The Patient Impact of 11 Years of Ocrelizumab Treatment in Multiple Sclerosis: Long-Term Data from the Phase III OPERA and ORATORIO Studies

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Supplementary Materials

METHODS
OPERA I/II and ORATORIO: Efficacy Outcomes

Measures of disability progression[a]

CDP–EDSS
Defined as ≥1.0 increase in EDSS score from baseline (or 0.5 increase in EDSS score if baseline EDSS score >5.5) confirmed at 48 weeks

CDP–T25FW
Defined as ≥20% increase in T25FW from baseline confirmed at 48 weeks

CDP–9HPT
Defined as ≥20% increase in 9HPT from baseline confirmed at 48 weeks

Composite measure: cCDP[b]

cCDP
Defined as 48-week CDP–EDSS, CDP–T25FW or CDP–9HPT

REPEATED CDP–EDSS
Defined by expanding the first-event definition such that the subsequent event was rebaselined to the EDSS at the onset of the previous event

Annualised repeated CDP-EDSS event rate
i.e. the average number of events per year, used to establish the time between two disability progression events

Time to key disability milestones

RMS: Requiring a walking aid
EDSS score ≥6 from baseline ≤5.5
EDSS score ≥6 CDP

PPMS: Requiring a wheelchair
EDSS score ≥7 from baseline ≤6.5
EDSS score ≥7 CDP

Disease Activity
Annualised relapse rate
MRI N/E T2 lesions

OPERA I/II: OCR vs IFN β-1a in RMS; NCT01247324/NCT01412333
FPI: 31 August 2011/20 September 2011

ORATORIO: OCR vs placebo in PPMS; NCT01194570
FPI: 3 March 2011

[a]CDP is also termed confirmed disability worsening; [b]cCDP requires at least one of the following: (1) an increase in EDSS score of ≥1.0 points from a BL score of ≤5.5 points, or a ≥0.5-point increase from a BL score of >5.5 points; (2) a 20% increase from BL in time to complete the 9HPT; (3) a 20% increase from BL in the T25FW.
9HPT, Nine-Hole Peg Test; BL, baseline; CDP, confirmed disability progression; cCDP, composite confirmed disability progression; EDSS, Expanded Disability Status Scale; FPI, first patient in; IFN, interferon; N/E, new/enlarging; OCR, ocrelizumab; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; T25FW, Timed 25-Foot Walk.

RESULTS
Patient Populations, Baseline Demographics and Disease Characteristics[a]

OPERA I/II PATIENT POPULATION	ORATORIO PATIENT POPULATION
RMS diagnosis (McDonald 2010)[1]	PPMS diagnosis (McDonald 2005)[2]
Age 18–55 years, inclusive	Age 18–55 years, inclusive
MRI consistent with MS	MS disease duration <10 years if EDSS score ≤5.0 <15 years if EDSS score >5.0
EDSS score 0.0–5.5, inclusive	EDSS score 3.0–6.5, inclusive
≥2 relapses in the previous 2 years or one relapse in prior 12 months	Documented history or presence of elevated IgG or ≥1 IgG OCB
Treatment naïve or previously treated	Treatment naïve or previously treated

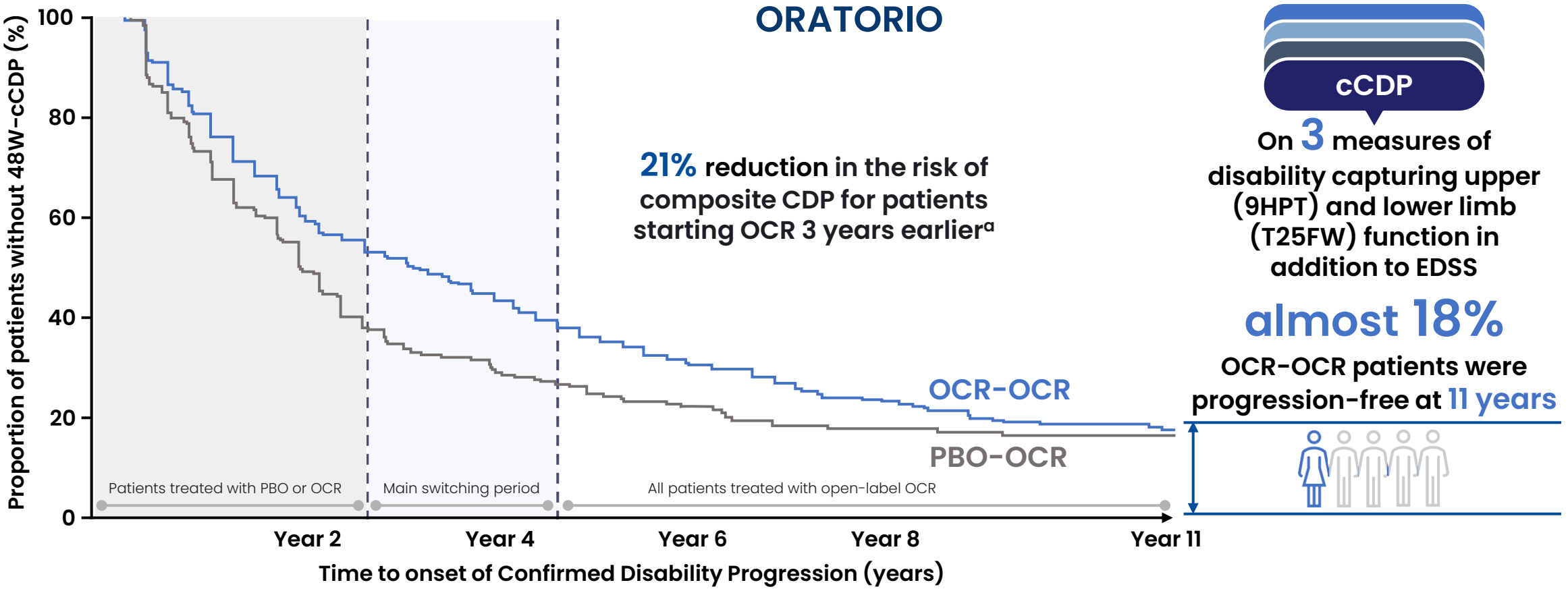
	OPERA I/II RMS (OCR; N=827)	OPERA I/II RMS (IFN; N=829)	ORATORIO PPMS (OCR; N=488)	ORATORIO PPMS (PBO; N=244)
Age years, mean ± SD	37.1 ± 9.2	37.2 ± 9.2	44.7 ± 7.9	44.4 ± 8.3
Female n (%)	541 (65.4)	552 (66.6)	237 (48.6)	124 (50.8)
Time since symptom onset years, mean ± SD	6.7 ± 6.2	6.5 ± 6.1	6.7 ± 4.0	6.1 ± 3.6
EDSS score, mean ± SD	2.8 ± 1.3	2.8 ± 1.3	4.7 ± 1.2	4.7 ± 1.2
T25FW seconds, mean ± SD	7.9 ± 9.9	7.2 ± 9.2	14.8 ± 21.2	12.9 ± 15.5
9HPT seconds, mean ± SD	24.5 ± 13.1	24.0 ± 8.3	31.9 ± 23.3	30.6 ± 13.4

