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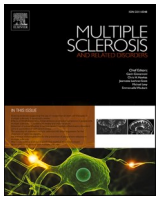

Review article

Efficacy, safety and patient reported outcomes in patients with active relapsing multiple sclerosis treated with ocrelizumab: Final results from the PRO-MSACTIVE study

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ABSTRACT

Background: Ocrelizumab, a humanized anti-CD20 monoclonal antibody, has been approved in Europe for the treatment of adult patients with active relapsing multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS), on the basis of previous phase III studies. However, limited data were available on ocrelizumab efficacy in RMS according to the Lublin definition of activity (clinical and/or imaging features) used in the current drug label. The PRO-MSACTIVE study was thus designed to provide additional data on ocrelizumab efficacy according to this definition, and also on safety and patient reported outcomes (PROs).

Methods: PRO-MSACTIVE is a national, multicenter, open-label, single-arm phase IV French study, conducted in patients with active RMS (relapsing-remitting multiple sclerosis, RRMS, or secondary progressive multiple sclerosis, SPMS). The primary endpoint, which was assessed at week (W) 48, was defined as the proportion of patients free of disease activity (defined by no relapses and no T1 gadolinium-enhancing nor new and/or enlarging T2 lesions using brain MRI). Disease activity, disability and PROs using 6 questionnaires for disease severity, quality of life, impact on work productivity, and treatment satisfaction were described at W24 and W48. Adverse events were described until W72.

Results: Among the 422 analyzed patients (RRMS: 376, SPMS: 46), 63.3% (95% CI [58.5%; 67.9%]) were free of disease activity at W48 (RRMS: 62.2% [57.1%; 67.2%], SPMS: 71.7% [56.5%; 84.0%]). A total of 358 patients (84.8%; RRMS: 84.6%, SPMS: 87.0%) were relapse-free up to W48, and the overall adjusted annualized relapse rate was 0.14 (RRMS: 0.15, SPMS: 0.09). Overall, 67.8% of patients (RRMS: 66.8%, SPMS: 76.1%) had no evidence of MRI activity (no T1 gadolinium-enhancing lesions [83.4%] and no new/enlarging T2 lesions [75.1%]); 58.5% of patients (RRMS: 57.7%, SPMS: 65.2%) achieved No Evidence of Disease Activity (NEDA: no relapses, no confirmed disability progression, and no MRI activity) at W48. All PRO scores were stable between the first dose of ocrelizumab and W48 and better outcomes were seen for patients having an EDSS score $\geq$4. Overall, 89.3% of patients reported adverse events, 62.3% adverse events assessed as related to ocrelizumab, and 8.5% serious adverse events. No serious infusion-related reactions, opportunistic infections, progressive multifocal leukoencephalopathy, nor deaths were reported. No new safety signal was identified.

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Conclusion: These data confirm the efficacy of ocrelizumab in a pragmatic setting and its favorable benefit-risk profile in patients with RMS.
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1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory condition of the central nervous system involving immune mediated processes leading to demyelination and neurodegeneration (Leray et al., 2016). Swift action to prevent or slow disease activity and progression is crucial and early treatment optimization is critical to achieve favorable outcomes. In this context, MS therapeutic landscape is rapidly evolving and the number of disease-modifying therapies (DMTs) has been steadily increasing, with among others the advent of monoclonal antibodies, which have opened up a new era in the treatment of MS (Voge and Alvarez, 2019; Wootla et al., 2016). Ocrelizumab is a recombinant humanized monoclonal antibody that selectively targets CD20-expressing B cells (Klein et al., 2013). Ocrelizumab was approved for use in the USA in March 2017 and in the EU in January 2018 (McCool et al., 2019), after the demonstration of its favorable benefit/risk profile in relapsing forms of MS (RMS) (pivotal studies OPERA I, NCT01247324; OPERA II, NCT01412333) (Hauser et al., 2017) and in primary progressive MS (PPMS) (pivotal study ORATORIO, NCT01194570) (Montalban et al., 2017).

However, in OPERA phase III studies, disease activity was only defined by clinical criteria for eligibility (at least 2 documented clinical relapses within the previous 2 years, or one clinical relapse within the last year). Consequently, patients with a diagnosis of MS and for whom disease activity was only assessed by brain imaging techniques were not included in these trials. Moreover, despite the efficacy assessment of ocrelizumab by using the proportion of patients with no evidence of disease activity (NEDA: no relapses, no confirmed disability progression, and no MRI activity) at 2 years, data were not analyzed according to the Lublin definition (clinical and/or imaging features) used in ocrelizumab current label (Lublin et al., 2014). At last, secondary progressive MS (SPMS) was not specifically identified in OPERA studies.

Over the past 20 years, there has been a growing interest in qualitative data and better insight into patient perception of their quality of life and health care experiences. This is particularly relevant in MS where patients' quality of life (QoL) is impaired due to long-term accumulation of physical and cognitive disability. Patient-reported outcomes (PROs), which include a variety of questionnaires are thus relevant to assess patients' disease burden and to provide valuable insight into treatment benefits.

In this context, PRO-MSACTIVE, a phase IV study, was designed to provide additional data on ocrelizumab efficacy, safety and PRO measures in patients with RMS in a pragmatic setting.

2. Material and methods

2.1. Study design

PRO-MSACTIVE is a national, multicenter, open-label, single-arm interventional phase IV French study.

