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Safety of Ocrelizumab in Multiple Sclerosis: Updated Analysis in Patients With Relapsing and Primary Progressive Multiple Sclerosis

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INTRODUCTION AND PURPOSE

- The safety and efficacy of ocrelizumab (OCR) have been characterised in a Phase II study in patients with relapsing-remitting multiple sclerosis (RRMS; NCT00676715),[1] and in the ORCHESTRA Phase III studies encompassing patients with relapsing multiple sclerosis (RMS; OPERA I [NCT01247324] and OPERA II [NCT01412333])[2] or primary progressive multiple sclerosis (PPMS; ORATORIO [NCT01194570])[3]
  - — OCR reduced disease activity and disability progression in patients with RMS (vs interferon [IFN] β-1a)[2] and PPMS (vs placebo)[3]
- In the Phase III trials, the most common adverse events (AEs) associated with OCR included infusion-related reactions (IRRs), nasopharyngitis, upper respiratory tract infections, headache and urinary tract infections (UTIs)[2,3]
- In the Phase III multiple sclerosis (MS) clinical trial programme, an imbalance of malignancies was observed between the OCR- and comparator-treated patients
  - — A higher incidence rate of malignancies, driven by a higher number of female breast cancer events, was observed in OCR-treated patients compared with pooled IFN β-1a- or placebo-treated patients
- Safety surveillance is crucial to understanding the long-term benefit–risk profile of OCR in patients with MS
- The purpose of the current analyses was to report ongoing safety evaluations from OCR clinical trials and associated open-label extension (OLE) periods up to January 2019, and selected post-marketing safety data

METHODS

General Safety

- Safety analyses are based on integrated data for all patients who received OCR in the following MS clinical trials (**Figure 1**), as of January 2019 (OCR all-exposure population):
  - — The Phase II and Phase III MS clinical trials and associated OLE periods (termed the "Phase [Ph] II/Ph III and OLEs population"), plus the ongoing Phase IIIb trials VELOCE (NCT02545868), CHORDS (NCT02637856), CASTING (NCT02861014; and associated long-term extension, LTE [NCT03599245]), OBOE (NCT02688985) and ENSEMBLE (NCT03085810)
- To account for the different exposure lengths, the rate per 100 patient years (PY) is presented
- AEs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA)

Malignancies

- Standardised incidence rates of (i) all malignancies (excluding non-melanoma skin cancer [NMSC]) and (ii) female breast cancer were calculated in the context of data from published MS-specific epidemiological sources (Danish MS registry[4]) and the general population (National Cancer Institute [NCI] Surveillance, Epidemiology, and End Results [SEER] database[5])
- Standardised incidence rates of malignancies have been calculated previously using the "age at enrolment" methodology, based on the age of the patient at study baseline; this methodology has been used up to July 2018[6]
  - — However, as study follow-up continues and patients become older, the "age at event onset" methodology, based on the age of the patient at the onset of malignancy, is a more accurate method of calculating the standardised incidence rate; from September 2017 onwards, the "age at event onset" methodology has been used
  - — Standardised incidence rates using both methodologies have been presented concurrently from September 2017 up to July 2018; from January 2019, only rates using the "age at event onset" methodology will be presented
- The standardised incidence ratio (SIR) of (i) all malignancies (excluding NMSC) and (ii) female breast cancer is calculated as observed to expected number of events, using SEER database[5] and Danish MS registry[4] as reference populations

For study designs (Figure 1), please scan here

RESULTS

Treatment Exposure

- As of January 2019, 4,611 patients with MS received OCR in the OCR all-exposure population, resulting in 14,329 PY of exposure (**Table 1**)
- As of August 2019, more than 120,000 patients with RMS and PPMS have started OCR treatment globally, amounting to a total of more than 120,000 PY:
  - — Over 6,000 patients in clinical trials and OLEs
  - — Over 114,000 patients with post-marketing experience

