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Long-Term Treatment With First-Line Ocrelizumab in Patients With Early RMS: 9-Year Follow-Up Data From the OPERA Trial

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Background

Patients with MS are often started on lower efficacy drugs and then escalated to higher efficacy therapies following clinical disease progression[1]

Early treatment with higher efficacy drugs may be more beneficial to patients in terms of preventing disability accrual[2]

OCR is a monoclonal anti-CD20 antibody[3] that has been shown to be a highly efficacious treatment for patients with RMS[4] and PPMS[3]

Objectives: To assess the efficacy and safety of the high-efficacy therapy OCR as a first-line therapy in treatment-naive patients with early RMS over 9 years

MS, multiple sclerosis; OCR, ocrelizumab; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis.

1. Fernandez O, *et al. Eur J Neurol* 2017;24(3):516–522. 2. Hutchinson M, *et al. J Neurol* 2009;256(3):405–415. 3. OCREVUS [ocrelizumab] Full Prescribing Information. Genentech, Inc., 2021.
4. Hauser SL, *et al. N Engl J Med* 2017;376(3):221–234.

Methods

PATIENT POPULATION

RMS diagnosis (McDonald 2010)[1]

Age 18–55 years, inclusive

Disease duration ≤2 years since diagnosis (early-stage MS)

Treatment naive (no DMT in the preceding 2 years)

STUDY DESIGN

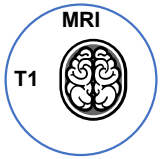
- The OPERA I/II trials (NCT01247324/NCT01412333)[2] are Phase III studies evaluating the efficacy and safety of OCR vs IFN in patients with RMS with double-blind and open-label phases
- This study analyzed data from a subgroup of early RMS, treatment-naive patients from OPERA I/II

KEY ENDPOINT

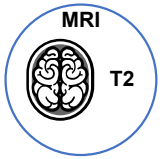
NEDA is a composite measure of the **absence of**:

Relapses

24W-CDP



T1w-CEL



New/enlarging T2w-L

MRI measurements were **rebaselined at Week 24**

ADDITIONAL ENDPOINTS

ARR

Time to 24W-CDP

Safety

Cut-off date: November 26, 2021.
24W-CDP, 24-week confirmed disability progression; ARR, annualized relapse rate; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; IFN, interferon β-1a; MRI, magnetic resonance imaging; MS, multiple sclerosis; NEDA, no evidence of disease activity; OCR, ocrelizumab; RMS, relapsing multiple sclerosis; T1w-CEL, T1-weighted contrast enhancing lesion; T2w-L, T2-weighted lesion.
1. Polman CH, *et al. Ann Neurol* 2011;69(2):292–302. 2. Hauser SL, *et al. N Engl J Med* 2017;376(3):221–234.