Eligible patients were adults aged $\geq$ 18 years with active RMS (RRMS or SPMS) defined by clinical and/or imaging features and who might have received prior DMTs. Specifically, active RMS was defined as patients having (1) $\geq$ 1 clinically reported relapse over the 6-month period prior to screening and/or (2) as detected by brain magnetic resonance imaging (MRI) performed over a 3-month period prior to screening, with no DMT changes, at least: (2a) $\geq$ 1 T1 gadolinium-enhancing lesion or (2b) $\geq$ 1 new or enlarging T2 lesion compared to a previous MRI performed within 24 months before screening. Key exclusion criteria included diagnosis of PPMS or other neurological disorders, current active infections, and severely immunocompromised state.

After a 4-week screening period, eligible patients entered the 48-week treatment period and received an initial dose of two 300 mg intravenous (IV) ocrelizumab infusions given at 14 days apart (i.e., Days 1 and 15), followed by one single 600 mg IV ocrelizumab infusion 24 weeks after the initial ocrelizumab dose. Premedication with intravenous methylprednisolone and antihistamine had to be administered prior to each ocrelizumab infusion. At week (W) 48, patients could either receive ocrelizumab in a post-marketing setting or another DMT. The safety period covered 72 weeks from the first ocrelizumab administration (including an additional 24-week follow-up after the 48-week treatment period).

Patients were assessed by investigators for efficacy and safety at day (D) 15, W24, and W48, and for safety until W72.

Patients completed the following self-reported PRO questionnaires during the study: MS symptoms' severity scale (SymptoMScreen), Modified Fatigue Impact Scale (MFIS, impact of fatigue on activities), EuroQol 5-dimension 5-level version with visual analog scale (EQ-5D-5L with VAS, health-related quality of life), Multiple Sclerosis International Quality of Life questionnaire (MusiQoL, MS-related quality of life), Work Productivity and Activity Impairment scale: Specific Health Problem (WPAI:SHP, work productivity and impairment due to problems), and Treatment Satisfaction Questionnaire for Medication (TSQM-14, satisfaction to treatment).

The study visits and main assessments are captured in Fig. 1.

The study was performed according to principles in the Declaration of Helsinki and International Council for Harmonization Guidelines for Good Clinical Practice (ICH GCP). Approval from the 'Sud-Ouest et Outre-Mer 4' Institutional Review Board/Independent Ethics Committee was obtained on May 03, 2018, before study set-up. All the patients provided written informed consent before any trial-related activities were carried out.

2.2. Endpoints

The primary efficacy objective of the study was to evaluate the impact of ocrelizumab on disease activity at W48. Ocrelizumab efficacy was consequently assessed based on the proportion of patients free of disease activity at W48, defined by no protocol-defined relapses and no gadolinium-enhancing T1 lesions nor new or unequivocally enlarging T2 lesions on brain MRI according to the investigator. Protocol-defined relapses consisted on symptoms attributable to MS only in the absence of fever or infection, persisting for over 24 h, preceded by a neurological stability for $\geq$ 30 days, accompanied by objective neurological worsening consistent with an increase of at least: 0.5 step on the Expanded Disability Status Scale (EDSS), or 2 points in one of the following functional system score (FSS) (pyramidal, ambulation, cerebellar, brainstem, sensory, or visual), or 1 point in each of $\geq$ 2 on previously described FSS.

Secondary endpoints included the annualized relapse rate (ARR), the proportion of patients with confirmed disability progression at W24 (CDP24; change in EDSS $\geq$ 1 step when baseline score was within the interval of [0.0; 5,5], and $\geq$ 0.5 when baseline score was $>$ 5.5), the proportion of patients with no MRI activity at W48 (no T1 gadolinium-enhancing and no new or enlarging T2 lesions), the proportion of patients with No Evidence of Disease Activity (NEDA) at W48 (no protocol-defined relapses, no CDP24, and no MRI activity), the proportion of patients with changes in PRO scores, and treatment-emergent adverse events (AEs).

2.3. Statistical analysis

Efficacy and safety analyses were performed in all enrolled patients with at least one ocrelizumab dose (full set analysis [FAS] and safety analysis set [SAF] populations), and according to the diagnosis cohort at baseline (RRMS *versus* SPMS). The primary efficacy criterion was also analyzed in the Per Protocol (PP) population (no major protocol deviation impacting the primary endpoint and no ocrelizumab discontinuation during the 48-week treatment period), and in the modified PP population (after enlarging the time-window for assessments at W48, from ± 14 days to ± 56 days, to take into account the pragmatic patient management in this phase IV study). QoL populations consisted in all the patients from the FAS with ≥ 1 baseline QoL score for each PRO questionnaire.

The proportion of patients free of disease activity at W48 (primary endpoint) was described with its associated two-sided 95% confidence interval (CI) using the Clopper-Pearson method. Patients who discontinued early during the 48-week treatment period or with missing data were considered as failure. A sensitivity analysis was performed on the FAS population without considering missing data as failure.