Overall Adverse Events

- As of January 2019, the rate of AEs was 252 (95% CI 249–254) per 100 PY in the OCR all-exposure population (**Table 2**), consistent with the rate observed at the primary analysis cut-off date (based on the clinical cut-off dates of the individual studies: Phase II, January 2015; OPERA I, April 2015; OPERA II, May 2015; ORATORIO, July 2015)
  - — The most common AEs included IRRs, nasopharyngitis, UTIs and upper respiratory tract infections
- As of January 2019, serious AEs were reported at a rate of 7.33 (95% CI 6.89–7.79) events per 100 PY in the OCR all-exposure population
  - — The most common serious AEs were coded to the MedDRA system order class (SOC) term Infections and infestations
- As of January 2019, the rate of AEs leading to treatment discontinuation was 1.08 (95% CI 0.92–1.27) per 100 PY in the OCR all-exposure population (**Table 3**)
  - — The most common AEs per 100 PY leading to discontinuation were IRRs (0.21 [95% CI 0.14–0.30]) and events coded to the MedDRA version 21.1 SOC terms Neoplasms benign, malignant and unspecified (0.20 [95% CI 0.13–0.28]) and Infections and infestations (0.19 [95% CI 0.12–0.27]) (**Table 3**)
  - — The rate of AEs leading to discontinuation remained stable with additional patient exposure
  - — The pattern of AEs leading to discontinuation was consistent with the pattern of AEs observed at the end of the controlled treatment periods (2015) (**Table 4**)

For treatment exposure (Table 1), the safety profile of OCR at previous data-cuts (extended Table 2), and AEs leading to discontinuation (Table 3 and Table 4), please scan here

