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Ocrelizumab in Early-Stage Relapsing-Remitting Multiple Sclerosis

The Phase IIIb ENSEMBLE 4-Year, Single-Arm, Open-Label Trial

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Abstract

Background and Objectives

Early treatment of multiple sclerosis (MS) reduces disease activity and the risk of long-term disease progression. Effectiveness of ocrelizumab is established in relapsing MS (RMS); however, data in early RMS are lacking. We evaluated the 4-year effectiveness and safety of ocrelizumab as a first-line therapy in treatment-naive patients with recently diagnosed relapsing-remitting MS (RRMS).

Methods

ENSEMBLE was a prospective, 4-year, international, multicenter, single-arm, open-label, phase IIIb study. Patients were treatment naive, aged 18–55 years, had early-stage RRMS with a disease duration ≤3 years, Expanded Disability Status Scale (EDSS) score ≤3.5, and ≥1 clinically reported relapse(s) or ≥1 signs of brain inflammatory activity on MRI in the prior 12 months. Patients received IV ocrelizumab 600 mg every 24 weeks. Effectiveness endpoints over 192 weeks were proportion of patients with no evidence of disease activity (NEDA-3; defined as absence of relapses, 24-week confirmed disability progression [CDP], and MRI measures, with prespecified MRI rebaselining at week 8), 24-week/48-week CDP and 24-week confirmed disability improvement, annualized relapse rate (ARR), mean change in EDSS score from baseline, and safety. Cognitive status, patient-reported outcomes, and serum neurofilament light chain (NfL) were assessed. Descriptive analysis was performed on the intention-to-treat population.

Results

Baseline characteristics (N = 678) were consistent with early-stage RRMS (n = 539 patients, 64.6% female, age 40 years and younger; median age: 31.0 years; duration since: MS symptom onset 0.78 years, RRMS diagnosis 0.24 years; mean baseline EDSS score [SD] 1.71 [0.95]). At week 192, most of the patients had NEDA-3 (n = 394/593, 66.4%), 85.0% had no MRI activity, 90.9% had no relapses, and 81.8% had no 24-week CDP over the study duration. Adjusted ARR at week 192 was low (0.020, 95% CI 0.015–0.027). NfL levels were reduced to and remained within the healthy donor range, by week 48 and week 192, respectively. No new or unexpected safety signals were observed.

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Class of Evidence
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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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Glossary

AE = adverse event; **ANCOVA** = analysis of covariance; **ARR** = annualized relapse rate; **BICAMS** = Brief International Cognitive Assessment for Multiple Sclerosis; **BVL** = brain volume loss; **BVMT-R** = Brief Visuospatial Memory Test-Revised; **cCDP** = composite CDP; **CDI** = confirmed disability improvement; **CDP** = confirmed disability progression; **COVID-19** = coronavirus disease 2019; **CVLT-II** = California Verbal Learning Test; **DMT** = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **FLAIR** = fluid-attenuated inversion recovery; **GMV** = gray matter volume; **HA-RMS** = highly active RMS; **HA-RRMS** = highly active RRMS; **IFN** = interferon; **IRR** = infusion-related reaction; **ITT** = intention-to-treat; **MS** = multiple sclerosis; **MSIS-29** = Multiple Sclerosis Impact Scale-29; **NE** = not evaluable; **NEDA** = no evidence of disease activity; **NfL** = neurofilament light; **PDR** = protocol-defined relapse; **PRO** = patient-reported outcome; **RMS** = relapsing MS; **RRMS** = relapsing-remitting MS; **SAE** = serious AE; **SDMT** = Symbol Digit Modalities Test; **SI** = serious infection; **SMS** = SymptoMScreen; **T2w** = T2-weighted; **WMV** = white matter volume; **WPAI** = Work Productivity and Activity Impairment.

Discussion

Disease activity based on clinical and MRI measures was absent in most of the patients treated with ocrelizumab over 4 years in the ENSEMBLE study. Safety was consistent with the known profile of ocrelizumab. Although this single-arm study was limited by lack of a parallel group for comparison of outcome measures, the positive benefit–risk profile observed may provide confidence to adopt ocrelizumab as a first-line treatment in newly diagnosed patients with early RMS.

Classification of Evidence

This study provides Class IV evidence that adult patients with early-stage MS who were treatment naive maintained low disease activity (NEDA-3) over 4 years with ocrelizumab treatment; no new safety signals were detected.

Trial Registration Information

ClinicalTrials.gov Identifier NCT03085810; first submitted March 16, 2017; first patient enrolled: March 27, 2017; available at clinicaltrials.gov/ct2/show/NCT03085810.

Introduction

Disease activity, manifested clinically as relapses and as new and enlarging T2-weighted (T2w)/fluid-attenuated inversion recovery (FLAIR) hyperintense or contrast-enhancing lesions on MRI, contributes to meaningful neurologic disability and affects quality of life of patients with multiple sclerosis (MS).[1-3] Relapses also contribute to disability accumulation, primarily early in MS.[3] Neuroaxonal damage, and the resulting global and regional brain atrophy, is detectable early in the disease course,[4-6] and although not always clinically evident,[7] it is associated with an increased risk of progressive disability accumulation.[8,9]

Because early and sustained high-efficacy treatment of MS reduces disease activity and the risk of long-term disease progression,[10-22] treatment guidelines now include this approach to managing relapsing MS from disease onset, particularly in patients with highly active relapsing MS (HA-RMS),[23-26] although clinical implementation of these guidelines is limited. This is in contrast to "watchful waiting" coupled with disease-modifying therapy (DMT) escalation, which commences with lower efficacy therapies, can involve frequent DMT switching, and has been a widely used treatment paradigm in MS.[23-26] No evidence of disease activity (NEDA-3), a composite measure of the absence of confirmed disability worsening, relapses, and MRI activity (T1 gadolinium-enhancing lesions and new/enlarging T2w lesions), is a sensitive and comprehensive measure of overall treatment benefit of DMTs in the clinical trial setting and represents an important treatment goal for patients with RMS.[27-29]

Ocrelizumab is an anti-CD20 monoclonal antibody approved for the treatment of RMS and primary progressive MS.[30,31] Phase III study data showed significant benefit in clinical and MRI measures (including NEDA-3)[32,33] with sustained efficacy in the open-label extension studies, where adverse events were consistent with past reports and no new safety signals emerged with prolonged treatment.[34,35] However, our understanding of ocrelizumab effectiveness in early-stage MS is still limited.[36]

ENSEMBLE (NCT03085810) was a prospective, 4-year (192 weeks, where a study year is defined as 48 weeks), multicenter, interventional, open-label, single-arm, phase IIIb study, evaluating the effectiveness and safety of ocrelizumab as a first-line therapy in treatment-naive patients with early-stage relapsing-remitting MS (RRMS). Ocrelizumab effectiveness was assessed using multiple clinical and