3. Results

3.1. Patient characteristics

Overall, 422 included patients were eligible and retained for analysis (FAS and SAF populations) (Fig. 2). Of these 422 patients, 376 (89.1%) suffered from RRMS and 46 (10.9%) from active SPMS. The PP population comprised 255 patients, and the modified PP population 317 patients after enlarging the time-window for assessments at W48. The six PRO questionnaires were fulfilled and then analyzed in most patients, whatever the self-reported questionnaire was: 417 patients with at least one baseline score for the SymptoMScreen, 416 for the MFIS, 414 for the EQ-5D-5L, 410 for the WPAI:SHP, 416 for the MusiQoL, and 392 for the TSQM-14. Overall, 384 patients (91.0%) of the FAS population completed the study.

At baseline, SPMS patients were older than RRMS patients (50.7 ± 8.5 *versus* 38.3 ± 9.9 years) and had a higher EDSS score (5.6 ± 1.7 *versus* 2.5 ± 1.8). Their MS was diagnosed longer ago (16.7 ± 9.4 *versus* 6.4 ± 7.1 years) and they were more susceptible to be relapse-free for the last 12 months prior to enrollment (34.8% *versus* 15.7%). They also received more DMTs prior to ocrelizumab (3.8 ± 1.9 *versus* 2.3 ± 1.3) (Table 1).

3.2. Efficacy

3.2.1. Patients free of disease activity (primary endpoint)

Overall, 267/422 patients (63.3%, 95% CI [58.5; 67.9%]) were free of disease activity at W48 (Fig. 3A). This proportion was higher in SPMS patients than in RRMS patients (71.7% [56.5%; 84.0%] *versus* 62.2% [57.1%; 67.2%]). Excluding missing data from analysis, the proportion of patients free of disease activity was higher: 267/393 patients (67.9% [63.1%; 72.5%]) (Fig. 3B). This proportion was also higher in the PP population: 185/255 patients (72.5% [66.6%; 77.9%]) (Fig. 3C) and in the modified PP population: 228/317 patients (71.9% [66.6%; 76.8%]) (Fig. 3D).

3.2.2. Disease activity

A total of 46/422 patients (10.9%) (RRMS: $n = 43$, 11.4%; SPMS: $n = 3$, 6.5%) experienced at least one protocol-defined or clinical relapse up to W48. Among these patients, 36 (78.3%) experienced a single relapse, and the majority of relapses occurred before W24, meaning within 6 months following ocrelizumab initiation. The overall adjusted ARR at W48 was 0.14 (i.e., 1.4 relapse every 10 years), higher in RRMS patients than in SPMS patients (0.15 and 0.09, respectively).

At W48, 286/422 patients (67.8%) had no evidence of MRI activity (no gadolinium-enhancing T1 lesions [83.4%] and no new or enlarging T2 lesions [75.1%]), considering missing data as failure (Fig. 3A). This

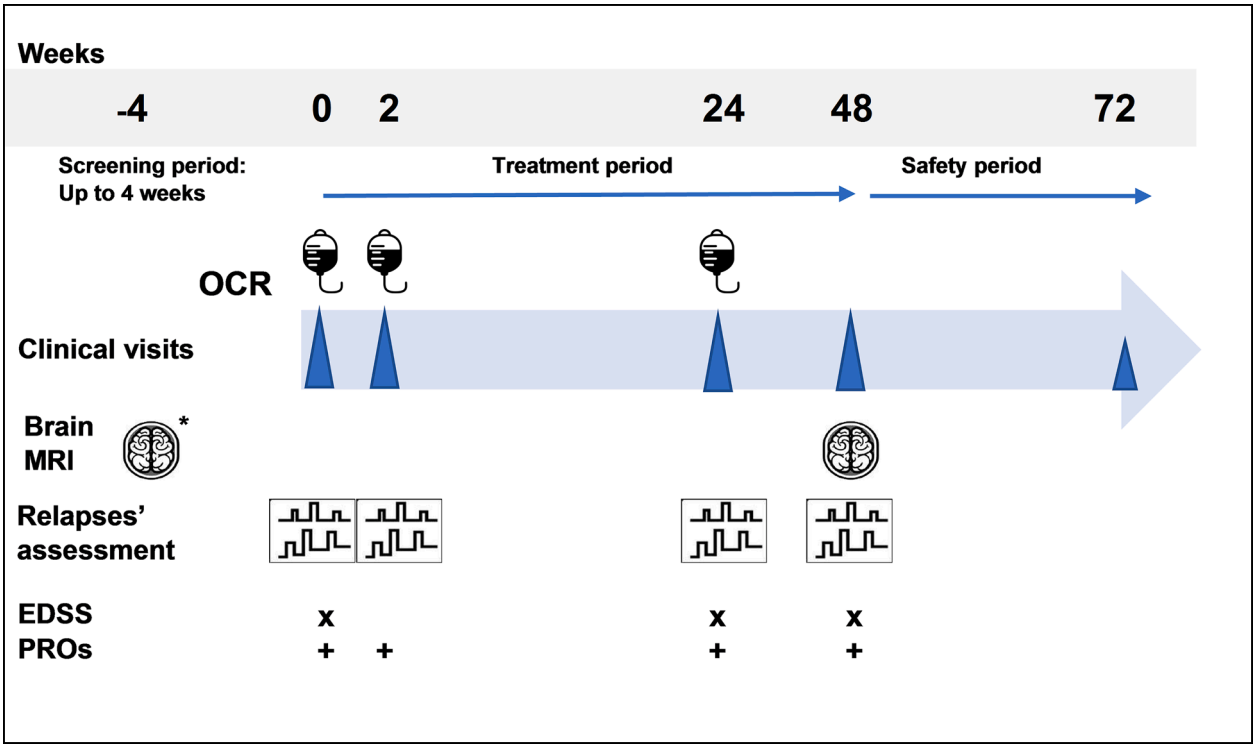

Fig. 1. Study design.
EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; PROs, patient reported outcomes; OCR, ocrelizumab
* Unless documented MRI performed within 3 months prior to screening with no changes in disease modifying treatments.

