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Efficacy and Safety of Patients With Relapsing Multiple Sclerosis Switching to Ocrelizumab Due to Suboptimal Treatment Response: Results of the 4-Year CASTING–LIBERTO Trial

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ABSTRACT

Background: Almost 75% of patients with relapsing multiple sclerosis (pwRMS) with suboptimal response to other disease-modifying therapies (DMTs) showed no evidence of disease activity (NEDA-3) when treated with ocrelizumab in a large single-arm multicentre trial over 2 years. We aimed to assess the 4-year effectiveness and safety of ocrelizumab in pwRMS who entered a 2-year extension trial.

Methods: PwRMS completing CASTING were eligible to rollover into LIBERTO if available in the country of residence. PwRMS received ocrelizumab every 24 weeks; the same frequency was used for clinical assessments. Primary endpoint was the proportion of patients who had NEDA-3 over 4 years. Safety was assessed by rate and nature of adverse events (AEs).

Results: A total of 439 pwRMS rolled over to LIBERTO, of which 68.1% completed the study; most patients discontinued from LIBERTO due to country-specific changes in reimbursement but most remained on ocrelizumab outside the trial. Over 4 years, 79.5% of patients showed no 24-week confirmed disability progression, 87.5% no relapses, and 90.0% no radiological activity. A total of 65.6% of patients ($n = 290$) showed NEDA-3, with the proportion of patients achieving NEDA-3 yearly remaining above

†Giancarlo Comi passed away in November 2024. Giancarlo contributed to the design of the study and the interpretation of the results and reviewed the first draft of the manuscript. All co-authors would like to acknowledge Giancarlo Comi's extraordinary contribution to the field of MS, with his groundbreaking work in early diagnosis and treatment strategies. His visionary leadership, dedication to patient care, and passion for scientific advancement have left an indelible mark on the field of MS. But beyond his scientific achievements, what truly set him apart was his generous and kind spirit. He had this extraordinary ability to inspire and guide others with wisdom, encouragement, and an unshakable belief that the best was still to come. In doing so, he nurtured many young neurologists who are today beacons in the MS field. To those of us privileged to have crossed his path, he was not just a colleague or a friend but a role model, someone whose passion and dedication remained until his very last days with us. His absence is deeply felt, but his work, his vision, and his kindness will endure and continue to influence generations to come.

During completion of the work related to this manuscript, Regine Buffels and Petra Dirks were employees of F. Hoffmann-La Roche Ltd, Basel, Switzerland.

84.8%. Over 4 years, infections (72.9% of patients) and infusion-related reactions (44.2%) were the most reported AEs. Serious AEs were reported in 9.3% of patients. Five (1.1%) patients discontinued due to AEs.
Conclusions: Findings suggest that switching to ocrelizumab is safe for patients with early RRMS and suboptimal response to previous DMTs, resulting in significant and durable control of disease activity.
Trial Registration: LIBERTO (NCT03599245), extension study to CASTING (NCT02861014); first patient enrolled 12.07.2018; https://clinicaltrials.gov/study/NCT03599245. CHORDS (NCT02637856), ENSEMBLE (NCT03085810)

1 | Introduction

Ocrelizumab, a humanised monoclonal anti-CD20 antibody, was the first therapy targeting B cells approved for relapsing multiple sclerosis (RMS) [1–3]. In the pivotal phase 3 studies, ocrelizumab demonstrated significant benefit versus interferon β-1a on clinical and MRI measures, and a comparable safety over a 2-year period [4–6]. However, participants included in pivotal trials were mainly treatment-naive at enrolment or, when previously treated, had received mostly first-line injection therapies such as interferons and glatiramer acetate [7].

To investigate the effectiveness of ocrelizumab in people with RMS (pwRMS) experiencing disease activity while receiving another disease-modifying therapy (DMT), including fingolimod, dimethyl fumarate, and teriflunomide, two interventional phase 3b studies were designed: CASTING and CHORDS [3, 7]. We previously reported that most patients in CASTING showed no evidence of disease activity (NEDA-3) over a 2-year period [7], with a safety profile consistent with that observed in pivotal phase 3 studies [6]. However, longer-term data on the effectiveness and safety of ocrelizumab in patients switching from other DMTs remain limited.

The LIBERTO study was an extension study, designed to assess the long-term effectiveness, safety, and tolerability of ocrelizumab in patients who had been enrolled in phase 3b trials (CASTING and ENSEMBLE). Here, we report the 4-year effectiveness and safety of ocrelizumab in pwRMS who completed the 2-year CASTING study and rolled over into the LIBERTO study.

2 | Methods and Materials

2.1 | Study Population

The LIBERTO study was a multicentre, single-arm, 2-year open-label extension study for two phase 3b trials investigating the effectiveness and safety of ocrelizumab in pwRMS, diagnosed according to the 2010 McDonald diagnostic criteria [8]. The first patient enrolled on 12 July 2018.

All pwRMS completing the 2-year phase 3b CASTING study were eligible to rollover into the LIBERTO study, if this option was available in the country of residence, and if the following exclusion criteria were not present: hypersensitivity to ocrelizumab treatment; unresolved severe immunocompromising state; evidence of any adverse events (AEs) for which the local label recommended permanent discontinuation; intention to become pregnant; and prohibited concomitant medication. Detailed eligibility criteria at screening of CASTING have been previously reported (Methods S1) [7].

2.2 | Study Design and Procedure

Eligible patients received ocrelizumab every 24 weeks up to week 168 of LIBERTO (Figure 1A). Assessments of effectiveness such as Expanded Disability Status Scale (EDSS) score and relapses were conducted at baseline and subsequently every 24 weeks up to year 4 (week 192 of LIBERTO). Magnetic resonance imaging (MRI) was acquired at baseline, week 8 (for rebaselining purposes, in line with findings from the ocrelizumab phase 2 trial [9, 10]), weeks 24, 48, and 96 of CASTING and weeks 120, 144, and 192 of LIBERTO (Figure 1A). Upon discontinuation or at the end of the 2-year and 4-year periods, patients could enter a safety follow-up period for 48 weeks from the date of their last infusion (up to 24 weeks after the last study visit).

2.3 | Efficacy Endpoints

The primary clinical endpoint was the proportion of patients with NEDA-3 over a 4-year treatment period, defined as the absence of: 24-week confirmed disability progression (CDP) or sustained disability progression (SDP) (see below); protocol-defined relapses; and MRI activity, defined as the presence of T1-weighted contrast-enhancing lesions (T1w-CEL) and new/enlarging T2-weighted lesions (N/E-T2wL) from week 8 [11].

Key secondary clinical endpoints included: proportion of patients with 24-week and 48-week CDP; proportion of patients with 24-week and 48-week confirmed disability improvement (CDI), defined as a reduction in EDSS score by ≥ 1.0 points if EDSS ≤ 5.5, and ≥ 0.5 points if EDSS > 5.5 in patients with a baseline EDSS of ≥ 2.0; proportion of patients with SDP, defined as a 48-week CDP event at any time during the study period, which is still confirmed at the last study visit or last known follow-up (this is a more stringent measure likely to capture accumulation of irreversible disability [12], and accounts for patients who improve after experiencing disability progression); annualised relapse rate (ARR) and proportion of patients free of relapses; and change in cognitive performance as measured by the Symbol Digit Modalities Test (SDMT) using validated alternate forms to control for practise effect [13]. MRI endpoints, counted from week 8 (rebaseline), included: total number of T1w-CEL and N/E-T2wL, changes in T1w hypointense lesion volume, and changes in whole brain volume (WBV) using SIENA, and grey and white matter volume changes using the longitudinal Freesurfer pipeline. Whole brain volume changes were contextualised using rates observed in healthy 30–50-year-old individuals [14].