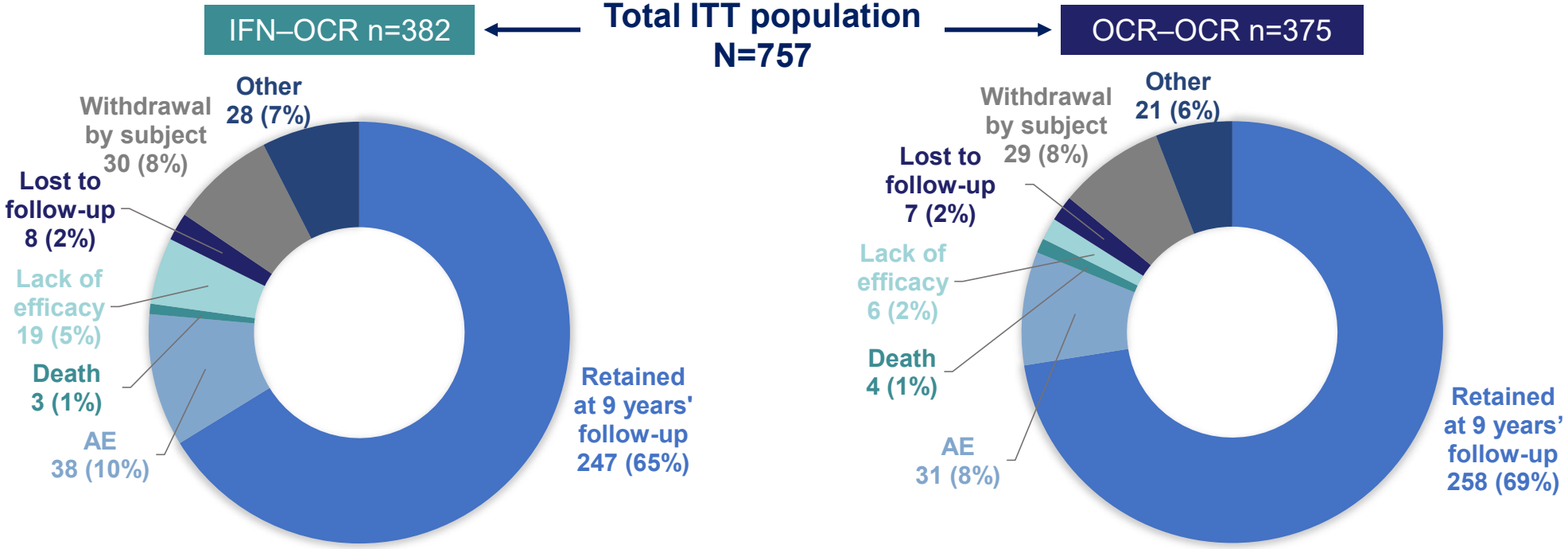
Results: Demographic and baseline characteristics

Baseline demographics and disease characteristics	IFN (N=382)	OCR (N=375)
Baseline age, mean (SD)	36.3 (9.3)	35.5 (9.3)
Baseline age, median	36.0	37.0
Sex, n (%)		
Female	251 (65.7)	240 (64.0)
Male	131 (34.3)	135 (36.0)
Duration since diagnosis (years), mean (SD)	0.6 (0.5)	0.6 (0.4)
Duration since MS symptom onset (years), mean (SD)	3.4 (4.1)	3.1 (4.0)
Baseline EDSS, mean (SD)	2.4 (1.2)	2.4 (1.1)
Baseline T1w-CEL, n (%)		
0	219 (58.1)	209 (56.5)
>0	158 (41.9)	161 (43.5)
Baseline number of T2 lesions, mean (SD)	44.8 (36.3)	44.8 (38.8)

Baseline demographics and disease characteristics were consistent with early-stage RMS
Similar characteristics were observed in both treatment arms

EDSS, Expanded Disability Status Scale; IFN, interferon β-1a; MS, multiple sclerosis; OCR, ocrelizumab; RMS, relapsing multiple sclerosis; SD, standard deviation; T1w-CEL, T1-weighted contrast enhancing lesion.