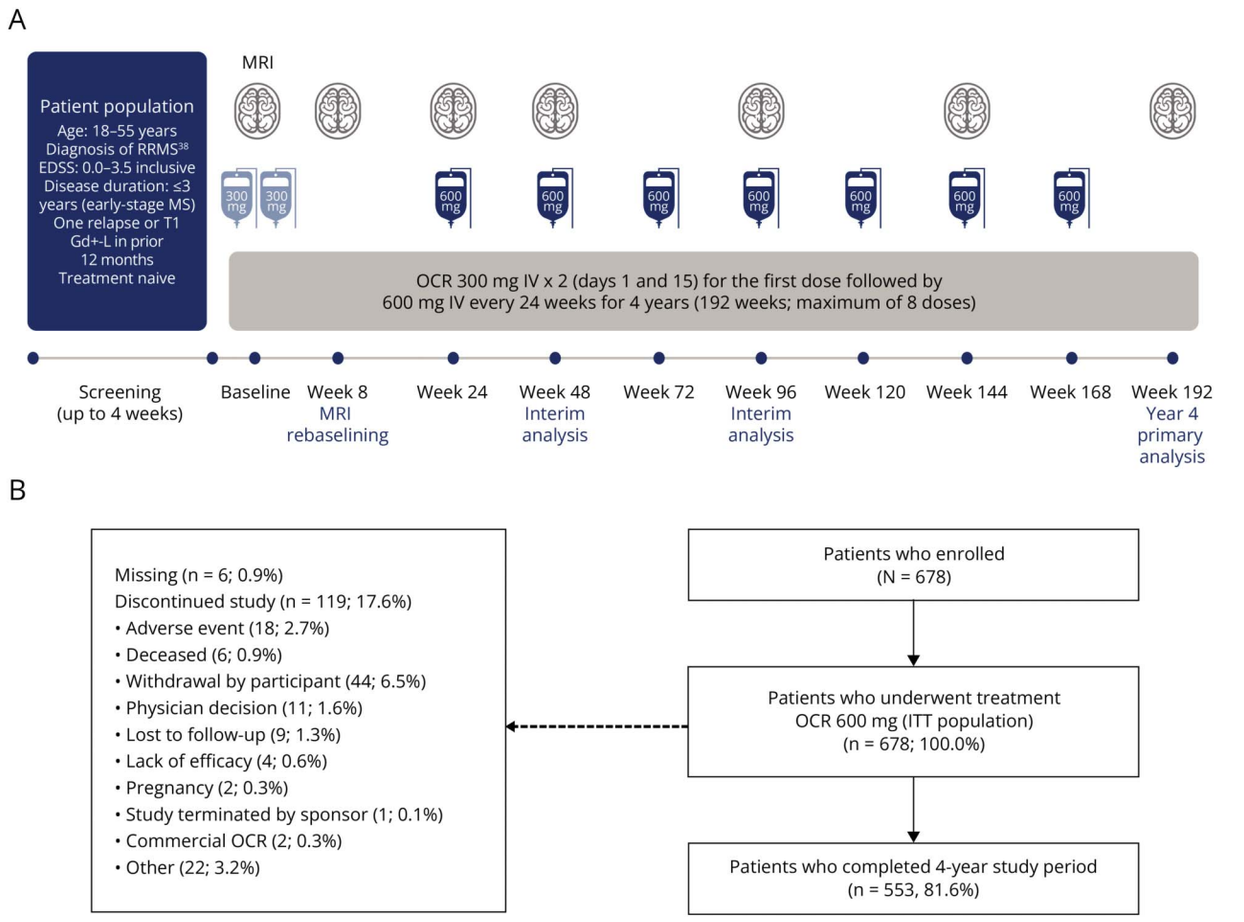
MRI endpoints, including the proportion of patients with NEDA-3 (with MRI baselining at week 8[37]), overall population and patients with highly active RRMS (HA-RRMS), measures of disability progression and relapse activity, cognitive assessments, patient-reported outcomes (PROs), and a fluid biomarker of neuroaxonal damage (neurofilament light chain [NfL]).

Methods

Trial Design and Procedures

ENSEMBLE (NCT03085810) was a multicenter, open-label, single-arm, phase IIIb study investigating the effectiveness and safety of ocrelizumab in treatment-naive patients with early-stage RRMS (Figure 1). Details of the determination of the study sample size are provided in the eMethods. The study consisted of a screening period (up to 4 weeks), after which eligible patients received an IV infusion of ocrelizumab 600 mg every 24 weeks throughout the 192-week open-label treatment period (last dose on week 168) for a maximum of 8 doses (first dose administered as two 300 mg infusions, 14 days apart). Assessments of Expanded Disability Status Scale (EDSS) score, relapse, and MRI were conducted at baseline and at weeks 24, 48, 96, 144, and 192 (NB: for MRI rebaselining purposes, to exclude MRI activity that occurs during the first 8 weeks of treatment before the potential treatment effect of ocrelizumab is realized, an additional MRI assessment was made at week 8).[37] MRI analyses were supervised with manual editing by expert raters and finally approved by board-certified neuroradiologists from an independent imaging contract research organization (MIAC AG, Basel, Switzerland). These include longitudinal T2w/FLAIR lesion segmentation and volumetry for all individual lesions, enabling the determination of enlarging T2w lesions. Eligible patients could enroll in a separate long-term extension study at the end of the treatment period to further evaluate the effectiveness and safety of ocrelizumab. Patients who discontinued treatment early entered a safety follow-up for at least 48 weeks. The clinical cutoff date for data included in the analysis was April 19, 2022.

Figure 1 (A) Study Design and (B) Patient Disposition



EDSS = Expanded Disability Status Scale; ITT = intention-to-treat; MS = multiple sclerosis; OCR = ocrelizumab; RRMS = relapsing-remitting multiple sclerosis; T1 Gd+-L = T1 gadolinium-enhancing lesion.

Standard Protocol Approvals, Registrations, and Patient Consents

The trial protocol (ClinicalTrials.gov identifier number NCT03085810) was approved by the relevant institutional review boards/ethics committees. All patients provided written informed consent.

Patients

Key eligibility criteria included age 18–55 years, diagnosis of MS (2010 revised McDonald criteria),[38] treatment-naive patients, early-stage RRMS (defined as disease duration ≤3 years), EDSS score ≤3.5 at screening, 1 or more clinically reported relapse(s) or 1 or more signs of MRI activity in the prior 12 months. Within the overall population, effectiveness was also analyzed in patients with HA-RRMS, defined as having ≥2 prior relapses and MRI activity (T1 gadolinium-enhancing lesions, new or enlarging T2w lesions) in the 12 months preceding screening.