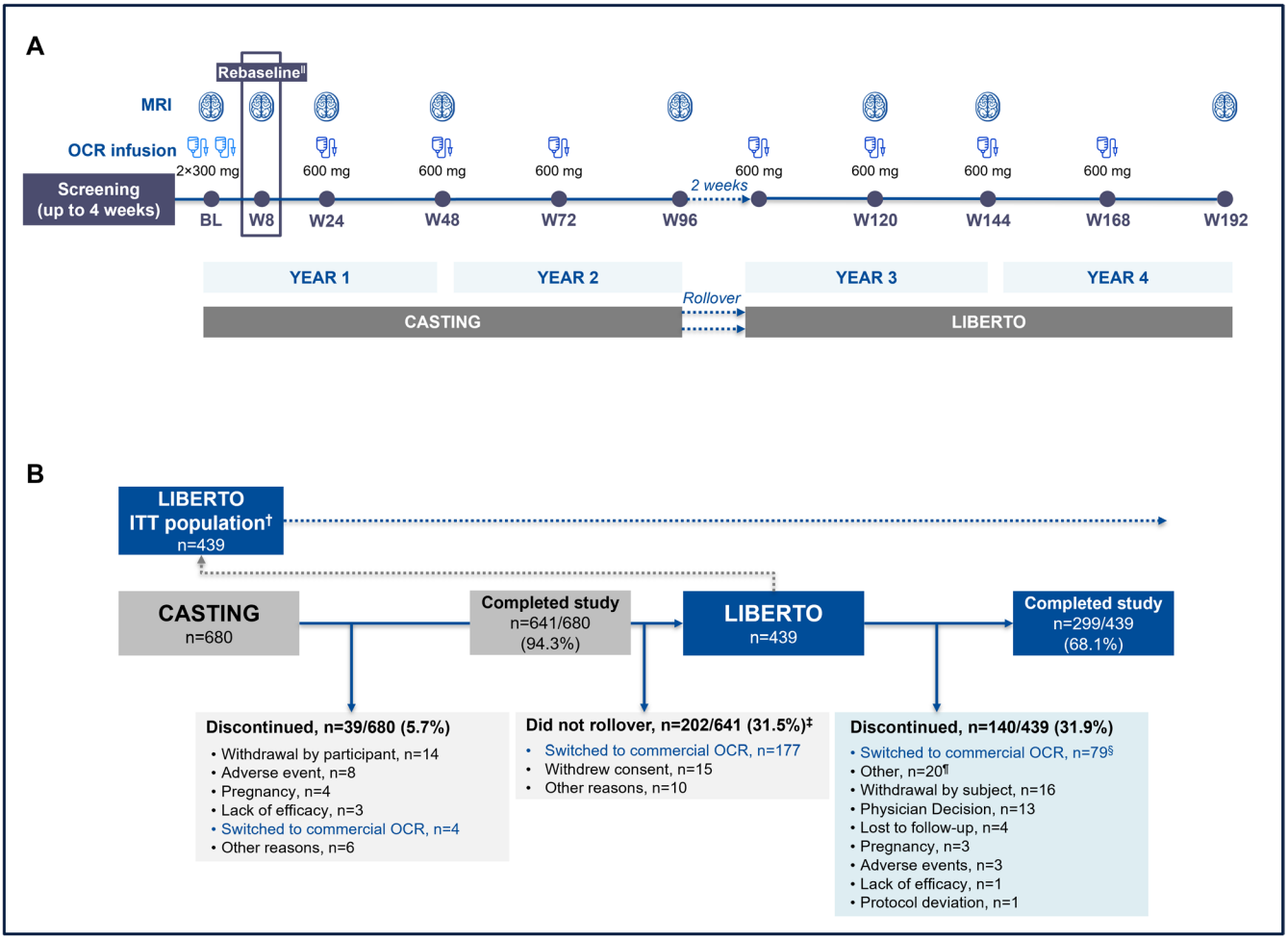

FIGURE 1 | CASTING–LIBERTO study design (A) and patient disposition (B). BL, baseline; ITT, intention-to-treat; OCR, ocrelizumab; W, week. ‖All results from CASTING use week 8 for rebaselining purposes; the first 8 weeks are excluded from the analysis of the first 24 weeks. †LIBERTO ITT population includes all the patients who enrolled into LIBERTO, and the 4-year outcomes are reported. ‡A total of 202/641 (31.5%) patients who completed CASTING did not rollover to LIBERTO, mostly because a decision was made by some participating countries (Belgium, Germany, Switzerland, and Turkey) to opt out of the trial and switch patients to commercial OCR. §Early closure of the trial (after the first dose was administered at baseline in LIBERTO) occurred in Spain, and patients (*n*/*N*, 75/79) continued ocrelizumab outside the study. ¶One patient left the study but did not have a discontinuation visit; therefore, no reason for discontinuation was recorded.

2.4 | Patient-Reported Outcomes

The MS Impact Scale (MSIS)-29, a 29-item questionnaire, was used to measure the physical and psychological impact of MS on health-related quality of life [15]. Impact of treatment with ocrelizumab on absenteeism, presenteeism, work productivity loss, and activity impairment were measured using the Work Productivity and Activity Impairment (WPAI) questionnaire [16].

2.5 | Safety

Safety outcome measures included the incidence and types of AEs, assessments of severity (Common Terminology Criteria for Adverse Events [CTCAE] classification) [17, 18] and seriousness, and discontinuations due to AEs, from baseline until the final visit in the safety follow-up.

2.6 | Statistical Analyses

The estimation of the probability of NEDA-3 and its components was evaluated through Kaplan–Meier survival analysis as time to disease activity (estimates of event-free rates) in the intention-to-treat (ITT) population, with the 95% confidence intervals (CI) calculated by the Greenwood method using log–log transformation. Participants discontinuing due to lack of efficacy or death were imputed as having a protocol-defined event. Further analyses evaluated the proportion of pwRMS with yearly rates of NEDA-3, where all components of NEDA-3 (including CDP) were re-baselined to the start of each year; evaluable populations were determined at the start of each year (Methods S1). Percentage change from baseline in WBV was calculated using a mixed-effect model of repeated measures (MMRM) and compared with normative brain volume data derived from Battaglini et al. [14]. An analysis on time to first relapse and 24-week CDP was performed in the following three subgroups of patients

defined according to their previous DMTs: natalizumab + fingolimod, interferons and glatiramer acetate, and dimethyl fumarate + teriflunomide.

2.7 | Ethical Approval and Informed Consent Statements

The relevant institutional review boards/ethics committees approved the trial protocols, and all participants provided written informed consent.

3 | Results

3.1 | Baseline Demographics and Disposition

A total of 680 pwRMS were enrolled into CASTING and received ≥1 dose of ocrelizumab, as previously reported [7], and 641 (94.3%) completed the study (Figure 1B). A subset of 439 patients rolled over to the LIBERTO study (ITT population), of whom 299 (68.1%) completed the study. Most pwRMS who did not enrol (*n*/*N*, 177/202; 87.6%) or discontinued prematurely (79/140; 56.4%) in LIBERTO switched to commercially available ocrelizumab, following country-specific changes in reimbursement conditions.