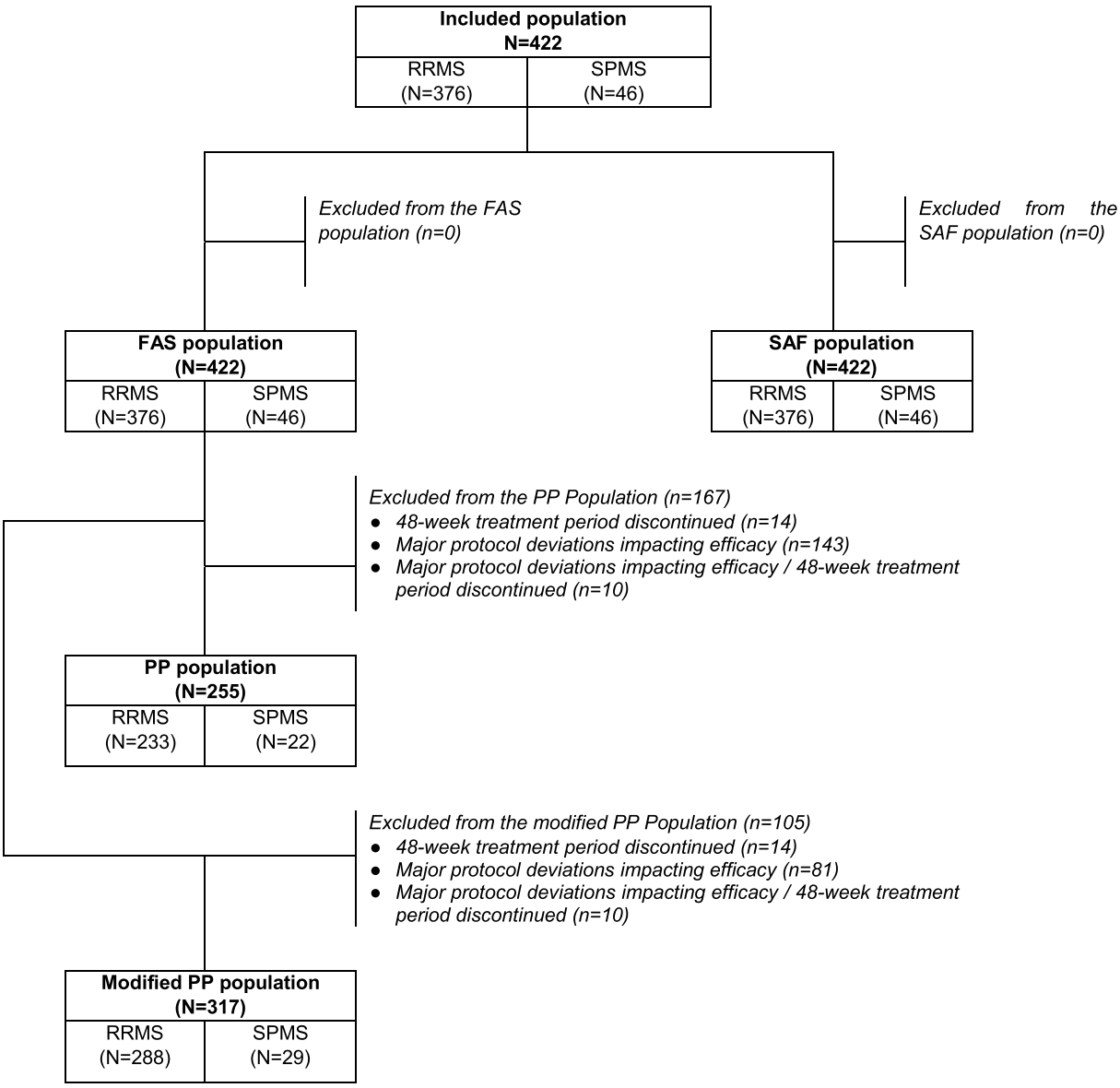

Fig. 2. Disposition of patients.
FAS, full analysis set; PP, Per-Protocol, RRMS, relapsing-remitting multiple sclerosis; SAF, safety analysis set; SPMS, secondary progressive multiple sclerosis.

proportion was higher in SPMS patients (76.1%) than in RRMS patients (66.8%). After excluding missing data from analysis, the proportion of patients with no evidence of MRI activity was higher: 286/390 patients (73.3%) had no evidence of MRI activity (no gadolinium-enhancing T1 lesions [92.4%] and no new or enlarging T2 lesions [79.3%]).

3.2.3. Disability

A minority of patients had disability progression at W24 confirmed at W48 (CDP24): 55/422 patients (13.0%, 95% CI [10.0%; 16.6%]). This proportion was higher in SPMS patients than in RRMS patients (17.4% and 12.5%, respectively). After excluding missing data from analysis, this overall proportion was lower: 26/393 patients (6.6%, 95% CI [4.4%; 9.5%]).