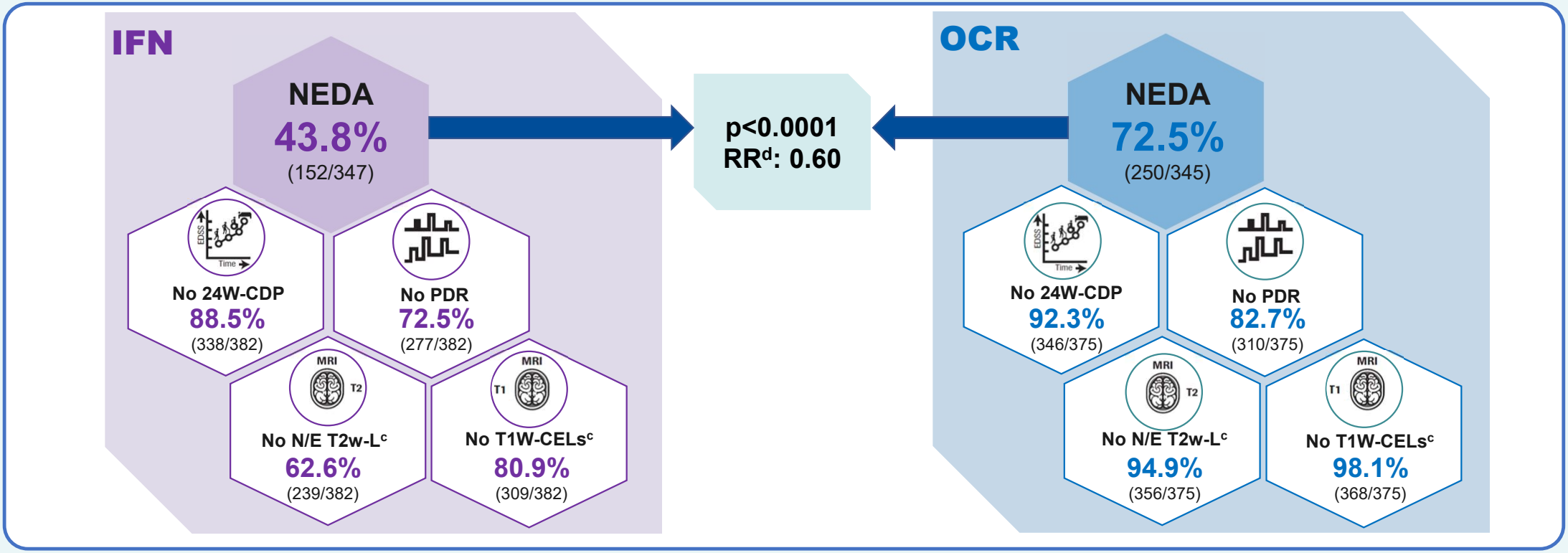
Results: Treatment disposition at 9 years[a] of follow-up



The majority of treatment-naive patients with early RMS diagnosis (67%) remained on OCR treatment throughout the 9 years of follow-up

[a]96 weeks in the double-blind period plus 336 weeks in the open-label extension.
AE, adverse event; IFN, interferon β-1a; ITT, intention-to-treat; OCR, ocrelizumab; RMS, relapsing multiple sclerosis.

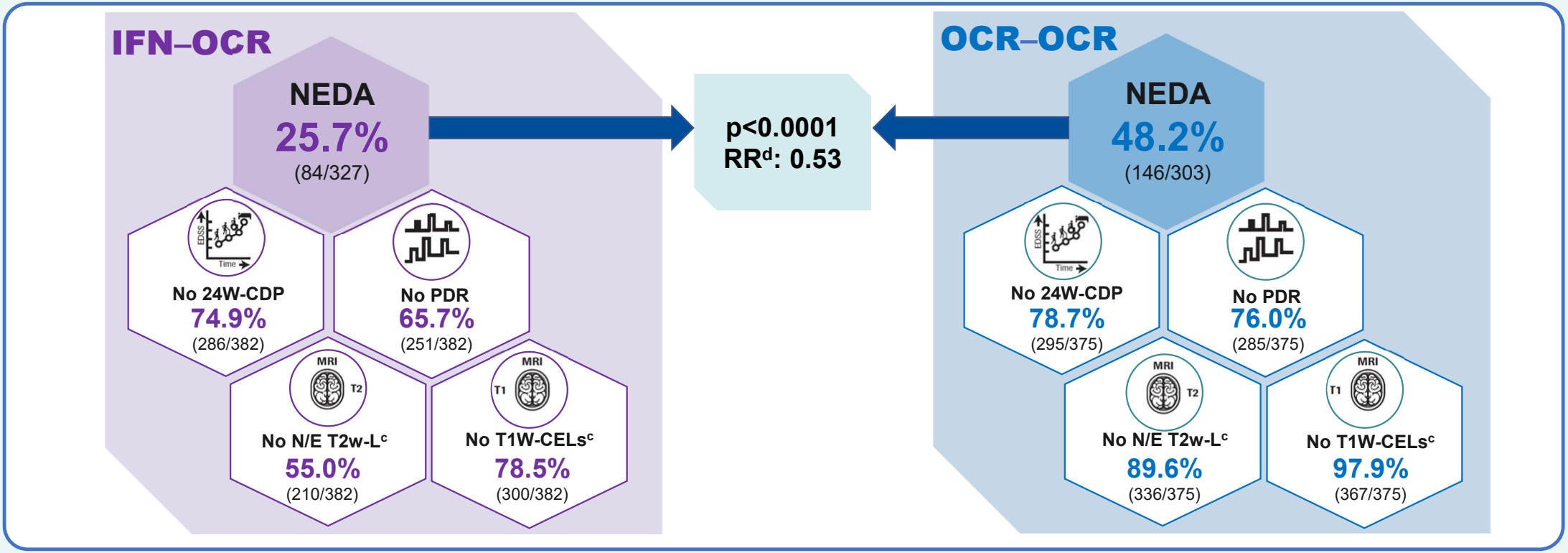
Results: NEDA[a] at 2 years[b] of follow-up (during the DBP)