Baseline demographics and disease characteristics were representative of relapsing and primary progressive MS disease, and were similar between treatment and comparator arms

[a]Data shown for DBP; clinical cut-off date for the analyses was 24 November 2023; for OPERA I/II and ORATORIO, data from patients up to Week 576 were used for the 11-year analyses.
9HPT, Nine-Hole Peg Test; DBP, double-blind period; EDSS, Expanded Disability Status Scale; IFN, interferon β-1a; IgG, immunoglobulin G; MS, multiple sclerosis; OCB, oligoclonal band; OCR, ocrelizumab; PBO, placebo; PPMS, primary progressive MS; RMS, relapsing MS; SD, standard deviation; T25FW, Timed 25-Foot Walk.
1. Polman CH, *et al. Ann Neurol* 2011;69:292–302; 2. Polman CH, *et al. Ann Neurol* 2005;58:840–846.

RESULTS

Disability Accumulation on Three Measures of Function (48W-cCDP) in PPMS



No. patients at risk:

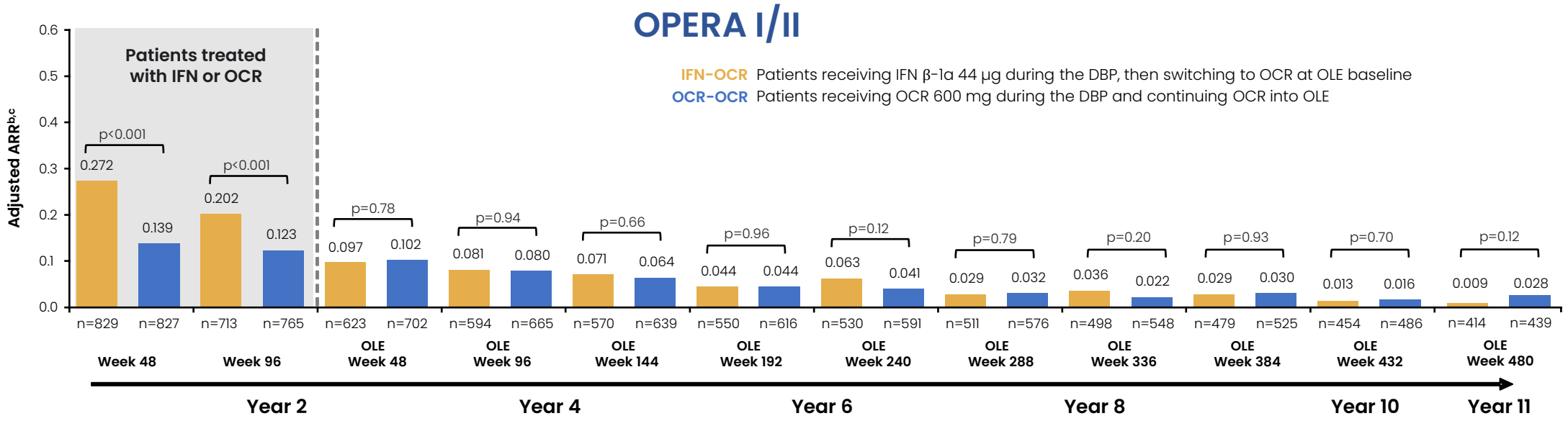
PBO/OCR 600mg (N=244) 244	169	122	72	62	48	41	33	29	27	26	16
OCR 600mg/OCR 600mg (N=488) 488	376	289	230	187	148	125	107	90	73	58	33

[a]Average HR over 11-year period: ORATORIO: HR (95% CI): 0.79 (0.66–0.94) p=0.0079. Risk reduction: 21%.

9HPT, Nine-Hole Peg Test; cCDP, composite CDP; CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; HR, hazard ratio; OCR, ocrelizumab; PBO, placebo; PPMS, primary progressive multiple sclerosis; T25FW, Timed 25-Foot Walk; W, week.

RESULTS
OPERA I/II Annualised Protocol Defined Relapse Rate by Year

Over the long-term (11 years[a]) continuous treatment with OCR was highly effective in suppressing relapses in PwRMS

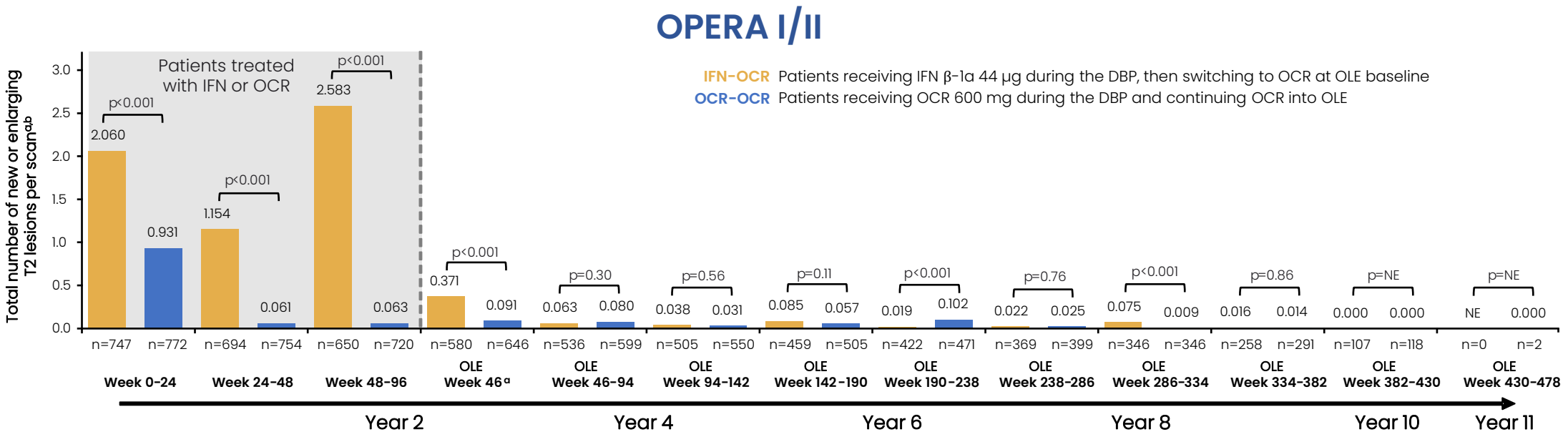


ARR decreased year-on-year from the pre-switch year to Year 11 in IFN–OCR switchers, and was maintained at low levels in all patients treated with OCR