Table 2. Safety profile observed with OCR

Event	OPERA (pooled) controlled treatment period[a]		ORATORIO controlled treatment period[a]		Ph II/Ph III and OLEs population[b]	OCR all-exposure population[c]
	IFN β-1a rate per 100 PY (95% CI)[d]	OCR rate per 100 PY (95% CI)[d]	Placebo rate per 100 PY (95% CI)[d]	OCR rate per 100 PY (95% CI)[d]	Jan 2019 rate per 100 PY (95% CI)[d,e]	Jan 2019 rate per 100 PY (95% CI)[d,e]
Total PY	**1,399**	**1,448**	**729**	**1,606**	**11,025**	**14,329**
Any adverse events[f]	**296 (287–305)**	**290 (281–299)**	**259 (247–271)**	**252 (244–260)**	**214 (211–217)**	**252 (249–254)**
Adverse events leading to treatment discontinuation[f]	**3.93 (2.96–5.12)**	**2.35 (1.63–3.28)**	**1.10 (0.47–2.16)**	**1.25 (0.76–1.92)**	**1.13 (0.94–1.35)**	**1.08 (0.92–1.27)**
Infections and infestations[f]	**67.8 (63.5–72.2)**	**84.5 (79.9–89.4)**	**72.5 (66.5–79.0)**	**70.8 (66.8–75.0)**	**71.0 (69.5–72.6)**	**76.7 (75.3–78.2)**
Urinary tract infection	9.7 (8.1–11.4)	11.6 (9.9–13.5)	17.8 (14.9–21.2)	15.1 (13.2–17.1)	13.0 (12.3–13.7)	12.4 (11.9–13.0)
Nasopharyngitis	8.3 (6.9–9.9)	13.0 (11.2–15.0)	17.7 (14.8–21.0)	12.8 (11.1–14.6)	10.8 (10.2–11.5)	13.4 (12.8–14.0)
Upper respiratory tract infection	9.4 (7.8–11.1)	13.3 (11.5–15.3)	2.9 (1.8–4.4)	5.2 (4.2–6.5)	9.7 (9.1–10.3)	10.0 (9.5–10.5)
Bronchitis	2.2 (1.5–3.1)	3.5 (2.6–4.6)	2.9 (1.8–4.4)	2.6 (1.9–3.5)	3.2 (2.9–3.6)	3.1 (2.8–3.4)
Influenza	3.3 (2.4–4.4)	3.1 (2.3–4.2)	3.4 (2.2–5.1)	4.6 (3.6–5.7)	2.9 (2.6–3.3)	3.7 (3.4–4.1)
Injury, poisoning, and procedural complications[f]	**17.1 (15.0–19.4)**	**45.9 (42.4–49.5)**	**36.3 (32.1–41.0)**	**43.5 (40.3–46.8)**	**28.2 (27.2–29.2)**	**37.2 (36.2–38.2)**
Infusion-related reactions	7.9 (6.5–9.5)	34.9 (31.9–38.1)	20.3 (17.2–23.8)	31.0 (28.3–33.9)	17.9 (17.1–18.7)	26.1 (25.3–26.9)
Nervous system disorders[f]	**34.8 (31.8–38.0)**	**31.6 (28.8–34.7)**	**22.4 (19.1–26.1)**	**22.6 (20.3–25.1)**	**19.1 (18.3–19.9)**	**25.5 (24.7–26.3)**
Headache	12.4 (10.6–14.4)	9.5 (8.0–11.3)	6.7 (5.0–8.9)	6.3 (5.1–7.6)	4.5 (4.2–5.0)	7.9 (7.5–8.4)
Musculoskeletal and connective tissue disorders[f]	**25.0 (22.5–27.8)**	**24.3 (21.8–27.0)**	**31.7 (27.7–36.0)**	**22.8 (20.5–25.3)**	**18.7 (17.9–19.5)**	**21.3 (20.5–22.0)**
Back pain	3.1 (2.2–4.1)	4.1 (3.1–5.3)	7.4 (5.6–9.7)	4.8 (3.8–6.0)	3.2 (2.9–3.6)	3.7 (3.4–4.0)
Arthralgia	3.9 (3.0–5.1)	3.5 (2.6–4.6)	4.3 (2.9–6.0)	3.0 (2.2–4.0)	2.6 (2.3–2.9)	2.9 (2.6–3.2)
Pain in extremity	2.9 (2.1–4.0)	3.7 (2.7–4.8)	4.7 (3.2–6.5)	2.4 (1.7–3.2)	2.2 (1.9–2.4)	2.8 (2.5–3.1)
General disorders and administration site conditions[f]	**51.3 (47.6–55.2)**	**17.3 (15.2–19.5)**	**15.6 (12.9–18.8)**	**12.7 (11.0–14.6)**	**10.2 (9.6–10.8)**	**13.8 (13.2–14.4)**
Fatigue	5.7 (4.5–7.1)	5.4 (4.3–6.7)	4.4 (3.0–6.2)	1.9 (1.3–2.7)	2.7 (2.4–3.1)	4.1 (3.7–4.4)
Psychiatric disorders[f]	**14.2 (12.3–16.3)**	**14.4 (12.5–16.5)**	**11.8 (9.4–14.6)**	**7.7 (6.4–9.2)**	**7.3 (6.8–7.8)**	**8.5 (8.1–9.0)**
Depression	4.2 (3.2–5.4)	4.9 (3.8–6.2)	5.1 (3.6–7.0)	2.4 (1.7–3.3)	2.4 (2.1–2.7)	2.5 (2.3–2.8)
Malignancies[f,g,h,i]	**0.14 (0.02–0.52)**	**0.28 (0.08–0.71)**	**0.27 (0.03–0.99)**	**0.93 (0.52–1.54)**	**0.51 (0.39–0.67)**	**0.46 (0.35–0.58)**
Serious adverse events[f]	**6.29 (5.05–7.75)**	**5.39 (4.26–6.72)**	**12.07 (9.68–14.87)**	**10.15 (8.65–11.83)**	**7.84 (7.32–8.38)**	**7.33 (6.89–7.79)**
Serious infections[j]	1.79 (1.16–2.64)	0.83 (0.43–1.45)	3.02 (1.89–4.57)	2.74 (1.99–3.68)	2.21 (1.94–2.51)	1.99 (1.77–2.23)
No. of potential serious OIs[k]	0	0	0	0	5	6
Fatalities[f]	**0.14 (0.02–0.52)**	**0.07 (0–0.38)**	**0.41 (0.08–1.20)**	**0.25 (0.07–0.64)**	**0.19 (0.12–0.29)**	**0.16 (0.10–0.24)**