Patients receiving OCR as a first-line therapy had favorable NEDA outcomes

[a]NEDA calculated for patients with no disease activity on all four components; [b]96 weeks; [c]Rebaselined at 24 weeks. [d]RR: Risk ratio from a Cochran-Mantel-Haenszel test stratified by Region and baseline EDSS category (<2, ≥2). 24W-CDP, 24-week confirmed disability progression; DBP, double-blind period; EDSS, Expanded Disability Status Scale; HR, hazard ratio; IFN, interferon β-1a; NEDA, no evidence of disease activity; N/E T2w-L, new/enlarging T2-weighted lesion; OCR, ocrelizumab; PDR, protocol-defined relapse; T1w-CEL, T1-weighted contrast enhancing lesion.

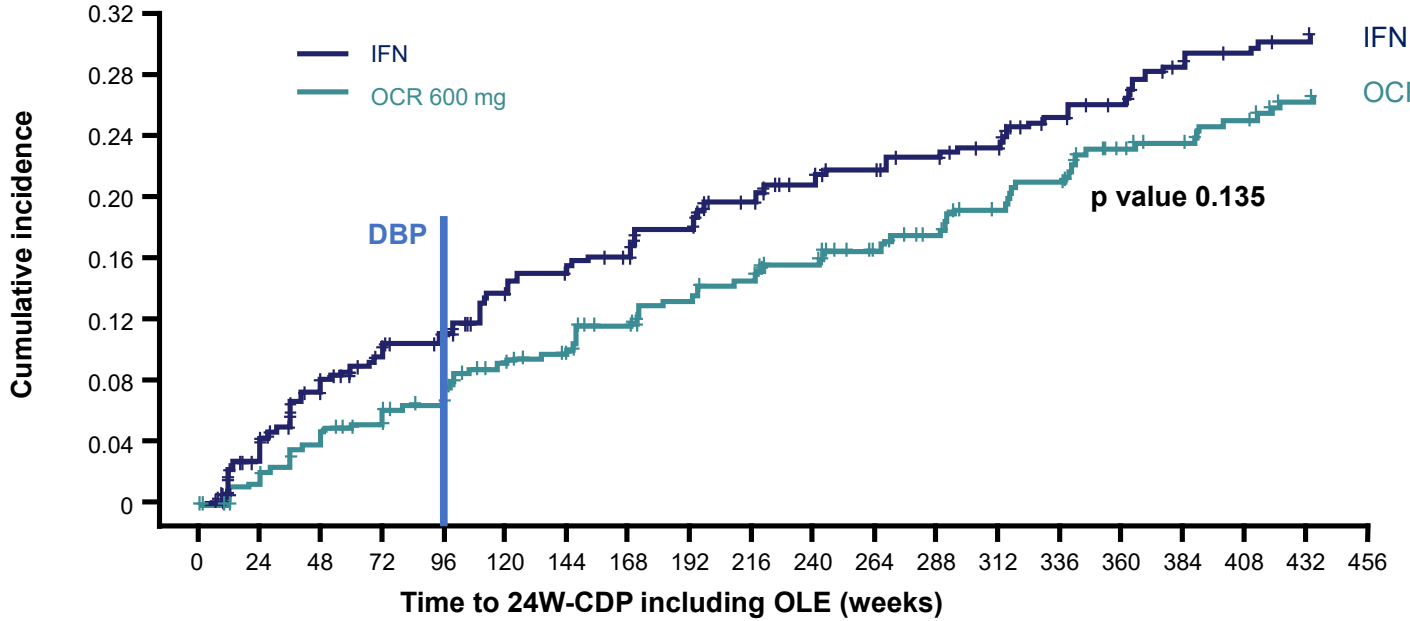
Results: NEDA[a] at 9 years[b] of follow-up (7 years in the OLE)