[a]The median follow-up time for patients continuously treated with OCR in the pooled OPERA I/II population was 10.5 years (range 0.0–12.0); [b]The total number of relapses for all patients in the treatment group divided by the total patient-years of exposure to that treatment; [c]DBP Year 1 and DBP Year 2 data include the ITT population (number of patients available); for years 4-11 (OLE years 1-9), data include the OLE ITT population (number of patients available). Clinical cut-off date: 24 November 2023. GEE Poisson Model ITT population. Adjusted ARRs from Week 48 to OLE Week 480 (Year 11). Adjusted by randomised treatment, study, baseline EDSS score (<4.0 vs ≥4.0), geographical region (US vs ROW), year and treatment-by-year interaction.
ARR, annualised relapse rate; DBP, double-blind period; EDSS, Expanded Disability Status Scale; GEE, generalised estimating equation; IFN, interferon; ITT, intention-to-treat; OCR, ocrelizumab; OLE, open-label extension; PwRMS, patients with RMS; ROW, rest of world; RMS, relapsing multiple sclerosis.

RESULTS
OPERA I/II MRI – Mean New/Enlarging T2 Lesions

In PwRMS treated early and continuously with OCR, consistent and persistent effects were evident on MRI measures of inflammatory disease activity, i.e. the near complete suppression of subclinical disease activity, as measured by MRI



Over 11 years, early and continuous OCR treatment led to an almost complete suppression of MRI activity in PwRMS; these benefits were also seen in patients once they switched from IFN β-1a to OCR

[a]The number of new T1 Gd-enhancing lesions and the number of new or enlarging T2 lesions were analysed using a negative binomial model; in a previously reported analysis[1] of lesion outcomes during the DBP, results were adjusted for study, T1 Gd-enhancing lesion status (present or not) or baseline T2 lesion volume, baseline EDSS score (≤4.0 vs >4.0) and geographic region (US vs ROW). However, as patients had no new T1 Gd-enhancing lesions/new or enlarging T2 lesions at several time points, it was impossible to fit a statistical model, and unadjusted rates were adopted for the OLE instead. Baseline number of T2 lesions, mean (adjusted) T2 lesion rates: IFN-OCR, 51.0; OCR-OCR, 50.1.

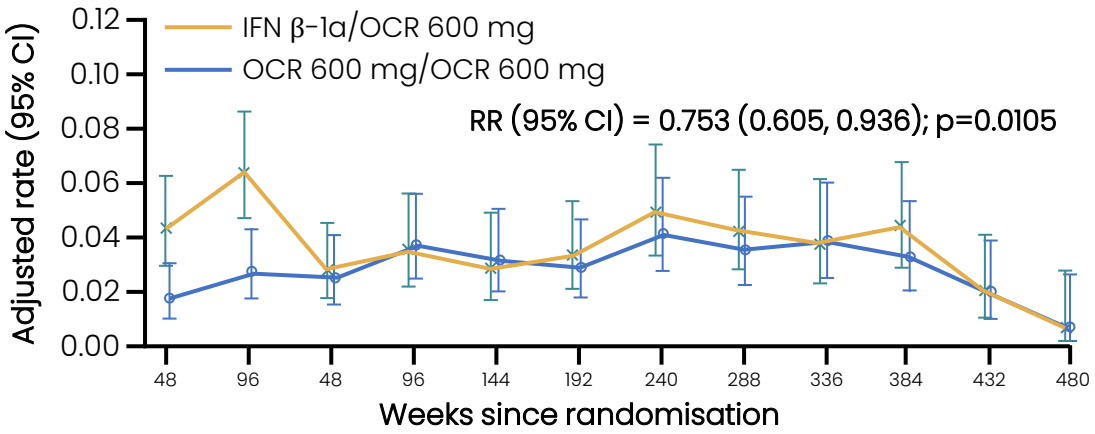
IFN, interferon; Gd, gadolinium; NE, not evaluable; OCR, ocrelizumab; PwRMS, patients with RMS; RMS, relapsing multiple sclerosis; ROW, rest of world.

1. Hauser SL, *et al. N Engl J Med* 2017;376:221–234.

RESULTS

Disability Event Rate Expressed as Annualised Repeated 48W-CDP EDSS

OPERA I/II



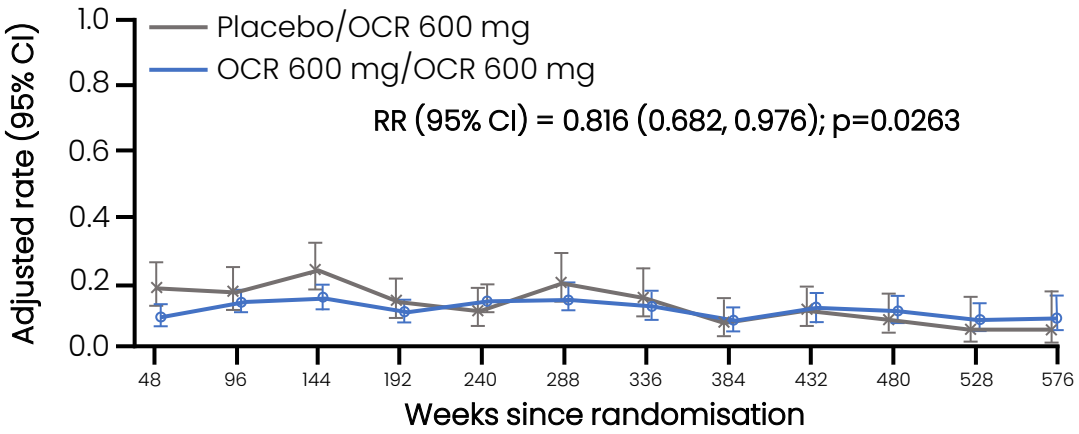
Number of patients at risk

IFN β-1a/OCR 600 mg	828	713	623	594	570	550	530	511	498	479	454	414
OCR 600 mg/OCR 600 mg	827	765	702	665	639	616	591	576	548	525	486	439