Baseline demographic and disease characteristics for the LIBERTO ITT population ($N=439$), patients who completed LIBERTO ($n=299$), and patients who did not enter LIBERTO ($n=241$) are described in Table 1 (note: patient characteristics are reported for their baseline at the start of CASTING, Figure 1B). Compared with the ITT population, the group not rolling over into LIBERTO had a slightly higher proportion of female patients (66.4% vs. 62.9%), was more likely to present with relapses and T1 gadolinium-enhancing lesions and new/enlarging T2 lesions (20.3% vs. 13.0%), to have been previously treated with ≥2 DMTs (46.9% vs. 35.5%), in particular fingolimod (22.4% vs. 17.1%), teriflunomide (11.6% vs. 8.4%), and glatiramer acetate (19.1% vs. 15.9%), and had higher MSIS-29 scores. Other patient characteristics were comparable.

3.2 | Primary Endpoint: NEDA-3

After 4 years of treatment, most patients had experienced no clinical or radiological activity: 79.7% (95% CI: 75.3, 83.4) had no 24-week CDP, 87.7% (84.3, 90.6) had no sustained disability progression, 86.7% (83.0, 89.4) had no relapses, and 89.9% (86.6, 92.4) had no MRI activity from rebaselining at week 8. This corresponds to 65.6% of patients showing NEDA-3 over the 4-year period when 24-week CDP was considered as a disability component, and 71.8% of patients showing NEDA-3 over the 4-year period when 24-week SDP was considered as a disability component (Figure 2A).

The proportion of patients achieving NEDA-3 at each year of the study remained above 84.8% (Figure 2B, Table S1). A small minority of patients experienced evidence of disease activity (EDA) over time, with clinical disease activity being more commonly reported than MRI activity. Excluding patients who discontinued treatment, ≥85.9% of patients with NEDA-3 during any given year maintained NEDA-3 in the following year, and ≥76.3% of patients with EDA during a given year experienced NEDA-3 in the subsequent year (Figure 3).

3.3 | Other Clinical Outcomes

3.3.1 | Clinical Disability Improvement

Among patients with EDSS ≥2.0, improvement in disability status was observed in 24.0% (95% CI: 18.7, 29.9) of patients 24 weeks after the initial event was recorded; this decreased to 20.7% (15.7, 26.3) of patients when confirmed after 48 weeks.

3.3.2 | Relapses

In the ITT population, a total of 63 relapses were recorded over a period of 4 years, resulting in an adjusted ARR of 0.02 (95% CI: 0.02, 0.03), and 86.7% (83.0, 89.4) of patients remaining relapse free by year 4. A slightly lower proportion of patients experienced no relapses in the first year (93.6%, 90.9, 95.7), but in subsequent years the proportion of patients with no relapses remained stable and above 95% (Table S1). Patients switching from fingolimod or natalizumab were more likely to experience relapses in the first 24 weeks; but, by year 4, the proportion of patients with relapses was similar across different subgroups of patients clustered according to their previous DMT (Figure S1). Notably, patients switching from fingolimod and natalizumab had a lower risk of disability progression (Figure S2).

3.3.3 | Cognition (SDMT)

At baseline, the mean (SD) SDMT score in the ITT population was 54.5 (11.6). For most patients (61.4%), information processing speed remained stable by the end of the study, with 27.5% of patients experiencing improvement (≥8-point increase) and 11.1% of patients experiencing worsening (≥8-point decrease) in cognitive function.

3.4 | Brain MRI Metrics

3.4.1 | T1w-CEL and N/E-T2w Lesions Counts

At week 8 (rebaseline), 86.5% ($n=371$) of patients had no T1w-CEL, 8.2% ($n=5$) had one lesion and 5.3% ($n=23$) had two or more lesions. Over the 4-year period, after rebaselining at week 8, a total of 17 T1w-CELs were detected (most lesions were detected in the first 24 weeks), resulting in a minimal adjusted rate of 0.003 lesions per visit (95% CI: 0.002, 0.006) across all combined scans. Over the same period, a total of 57 N/E-T2wL were detected ($n=25$ detected in the first 24 weeks), resulting in an adjusted rate of 0.024 lesions per scan (95% CI: 0.018, 0.032) across all combined scans. This translated into near-complete suppression of acute MRI activity at year 1 (94.1%, 413/439), year 2 (97.3%, 427/439), year 3 (98.8%, 324/328), and year 4 (99.3%, 301/303).

TABLE 1 | Patient Baseline Demographics, Disease Characteristics, and Prior DMTs.

Baseline parameters	ITT population ($N=439$)[a]	Patients not rolling over ($N=241$)[b]	4-year completers ($N=299$)
Age, mean (SD), years	34.0 (8.5)	34.4 (8.7)	33.4 (8.4)
Age group, *n* (%)			
<40 years	318 (72.4)	181 (75.1)	234 (78.3)
≥40 years	121 (27.6)	60 (24.9)	65 (21.7)
Female, *n* (%)	276 (62.9)	160 (66.4)	180 (60.2)
Duration since MS onset, mean (SD)	4.9 (2.6)	5.2 (2.9)	4.8 (2.7)
Duration since MS diagnosis, mean (SD)	3.6 (2.5)	3.8 (2.5)	3.5 (2.5)
EDSS			
Median (IQR)	2.0 (1.5–3.0)	2.0 (1.5–3.0)	2.0 (1.5–3.0)
Range	0.0–6.0	0.0–4.5	0.0–5.5
SDMT			
Mean (SD)	54.5 (11.6)	52.5 (15.2)	54.8 (11.3)
Range	17–90	0–91	20–90
MSIS-29, physical subscale			
Mean (SD)	21.2 (20.6)	25.8 (21.7)	20.2 (19.7)
Range	0.0–90.0	0.0–83.3	0.0–90.0
MSIS-29, psychological subscale			
Mean (SD)	32.0 (23.7)	34.9 (23.7)	31.5 (22.9)
Range	0.0–96.3	0.0–96.3	0.0–96.3
Normalised brain volume at week 8, mean (SD), cm^3	1435.6 (84.4)	1439.3 (82.2)	1435.1 (84.8)
Patients with no T1w-CEL at week 8, *n* (%)	371 (86.5)	195 (84.8)	253 (85.5)
T1w hypointense lesions volume at week 8, mean (SD), mm^3	3976.8 (5332.8)	4478.6 (6904.5)	3772.9 (5461.4)
Patients pretreated, *n* (%)			
1 DMT	283 (64.5)	128 (53.1)	196 (65.6)
≥2 DMTs	156 (35.5)	113 (46.9)	103 (34.4)
Treatment duration with last DMT, mean (SD), months	26.9 (20.4)	25.8 (21.0)	26.4 (20.4)
Time from last DMT to first ocrelizumab infusion, mean (SD), months	1.8 (1.8)[c]	N/A	N/A
Last DMT prior to study entry, *n* (%)			
Interferon-based regimens	134 (30.5)	64 (26.6)	90 (30.1)
Dimethyl fumarate	121 (27.6)	47 (19.5)	81 (27.1)
Fingolimod	75 (17.1)	54 (22.4)	50 (16.7)
Glatiramer acetate	70 (15.9)	46 (19.1)	50 (16.7)
Teriflunomide	37 (8.4)	28 (11.6)	27 (9.0)
Natalizumab	2 (0.5)	2 (0.8)	1 (0.3)

(Continues)

TABLE 1 | (Continued)

Baseline parameters	ITT population ($N=439$)[a]	Patients not rolling over ($N=241$)[b]	4-year completers ($N=299$)
Disease activity prior to enrolment, *n* (%)			
Relapses only	162 (36.9)	76 (31.5)	110 (36.8)
Relapses + T1 Gd^+ lesions	38 (8.7)	27 (11.2)	19 (6.4)
Relapses + N/E T2 lesions	69 (15.7)	35 (14.5)	53 (17.7)
Relapses + T1 Gd+ lesions + N/E T2 lesions	57 (13.0)	49 (20.3)	41 (13.7)
MRI activity only	113 (25.7)	54 (22.4)	76 (25.4)