Patients who had started on OCR initially maintained benefits to NEDA at 336 weeks in the OLE vs IFN–OCR switchers

[a]NEDA calculated for patients with no disease activity on all four components; [b]336 weeks; [c]Rebaselined at 24 weeks. [d]RR: Risk ratio from a Cochran-Mantel-Haenszel test stratified by Region and baseline EDSS category (<2, ≥2). 24W-CDP, 24-week confirmed disability progression; EDSS, Expanded Disability Status Scale; HR, hazard ratio; IFN, interferon β-1a; NEDA, no evidence of disease activity; N/E T2w-L, new/enlarging T2-weighted lesion; OCR, ocrelizumab; OLE, open-label extension; PDR, protocol-defined relapse; T1w-CEL, T1-weighted contrast enhancing lesion.

Results: Time to 24W-CDP over 9 years[a] of follow-up



Number of patients at risk:

OCR 600 mg	375	352	339	327	317	294	288	277	270	265	257	247	239	230	225	209	204	198	187	0
IFN	382	350	321	298	289	256	251	245	234	222	215	210	205	199	189	183	173	169	166	0

The majority of patients demonstrated no disease progression over 9 years on OCR, with numerical benefits observed in those who started treatment on OCR earlier

[a]336 weeks.
24W-CDP, 24-week confirmed disability progression; DBP, double-blind period; IFN, interferon β-1a; OCR, ocrelizumab; OLE, open-label extension.

Results: AE rates

AE Rate per 100 PY (95% CI)	*Early RMS, treatment-naive,* OPERA OLE DBP+OLE OCR (N=668; 4,695 PY)	OCR all-exposure (N=5,848; 25,153 PY)
Any AEs	**199.04 (195.03–203.12)**	232.71 (230.83–234.60)
AEs leading to discontinuation of treatment	**1.21 (0.92–1.57)**	0.97 (0.85–1.10)
Serious AEs	**6.69 (5.97–7.47)**	7.61 (7.27–7.96)
Fatal outcomes	**0.17 (0.07–0.34)**	0.30 (0.24–0.38)
Malignancies	**0.53 (0.34–0.79)**	0.47 (0.39–0.57)
Infections and infestations	**68.86 (66.51–71.28)**	69.89 (68.86–70.93)
Serious infections	**2.13 (1.73–2.59)**	2.74 (2.54–2.96)

AE rates in early RMS patients over 9 years of follow-up were low and comparable to the OCR all-exposure population
Infections were among the most frequently reported AEs in patients treated with OCR
However, these rates remained stable over time with additional exposure, and were similar to rates that have been observed in the wider MS population[1]

AE, adverse event; CI, confidence interval; DBP, double-blind period; MS, multiple sclerosis; OCR, ocrelizumab; OLE, open-label extension; PY, patient years; RMS, relapsing multiple sclerosis.