11-year annualised event rate

IFN–OCR	OCR–OCR
0.038	0.029

ORATORIO



Number of patients at risk

Placebo/OCR 600 mg	243	222	196	171	163	156	146	135	128	119	104	83
OCR 600 mg/OCR 600 mg	481	452	428	399	366	349	325	308	289	268	245	187

11-year annualised event rate

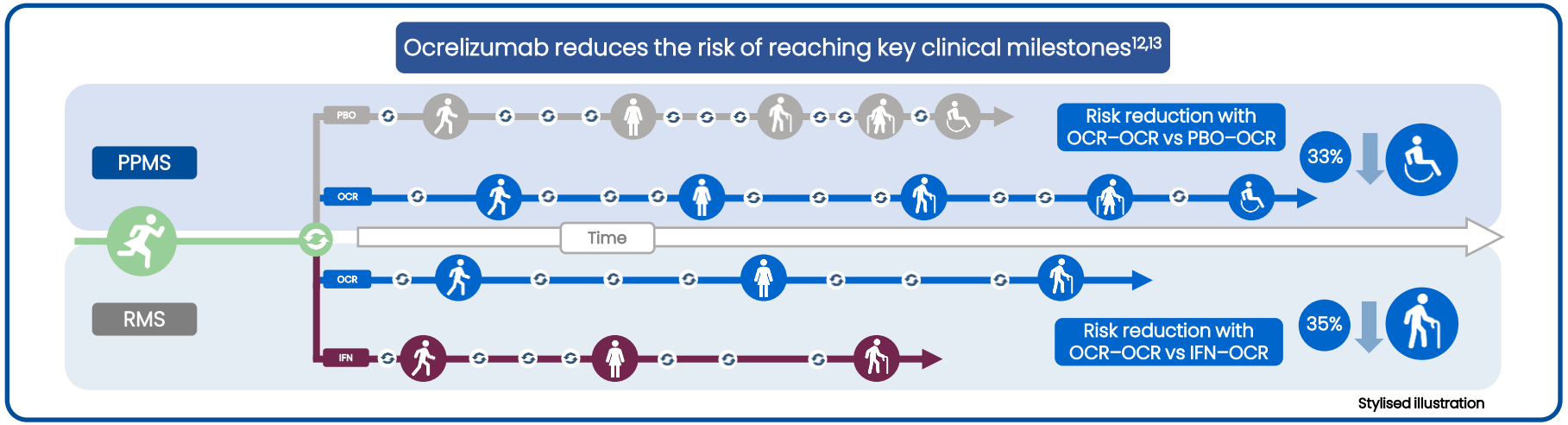
PBO–OCR	OCR–OCR
0.149	0.121

Over 11 years, the annualised, repeated 48W-CDP–EDSS event rate infers patients would be expected to be progression-free for the next 34.5 and 8.3 years after the last event, in PwRMS and PwPPMS, respectively

CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; IFN, interferon; OCR, ocrelizumab; PPMS, primary progressive multiple sclerosis; PwPPMS, patients with PPMS; PwRMS, patients with RMS; RMS, relapsing multiple sclerosis; RR, rate ratio; W, week.

BACKGROUND

- In MS, reaching irreversible key clinical milestones is usually the result of repeated progression events[1–3]
- Progression to requiring a walking aid (EDSS score ≥6.0) or wheelchair (EDSS score ≥7.0) is associated with a major reduction in patients' QoL and increased societal burdens, e.g. decreased employment rates; physical, emotional and financial challenges[4–8]
  - Long-term disability is an important outcome for patients with MS;[9] delaying the time to reach disability milestones is a significant treatment goal in RMS and PPMS
- In patients with MS, OCR reduced the risk of reaching key disability milestones vs comparator[10–13]
  - Using extrapolation analysis, OCR delayed the time to requiring a wheelchair by 7 years in patients with MS, vs comparator[11]



Ocrelizumab reduces the risk of reaching key clinical milestones

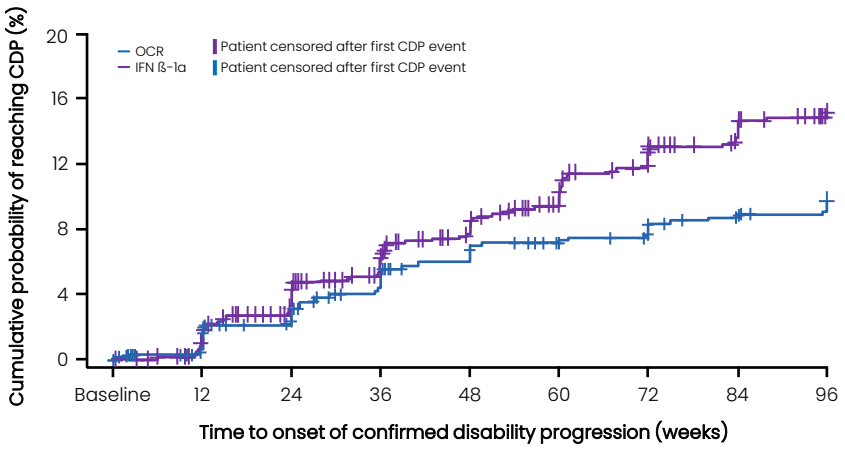
EDSS, Expanded Disability Status Scale; IFN, interferon; MS, multiple sclerosis; OCR, ocrelizumab; PBO, placebo; PPMS, primary progressive MS; QoL, quality of life; RMS, relapsing MS.