3.2.4. No evidence of disease activity at W48

Overall, 247/422 patients (58.5%, 95% CI [53.7%; 63.3%]) achieved NEDA at W48. This proportion was higher in SPMS patients (65.2% [49.8%; 748.6%]) than in RRMS patients (57.7% [52.5%; 62.8%]). After excluding 48 patients with missing data from analysis, 66.0% (95% CI [61.0%; 70.8%]) of patients achieved NEDA.

3.2.5. Patients reported outcomes

Table 2 presents the main results of PROs related to patients' daily lives. PRO questionnaires assessing different aspects of patients' quality of life (SymptoMScreen, MFIS, EQ-5D-5L, MusiQoL, and WPAI:SHP) showed a similar trend: the total score and per dimension of each scale remained broadly stable from baseline to W48, whatever the type of RMS was. It should be pointed out that the impact of MS on patient daily life was stronger at W48 in patients with a high EDSS score at baseline, whatever the PRO used was. Regarding patient satisfaction to treatment (TSQM-14), the mean global score (60.3 ± 19.5 at D15 on a 0–100 scale) and scores per dimension slightly improved until W48, in particular in RRMS patients for effectiveness (median change of 11.1), and in patients with a low baseline EDSS score (median change of 20.0 when EDSS $<$ 2.0).

3.3. Safety

From the first ocrelizumab infusion, a total of 377 patients (89.3%) experienced at least one emergent adverse event (AE) (Table 3). The most common AEs were infusion-related reactions (IRRs) related to

Table 1
Baseline characteristics of patients.

	RRMS(N = 376)	SPMS(N = 46)	Total(N = 422)
Mean age – years ±SD	38.3 ± 9.9	50.7 ± 8.5	39.7 ± 10.5
Female sex – no. (%)	280 (74.5)	31 (67.4)	311 (73.7)
Mean time since MS symptoms onset – years ±SD	7.7 ± 7.6	18.5 ± 9.5	8.9 ± 8.5
Mean time since MS diagnosis – years ±SD	6.4 ± 7.1	16.7 ± 9.4	7.5 ± 8.0
Mean EDSS score ± SD	2.5 ± 1.79	5.64 ± 1.67	2.81 ± 2.03
Type of MS activity at screening – no. (%):	180 (47.9)	17 (37.0)	197 (46.7)
• Only clinical relapses in previous 6 months			
• Only MRI features	88 (23.4)	20 (43.5)	108 (25.6)
• Clinical relapses and MRI	108 (28.7)	9 (19.6)	117 (27.7)
Previous DMT(s) – no. (%)	278 (73.9)	38 (82.6)	316 (74.9)
Mean no. of previous DMTs (316 non-naive patients) ±SD	2.3 ± 1.3	3.8 ± 1.9	2.4 ± 1.5
Main previous DMTs (316 non-naive patients) – no. (%)			
Beta interferon and assimilated products*	185 (66.6)	32 (84.2)	217 (68.7)
Fingolimod	115 (41.4)	14 (36.8)	129 (40.8)
Teriflunomide	92 (33.1)	10 (26.3)	102 (32.3)
Dimethyl Fumarate	92 (33.1)	5 (13.2)	97 (30.7)
Natalizumab	58 (20.9)	12 (31.6)	70 (22.2)

DMT, disease modifying treatment; MRI, magnetic resonance imaging; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation; SPMS, secondary progressive multiple sclerosis

* Including glatiramer acetate

ocrelizumab or to the pre-medication prophylaxis with methylprednisolone and/or antihistamine drug (reported in 47.6% of patients), headache (14.7%), nasopharyngitis (11.4%), and urinary tract infection (10.0%). AEs of grade ≥ 3 were reported in 10.7% of patients. Serious AEs were reported in 36 patients (8.5%), and this proportion was higher in SPMS patients (15.2%) compared to RRMS patients (7.7%).

Most of the IRRs experienced by 201 patients occurred at the first infusion of the first ocrelizumab dose (in 40.8% of patients at D1, 8.6% at D15) and 16.3% at W24. All IRRs were non-serious events but 2 IRRs led to ocrelizumab discontinuation (0.5%).

A total of 193 patients (45.7%) experienced infections, including 12 patients (2.8%) with serious infections (6 urinary tract infections, 3 pyelonephritis, 1 COVID-19 pneumonia, 1 influenza, 1 oral candidiasis, 1 facial cellulitis, 1 pneumonitis). No infections led to ocrelizumab discontinuation and there was no opportunistic infection nor progressive multifocal leukoencephalopathy. Two patients (0.5%) experienced neoplasms over the study period, a glioblastoma and a melanoma assessed as not related to ocrelizumab.

During patients' follow-up, 8 pregnancies including 3 ectopic pregnancies were reported.

No deaths occurred during the study.