1. Persson R, *et al. Mult Scler Relat Disord* 2020;41:101982.

Results: IgG<LLN and associated SIs

	Early RMS and treatment-naive subgroup (n=668)	
Serious infections	**IgG<LLN (n=89)**	**IgG≥LLN (n=579)**
No. of SIs	12	88
SIs per 100 PY	6.46	1.94
95% CI	3.34–11.29	1.56–2.39

- Twelve SI events in 10 patients were reported during episodes of IgG<LLN
- Eight events fully recovered, one case recovered with sequelae and three deaths related to COVID-19 were reported
- Type of SIs reported were comparable to those reported in the all-exposure group
- Only one SI case required OCR discontinuation

SIs were not more frequent in OCR-treated patients with IgG<LLN than in patients with normal IgG levels
SIs were typical in character, not treatment limiting and consistent with SIs reported in the all-exposure patient population, with and without decreased IgG levels[1]

CI, confidence interval; IgG, immunoglobulin G; LLN, lower limit of normal; OCR, ocrelizumab; PY, patient years; RMS, relapsing multiple sclerosis; SI, serious infection.
1. Hauser SL, *et al. ECTRIMS* 2022; Poster 326.

Conclusions

The safety profile observed in the early RMS, treatment-naive subgroup is similar to that observed in the overall OPERA population

A significantly higher proportion of patients continuously treated with ocrelizumab achieved NEDA; ARR and disease progression (24W-CDP) were also significantly reduced over 9 years of follow-up

Ocrelizumab as a first-line therapy is shown to be effective in reducing disease progression and disease activity in patients with RMS
Earlier treatment with the high-efficacy therapy ocrelizumab associates with improved long-term clinical outcomes

24W-CDP, 24-week confirmed disability progression; ARR, annualized relapse rate; NEDA, no evidence of disease activity; RMS, relapsing multiple sclerosis.

Acknowledgments: We would like to thank all patients, their families and the investigators who participated in this study

Supplemental Materials

Methods: Eligibility criteria in the OPERA studies[1]

INCLUSION CRITERIA

- Age 18 to 55 years
- A diagnosis of MS (according to the 2010 revised McDonald criteria)[2]
- An EDSS score of 0.0 to 5.5 at screening
- At least two documented clinical relapses within the previous 2 years or one clinical relapse within the year before screening
- MRI of the brain showing abnormalities consistent with MS
- No neurologic worsening for at least 30 days before both screening and baseline

EXCLUSION CRITERIA

- A diagnosis of PPMS
- Previous treatment with any B-cell–targeted therapy or other immunosuppressive medication as defined in the protocol
- A disease duration of more than 10 years in combination with an EDSS score of 2.0 or less at screening

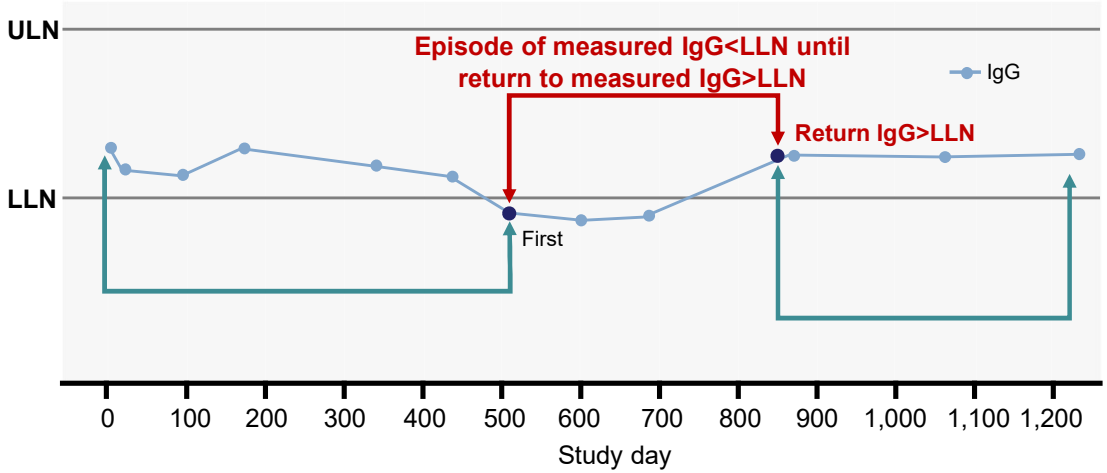
EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis.