Study Endpoints

Effectiveness

The following registered, key effectiveness endpoints for the ENSEMBLE population over the 192-week treatment period were determined:

- The proportion of patients with NEDA-3 (with MRI rebaselining at week 8), defined as an absence of protocol-defined relapse (PDR);
- 24-week confirmed disability progression (CDP);
- T1 gadolinium-enhancing lesions and new and enlarging T2w lesions[27];
- The proportion of patients with NEDA-3 as determined in the HA-RRMS population (not registered);
- Time to onset of CDP, sustained for at least 24 weeks and 48 weeks (defined as an increase of at least 1.0 point from the baseline EDSS score, or increase of ≥1.5 points if baseline EDSS score was <1.0);
- Time to onset of composite CDP (cCDP; a more sensitive measure of disability progression than EDSS)[39], defined as the presence of 24-week CDP or the presence of confirmed ≥20% increase in Timed 25-Foot Walk or Nine-Hole Peg Test sustained for 24 weeks (not registered);
- Mean change from baseline at 48-week intervals in EDSS score;
- Proportion of patients with CDP, stable disability, or confirmed disability improvement (CDI; defined as a reduction in EDSS score ≥1.0 point compared with baseline, in patients with a baseline EDSS score ≥2);
- Annualized relapse rate (ARR), calculated as the total number of PDRs (defined as the occurrence of new or objective worsening of neurologic symptoms that were attributable to MS) for all patients divided by the total patient years of exposure to the treatment;
- Percentage brain volume change, cortical gray matter volume (CGMV), and white matter volume (WMV) at weeks 24, 48, 96, 144, and 192 (rebaselined at week 8), were quantified using Structural Image Evaluation, using Normalization, of Atrophy/X[40];
- Cognitive status assessed at baseline and 48-week intervals using the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS),[41] consisting of performance outcome assessments including validated, alternate forms of the Symbol Digit Modalities Test (SDMT), California Verbal Learning Test (CVLT-II), and Brief Visuospatial Memory Test-Revised (BVMT-R);
- PROs, including the Multiple Sclerosis Impact Scale-29 (MSIS-29) questionnaire (physical and psychological impact of MS); the SymptoMScreen (SMS; symptom limitations); the Work - Productivity and Activity Impairment (WPAI) questionnaire (working status and the impact of MS on absenteeism, presenteeism, and the ability to perform regular activities; see eMethods for additional details).

The following exploratory (not registered) endpoints the ENSEMBLE population over the 192-week treatment period included:

- NfL in serum, measured at baseline and 48-week intervals;
- Baseline predictors/indicators of NEDA-3 at week 192.

Safety

All enrolled patients who received any dose or part of a dose of ocrelizumab were included in the safety population. Safety measures included the incidence and nature of adverse events (AEs), serious AEs (SAEs), discontinuations for AEs, vital sign measurements, physical and neurologic examinations, clinical laboratory tests, locally reviewed MRI for safety (non-MS CNS pathology), and concomitant medications. The severity of AEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events.

AEs of interest included infections and serious infections (SIs), coronavirus disease 2019 (COVID-19)-related SAEs, infusion-related reactions, and neoplasms.

Statistical Analyses

The analysis of this single-arm, noncomparative study was primarily based on descriptive statistical methods. No formal hypothesis was tested. The effectiveness analyses were performed on the intention-to-treat (ITT) population, which included all enrolled patients who received any dose of ocrelizumab, including those who prematurely withdrew and did not undergo any assessments. The safety population consisted of all patients who received at least 1 dose of ocrelizumab. For the key effectiveness endpoint, the proportion of patients with NEDA-3 during the 192-week treatment period in the modified ITT population (where patients receiving any dose and who discontinued early without a protocol-defined event were imputed as having an event if the treatment discontinuation reason was lack of efficacy or death; others were excluded), and in the subgroup of patients with HA-RRMS, descriptive statistics were used. Cox proportional hazards

regression was used to identify baseline predictors for NEDA-3. The time to onset of the first protocol-defined event of disability progression (CDP and cCDP) was estimated using Kaplan-Meier analysis. EDSS score, mean change from baseline in EDSS score, and percentage change in whole-brain volume were analyzed using the longitudinal mixed-effect model of repeated measures. The proportion of patients who had CDP or CDI was analyzed using the ITT population. The ARR, total number of T1 gadolinium-enhancing lesions, and number of new and enlarging T2w lesions were analyzed using a Poisson model and the ITT population. The change from baseline in BICAMS components and PRO scores (WPAI, MSIS-29) and SMS scores were analyzed using Wilcoxon signed-rank test. Descriptive and covariance analyses (ANCOVA) of change from baseline and regression analysis of factors affecting baseline levels were used for serum NfL; a healthy donor NfL cohort was included for comparison.[42] Analyses were conducted on age-adjusted NfL values where necessary to remove the known relationship of higher NfL values in older patients (i.e., covariance analysis; see eMethods for additional description of the age adjustment for NfL levels).

Data Availability

The study protocol and statistical analysis plan are available in eSAP 1 and eSAP 2, respectively. For eligible studies, qualified researchers may request access to individual patient-level data through the clinical study data request platform. At the time of writing, this request platform was Vivli.[43] 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 the Roche data-sharing platform (go.roche.com/data_sharing). Anonymized records for individual patients across more than 1 data source external to Roche cannot, and should not, be linked because of a potential increase in risk of patient reidentification.

Results

Patient Demographics, Disease Characteristics, and Disposition

The ENSEMBLE study (March 27, 2017, to April 15, 2022) enrolled 678 of 739 screened patients in the primary analysis cohort, across 186 centers in 29 participating countries across Europe, North America, and the rest of the world. Patients were most frequently enrolled for reason of relapse (89.7%, n = 608/678) alone (15.0%, n = 102/678), with ≥1 T1 gadolinium-enhancing lesion on brain MRI (28.0%, n = 190/678), with a new or enlarging T2w lesion on brain MRI (17.0%, n = 115/678), or with ≥1 T1 gadolinium-enhancing lesion and new or enlarging T2w lesion on brain MRI (29.6%, n = 201/678); 10.3% (n = 70/678) were enrolled because of MRI activity only. A total of 553 of 678 patients (81.6%) completed the treatment period in this 4-year study, and 119 of 678 patients (17.6%) withdrew from study treatment prematurely, of which 18 (2.7%) discontinued because of AEs (Figure 1). Baseline demographic data and disease characteristics are provided in Table 1.

Table 1 Baseline Demographics and Disease Characteristics

Variable	ITT population (N = 678)
Age, y, mean (SD)	32.4 (9.1)
Age category, n (%); ≤40/>40	539 (79.5)/139 (20.5)
Sex, male/female, n (%)	240 (35.4)/438 (64.6)
Ethnicity, n (%)	
Hispanic or Latino/not Hispanic or Latino	67 (9.9)/505 (74.5)
Not reported	54 (8.0)
Unknown	52 (7.7)
Race, n (%)	
American Indian or Alaskan Native	6 (0.9)
Asian	11 (1.6)
Black or African American	12 (1.8)
Native Hawaiian or other Pacific Islander	1 (0.1)
White	555 (81.9)
Other	0 (0.0)
Multiple	5 (0.7)
Unknown	88 (13.0)
Duration since MS symptom onset,[a] y, median (IQR)	0.78 (0.44–1.63)
Duration since RRMS diagnosis, y, median (IQR)	0.24 (0.15–0.42)
EDSS at baseline,[b] median (IQR)	1.5 (1.0–2.5)
EDSS at baseline category,[b] <2.5/≥2.5, n (%)	508 (74.9)/170 (25.1)
No. of relapses in the year before enrollment, n (%)	
0	38 (5.6)
1	438 (64.6)
2	166 (24.5)
3	27 (4.0)
≥4	9 (1.3)

Abbreviations: EDSS = Expanded Disability Status Scale; IQR = interquartile range; ITT = intention-to-treat; MS = multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis.
Snapshot date: July 8, 2022; cutoff date: April 19, 2022. The snapshot contains data up to week 192 of the treatment period of each individual patient.
[a] n = 673.
[b] Baseline EDSS is defined as the average of the EDSS scores at the screening and baseline visits. If one of the EDSS scores from the screening or baseline visits was missing, the other was used for baseline EDSS.