Abbreviations: DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; IQR, interquartile range; ITT, intention-to-treat; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSIS, Multiple Sclerosis Impact Scale; N/A, not available; N/E, new/enlarging; SD, standard deviation; SDMT, Symbol Digit Modalities Test; T1 Gd^+, T1 gadolinium-enhancing; T1w-CEL, T1-weighted contrast-enhancing lesion.
[a]ITT population includes patients available at LIBERTO baseline (year 2); patient characteristics are reported for their baseline at the start of CASTING.
[b]Includes patients enrolled into CASTING but discontinued the study (n=39) or did not rollover to LIBERTO at the end of CASTING ($n=202$), as described in Figure 1B.
[c]Time from last DMT to first ocrelizumab infusion by DMT type, mean (SD), months: Interferon 1.5 (1.9), Glatiramer acetate 1.3 (1.9), Dimethyl fumarate 1.6 (1.1), Fingolimod 2.9 (1.7), Teriflunomide 1.6 (1.6), Natalizumab 6.7 (5.8).

3.4.2 | T1-Weighted Hypointense Lesion Volume

The T1w hypointense lesion volume decreased by a median (IQR) of 11.6% (−19.4 to −4.7) from week 8 to year 2, and 10.8% (−19.6 to −3.1) from week 8 to year 4, with the greatest reduction observed in the first year (8.3% [−16.2 to −2.3]), but continuing in subsequent years.

3.4.3 | Brain Volume

A mean whole brain atrophy rate of −1.59% (95% CI −1.78, −1.39) was observed from week 8 to year 4, corresponding to an average yearly whole brain atrophy rate of −0.39% (Figure 4). This is within the ranges of normal brain volume loss observed in a cohort of healthy subjects, with an average of −0.23% per year, and an 80th percentile of −0.55% to −0.44% per year [14] (see Figure 4 for more details).

3.5 | Patient-Reported Outcomes

3.5.1 | MSIS-29

Over 4 years, an improvement was observed in the physical domain score (mean [SD], −2.4 [16.3]) and the psychological domain score (−8.3 [19.9]).

3.5.2 | Work Productivity and Activity Impairment

Treatment with ocrelizumab resulted in a reduction in: missed work days (absenteeism, mean [SE]: baseline, 10.3% [1.6] to 3.6% [0.9] at year 4), impairment levels while at work (presenteeism: baseline, 19.9% [1.4] to 14.4% [1.4] at year 4), work productivity loss (baseline, 22.9% [1.7] to 16.5% [1.5] at year 4), and impairment of other non-work activities (baseline, 29.7% [1.4] to 22.9% [1.5] at year 4), suggesting a reduction in the impact of MS symptoms on work and non-work activities (Figure 5).

3.6 | Safety Endpoints

Over the 4-year period, 92.9% of patients (408/439) experienced ≥1 AE and 9.3% of patients (41/439) experienced ≥1 SAE (Table 2). The most common AEs were infections and infusion-related reactions (IRRs), while infections and nervous system disorders were the most common SAEs (Table S2). Most patients had mild or moderate AEs (78.4%); 13.4% of patients (59/439) experienced severe AEs (not all severe AEs were reported by investigators as SAEs) and 1.1% (5/439) experienced life-threatening events (Table 2). No deaths were recorded. A total of five patients (1.1%) discontinued the study due to AEs: female breast cancer ($n=2$), *Clostridium difficile* colitis ($n=1$), depression ($n=1$), and hypogammaglobulinemia ($n=1$) reported as a non-serious event.

Infusion-related reactions were reported in 44.2% of patients (194/439). For most patients this occurred at the first infusion (140/439; 31.9%) with frequency decreasing to <4% in subsequent infusions. Most IRRs were mild or moderate (grade 1 or 2), with only three patients experiencing a grade 3 IRR. In LIBERTO, no IRRs led to treatment discontinuation.

A total of 320 patients (72.9%) had at least one infection, with nasopharyngitis ($n=126$, 28.7%), influenza ($n=81$, 18.5%), urinary tract infections (UTI, $n=70$, 15.9%), oral herpes ($n=43$, 9.8%), and upper respiratory tract infections ($n=38$, 8.7%) being the most common. For most patients (297/320, 92.8%), infections were mild or moderate. Serious infections were observed in only 2.7% of patients (12/439), all leading to hospitalisation, with sinusitis ($n=3$) and UTIs ($n=2$) being most common (Table 2, Table S2). All serious infections resolved except one case of COVID-19 pneumonia (see below). Treatment was discontinued due to infections in one patient with *Clostridium difficile* colitis who was subsequently