4. Discussion

After the previous positive OPERA I and OPERA II phase III studies conducted in RMS patients (Hauser et al., 2017), the PRO-MSACTIVE study provided complementary ocrelizumab efficacy and safety data in patients with active RMS (i.e., both RRMS and SPMS) in a pragmatic setting. In particular, the definition of disease activity for patient eligibility was consistent with the Lublin definition (clinical and/or imaging features) used in ocrelizumab current European label (Lublin et al., 2014; OCREVUS, 2022), and not only focused on relapses. The PRO-MSACTIVE study was also set up with less strict requirements and patient management, and was closer to real-world conditions than in both pivotal trials. In this context of pragmatic evaluations mimicking current practice, not all requested assessments were consistently completed within the timeframe required by the protocol. The March 2020 COVID-19 related lockdown also had an impact on patient assessments. The sensitivity analysis excluding missing data and the PP analysis therefore allowed us to complete the analysis. In addition, considering the growing interest in patient perceptions and disease burden, several PRO questionnaires were used to better understand the impact of active RMS on symptom severity, fatigue, health-related quality of life, work productivity, as well as treatment satisfaction.

The efficacy of ocrelizumab in RMS was confirmed with a proportion of patients free of disease activity (no protocol-defined relapses, no gadolinium-enhancing T1 lesions and no new or enlarging T2 lesions) of 63.3% (95% CI [58.5%; 67.9%]) 48 weeks after ocrelizumab initiation, supported by complementary analyses (exclusion of missing data, enlarged time-window for assessments at W48). The proportion of patients free of disease activity was higher in SPMS patients than in RRMS patients (71.7% *versus* 62.2%). This difference between phenotypes is consistent with the action of a high efficacy DMT such as ocrelizumab, but also with physiopathologic findings suggesting that later stages of MS are mainly driven by chronic CNS-compartmentalized inflammatory responses and neurodegeneration (Cree et al., 2021). SPMS which typically follows an initial course of RRMS, with progressively worsening disability, is indeed mainly driven independently of relapse and acute inflammation activity (Lorscheider et al., 2016).

Regarding individual MS activity events, findings are close to the OPERA studies: 84.8% of patients were relapse-free up to W48 in the PRO-MSACTIVE study (*versus* 87.4% in OPERA; Havrdova et al. 2018); the adjusted annualized relapse rate was at 0.14 (*versus* 0.16 as assessed by W96; Hauser et al. 2017); 67.8% of patients had no evidence of MRI activity at W48 (*versus* 63.7%; Havrdova et al. 2018), and 58.5% of patients achieved NEDA at W48 (*versus* 54.6% in OPERA; Havrdova et al. 2018 and 74.8% with MRI rebaselining in CASTING; Vermersch et al. 2022). Some differences were reported in the gadolinium-enhancing T1 lesions results, where the percentage of patients having these lesions was higher than in other studies evaluating ocrelizumab ($n = 70$, 16.6%). Of these 70 patients, 41 were considered as having an activity by statistical imputation (21 missing and 20 with an interruption of the treatment period), no rebaselining and no centralized review of the MRIs were performed, and after excluding missing data from analysis, the results were more consistent with what is usually reported.

Regarding PROs, as self-reported questionnaires were fully completed by most patients in this study close to real-world conditions, they could probably be routinely administered in clinical practice. A stability between the initiation of ocrelizumab and W48 was shown, which still remains good over 1 year of treatment in the context of a progressive disease without curative treatment. However, it also should be noted that the study duration was probably too short to measure any potential improvement. As expected, PRO scores were always worse in patients with a high EDSS score at baseline compared to other patients; however, they had a more favorable PRO evolution until W48. Regarding safety data, AEs were reported in 89.3% of patients and serious AEs in 8.5% up to W72. Similar proportions were observed in the OPERA studies up to W96 (OPERA I: 80.1% and 6.9%; OPERA II: 86.3% and 7.0%) (Hauser et al., 2017). In the PRO-MSACTIVE study, infections were reported in 45.7% of patients, which is consistent with the risk of infections in MS patients and with the immunosuppressive mechanism of ocrelizumab. The most reported infections were nasopharyngitis (11.4%) and urinary tract infection (10.0%) which are common in patients with MS with bladder dysfunction such as urine retention. By comparison in the OPERA studies, 56.9% (OPERA I) and 60.2% (OPERA II) experienced in the ocrelizumab arm at least one infection up to W96, with the same type of most reported events (Hauser et al., 2017). No opportunistic infections were reported and serious infections were reported in only 2.8% of patients until W48 (1.3% in the ocrelizumab arms