1. Roche/Genentech. Data on file; 2. Kappos L, *et al. JAMA Neurol* 2020;77:1132–1140; 3. Lublin FD, *et al. Brain* 2022;145:3147–3161; 4. Jones E, *et al. BMC Health Serv Res* 2016;16:294; 5. Tomassini V, *et al. Mult Scler* 2019;25:1306–1315; 6. Kobelt G, *et al. Mult Scler* 2017;23:1123–1136; 7. Jones KH, *et al. PLoS One* 2014;9:e104604; 8. Sutliff MH. *Curr Med Res Opin* 2010;26:109–119; 9. Wilson LS, *et al. Int J MS Care* 2015;17:74–82; 10. Giovannoni G, *et al. Eur J Neurol* 2021;29:1238–1242; 11. Butzkueven H, *et al. Eur J Neurol* 2021;29:1082–1090; 12. Wolinsky J, *et al. ECTRIMS* 2021; Poster 158; 13. Giovannoni G, *et al. ECTRIMS* 2021;Poster 723.

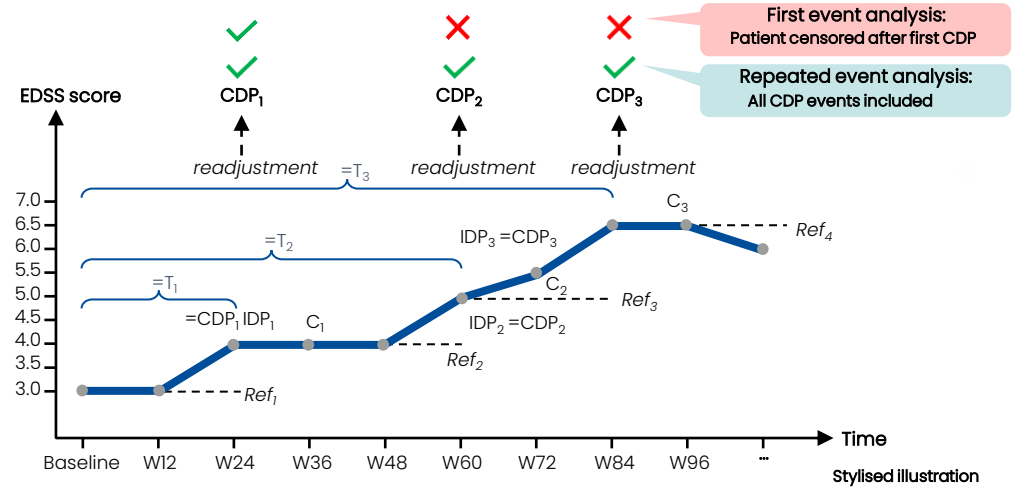
BACKGROUND

- The current gold standard **endpoint** to assess **disability accumulation** in Phase III MS clinical trials is the **time to the first** disability progression[a]
- This time-to-first event approach **does not** take into **account subsequent** on-trial **repeated progression events** that may occur but are excluded from analysis, thereby potentially missing the overall effect of a DMT
- Including **repeated progression events** in trial analysis may permit a more **comprehensive assessment of DMT** effects on disability progression
  - Repeated disability progression events can be defined by expanding the first-event definition such that the EDSS score is rebaselined at the onset of a confirmed event
  - Compared with conventional time-to-first-event analyses, repeated-event analyses captured more progression events, reflecting an increase of 9.5% to 29.0% in the control arms of studies in RMS and PPMS respectively[1]

Disability progression: Example of time to first event KM plot



Disability progression: Repeated-event illustration for a stylised PwMS



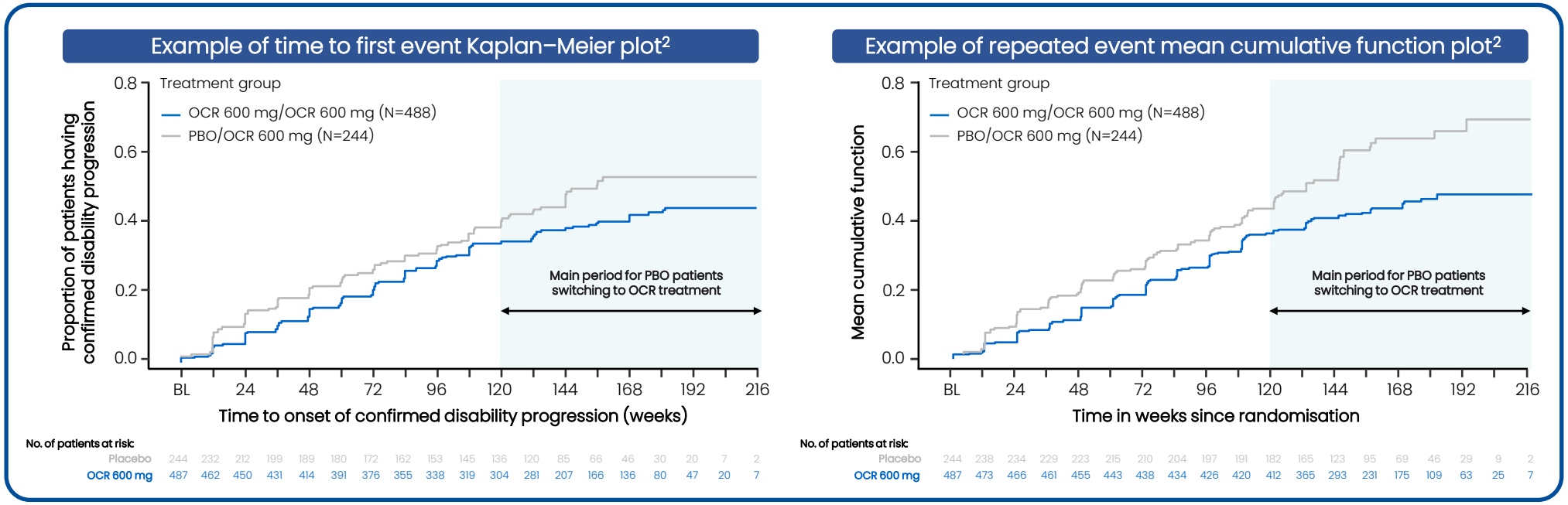
Repeated progression event analyses may improve estimates of treatment effects, and better capture patients' long-term disability progression experience

[a]Typically confirmed at 12-weeks; 12-week CDP.
C, confirmation of initial disability progression; CDP, confirmed disability progression (event); DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; IDP, initial disability progression; IFN, interferon; KM, Kaplan–Meier; MS, multiple sclerosis; OCR, ocrelizumab; PPMS, primary progressive MS; PwMS, patient with MS; *Ref*, reference EDSS score for confirmed disability progression; RMS, relapsing MS; T, time to onset of the confirmed disability progression; W, week.