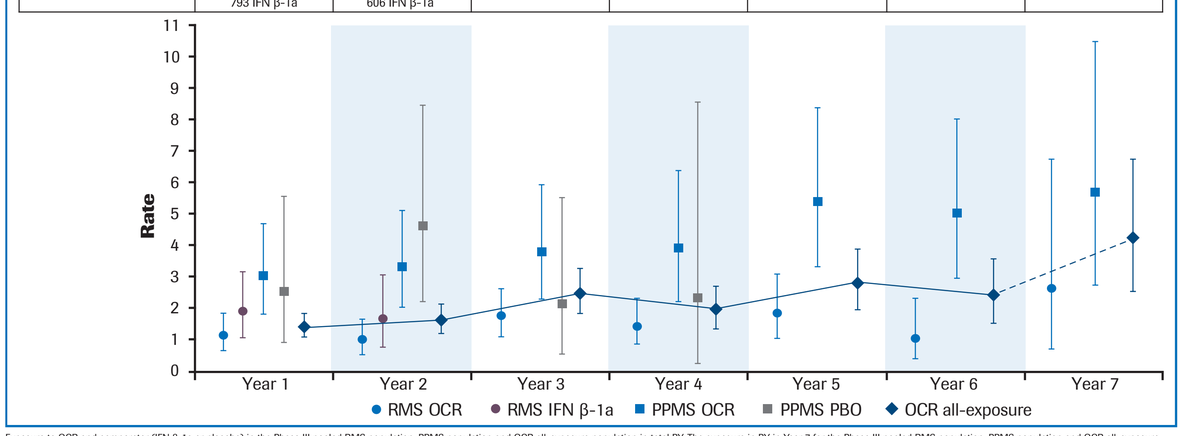
[a]Includes patients who received placebo or IFN β-1a during the controlled treatment period of the Phase III studies; [b]Includes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the Phase II and Phase III studies; data from patients who were originally randomised to comparator (IFN β-1a or placebo) are included after the switch to open-label OCR treatment; [c]Includes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the Phase II and Phase III studies, plus VELOCE, CHORDS, CASTING (and associated LTE), OBOE and ENSEMBLE; data from patients who were originally randomised to comparator (IFN β-1a or placebo) are included after the switch to open-label OCR treatment; [d]Multiple occurrences of the same adverse event (except for malignancies") in one patient are counted multiple times; [e]Rate per 100 PY (95% CI) as of January 2019; [f]Includes adverse events falling into the MedDRA versions 18.0, 18.1 and 21.1; [g]Malignancies are identified using adverse events falling into the standard MedDRA query 'Malignant tumours (narrow)'; [h]From January 2016, multiple occurrences of the same adverse event in one patient are counted only once; [i]From January 2016, for patients with malignancies, exposure in PY was calculated from first treatment to onset of first malignancy; [j]Serious infections are defined using adverse events falling into the MedDRA SOC Infections and infestations, and using 'Is the event non-serious or serious?' from the adverse event case report form; [k]Potential serious OIs were medically reviewed.
IFN, interferon; LTE, long-term extension; MedDRA, Medical Dictionary for Regulatory Activities; OCR, ocrelizumab; OI, opportunistic infection; OLE, open-label extension; Ph, Phase; PY, patient years; SOC, system organ class.

Infections and Serious Infections

- As of January 2019, the rate of infections was 76.7 (95% CI 75.3–78.2) per 100 PY in the OCR all-exposure population (**Table 2**), consistent with the rate observed at the primary analysis cut-off date
- The most common serious infections were UTIs and pneumonia
- In the OCR all-exposure population, the overall rate per 100 PY of serious infections as of January 2019 (1.99 [95% CI 1.77–2.23]) was similar to the rate observed at the primary analysis cut-off date (**Table 2**)
- In the OCR all-exposure population, point estimates fluctuate though the rate per 100 PY of serious infections by year appears to increase numerically over time (**Figure 2**)
  - — In the pooled RMS population, the rate per 100 PY of serious infections by year increases to Year 3, with no further increase until Year 5 (**Figure 2**)
  - — In the PPMS population, the rate per 100 PY of serious infections by year was higher than in the RMS population (**Figure 2**)
  - — As observed in previous data-cuts, there was no change in the type or pattern of serious infections identified by year in patients with RMS or PPMS treated with OCR and no pattern was identified with regard to demography, duration or latency