1. Hauser SL, *et al. N Engl J Med* 2017;376(3):221–234. 2. Polman CH, *et al. Ann Neurol* 2011;69(2):292–302.

Methods: Single-drop method for measurement of SI rates per 100 PY

- The rates per 100 PY of SIs during the single-drop IgG<LLN (<5.65 g/L) were compared with the rates of SIs during episodes of normalized IgG≥LLN episodes
- The duration of exposure of single-drop <LLN is defined as from the day the first laboratory value <LLN until the day the laboratory value is normalized to ≥LLN; the SIs with onset dates in between are counted

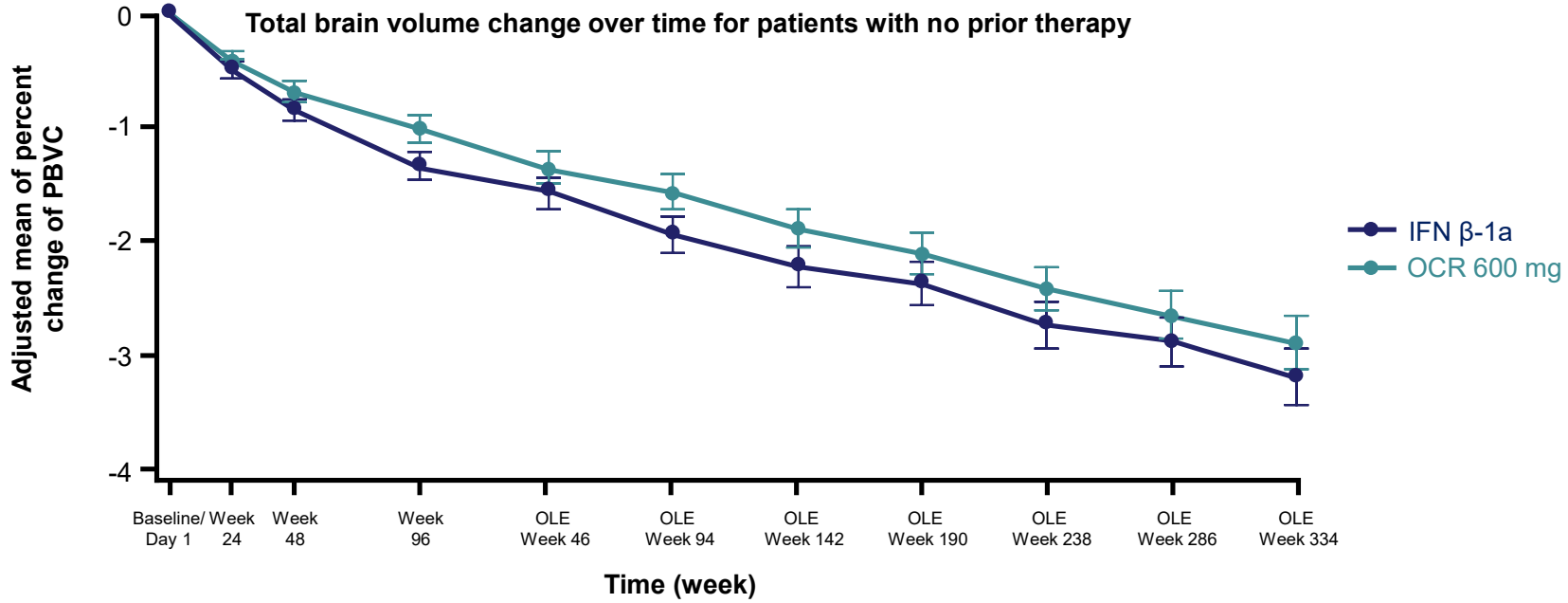
Episode of single-drop IgG<LLN and occurrence of SIs



The single-drop method was used to examine the risk of infections during the period of IgG<LLN, compared with the risk of infections during the period of IgG≥LLN

IgG, immunoglobulin G; LLN, lower limit of normal; PY, patient years; SI, serious infection; ULN, upper limit of normal.