1. Bühler A, *et al. Mult Scler.* 2023;29:130–139.

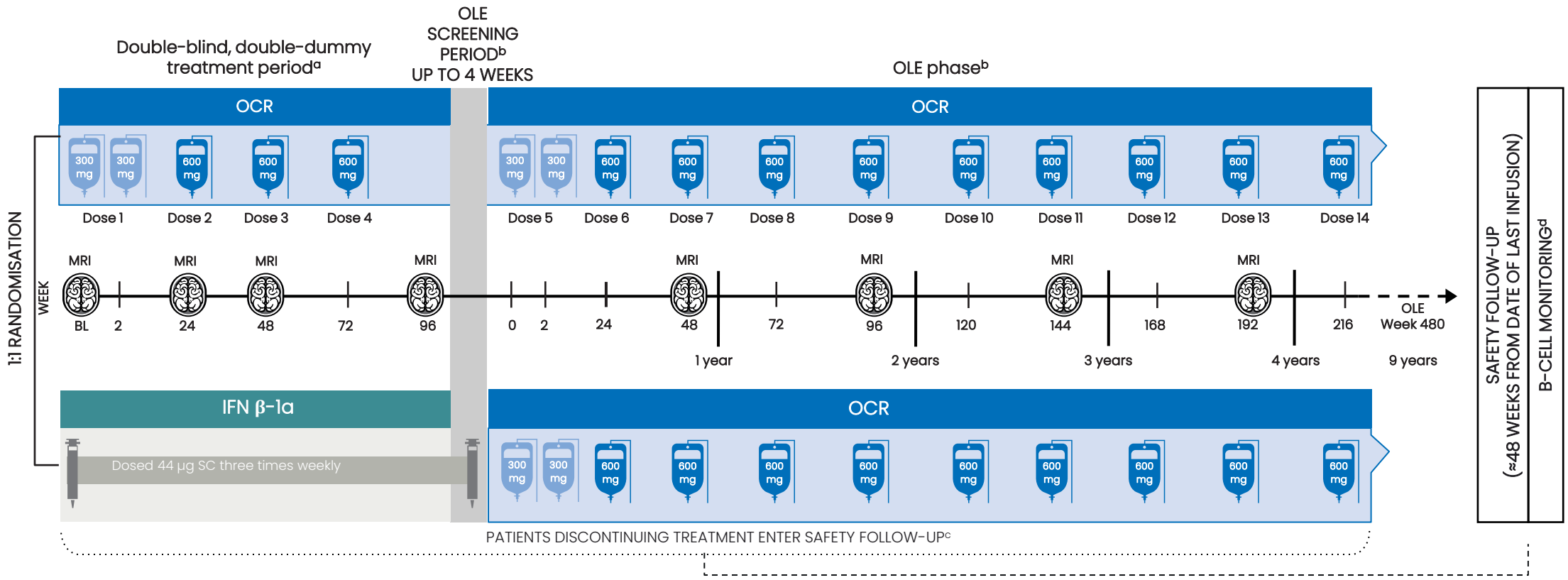
METHODS
Statistical Analysis

- A rate-based method, the Negative Binomial model, was used for the analysis of repeated CDP events[1]
  - The treatment effect estimate can be interpreted as a rate ratio (RR)
- Repeated events over time were visualised by estimates of the mean cumulative function (MCF)
  - The MCF represents the estimated average number of progression events per patient, over time
- Adjusted annualised repeated event rates and CIs were plotted over time



At Week 120, the start of the main switching period in the ORATORIO study, 494 patients were available for analysis using repeated CDP events vs 404 patients using the Kaplan–Meier approach.
BL, baseline; CDP, confirmed disability progression; MCF, mean cumulative function; OCR, ocrelizumab; PBO, placebo; RR, rate ratio.
1. Lin D, *et al. J R Stat Soc Ser B Stat Methodol* 2000;62:711–730. 2. Bühler A, *et al. Mult Scler* 2023;29:130–139.

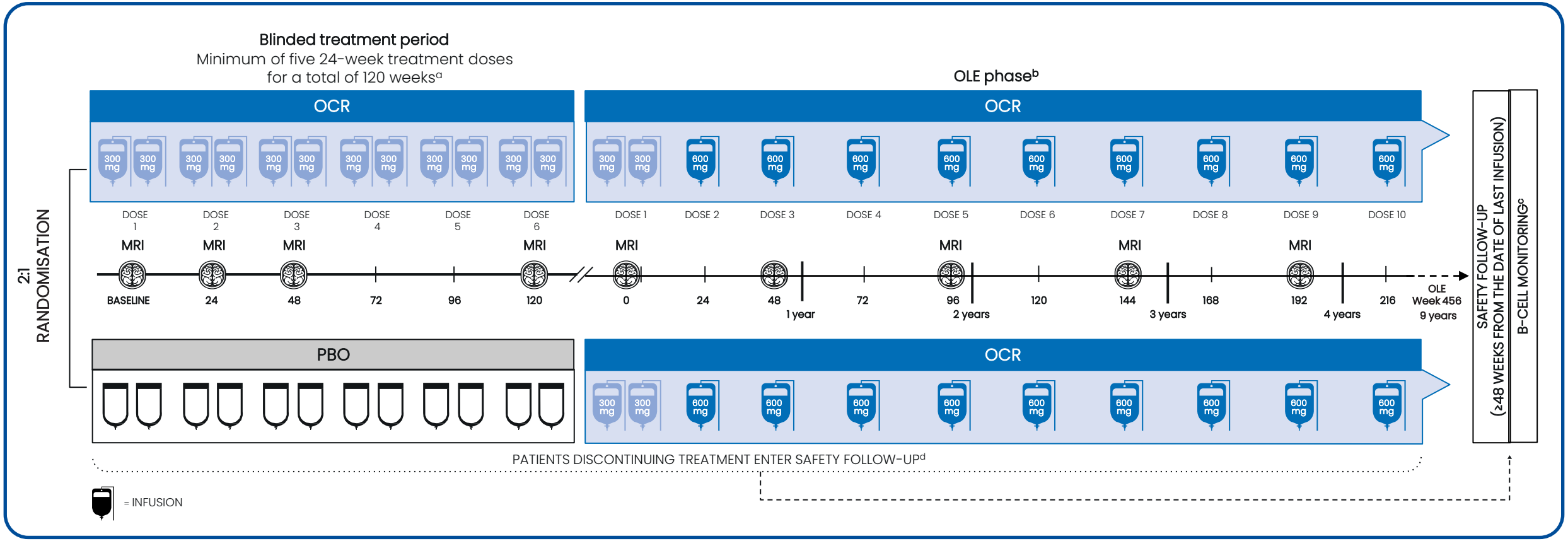
METHODS
OPERA I/OPERA II Study Design



In the DBP, patients were randomised to OCR or comparator (IFN β-1a).
At OLE initiation, patients continued OCR or switched from IFN β-1a to OCR