Figure 2. Rate per 100 patient years of serious infections

OCR all-exposure[a] (PY):	4,362	3,304	2,063	1,715	1,286	1,008	423
PPMS exposure[b] (PY):	635 OCR; 235 PBO	607 OCR; 217 PBO	564 OCR; 186 PBO	409 OCR; 85 PBO	370 OCR	340 OCR	176 OCR
RMS exposure[c] (PY):	1,422 OCR; 793 IFN β-1a	1,360 OCR; 606 IFN β-1a	1,277 OCR	1,183 OCR	807 OCR	568 OCR	153 OCR



Exposure to OCR and comparator (IFN β-1a or placebo) in the Phase III pooled RMS population, PPMS population and OCR all-exposure population in total PY. The exposure in PY in Year 7 for the Phase III pooled RMS population, PPMS population and OCR all-exposure population was lower compared with earlier years. The dotted line between Year 6 and Year 7 is due to the immaturity of the data due to limited exposure. Investigator text for adverse events was encoded using MedDRA versions 18.1 and 21.1. Multiple occurrences of the same adverse event in one patient are counted multiple times. Serious infections are defined using adverse events falling into the MedDRA SOC Infections and infestations, and using 'Is the event non-serious or serious?' from the adverse event case report form. 95% CIs were calculated using an exact method based on the Poisson distribution. Patients are considered in the ongoing year, e.g. Year 6 contains patients completing at least 5 years in the study and ongoing during the sixth year.
[a]Includes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the Phase II and Phase III studies, plus VELOCE, CHORDS, CASTING (and associated LTE), OBOE and ENSEMBLE; [b]Includes patients who received placebo during the controlled treatment period, and any dose of OCR during the controlled treatment and associated OLE period of the ORATORIO study; [c]Includes patients who received IFN β-1a during the controlled treatment period, and any dose of OCR during the controlled treatment and associated OLE period of the OPERA I and OPERA II studies.
IFN, interferon; LTE, long-term extension; MedDRA, Medical Dictionary for Regulatory Activities; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; PPMS, primary progressive multiple sclerosis; PY, patient years; RMS, relapsing multiple sclerosis; SOC, system organ class.