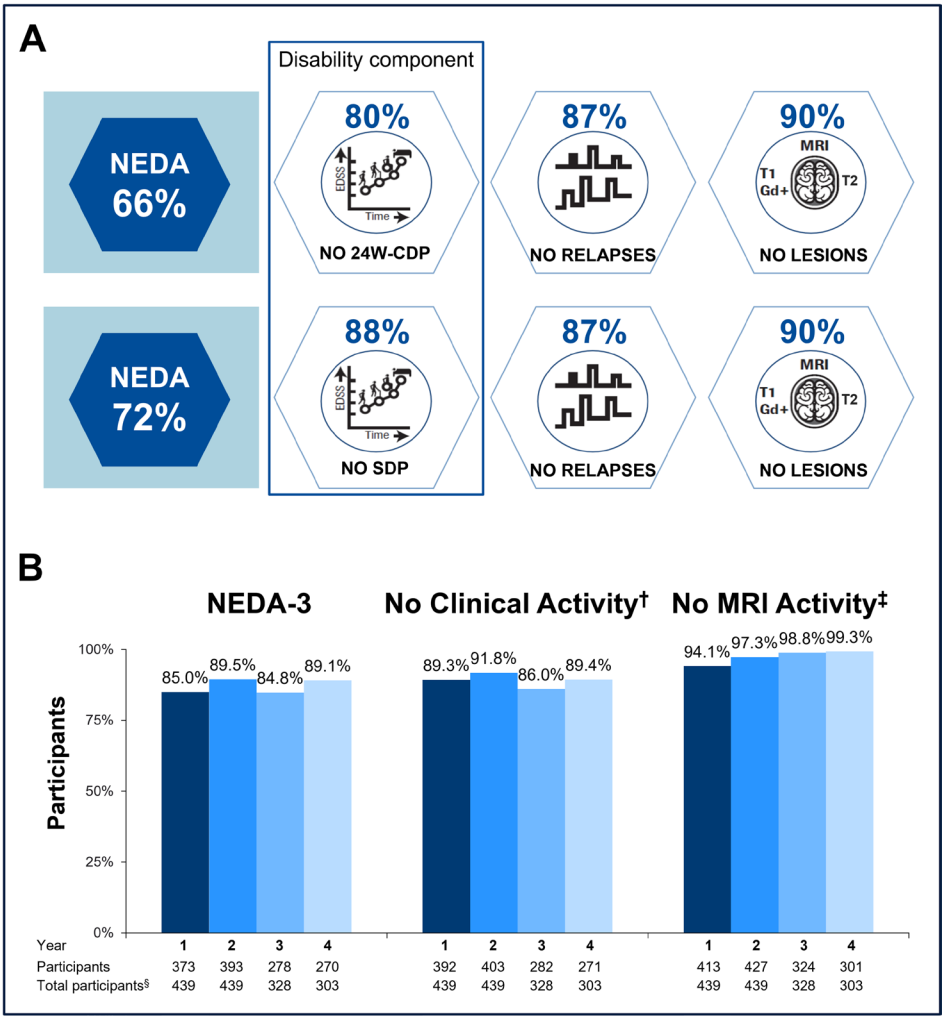

FIGURE 2 | Rate of NEDA-3 and subcomponents over a period of 4 years (A) and annual rates of NEDA-3 (B). 24W-CDP, 24-week confirmed disability progression; CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; NEDA, no evidence of disease activity; N/E-T2wL, new/enlarging T2-weighted lesion; SDP, sustained disability progression; T1 Gd+, T1 gadolinium-enhancing; T1w-CEL, T1-weighted contrast-enhancing lesion. Panel A: Two NEDA rates are presented over the 4-year period, using two different disability progression definitions: Disability progression sustained for at least 24 weeks (24-week CDP) or sustained by the end of the study (SDP); Kaplan–Meier estimates rounded up to the nearest whole number are presented. Panel B: Annual rates of NEDA and subcomponents (using 24-week CDP) are presented, with all components of NEDA rebaselined to the start of each year. †Defined as no 24-week CDP and no relapse. ‡Defined as no T1w-CELs and no N/E-T2wL after week 8. §Total patients at the start of each year.

diagnosed with Crohn's disease. Among 33 patients still in the study as of 11 March 2020 (when the pandemic was officially declared), nine cases of COVID-19 were observed. Only one case resulted in hospitalisation, with the patient admitted to intensive care and recovering but with some sequelae (post-intensive care syndrome); the patient subsequently continued treatment with ocrelizumab outside of the trial.

Immunoglobulin (Ig) levels were not measured systematically and were only reported if considered as AEs by the investigator. Three cases of hypogammaglobulinaemia were reported, one of which led to treatment discontinuation.

Four malignancies were reported in four patients (0.9%), including three female breast cancers. Two of the patients with breast cancer (mother and grandmother) had a significant family history of breast cancer. A fourth patient was diagnosed with a grade 2 malignant melanoma in situ after removal of a nevus, and the procedure was considered curative.

4 | Discussion

Escalation remains a frequently utilised treatment approach for patients with RMS [19–21]. In this 4-year study, we assessed the effectiveness and safety of escalating pwRMS to ocrelizumab, following suboptimal disease control on prior therapies (which, in nearly all patients, were: interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod).

Following this treatment escalation, patients demonstrated robust and sustained disease control. Over the 4-year period, nearly 70% of patients achieved NEDA-3, with approximately 80% remaining free from disability progression and 90%

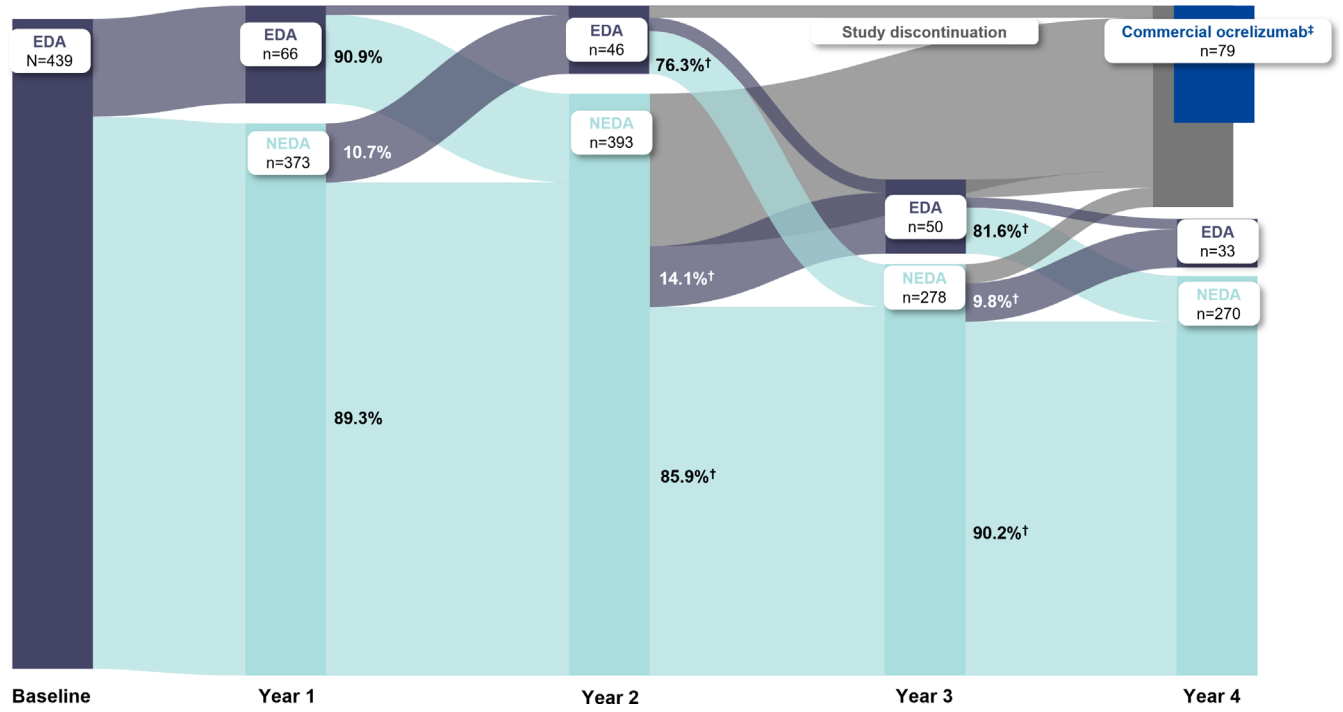

FIGURE 3 | Sankey plot showing transition between states of disease activity (NEDA and EDA). EDA, evidence of disease activity; NEDA, no evidence of disease activity; OCR, ocrelizumab; pwRMS, patients with relapsing multiple sclerosis. †Proportions of pwRMS transitioning between NEDA and EDA from year 2 onward were calculated excluding patients who discontinued the study. The Sankey plot visually summarises the direction of flow through the states of disease activity (NEDA and EDA) from baseline to year 4.