Clinical Effectiveness Outcomes

After 4 years, at the end of the treatment period (week 192) most of the patients (66.4% [95% CI 62.5–70.2], n/N = 394/593) had NEDA-3, with MRI rebaselining at week 8 (key endpoint; Table 2). 77.9% (95% CI 74.4–81.2, n/N = 462/593) of patients had no evidence of clinical activity

Table 2 Four-Year Efficacy Endpoints in Patients With RRMS Treated With OCR, (A) NEDA-3, (B) ARR, and (C) Change in EDSS

Variable	
A. Proportion of patients with NEDA,[a] % (n/N)	66.4 (394/593)
Proportion of patients with no 24W-CDP and no relapses, % (n/N)	77.9 (462/593)
Proportion of patients with no 24W-CDP, % (n/N)	81.8 (485/593)
Proportion of patients with no relapses, % (n/N)	90.9 (539/593)
Proportion of patients with no brain MRI activity, % (n/N)	85.0 (504/593)
Proportion of patients with no new or enlarging T2 lesions, % (n/N)	90.4 (536/593)
Proportion of patients with no T1 Gd+ lesions, % (n/N)	90.6 (537/593)
B. Adjusted annualized relapse rate[b] (95% CI)	0.02 (0.02–0.03)
Total number of relapses (n)	54
Total patient-years followed (n)	2,385
Unadjusted annualized relapse rate[c]	0.023
C. Change in EDSS (stable/improved), % (n/N)	82.1 (461/562)
Improved	22.8 (128/562)
Stable	59.3 (333/562)
Worsened	18.0 (101/562)

Abbreviations: 24W-CDP = 24-week confirmed disability progression; ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; N/E = new/enlarging; NEDA = no evidence of disease activity; T1 Gd+-L = T1 gadolinium-enhancing lesion; T2w-L = T2-weighted lesion.
[a] Patients receiving any dose and who discontinued early without a protocol-defined event were imputed as having an event if the treatment discontinuation reason was lack of efficacy or death; others were excluded. Clinical cutoff date: April 19, 2022; snapshot date: July 8, 2022; the snapshot contains data up to week 192 of the treatment period of each individual patient.
[b] Adjusted by age at disease diagnosis, baseline EDSS score, presence of T1-weighted gadolinium-enhancing lesions at screening, presence of relapses in the last year before enrollment. Log-transformed exposure time is included as an offset variable.
[c] The total number of relapses for all patients divided by the total patient-years of exposure (defined as the duration of the treatment period).

(absence of PDR and 24-week CDP), and 85.0% (95% CI 81.9–87.8, n/N = 504/593) of patients were free from MRI activity (absence of T1 gadolinium-enhancing lesions and new and enlarging T2w lesions). Comparable NEDA-3 rates were seen in the population of patients with HA-RRMS (64.4% [95% CI 57.0–71.4], n/N = 116/180; no evidence of clinical activity 77.8% [95% CI 71.0–83.6], n/N = 140/180; no evidence of MRI activity 83.9% [95% CI 77.7–88.9], n/N = 151/180; eFigure 1). Regression analysis revealed age (years) at disease diagnosis was the only significant predictor of NEDA-3 from baseline to week 192 (odds ratio 0.98, 95% CI 0.96–1.00; $p = 0.034$; an increase in 1 year leads to an increased risk of disease activity of 2.0%); sex, number of relapses 1 year before enrollment, baseline EDSS score, and baseline MRI lesion activity did not influence NEDA-3 status at week 192 (eTable 1). A total of 539 of 593 (90.9%, 95% CI 88.3–93.1) patients with RRMS and 163 of 180 (90.6%, 95% CI 85.3–94.4) patients with HA-RRMS had no relapses.

For other key clinical outcomes, CDP and cCDP, the Kaplan-Meier estimates of event-free rate over the study duration are shown in Figure 2. At week 192, the chance of not having had a disability progression event (event-free rate) was 84.2% (95% CI 81.1–86.8, patients at risk n = 402) for 24-week CDP and 69.2% (95% CI 65.4–72.6, patients at risk n = 325) for 24-week cCDP. For 48-week CDP, the rate was 86.5% (95% CI 83.5–88.9, patients at risk n = 414) at week 192 (eFigure 2).

Mean (SD) EDSS scores over the treatment period were stable (baseline: 1.71 [0.95] vs week 192: 1.66 [1.25]); this was reflected in the proportion of evaluable patients (n = 562; only patients with nonmissing values) with no change from baseline in EDSS score (59.3%, n = 333/562; change ≤0.5 and ≥−0.5) at week 192, whereas 22.8% (n = 128/562) had improved (<−0.5) and 18.0% (n = 101/562) had worse (>0.5) EDSS scores. Over the 4-year study duration, a total of 54 PDRs were recorded; at week 192, the adjusted ARR was 0.02 (95% CI 0.02–0.03).