Potential Serious Opportunistic Infections

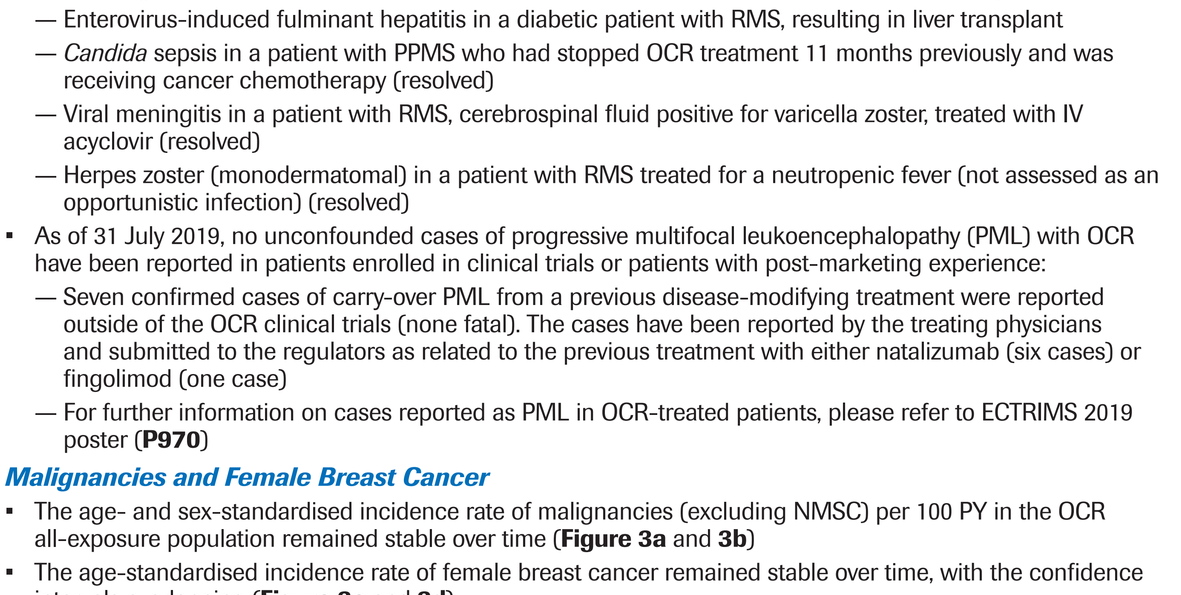
- As of January 2019, no additional potential serious opportunistic infections had been reported from OCR clinical trials since the last data cut-off (July 2018)[6] (**Table 2**)
- As of January 2019, six potential serious opportunistic infections had been reported from OCR clinical trials
  - — Systemic *Pasteurella* infection in a patient with RMS following a cat bite (resolved)
  - — Multisegmental herpes zoster infection in a patient with RMS, treated with intravenous (IV) acyclovir (resolved)
  - — Enterovirus-induced fulminant hepatitis in a diabetic patient with RMS, resulting in liver transplant
  - — *Candida* sepsis in a patient with PPMS who had stopped OCR treatment 11 months previously and was receiving cancer chemotherapy (resolved)
  - — Viral meningitis in a patient with RMS, cerebrospinal fluid positive for varicella zoster, treated with IV acyclovir (resolved)
  - — Herpes zoster (monodermatomal) in a patient with RMS treated for a neutropenic fever (not assessed as an opportunistic infection) (resolved)
- As of 31 July 2019, no unconfounded cases of progressive multifocal leukoencephalopathy (PML) with OCR have been reported in patients enrolled in clinical trials or patients with post-marketing experience:
  - — Seven confirmed cases of carry-over PML from a previous disease-modifying treatment were reported outside of the OCR clinical trials (none fatal). The cases have been reported by the treating physicians and submitted to the regulators as related to the previous treatment with either natalizumab (six cases) or fingolimod (one case)
  - — For further information on cases reported as PML in OCR-treated patients, please refer to ECTRIMS 2019 poster (**P970**)

Malignancies and Female Breast Cancer

- The age- and sex-standardised incidence rate of malignancies (excluding NMSC) per 100 PY in the OCR all-exposure population remained stable over time (**Figure 3a** and **3b**)
- The age-standardised incidence rate of female breast cancer remained stable over time, with the confidence intervals overlapping (**Figure 3c** and **3d**)
- SIRs for all malignancies (excluding NMSC) and female breast cancer vs SEER and Danish MS registry further confirmed that the observed incidence rates were within epidemiological references (**Table 5**)
- Yearly incidence rates of all malignancies and female breast cancer fluctuate and do not suggest a time-dependent exposure effect (**Table 6** and **Table 7**)

For yearly incidence rates of all malignancies (Table 6) and of female breast cancer (Table 7), please scan here

Figure 3. Incidence rates per 100 patient years over time compared with the Danish MS registry and SEER database: (a)(b) Age- and sex-standardised of all malignancies, (c)(d) age-standardised of female breast cancer



The incidence rate of first malignancy (number of first malignancy events per 100 PY) was calculated. Standardised incidence rates are presented using "age at enrolment" (panels a and c; age range: 15–59 years) and "age at event onset" (age range: 15–64 years).
Standardised incidence rate (95% CI) for panel a: SEER: 0.24 (0.24–0.24); Danish MS registry: 0.27 (0.24–0.31).
Standardised incidence rate (95% CI) for panel b: SEER: 0.31 (0.30–0.31); Danish MS registry: 0.30 (0.27–0.35).
Standardised incidence rate (95% CI) for panel c: SEER: 0.12 (0.12–0.13); Danish MS registry: 0.16 (0.13–0.20).
Standardised incidence rate (95% CI) for panel d: SEER: 0.14 (0.14–0.14); Danish MS registry: 0.17 (0.14–0.21).
[a]NMSC is not reported in SEER; [b]Includes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the Phase II and Phase III studies; [c]Includes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the Phase II and Phase III studies, plus VELOCE, CHORDS, CASTING, OBOE and ENSEMBLE; [d]Includes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the Phase II and Phase III studies, plus VELOCE, CHORDS, CASTING (and associated LTE), OBOE and ENSEMBLE.
LTE, long-term extension; MS, multiple sclerosis; NMSC, non-melanoma skin cancer; OCR, ocrelizumab; OLE, open-label extension; Ph, Phase; PY, patient years; SEER, Surveillance, Epidemiology, and End Results.