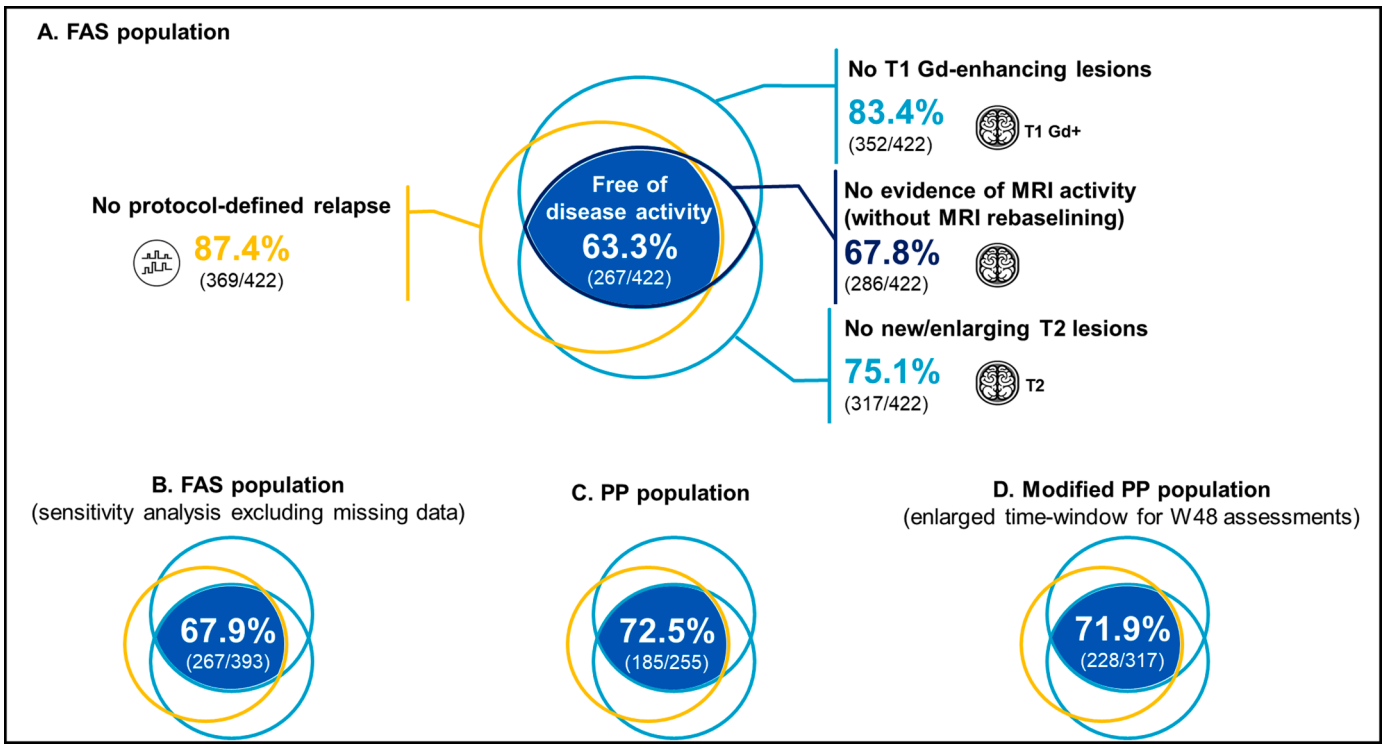

Fig. 3. Patients free of disease activity (primary endpoint).
FAS, full analysis set; Gd, gadolinium; MRI, magnetic resonance imaging; PP, Per-Protocol; W, week.
In the FAS population, patients who discontinued the infusion period (i.e., no W24 infusion) or have missing data have been considered as having a disease activity. For patients having completed the infusion period and discontinued the treatment between W24 and W48, disease activity at W48 has been evaluated based on the MRI at end of treatment (EoT) result and based on the protocol-defined relapse before EoT visit.
Protocol-defined relapses were defined as symptoms attributable to MS only in the absence of fever or infection, persisting for over 24 h, preceded by a neurological stability for $\geq$ 30 days, accompanied by objective neurological worsening consistent with an increase of at least: 0.5 step on the Expanded Disability Status Scale (EDSS), or 2 points in one of the following EDSS functional system score (FSS) (pyramidal, ambulation, cerebellar, brainstem, sensory, or visual), or 1 point in each of $\geq$ 2 EDSS functional system scores on previously described FSS (pyramidal, ambulation, cerebellar, brainstem, sensory, or visual).
All the MRI evaluations with non-missing results have been considered for the evaluation of the primary endpoint even if the MRI evaluations has been done more than 14 days before or after the W48 visit.

of the OPERA trials until W96). In addition, recent long-term safety ocrelizumab data up to 7 years, pooled from 11 clinical trials, showed similar results with a serious infections' rate of 2.01 per 100 patient-years (Hauser et al, 2021). IRRs were reported in 47.6% of the patients (34.3% in the OPERA studies; Hauser et al. 2017); all were non-serious events and only two IRRs led to treatment discontinuation. Most IRRs occurred at the first infusion of the first dose, as previously reported (Mayer et al., 2019). Neoplasms (one glioblastoma and one malignant melanoma, both assessed as not related to ocrelizumab) occurred in 0.5% of patients, as previously shown in the OPERA studies up to W96 (Hauser et al., 2017), and in 11 pooled clinical trials up to 7 years with a malignancies rate of 0.46 per 100 patient-years (Hauser et al, 2021). Safety data from the PRO-MSACTIVE study are consistent with the safety profile of ocrelizumab with no new signals observed, as known since its commercialization in France on the 28 February 2019.

The PRO-MSACTIVE study has several limitations. Even if analysis distinguished RRMS and SPMS patients, interpretation of results on the SPMS cohort should be cautious considering the limited number of SPMS patients enrolled ($n = 46$). In addition, considering that this trial was conducted as close as possible to current clinical practice and that the COVID-19 pandemic impacted the operational conduct of the study, all protocol-required assessments were not systematically performed at the requested time points. Complementary analyses were then added for efficacy outcomes (exclusion of missing data, enlarged time-window for assessments at W48); they confirmed main results. Still in line with the pragmatic evaluation framework of the study, no central MRI reading providing objective and standardized grading of images, and no MRI rebaselining were performed. Finally, the composite primary endpoint of the study did not include the CDP endpoint while progression is critical in the management of MS.