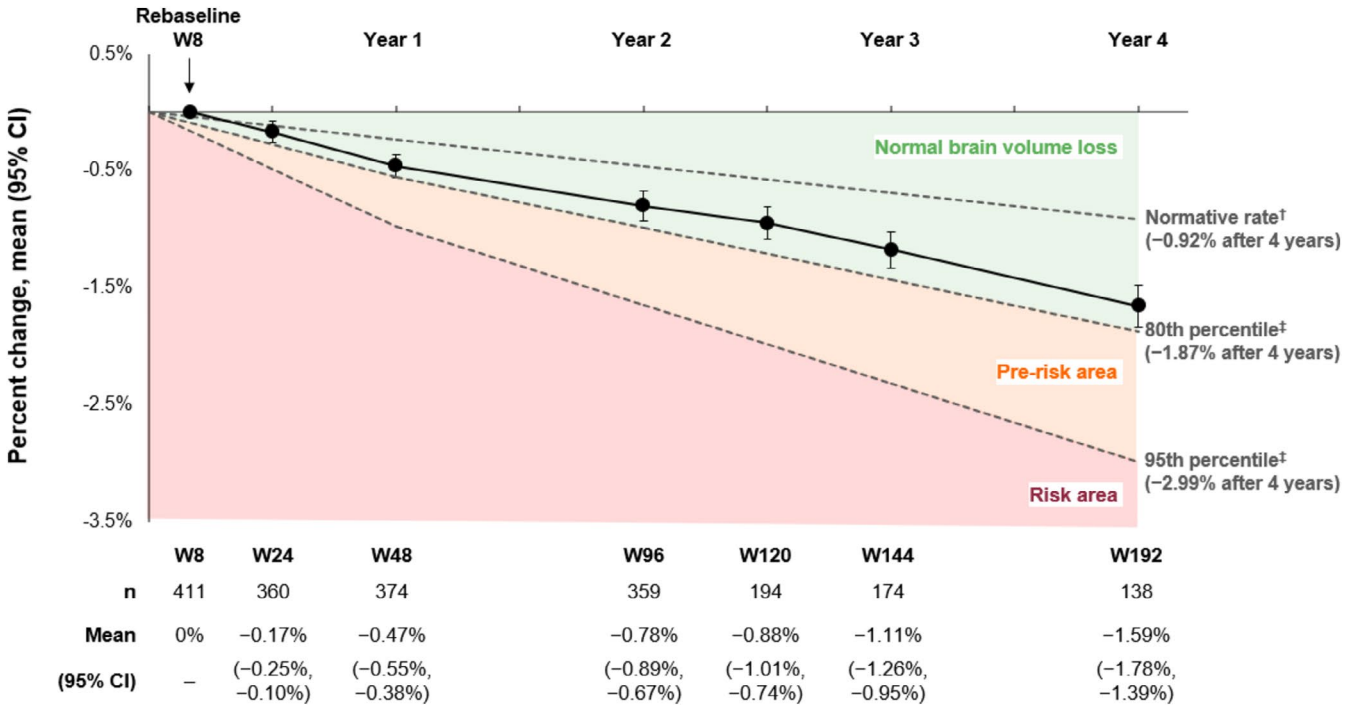

FIGURE 4 | Percentage change in whole brain volume. †Predicted annual brain atrophy rates in healthy subjects aged 30–40 years (−0.23% per year), with brain imaging performed in 1.5T scans; derived from Battaglini et al. [14]. In CASTING-LIBERTO, > 70% of patients were < 40 years old and most scanners had a field strength of 1.5T. ‡Normative 80th percentiles in 30–40-year-olds: −0.55% in year 1 and −0.44% from year 1 onwards, and normative 95th percentiles in 30–40-year-olds: −0.98% in year 1 and −0.67% from year 1 onwards; derived from Battaglini et al. [14]. Pre-risk (80th to 95th percentiles and risk, > 95th percentile) areas as defined by Battaglini et al. [14].

experiencing no relapses or MRI activity. The annual proportion of patients maintaining NEDA-3 consistently stayed at or above 85%. Furthermore, of those who did show evidence of disease activity in a given year, 76% to 91% converted to NEDA the following year, indicating sustained efficacy with ocrelizumab. Notably, these outcomes were achieved despite a highly active

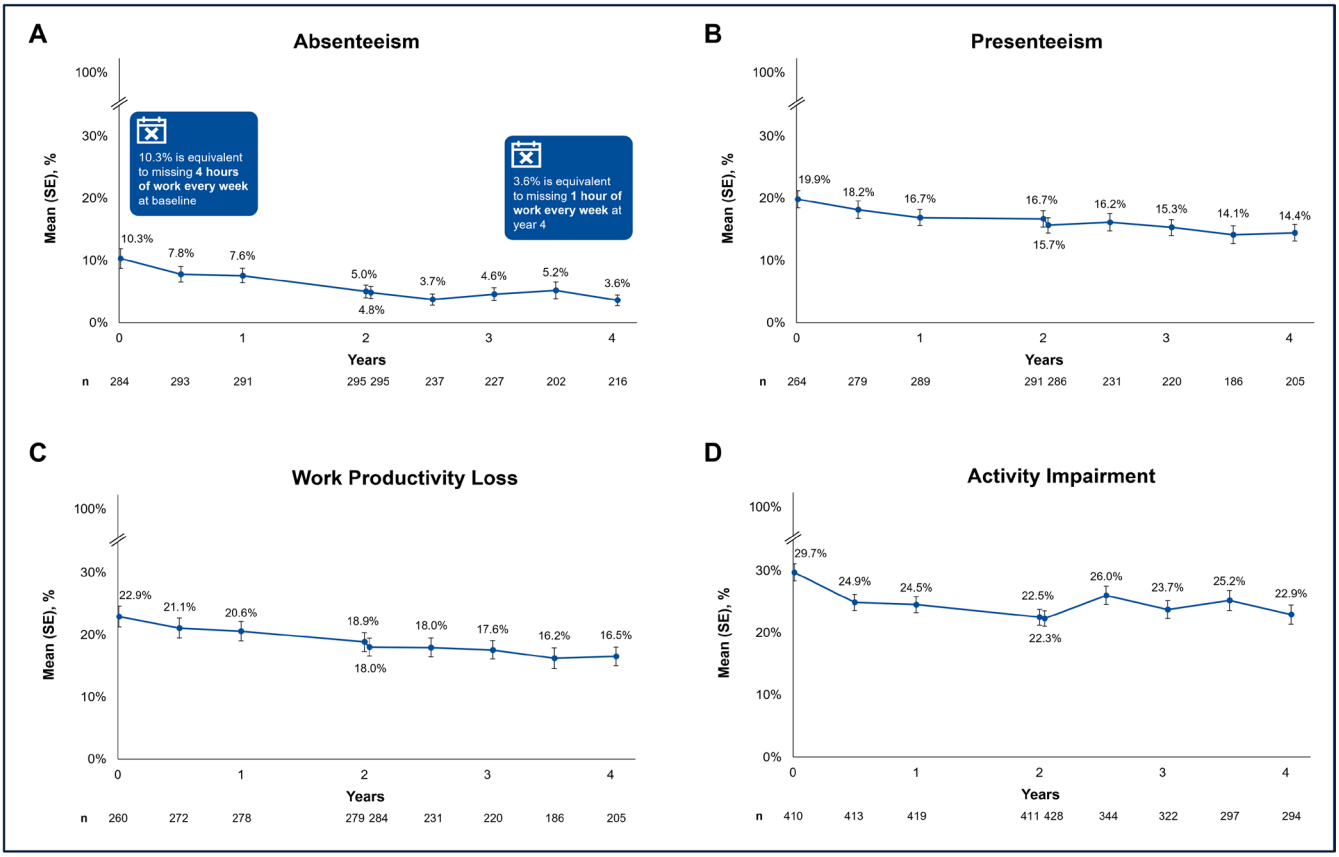

FIGURE 5 | WPAI scores for absenteeism (A), presenteeism (B), work productivity loss (C), and activity impairment (D) over a period of 4 years. SE, standard error; WPAI, Work Productivity and Activity Impairment.

baseline disease profile; prior to switching, 74% of the cohort had experienced recent relapses and 63% exhibited acute MRI activity. This sustained control was observed regardless of the previous DMT, although it is worth noting that patients transitioning from fingolimod or natalizumab were more likely to experience relapses early after the switch.

In a similar prospective, multicentre, single-arm study enrolling 608 patients (CHORDS), NEDA-3 was observed in only 48% of pwRMS over a 2-year period [22]. However, there was a notable difference in the design of the two studies. In CASTING–LIBERTO, data were rebaselined at week 8 to exclude MRI activity that developed before the initiation of ocrelizumab and would resolve in the first weeks post-ocrelizumab initiation; this rebaselining approach was based on results from the phase 2 trial [9] and reflects current clinical practise and guidelines [23]. When the MRI from the screening visit was used, NEDA-3 was attained by 46% of patients in CASTING-LIBERTO over the 4-year period.