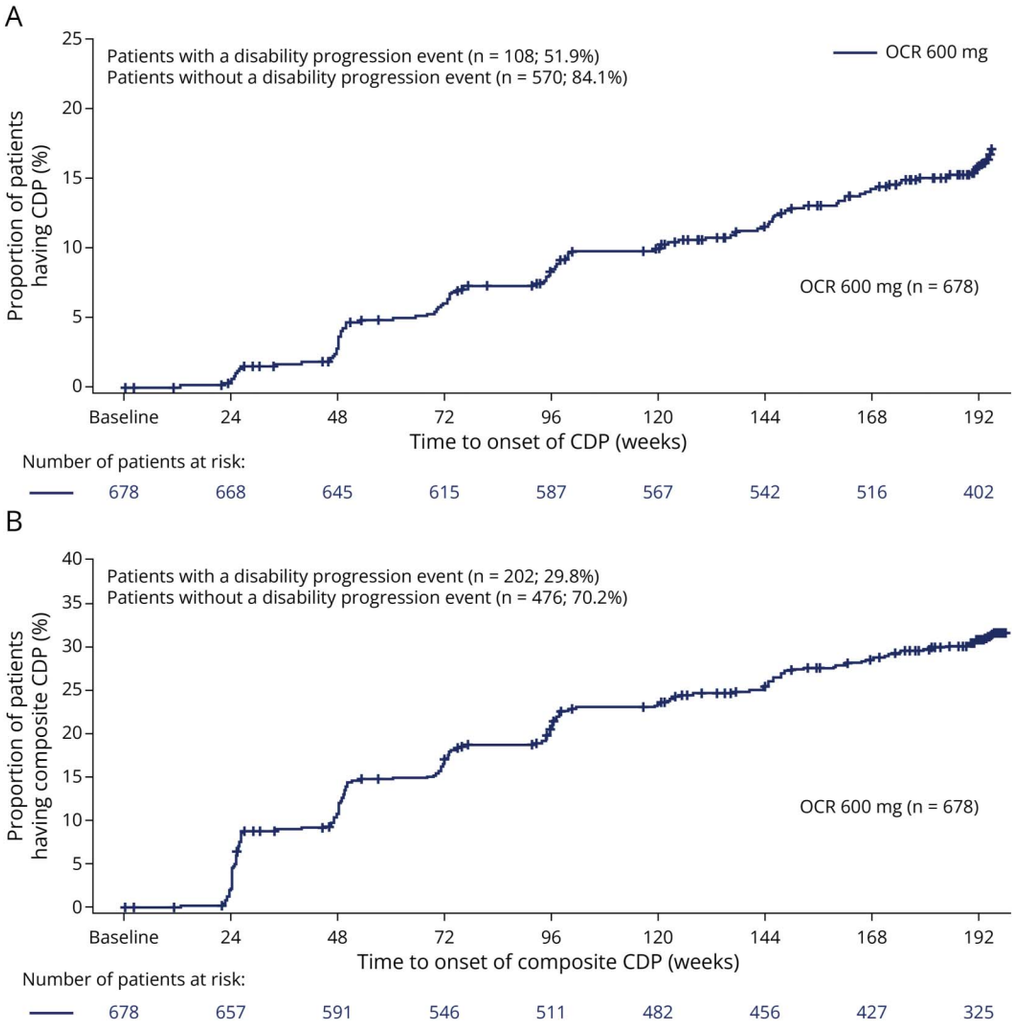
Changes in clinical parameters and event-free rates over the duration of the ENSEMBLE study are summarized in eTable 2.

MRI and Biomarker Outcomes

After week 8 rebaselining, from week 24 to 192, a near-complete suppression of MRI lesion activity was observed, with most of the patients having no T1 gadolinium-enhancing lesions and no new or enlarging T2w lesions (over weeks 24–192, only 23 T1 gadolinium-enhancing lesions were detected on a total of 3,096 brain MRI scans; eTable 2); adjusted rates of the total number of lesions were low (T1 gadolinium-enhancing lesions: 0.000; 95% CI 0.000–NE; new or enlarging T2w lesions: 0.016; 95% CI 0.0080–0.0341). Normalized brain volume decreased over time, with mean (SD) percentage change from week 8 baseline of −0.48% (0.73) at week 48, −0.91% (0.93) at week 96, −1.28% (1.16) at week 144, and −1.54% (1.31) at week 192 (Figure 3). Over the 4-year study period, this equated to an annualized rate of brain volume loss (BVL) of −0.38%. The mean (SD) percentage change from week 8 baseline to week 192 was −1.04% (2.24) in WMV and −1.61% (2.06) in CGMV.

At study baseline, serum NfL levels were higher than that in healthy donors (sNfL, pg/mL [median]: 12.8 vs 5.5; Figure 4, A and B). Regression analysis revealed baseline T1 gadolinium-enhancing lesion status was the strongest predictor of baseline NfL level, and although age and time since the last relapse may affect NfL levels, sex and EDSS score category did not influence baseline NfL levels in this early, treatment-naive cohort (Figure 4A).

Figure 2 Four-Year Kaplan-Meier Plot of Time to Onset of 24-Week (A) CDP and (B) Composite CDP in Patients With RRMS Treated With OCR



Time to onset of (A) CDP and (B) cCDP. Curves show Kaplan-Meier estimates of the proportion of patients with disability progression events relative to the baseline throughout the open-label treatment period. Patients who discontinued the study due to lack of efficacy or death without confirmed progression of disease were imputed as having an event at the time of discontinuation. ITT population. Clinical cutoff date: April 19, 2022; snapshot date: July 8, 2022; the snapshot contains data up to week 192 of the treatment period of each individual patient. cCDP = composite confirmed disability progression; CDP = confirmed disability progression; ITT = intention-to-treat; OCR = ocrelizumab; RRMS = relapsing-remitting multiple sclerosis.

The ANCOVA model for analysis of serum NfL levels showed that, following ocrelizumab administration, levels were significantly reduced from baseline to week 48 (sNfL, pg/mL [geometric mean]: 14.6 vs 6.5; $p < 0.001$), and this was maintained throughout the study (Figure 4B). Serum NfL levels reached healthy donor levels after 48 weeks (sNfL, pg/mL [median]: 6.4 vs 5.5).

Clinical Outcome Assessments (Cognition and PROs)

Improvements were seen on the BICAMS component scores over the duration of the study for SDMT, CVLT-II, and BVMT-R (baseline vs week 192, mean [SD]: 4.38 [10.38], 4.28 [13.76], and 1.06 [7.09], respectively; all $p < 0.001$; eFigure 3).

Patient-Reported Outcomes

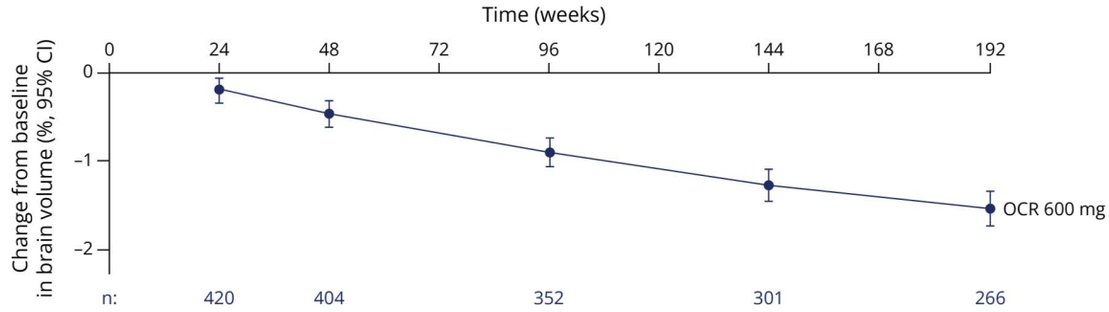
WPAI

At week 192, relative to baseline, patients missed less work (baseline: 18.38%; week 192: 3.94% work time missed; $p < 0.001$), had less impairment working because of their MS (baseline: 19.72% vs week 192: 13.11%; $p < 0.001$), had less overall work impairment because of their MS (baseline: 26.33% vs week 192: 15.80%; $p < 0.001$), and had less activity impairment (baseline: 23.23% vs week 192: 18.18%; $p < 0.001$).