5. Conclusions

Findings from the PRO-MSACTIVE study conducted in a pragmatic setting and aligned with ocrelizumab current label confirm its treatment benefit, measured by clinical and MRI outcomes. The use of 6 questionnaires (including QoL and treatment satisfaction) allows a better understanding of the patients' disease burden. Safety data are reassuring, and consistent with results from previous trials and with ocrelizumab safety profile as known since its commercialization, confirming its favorable benefit-risk profile for the treatment of active RMS.

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Data sharing statement

Data that support findings of this study are available from the corresponding author upon reasonable request.

Table 2
Patient reported outcomes.

PRO questionnaire used (range of the scale)	Mean score (SD) at baseline	Mean change (SD) in score between baseline and W48		
		Total	EDSS <4 at baseline	EDSS ≥4 at baseline
SymptoMScreen for MS symptom severity (0: not affected at all; 72: total limitation)	19.3 (13.7)	-0.94 (9.3)	-0.1 (8.6)	-2.7 (10.5)
MFIS for fatigue (0: no impact of fatigue on activities; 84: always impact of fatigue on activities)	36.1 (20.1)	-3.2 (13.6)	-2.6 (13.6)	-4.7 (13.5)
EQ-5D-5L for health-related QoL				
• Health state score (0: worst state; 100: best state)	66.8 (20.4)	+ 4.3 (17.2)	+ 3.0 (14.4)	+7.5 (21.6)
• Utility score (-0.530: worst state; 1: best state)	0.588 (0.303)	+ 0.050 (0.197)	+ 0.0407 (0.1650)	+0.0733 (0.2528)
MusiQoLfor MS-related QoL (0: worst QoL; 100: best QoL)	68.9 (16.7)	+1.76 (11.16)	+ 0.8 (11.0)	+4.1 (11.2)
WPAI:SHP for work productivity and impairment due to problem (0: no Impairment; 100: total impairment)				
• Percent overall work impairment *	30.1 (30.3)	-0.78 (25.08)	-0.4 (24.3)	-3.4 (29.8)
• Percent activity impairment	40.2 (29.9)	-6.09 (23.24)	-5.2 (22.7)	-8.3 (24.3)
TSQM-14 for treatment satisfaction (0: not satisfied; 100: very satisfied)	60.3 (19.5)	+ 8.3 (21.2)	+ 8.5 (20.4)	+8.2 (23.0)

EDSS, Expanded Disability Status Scale; EQ-5D-5L with VAS, EuroQol 5-dimension 5-level version with visual analog scale; MFIS, Modified Fatigue Impact Scale; MS, multiple sclerosis; MusiQoL, Multiple Sclerosis International Quality of Life questionnaire; PRO, patient reported outcomes; SymptoMScreen, MS symptoms' severity scale; QoL, quality of life; WPAI:SHP, Work Productivity and Activity Impairment scale

* *Assessed in working patients*

Table 3
Adverse events.

Variables - no. of patients (%)	*N* = 422
Any adverse event (AE)	377 (89.3)
• Infusion related reactions	201 (47.6)
• COVID-19 infections	5 (1.2)
AEs leading to permanent treatment discontinuation	4 (0.9)
AEs leading to temporary treatment discontinuation	36 (8.5)
AEs related to treatment	263 (62.3)
AEs of grade ≥3	45 (10.7)
• Infusion related reaction	4 (0.9)
• Neutropenia	4 (0.9)
• Urinary tract infection	3 (0.7)
• Fall	3 (0.7)
AEs of specific interest *	1 (0.2)
Serious AEs (SAEs)	36 (8.5)
• Serious Infections	13 (3.1)
• Serious infusion related reactions	0 (0.0)
Neoplasms #	2 (0.5)
Pregnancies ‡	8 (1.9)
Deaths	0 (0.0)

COVID-19, Coronavirus Disease 2019
* Transaminases increased
\# Glioblastoma and melanoma
‡ Including 3 ectopic pregnancies

CRediT authorship contribution statement

Eric Manchon: Conceptualization, Methodology, Investigation, Writing – review & editing. **David Laplaud:** Investigation, Writing – review & editing. **Sandra Vukusic:** Investigation, Writing – review & editing. **Pierre Labauge:** Investigation, Writing – review & editing. **Thibault Moreau:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Gisela Kobelt:** Conceptualization, Methodology, Writing – review & editing. **Jean-Marie Grouin:** Conceptualization, Methodology, Writing – review & editing. **Marie Lotz:** Conceptualization, Methodology, Writing – review & editing. **David Pau:** Conceptualization, Methodology, Formal analysis, Writing – review & editing. **Lebrun Frenay Christine:** Conceptualization, Methodology, Investigation, Writing – review & editing.

Declaration of Competing Interest

E. Manchon received honoraria and consulting fees from Sanofi, Merck, Novartis, and Roche.

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G. Kobelt has carried out projects and consulted for Biogen, Novartis, Roche, Teva, Merck Serono, and Sanofi Genzyme.

JM. Grouin reports no disclosures for this communication.

M. Lotz and D. Pau are employees of Roche SAS.

C. Lebrun Frenay has participated in expert boards for Biogen, Novartis, Roche, and Sanofi-Genzyme in the last 5 years. Expert and Speaker honoraria were either declined or donated to the URRIS research unit, University Cote d'Azur, Nice, France. She did not receive any financial compensation for her participation in the scientific committee of the French MS Society, ARSEP and ECTRIMS apart from travel expenses.

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Supplementary materials

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