The high control of disease activity observed in this study is consistent with recent real-world evidence on ocrelizumab. In an Italian cohort of 388 patients, 84.9% had NEDA-3 (94.8% having no relapses, 93.7% with no MRI activity, and 91.1% with no disability progression) after 2 years of treatment [24]. NEDA-3 was also achieved in 91% of 332 patients in a study in Kuwait, and 85% of 235 patients in a cohort study in Switzerland, both over a 2-year period [25, 26]. In a small cohort of 22 RRMS patients in Turkey, EDSS was stable or improved in 91% of patients over a 4-year period [27]. Finally, in a large German cohort of 1858 previously treated pwRMS, approximately 75% remained free of disability progression over a period of up to 5 years, similar to the 80% observed in CASTING–LIBERTO over 4 years [28].

The near-complete suppression of acute MRI activity observed in CASTING–LIBERTO aligned with results from the phase 3 OPERA trials [6] and other ocrelizumab studies [29]. Even more importantly, a significant reduction in the total volume of T1w hypointense lesions was observed. Chronically T1w hypointense lesions, also coined “black holes”, have been associated with long-term disability accrual. In the acute phase, T1w hypointense regions reflect increased water content due to inflammatory oedema but in the chronic phase, chronic T1w hypointensity reflects axonal loss and matrix destruction [30, 31]. In the present study, reduction of T1w hypointense volume was highest in the first year, indicating a likely resolution of oedema. However, the effect continued for the remaining 3 years, suggesting a potential restorative effect of ocrelizumab. This restorative effect against progression of disease-related neurodegeneration is further supported by the normalisation of brain volume loss, reflected in annual atrophy rates within normative values reported in healthy controls [14], and below the well-established pathological threshold of $>0.4\%$ per year, which is associated with clinically relevant EDSS worsening [32]. Accordingly, over the 4-year period of this study, the proportion of participants

TABLE 2 | Adverse events and discontinuation due to adverse events.

Variable	Number of patients ($n = 439$), n (%)
Total number of patients with, n (%)	
Any adverse event	408 (92.9)
Any serious adverse event[a]	41 (9.3)
Discontinuation due to adverse events	5 (1.1)
Death	0 (0.0)
Total number of patients with, n (%)	
Infusion-related reactions	194 (44.2)
Infections	320 (72.9)
Nasopharyngitis	126 (28.7)
Influenza	81 (18.5)
Urinary tract infection	70 (15.9)
Oral herpes	43 (9.8)
Upper respiratory tract infections	38 (8.7)
COVID-19	9 (2.1)
Serious infections[b]	12 (2.7)
Malignancies[c]	4 (0.9)

Abbreviations: COVID-19, coronavirus disease 2019; SAE, serious adverse event; UTI, urinary tract infection.
[a]A total of 49 SAEs were reported in 38 patients. This includes five life-threatening events: COVID-19 pneumonia ($n = 1$); road traffic accident ($n = 1$); suicide attempt ($n = 1$) where the patient was subsequently discontinued due to worsening of depression; hypoglycaemia ($n = 1$) and hypoglycaemic seizure ($n = 1$) occurring in the same patient with comorbid type 1 diabetes; and subarachnoid haemorrhage ($n = 1$).
[b]Twelve serious infections were reported in 12 patients, all hospitalised: sinusitis ($n = 3$), UTI ($n = 2$), *Clostridium difficile* colitis ($n = 1$), COVID-19 pneumonia ($n = 1$), localised infection ($n = 1$, infected toe in patient with type 1 diabetes), lower respiratory tract infection ($n = 1$), postoperative (knee replacement) wound infection ($n = 1$), vestibular neuronitis ($n = 1$, unknown cause), and viral (respiratory) infection ($n = 1$).
[c]Four malignancies were reported in four patients (breast cancer [$n = 3$] and malignant melanoma [$n = 1$]).

showing sustained disability progression, a more stringent measure likely to capture accumulation of irreversible disability [12], was low.

The treatment effect of ocrelizumab was also perceived by participants who reported an overall improvement in their quality of life as measured by the physical and psychological subscales of the MSIS-29. This is consistent with the results reported in a large real-world cohort of 1224 pwRMS treated with ocrelizumab over a 2-year period, where a mean reduction of 1.7 points in the Phy-MSIS29 and 4.0 points in the Psy-MSIS29 was observed [33]. In CASTING–LIBERTO, we also saw a reduction in the rates of absenteeism, presenteeism, work productivity loss, and activity impairment. Regarding absenteeism and considering someone working full-time (40 h/week), the observed decrease in percent of work time due to disease-related problems from 10.3% to 3.6% can be translated as an average reduction from 4 to 1 missed working hours in the past week. These are highly relevant findings for a cohort of patients likely to be at the beginning of their professional careers and are consistent with a previous real-world report on work productivity in patients treated with ocrelizumab [34]. These patient-reported outcomes may reflect the observed improvement in disability levels as measured by EDSS, and the overall stability or improvement in cognitive function as measured by the SDMT. This improvement may partly reflect practise effect [35, 36], although validated alternate forms of SDMT were used to control for it [13].

Several key aspects should be highlighted regarding the safety results in this population. Infections and IRRs were the most common AEs. IRRs were mostly observed with the first infusion; the majority were mild to moderate, and no patients discontinued treatment due to IRRs, which is consistent with findings from the phase 3 OPERA studies [37]. Upper respiratory tract infections and UTIs were the most common serious and non-serious infections, reflecting findings from other ocrelizumab clinical trials [38] and real-world MS cohorts [39–43]. Infections were manageable, with 93% reported as mild or moderate. All serious infections resolved without sequelae (except one case of COVID-19 pneumonia), and only one infection was treatment-limiting, a case of colitis by *Clostridium difficile*, which occurred in the context of underlying Crohn's disease. *Clostridium difficile* infections are a common complication of inflammatory bowel disease [44]. Association of infections with immunoglobulin levels could not be assessed in the current study as immunoglobulins were not measured routinely in a central laboratory. Three cases of hypogammaglobulinaemia were reported by local laboratories, one of which (IgG, 2.8 g/L) led to treatment discontinuation of ocrelizumab, although no concomitant infection was reported. In a recent large real-world study of patients treated with anti-CD20 agents (rituximab and ocrelizumab) over a mean time of 2.5 years, IgG < 500 mg/dL showed increased odds of serious infections [45]. However, in a recent 10-year analysis of the phase 3 OPERA study, hypogammaglobulinaemia and longer treatment duration with ocrelizumab were not associated with a higher risk of serious infections. Instead, the presence of 1 or ≥2 comorbidities, recent relapse activity, and EDSS ≥6.0 were shown to be significant risk factors for serious infections in a multivariate analysis [38]. Four malignancies were reported in four patients (female breast cancer [$n = 3$] and malignant melanoma [$n = 1$]); two of the patients with breast cancer had a family history of breast cancer. Previously, a numerical imbalance of malignancies was observed in patients treated with ocrelizumab relative to its comparators [4]. However, analysis of malignancy rates in pooled safety data from 5680 patients who received ocrelizumab from 11 clinical trials did not indicate an increased risk or a time-dependent exposure effect [3].