Table 5. Standardised incidence ratios of all malignancies and female breast cancer vs SEER database and the Danish MS registry

January 2019[a,b]	SIRs of all malignancies[c] (95% CI)	SIRs of female breast cancer (95% CI)
SIR OCR/SEER	0.81 (0.58–1.09)	1.10 (0.63–1.79)
SIR OCR/Danish MS registry	0.86 (0.62–1.17)	0.87 (0.50–1.42)

The SIR is calculated as observed to expected number of events.
[a]Includes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the Phase II and Phase III studies, plus VELOCE, CHORDS, CASTING (and associated LTE), OBOE and ENSEMBLE; [b]Incidence rate is calculated based on the age at event onset; [c]NMSC is not reported in SEER.
LTE, long-term extension; MS, multiple sclerosis; NMSC, non-melanoma skin cancer; OCR, ocrelizumab; OLE, open-label extension; SEER, Surveillance, Epidemiology, and End Results; SIR, standardised incidence ratio.

CONCLUSIONS

- The reported rates of AEs per 100 PY in the ocrelizumab MS all-exposure population continue to be generally consistent with those seen during the controlled treatment period in the RMS and PPMS populations
- In the ocrelizumab all-exposure population, point estimates fluctuate though the rate per 100 PY of serious infections by year appears to increase numerically over time
- Six potential serious opportunistic infections have been identified in patients from ocrelizumab clinical trials
- No unconfounded cases of PML with ocrelizumab have been reported
- The rate of malignancies in ocrelizumab-treated patients remained within the range reported in epidemiological data
- Post-marketing data remain consistent with those observed in clinical trials
- Long-term follow-up and post-marketing requirement studies will monitor safety over time in patients with MS receiving ocrelizumab, including identified and potential risks

DISCLOSURES

SL Hauser serves on the board of trustees for Neurona and on scientific advisory boards for Alector, Annexon, Bionure, Molecular Stethoscope and Symbiotix, and has received travel reimbursement and writing assistance from F. Hoffmann-La Roche Ltd for CD20-related meetings and presentations. L Kappos's institution (University Hospital Basel) received in the last 3 years and used exclusively for research support at the Department: steering committee, advisory board and consultancy fees from Actelion, Alkermes, Almirall, Bayer, Biogen, Celgene/Receptos, df-mp, Excemed, GeNeuro SA, Genzyme, Japan Tobacco, Merck, Minoryx, Mitsubishi Pharma, Novartis, Roche, Sanofi-Aventis, Santhera, Teva and Vianex, and royalties for Neurostatus-UHB products; the Research of the MS Center in Basel has been supported by grants from Bayer, Biogen, Novartis, the Swiss MS Society, the Swiss National Research Foundation, the European Union and Roche Research Foundations. X Montalban has received speaker honoraria and travel expense reimbursement for participation in scientific meetings, been a steering committee member of clinical trials or served on advisory boards of clinical trials for Actelion, Biogen, Celgene, Merck, Novartis, Oryzon, Roche, Sanofi Genzyme and Teva Pharmaceutical. L Craveiro is an employee of F. Hoffmann-La Roche Ltd. R Hughes is an employee of F. Hoffmann-La Roche Ltd. K Prajapati has received consulting fees from F. Hoffmann-La Roche Ltd for statistical assistance, and is an employee of GCE Solutions Inc. A Pradhan is an employee of Genentech, Inc. D Wormser is an employee and shareholder of F. Hoffmann-La Roche Ltd. H Koendgen is an employee and shareholder of F. Hoffmann-La Roche Ltd. JS Wolinsky has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with AbbVie, Actelion, Alkermes, Biogen, Bionest, Celgene, Clene Nanomedicine, EMD Serono, Forward Pharma A/S, GeNeuro, MedDay Pharmaceuticals, Novartis, Otsuka, PTC Therapeutics, Roche/Genentech and Sanofi Genzyme; royalties are received for outlicensed monoclonal antibodies through UTHealth from Millipore Corporation.