[a]Patients in the OCR group received placebo injections three times weekly, while patients in the IFN β-1a group received placebo infusions on Days 1 and 15 and at Weeks 24, 48 and 72;
[b]During OLE screening, patients received IFN β-1a or placebo until first infusion of Dose 5; [c]OLE was not mandatory – patients who declined to participate in the OLE entered safety follow-up;
[d]Continued monitoring occurs if B cells are not repleted. Data cut-off: 24 November 2023.
BL, baseline; DBP, double-blind period; IFN, interferon; OCR, ocrelizumab; OLE, open-label extension; SC, subcutaneous.

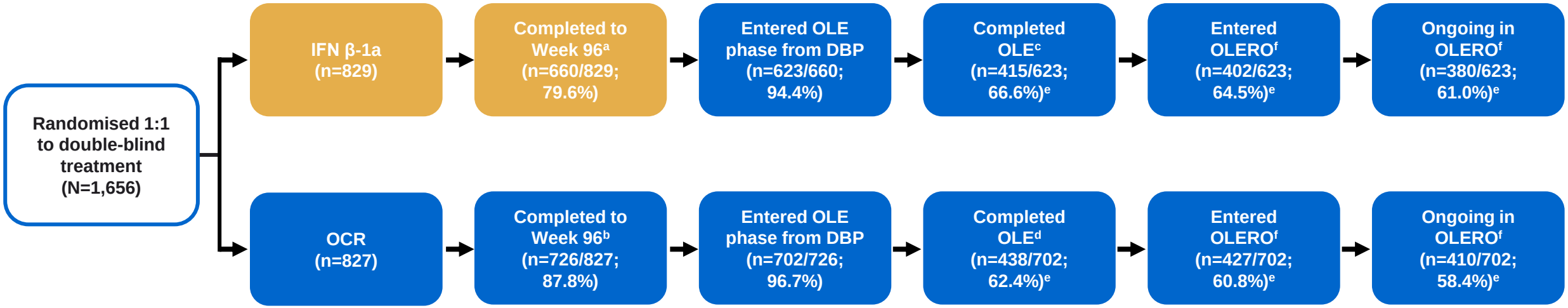
METHODS
ORATORIO Study Design



In the DBP, patients were randomised to OCR or PBO.
At OLE initiation, patients continued OCR or switched from PBO to OCR

[a]The blinded treatment period continued until the last patient completed 120 weeks and a target of 253 CDP events was reached;
[b]OLE was not mandatory – patients who declined to participate in the OLE entered safety follow-up;
[c]Continued monitoring occurs if B cells are not repleted. Data cut-off: 24 November 2023.
CDP, confirmed disability progression; DBP, double-blind period; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo.

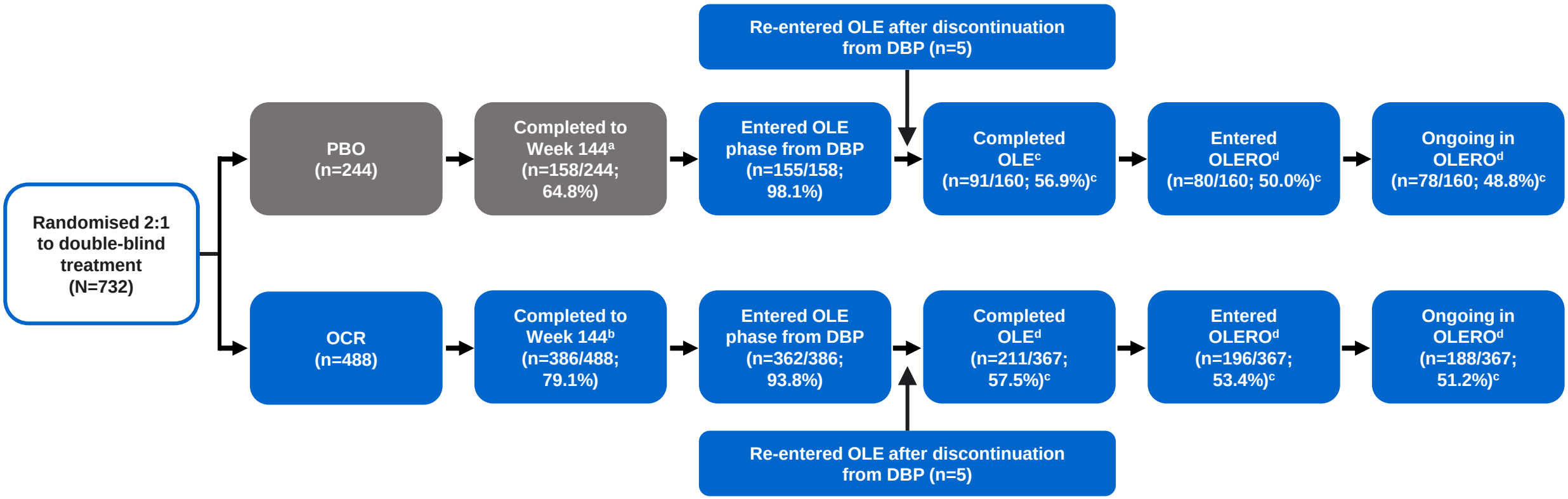
RESULTS
OPERA I/II OLE – Patient Disposition After 11 Years of Follow-Up



After 11 years, almost half (48%) of patients initially randomised in the OPERA I/II study were ongoing in the OLE roll-over period

Percentages in parentheses are of the ITT population. Clinical cut-off date: 24 November 2023.
[a]142 (17.2%) patients entered safety follow-up from DBP; [b]80 (9.7%) patients entered safety follow-up from DBP; [c]156 (25%) patients entered safety follow-up from OLE; [d]143 (20.4%) patients entered safety follow-up from OLE; [e]Percentages in parentheses are of the OLE population; [f]OLE roll-over period continuation of the OLE.
DBP, double-blind period; IFN, interferon; ITT, intention to treat; OCR, ocrelizumab; OLE, open-label extension; OLERO, OLE roll-over.