MSIS-29

At week 192, relative to baseline, improvements were seen in the physical (baseline: 16.90 vs week 192: 15.28; $p = 0.05$) and

Figure 3 Four-Year Percent Change in Whole-Brain Volume (Week 192, Rebaselined at Week 8) in Patients With RRMS Treated With OCR



The annualized rate of BVL reported in patients with MS ranges from −0.46% to −1.34% per year[e10] and that associated with healthy controls and normal aging is −0.05 to −0.50 per year.[e11,e12] Whole-brain volume loss over time in the ENSEMBLE RRMS ITT population (percent change [95% CI]). Whole-brain volume was recorded as an absolute normalized value at week 8; relative percentage change from week 8 was obtained for each subsequent visit using SIENA for whole brain.[41] Clinical cutoff date: April 19, 2022; snapshot date: July 8, 2022; the snapshot contains data up to week 192 of the treatment period of each individual patient. BVL = brain volume loss; ITT = intention-to-treat; MS = multiple sclerosis; OCR = ocrelizumab; PBVC = percentage brain volume change; RRMS = relapsing-remitting multiple sclerosis; SIENA = Structural Image Evaluation, using Normalization, of Atrophy.

psychological (baseline: 28.81 vs week 192: 21.64; $p < 0.001$) impact of MS on patients.

SMS

A reduction in patient's symptom limitations was seen at week 192 relative to baseline (baseline: 12.2; week 192: 11.4; $p < 0.05$).

Safety Outcomes

The incidence of AEs among all patients receiving ocrelizumab in the ENSEMBLE study is summarized in Table 3. No new safety signals were identified. A total of 647 of 678 patients (95.4%) reported AEs. The most common AEs (occurring in >10% of patients) were infusion-related reactions (IRRs; 351, 51.8%), nasopharyngitis (198, 29.2%), headache (185, 27.3%), urinary tract infection (106, 15.6%), fatigue (103, 15.2%), upper respiratory tract infection (97, 14.3%), cough (84, 12.4%), oropharyngeal pain (78, 11.5%), pain in extremity (78, 11.5%), back pain (76, 11.2%), arthralgia (73, 10.8%), and influenza (68, 10.0%). The incidence of hypogammaglobulinemia (3, 0.4%; all nonserious), neutropenia (8, 1.2%; 7 nonserious and 1 serious), and neutropenic sepsis (1, 0.1%; serious) was low.

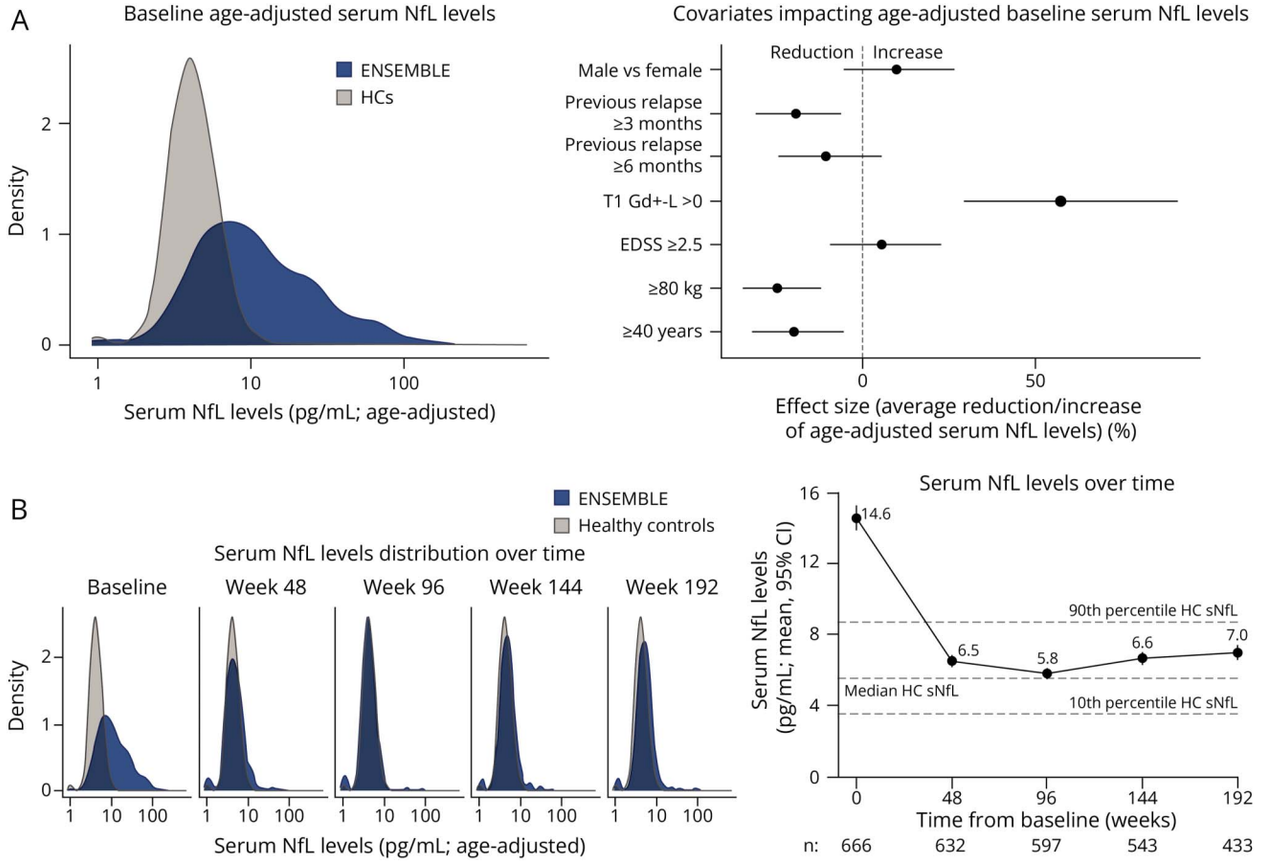
Most of the patients (75.8%, n = 514/678) had a maximum-grade AE of mild to moderate (grade 1/2). One hundred seventeen patients (17.3%) and 10 patients (1.5%) had a maximum of grade 3 or 4 AEs, respectively; there were 6 grade 5 AEs (0.9%; n = 2, COVID-19; n = 2, COVID-19 pneumonia; n = 1, pneumonia; n = 1, immune reconstitution inflammatory syndrome; see eAppendix 1 for details). The only treatment-related AEs occurring in ≥5% of patients were IRRs (51.6%, n = 350/678) and nasopharyngitis (9.0%, n = 61/678), urinary tract infection (6.0%, n = 41/678), and upper respiratory tract infection (5.0%, n = 34/678).

Infections were reported in 510 (75.2%) patients presenting with 1,845 infections, and 47 (6.9%) patients developed 51 serious infections. A total of 57 (8.4%) patients tested positive for COVID-19, 6 (0.9%) had suspected COVID-19, and 5 (0.7%) developed COVID-19 pneumonia. Neoplasms (n = 40) were reported in 34 (5.0%) patients, the most frequently reported being skin papilloma (9 patients, 1.3%), benign breast neoplasm (3 patients, 0.4%), and lipoma (3 patients, 0.4%).

