infusion.

Table 5
Summary of adverse events.

	Conventional infusion (N = 371)	Shorter infusion (N = 374)
Total number of AEs	**557**	**519**
Total no. of patients with ≥1 AE, n (%)	**218 (58.8)**	**205 (54.8)**
Grade 1	91 (41.7)[a]	79 (38.5)[a]
Grade 2	118 (54.1)[a]	120 (58.5)[a]
Grade 3	8 (3.7)[a]	6 (2.9)[a]
Grade 4	1 (0.5)[a]	0
Total no. of patients with ≥1:		
AE leading to withdrawal from OCR, n (%)	1 (.0.3)	0
AE leading to OCR temporary dose interruption, n (%)[b]	5 (1.3)	5 (1.3)
Total number of SAEs	**5**	**5**
Typhoid fever	1 (20.0)[c]	0
Fibula fracture	1 (20.0)[c]	0
Benign intraductal papilloma of breast	1 (20.0)[c]	0
Depressive symptom	2 (40.0)[c]	0
Appendicitis	0	1 (20.0)[c]
UTI	0	1 (20.0)[c]
Edema peripheral	0	1 (20.0)[c]
Neutropenia	0	1 (20.0)[c]
Hypotension	0	1 (20.0)[c]
Total no. of patients with ≥1 SAE, n (%)	**4 (1.1)**	**5 (1.3)**
Grade 1	0	0
Grade 2	0	3 (60.0)[d]
Grade 3	3 (75.0)[d]	2 (40.0)[d]
Grade 4	1 (25.0)[d]	0
Total no. of patients with ≥1:		
SAE leading to withdrawal from OCR, n (%)	1 (0.3)	0
SAE leading to OCR temporary dose interruption, n (%)[b]	1 (0.3)	1 (0.3)
Total no. of patients with infections, n (%)	**75 (20.2)**	**67 (17.9)**
Total no. of patients with serious infections, n (%)[e]	**1 (0.3)**	**2 (0.5)**
Typhoid fever	1 (0.3)	0
Appendicitis	0	1 (0.3)
UTI	0	1 (0.3)
Total no. of deaths, n	**0**	**0**

Investigator text for AEs is coded using MedDRA Version 22.1. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately. Treatment-emergent AEs (i.e. "1st Randomized Dose"-emergent AEs) are defined as either: a) AEs with an observed or imputed date of AE onset which is on or after the date of first Randomized Dose; or b) AEs with an observed or imputed date of AE onset which is before the date of first Randomized Dose and which later worsens in intensity.

AE, adverse event; eCRF, electronic Case Report Form; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; MS, multiple sclerosis; OCR, ocrelizumab; SAE, serious adverse event; UTI, urinary tract infection.

[a] Percentages based on total no. of patients with an AE.

[b] Based on the Adverse Event/IRR/MS Relapse eCRF page, where response to question "Action taken with Ocrelizumab due to SAE/AE" is "Drug temporarily interrupted" or "Dose delayed".

[c] Percentages are based on the number of SAEs.

[d] Percentages are based on total no. of patients with an SAE.

[e] Serious infections are defined using AEs falling into the MedDRA System Organ Class 'Infections and infestations', and using 'Is the event non-serious or serious?' from the Adverse Event CRF page. Non-serious relapses are excluded.

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Supplementary materials

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