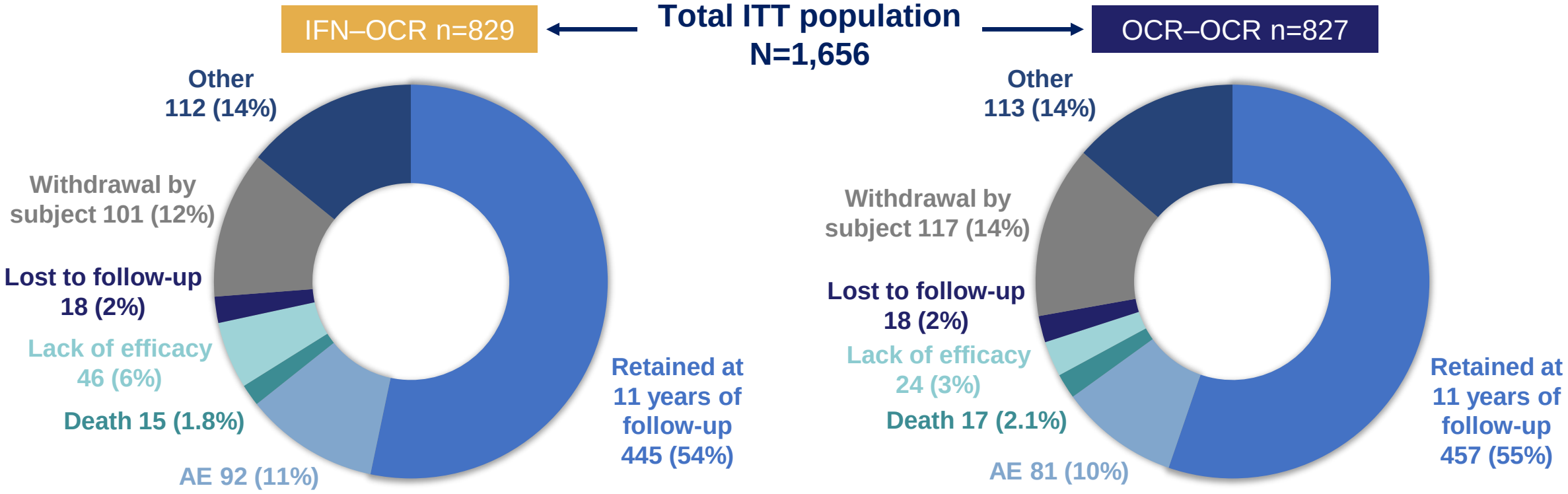
RESULTS
ORATORIO OLE – Patient Disposition After 11 Years of Follow-Up



After 11 years, over a third (36%) of patients initially randomised in the ORATORIO study were ongoing in the OLE roll-over period

Percentages in parentheses are of the ITT population. Clinical cut-off date: 24 November 2023.
[a]47 (19.3%) patients entered safety follow-up from DBP; [b]75 (15.6%) patients entered safety follow-up from DBP;
[c]Percentages in parentheses are of the OLE population;
[d]OLE roll-over period continuation of the OLE.
DBP, double-blind period; ITT, intention-to-treat; OCR, ocrelizumab; OLE, open-label extension; OLERO, OLE roll-over; PBO, placebo.

RESULTS
OPERA I/II Treatment Disposition at 11 Years of Follow-Up

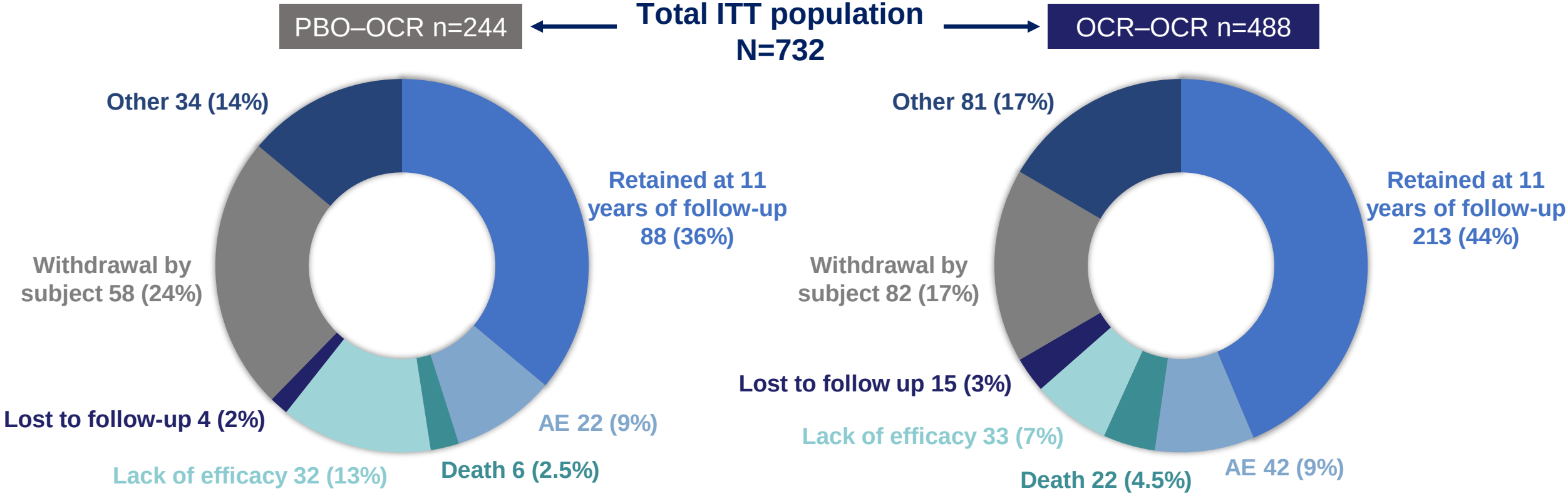


The majority of patients with RMS remained on OCR treatment throughout the 11 years of follow-up

AE, adverse event; IFN, interferon; ITT, intention-to-treat; OCR, ocrelizumab; RMS, relapsing multiple sclerosis.

RESULTS
ORATORIO Treatment Disposition at 11 Years of Follow-Up

Total ITT population N=732



Almost half of patients with PPMS receiving continuous OCR remained on treatment throughout the 11 years of follow-up

AE, adverse event; ITT, intention-to-treat; OCR, ocrelizumab; PBO, placebo; PPMS, primary progressive multiple sclerosis.