Overall, 105 of 678 patients (15.5%) reported a total of 136 SAEs during the treatment period. Most of the events were reported as recovered/resolved (111/136). At the time of analysis, 13 were recovered/resolved with sequelae, 1 was recovering/resolving, and 1 was not recovered/not resolved. A total of 6 grade 5 (fatal) SAEs were reported: immune reconstitution inflammatory syndrome (n = 1; see eAppendix 1 for details), pneumonia (n = 1), COVID-19 (n = 2), and COVID-19 pneumonia (n = 2). Serious infections (n = 51) were reported in 47 (6.9%) patients, serious injuries and procedural complications in 13 (1.9%), and serious nervous system disorders in 10 (1.5%); serious IRRs were reported in 3 (0.4%) patients (all received ocrelizumab administered over the conventional 3.5-hour infusion time). The most frequent SAEs by preferred term were COVID-19 (pneumonia) reported in 14 (2.1%) patients, followed by 7 (1.0%) showing MS relapses, 6 (0.9%) with a pneumonia (not COVID-19–related), and 5 (0.7%) reporting spontaneous abortion. Serious neoplasms developed in 8 patients (invasive ductal breast carcinoma [n = 2, 0.3%], benign breast neoplasm, intraductal papilloma of the breast, renal cell cancer, malignant melanoma, uterine leiomyoma, and papillary thyroid cancer [all n = 1, 0.1%]).

A total of 11 (1.6%) patients underwent dose modification or interruption because of AEs; 21 (3.1%) patients discontinued from the study because of AEs. There were 10 (1.5%)

Figure 4 Age-Adjusted Serum NfL Levels in the ENSEMBLE Population Compared With Healthy Donors at (A) Baseline (Plus Cofactors Affecting Baseline NfL Levels) and (B) Distribution Over Time (Plus Geometric Mean Serum NfL Levels Over Time, to Week 192)



Geometric means derived by using ANCOVA in the ENSEMBLE early-MS cohort (median age 31 years) demonstrated strong and significant reduction from baseline at week 48 and later visits ($p < 0.001$). The on-treatment (ocrelizumab) values of this MS cohort are comparable with a healthy donor cohort with similar demographics.[42] ANCOVA = analysis of covariance; EDSS = Expanded Disability Status Scale; HC = healthy control; MS = multiple sclerosis; NfL = neurofilament light; T1 Gd+-L = T1 gadolinium-enhancing lesion.

pregnancies. There were no notable findings in laboratory assessments, physical examinations, neurologic examinations, vital signs, and non-MS MRI pathology that changed the known safety profile of ocrelizumab.

Classification of Evidence

This study provides Class IV evidence that adult patients with early-stage MS who were treatment naive maintained low disease activity (NEDA-3) over 4 years with ocrelizumab treatment; no new safety signals were detected.

Discussion

The ENSEMBLE study in patients with early RRMS, enrolled largely for reason of relapse with concomitant MRI activity, showed that most patients treated with ocrelizumab had no disease activity over 4 years (66.4% NEDA-3; key endpoint). Furthermore, most patients had no disease progression measured by both 24-week CDP and composite CDP (84.1% and 70.2%, respectively); 82.1% of patients had stable or improved EDSS scores. The annualized relapse rate (0.020) over the 4 years of the ENSEMBLE study equated to 1 relapse every 50 years at the cohort level (i.e., on average, 50 patient-years in the cohort must be monitored to observe 1 relapse). This control of disease activity and progression with ocrelizumab treatment, also evident by improved cognitive test scores (where the SDMT score improvement was clinically meaningful [>4 points], reaching the mean score observed in healthy volunteers),[44,45] may have contributed to the significant effect on PROs, with improvements in work productivity, reductions in symptom limitations, and physical and psychological impacts of MS over the period of 4 years. In addition, an equally low level of disease activity was seen in the subgroup of patients with highly active RRMS (NEDA-3 64.4%) where the use of high-efficacy therapies is recommended in treatment guidelines.[23-26]

First-line DMTs, such as interferon (IFN)-β and glatiramer acetate, delay the conversion from clinically isolated syndrome to clinically definite MS[46,47] and are widely used in routine

Table 3 Safety Overview for Patients Receiving Ocrelizumab 600 mg in the ENSEMBLE Study

Variable	Ocrelizumab (N = 678) Total number of patients with event, n (%)
Adverse events	647 (95.4)
Serious adverse events	105 (15.5)
Death	6 (0.9)
Infusion-related reactions	351 (51.8)
Infections	510 (75.2)
Serious infections	47 (6.9)
AEs leading to discontinuation	21 (3.1)
SAEs leading to discontinuation	13 (1.9)
AEs leading to modification/interruption	11 (1.6)
SAEs leading to modification/interruption	2 (0.3)
AEs grade 3 and above	133 (19.6)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.
Adverse events were encoded using MedDRA version 21.0.

clinical practice coupled with watchful waiting. However, breakthrough disease activity occurs using the DMT escalation approach, necessitating a change in DMT, and is associated with poor long-term outcomes.[20-22] The reappraisal of treatment pathways in MS advocates earlier use of high-efficacy DMTs to reduce disease activity and the risk of long-term disability progression[10-26]; however, in Europe, only 23% of patients with MS received high-efficacy DMTs as first-line treatment.[48]

In patients with early RMS (MS symptom onset ≤2 years, who were also treatment naive) from the pooled OPERA I/II population, NEDA-3 (with rebaselining at week 24; time of first postbaseline MRI) was maintained in 72.5% of patients and was similar to the overall population (72.2%) after 2 years of treatment with ocrelizumab; both were significantly greater than the first-line treatment comparator, IFN β-1a.[29,49] The 4-year results of NEDA-3 (66.4%) in the ENSEMBLE study in patients with early RRMS, plus the interim analyses (NEDA-3: 6 months, 89.4%; 1 year, 83.5%; 2 years, 77.3%),[e1,e2] show early control of disease activity, which was maintained over the longer term. This is in line with NEDA-3 rates from the early-RMS subgroup analysis in the pooled OPERA I/II population and other ocrelizumab studies.[29,37,e1,e3] Furthermore, using the German NeuroTransData MS registry as an external, propensity score-matched control arm for the ENSEMBLE study, treatment with ocrelizumab in patients with early RRMS was associated with significantly lower risk of disease activity (NEDA-2) after 2 years compared with first-line treatment with other DMTs in the real world.[e4]

NEDA-3 is associated with reduced long-term disability progression in RRMS, with high-efficacy therapy decreasing the likelihood of progression, compared with low-efficacy DMT.[e5] As an evolving therapeutic goal, the incorporation of other novel biomarkers may improve the prognostic value of NEDA-3 in early RRMS, with one such candidate being serum NfL.[21] Serum NfL is a marker of neuroaxonal injury. Circulating NfL levels have been shown to increase before onset of clinical symptoms; elevated levels correlate with acute inflammatory disease (e.g., T1 gadolinium-enhancing lesions), accelerated brain volume loss, and disease worsening; and NfL is a biomarker of treatment effect, including ocrelizumab.[e6-e11] In line with the findings in the OPERA and ORATORIO studies,[e11] ocrelizumab treatment in the ENSEMBLE study lowered serum NfL levels to the healthy donor range after 1 year, and this was maintained over the duration of the study. Similarly, the annualized rate of BVL over the ENSEMBLE 4-year study period was below the range reported in patients with MS[e10] and approached, but remained above, that associated with normal aging.[e13,e14]

Adoption of an early treatment approach with high-efficacy DMTs in people living with RMS to improve long-term outcomes needs to be balanced with safety considerations because some of the more efficacious DMTs pose considerable risks, such as progressive multifocal leukoencephalopathy or secondary autoimmunity.[21] In the ENSEMBLE study, IRRs and infections were the most common AEs observed, there were low rates of SAEs and AE-related discontinuations over 4 years, and there were no new safety signals.