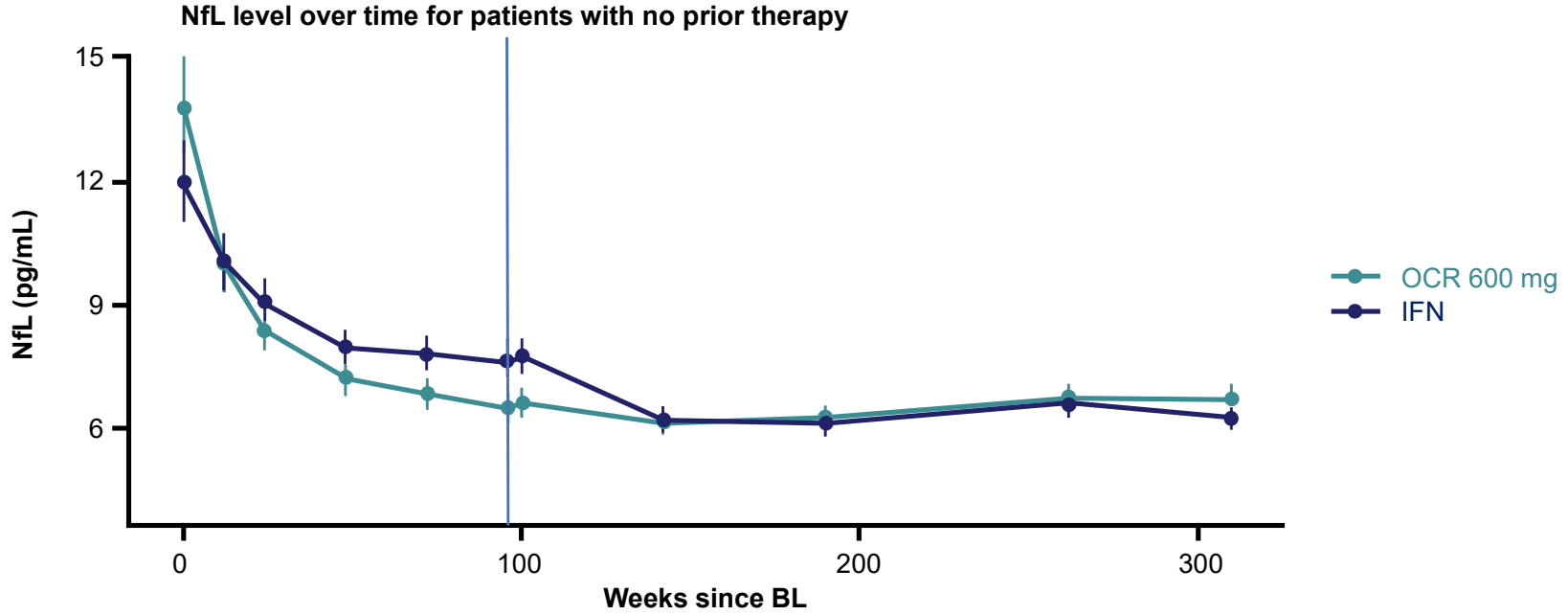
Results: Total brain volume change



Greater numerical brain volume loss was incurred in patients on IFN during the DBP, and this loss was not regained after switching to OCR during the OLE

DBP, double-blind period; IFN, interferon β-1a; OCR, ocrelizumab; OLE, open-label extension; PBVC, percentage brain volume change.

Results: NfL levels



Lower levels of NfL were observed in patients treated with OCR during the DBP
During the OLE, levels of NfL in the IFN–OCR group reached similar levels to those observed in the OCR–OCR group

BL, baseline; DBP, double-blind period; IFN, interferon β-1a; NfL, neurofilament light chain; OCR, ocrelizumab; OLE, open-label extension.