The present study has some limitations. Firstly, a single-arm trial lacking a comparator does not allow for conclusions to be drawn about treatment effects. However, as described above, the results are consistent with findings from several trials and real-world cohorts. Secondly, the studied population had a relatively short disease duration and, at most, had been previously treated with two DMTs; therefore the results may not be generalisable to other patients. Thirdly, the rollover design of the LIBERTO

study, where only a portion of the parent CASTING study population was included, may have resulted in some survivorship and attrition biases. Although most of the discontinuations (88%) were due to decisions in different countries to move patients to commercial ocrelizumab, we could not account for progression events on those patients. Given that the different populations of completers versus discontinuers were overall comparable, similar rates could be expected. Lastly, in CASTING–LIBERTO, we could not assess outcomes when switching from other high-efficacy DMTs; however, recent real-world studies have shown the superiority of ocrelizumab versus fingolimod or dimethyl fumarate following natalizumab cessation [46].

5 | Conclusion

Over a 4-year period, approximately 70% of patients showed NEDA-3, and efficacy was consistent across multiple clinical, MRI, and patient-reported measures. Safety in this population reflected that previously observed in other clinical trials and in real-world cohorts. This study suggests that, for patients with early RMS and suboptimal response to previous DMTs, switching to ocrelizumab is safe and results in significant and durable control of disease activity.

Author Contributions

Licinio Craveiro: writing – original draft, writing – review and editing. **Heinz Wiendl:** writing – original draft, writing – review and editing. **Bouchra El Azzouzi:** writing – original draft, writing – review and editing. **Jens Wuerfel:** writing – original draft, writing – review and editing. **Aksel Siva:** writing – original draft, writing – review and editing. **Patrick Vermersch:** writing – review and editing, writing – original draft. **Petra Dirks:** writing – original draft, writing – review and editing. **Bart Van Wijmeersch:** writing – original draft, writing – review and editing. **Regine Buffels:** writing – original draft, writing – review and editing. **Ralph H. B. Benedict:** writing – original draft, writing – review and editing. **Gary Cutter:** writing – original draft, writing – review and editing. **Thomas Kuenzel:** writing – original draft, writing – review and editing. **Ilya Kister:** writing – original draft, writing – review and editing. **Celia Oreja-Guevara:** writing – original draft, writing – review and editing. **Giancarlo Comi:** methodology, writing – review and editing.

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Conflicts of Interest

P. Vermersch has received consultancy fees from AB Science, Biogen, BMS/Celgene, Imcyse, Merck, Novartis, Sanofi, and Teva and performed contracted research for F. Hoffmann-La Roche Ltd. and Merck. R.H.B. Benedict has received research support from Biogen, BMS, the National Institutes of Health, the National Multiple Sclerosis Society, and Novartis, consultancy fees from BMS, F. Hoffmann-La Roche Ltd., Novartis, and Sanofi, speaking support from BMS and EMD Serono, and royalties from Psychological Assessment Resources Inc. B. Van Wijmeersch has received financial support/study grants or fees for speaking and serving on advisory boards from Actelion/Janssen, Almirall, Bayer, Biogen, BMS/Celgene, F. Hoffmann-La Roche Ltd., Merck, Novartis, Sanofi-Genzyme, and Teva. G. Cutter has served on the following data and safety monitoring boards: AI Therapeutics, AMO Pharma, Applied Therapeutics, Argenx, AstraZeneca, Avexis Pharmaceuticals, BMS, CSL Behring, Cynata Therapeutics, DiaMedica Therapeutics, Horizon Pharmaceuticals, Immunic, Inhibrix, Karuna Therapeutics, Kezar Life Sciences, Medtronic, Merck, Meiji Seika Pharma, Mitsubishi Tanabe Pharma Holdings, Prothena Biosciences, Novartis, Pipeline Therapeutics (Contineum), Regeneron, Sanofi, Teva Pharmaceuticals, United BioSource LLC, and the University of Texas Southwestern; consulting or advisory boards: Alexion, Antisense Therapeutics/Percheron, Avotres, Biogen, Clene Nanomedicine, Clinical Trial Solutions LLC, EMD Serono, Endra Life Sciences, Cognito Therapeutics, F. Hoffmann-La Roche Ltd., Genentech Inc., Genzyme, Hoya Corporation, Immunic, Immunosis Pty Ltd., Klein-Buendel Incorporated, Kyverna Therapeutics Inc., Linical, Perception Neurosciences, Protalix Biotherapeutics, Regeneron, Revelstone Consulting, SAB Biotherapeutics, Sapience Therapeutics, Scott&Scott LLP, and Tenmile. Dr. Cutter is employed by the University of Alabama at Birmingham and President of Pythagoras Inc., a private consulting company located in Birmingham, AL. l. Kister has served on advisory boards for Biogen, Genentech Inc., and Horizon, received research support for investigator-initiated grants from Biogen, EMD Serono, Genentech Inc., the Guthy Jackson Charitable Foundation, the National Multiple Sclerosis Society, and Sanofi-Genzyme. He received royalties from Walters-Kluwer for "Top 100 Diagnosis in Neurology". C. Oreja-Guevara has received honoraria for speaking and serving on advisory boards from Biogen, BMS, F. Hoffmann-La Roche Ltd., Janssen-Cilag, Merck, Neuraxpharm, Novartis, Sanofi-Genzyme, and Viatris. A. Siva has received research grants from Istanbul University Cerrahpaşa Research Support Funds, the Scientific and Technological Research Council of Türkiye, and the Turkish Multiple Sclerosis Society and has received honoraria or consultancy fees for participating on advisory boards, giving educational lectures, and/or travel and registration coverage for attending scientific congresses or symposia from Abdi Ibrahim Ilaç (Turkey), Alexion, Ali Raif Ilaç, EMD Serono, F. Hoffmann-La Roche Ltd., and Novartis. H. Wiendl has received grant/research support from Bayer HealthCare, Biogen, Deutsche Forschungsgesellschaft, Else Kröner-Fresenius Foundation, EMD Serono, German Federal Ministry of Education and Research, Hertie Foundation, Interdisciplinary Centre for Clinical Studies (Münster, Germany), Novartis, NRW Ministry of Education and Research, Sanofi-Genzyme, and Teva, and consulting fees from Bayer HealthCare, Biogen, BioVentures, EMD Serono, Fresenius Medical Care, GlaxoSmithKline, GW Pharmaceuticals, Novartis, Sanofi-Genzyme, and Teva. J. Wuerfel is an employee of F. Hoffmann-La Roche Ltd. At study start, he was an employee of MIAC AG, Switzerland; MIAC AG has received consultancy fees from Actelion, Bayer, Biogen, F. Hoffmann-La Roche Ltd., Genzyme-Sanofi, Idorsia, INmuneBio, Novartis, and Teva. B. El Azzouzi and T. Kuenzel are employees of F. Hoffmann-La Roche Ltd. P. Dirks and R. Buffels were employees of F. Hoffmann-La Roche Ltd. at the time of the study. L. Craveiro is an employee of and shareholder in F. Hoffmann-La Roche Ltd. G. Comi received consultancy fees from BMS, F. Hoffmann-La Roche Ltd., Janssen, and Novartis, performed contracted research for BMS and received consultancy and speaking fees from Almirall SpA, Celgene, EMD Serono, F. Hoffmann-La Roche Ltd., Janssen, Merck, Novartis, and Sanofi-Genzyme.

Data Availability Statement

For up-to-date 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://go.roche.com/data_sharing. Anonymised records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential

increase in risk of patient re-identification. For eligible studies, qualified researchers may request access to individual patient-level clinical data through a data request platform. At the time of writing this request platform is Vivli: https://vivli.org/ourmember/roche/.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Annual rates[†] of NEDA and subcomponents. **Table S2:** Serious adverse events from first CASTING intake to LIBERTO safety follow-up. **Figure S1:** Time to first protocol-defined relapse from CASTING baseline to LIBERTO week 96. **Figure S2:** Time to onset of 24-week CDP from CASTING baseline to LIBERTO week 96.