The single-arm ENSEMBLE study is limited by the lack of a parallel group for comparison of outcome measures; therefore, it is not possible to ascertain whether the NEDA-3 rate was higher than might have been observed if patients were treated with a first-line DMT. It is also not possible to

determine whether the NEDA-3 rate observed was due to the effect of ocrelizumab or to the natural history of the population. However, a significant proportion of patients who were previously experiencing disease activity maintained NEDA-3 for 4 years, thus supporting the benefit of ocrelizumab.

The 4-year ENSEMBLE study supports the early treatment of patients with RRMS with highly effective DMTs. The positive benefit-risk profile observed in this and other clinical studies including long-term extensions may provide additional confidence to adopt ocrelizumab as a first-line treatment strategy in newly diagnosed patients with early RMS.

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H.-P. Hartung has received honoraria for consulting, serving on steering committees, and speaking at scientific symposia with approval by the Rector of Heinrich-Heine University Düsseldorf from Bayer HealthCare, Biogen, BMS Celgene, F. Hoffmann-La Roche Ltd, GeNeuro SA, MedImmune, Merck-Serono, Novartis, Sanofi-Genzyme, TG Therapeutics, and Viela Bio. R.H.B. Benedict has received research support from Biogen, Bristol Myers Squibb, F. Hoffmann-La Roche Ltd, Genzyme, Genentech, Novartis, NIH, National Multiple Sclerosis Society, and VeraSci; consultancy fees from Immunic Therapeutics, Latin American Committee for Treatment and Research in Multiple Sclerosis, Merck, Novartis, and Sanofi; speaking support from Biogen, Bristol Myers Squibb, and EMD Serono; and royalties from Psychological Assessment Resources, Inc. T. Berger has participated in meetings sponsored by and received honoraria (lectures, advisory boards, consultations) from pharmaceutical companies marketing treatments for multiple sclerosis: Almirall, Bayer, Biogen, Biologix, Bionorica, BMS/Celgene, GW/Jazz Pharma, Horizon, Janssen-Cilag, MedDay, Merck, Novartis, Octapharma, Roche, Sandoz, Sanofi-Genzyme, TG Pharmaceuticals, Teva-Ratiopharm, and UCB. His institution has received financial support in the last 12 months by unrestricted research grants (Biogen, BMS/Celgene, Merck, Novartis, Roche, and Sanofi-Genzyme) and for participation in clinical trials in multiple sclerosis sponsored by Alexion, Biogen, BMS/Celgene, Merck, Novartis, Octapharma, Roche, Sanofi-Genzyme, and Teva. R. Bermel has received consultancy fees from Biogen, F. Hoffmann-La Roche Ltd, Genentech, Inc., Genzyme, and Novartis. B. Brochet or his institution has received honoraria for consulting, speaking at scientific symposia, or serving on advisory boards from Biogen Idec., BMS, Merck-Serono, Novartis, Roche, and Sanofi-Genzyme. W.M. Carroll has received honoraria for serving on steering committees, advisory boards, and for speaking at scientific meetings from Bayer, Biogen Idec., Merck, Novartis, Roche, and Sanofi-Genzyme. M.S. Freedman has received research or educational grants from Sanofi-Genzyme Canada; honoraria/consultancy fees from Alexion/AstraZeneca, Biogen Idec., EMD Inc./EMD Serono/Merck-Serono, Find Therapeutics, F. Hoffmann-La Roche Ltd, Novartis, Quanterix, Sanofi-Genzyme, and Teva Canada Innovation; is a member of a company advisory board, board of directors, or other similar group for Alexion/AstraZeneca, Atara Biotherapeutics, Bayer HealthCare, Celestra Health, EMD Inc./Merck-Serono, Find Therapeutics, F. Hoffmann-La Roche Ltd, Actelion/Janssen (J&J), Novartis, Sanofi-Genzyme, and Setpoint Medical; and has participated in a company sponsored speaker's bureau for Sanofi-Genzyme and EMD Serono. T. Holmøy has received honoraria/consultancy fees from Biogen Idec., Merck, Roche, Bristol Myers Squibb, Santen, and Sanofi-Genzyme. R. Karabudak received honoraria for consulting, lectures, and advisory boards from Sanofi-Genzyme, Roche, Novartis, Merck-Serono, Gen Ilac TR, and Teva. C. Nos has received funding for registration for scientific meeting from Novartis. F. Patti received personal compensation for speaking activities and serving on the advisory board by Almirall, Bayer, Biogen, Celgene, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva. He also received research grants by Biogen, Merck, FISM (Fondazione Italiana Sclerosi Multipla), RELOAD Onlus Association, and University of Catania. A. Perrin Ross has received honoraria/consultancy fees for serving on advisory boards from Alexion, Biogen Idec., EMD Serono, Merck, Mallinckrodt, Novartis, Roche, Sanofi-Genzyme, Genentech, Inc., Horizon, Janssen, BMS, TG Therapeutics, and Greenwich Biosciences. L. Vanopdenbosch has received compensation for lectures and consultancy from Biogen, F. Hoffmann-La Roche Ltd, Novartis, Merck-Serono, and Sanofi-Genzyme. T. Vollmer has received compensation for consultancy from Biogen Idec., Genentech/F. Hoffmann-La Roche Ltd, and Novartis; and has received research support from Rocky Mountain Multiple Sclerosis Center, Celgene, Biogen Idec., Anokion, Genentech/F. Hoffmann-La Roche Ltd, GW Pharma, and TG Therapeutics. J. Wuerfel was an employee of MIAC AG during the active study period, and is now an employee of F. Hoffmann-La Roche Ltd. He has received grants from EU (Horizon2020), Else Kröner-Fresenius Foundation, and Novartis Foundation; and his institution has received consultancy fees from Actelion, Bayer, Biogen, F. Hoffmann-La Roche Ltd, Genzyme/Sanofi, Idorsia, INmuneBio, Novartis, and Teva. K Kadner is an employee of F. Hoffmann-La Roche Ltd. I. Kulyk, T. Kuenzel, and C. Raposo, and G-A Thanei are employees of F. Hoffmann-La Roche Ltd. J. Killestein has carried out contracted research for F. Hoffmann-La Roche Ltd, Biogen, Teva, Merck, Novartis, and Sanofi-Genzyme. Go to Neurology.org/N for full disclosures.

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See eReferences for additional references e1-e14.