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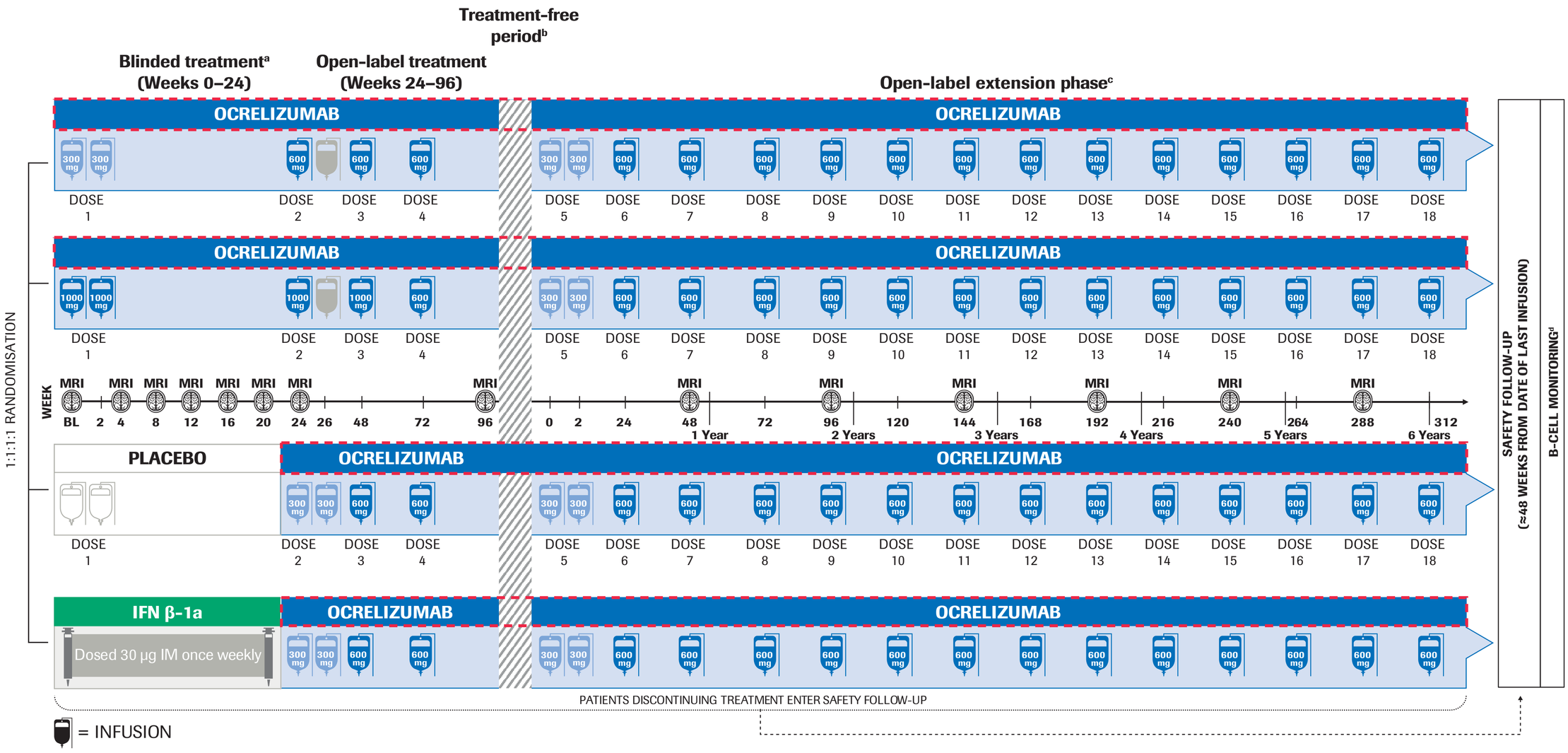
Poster P648

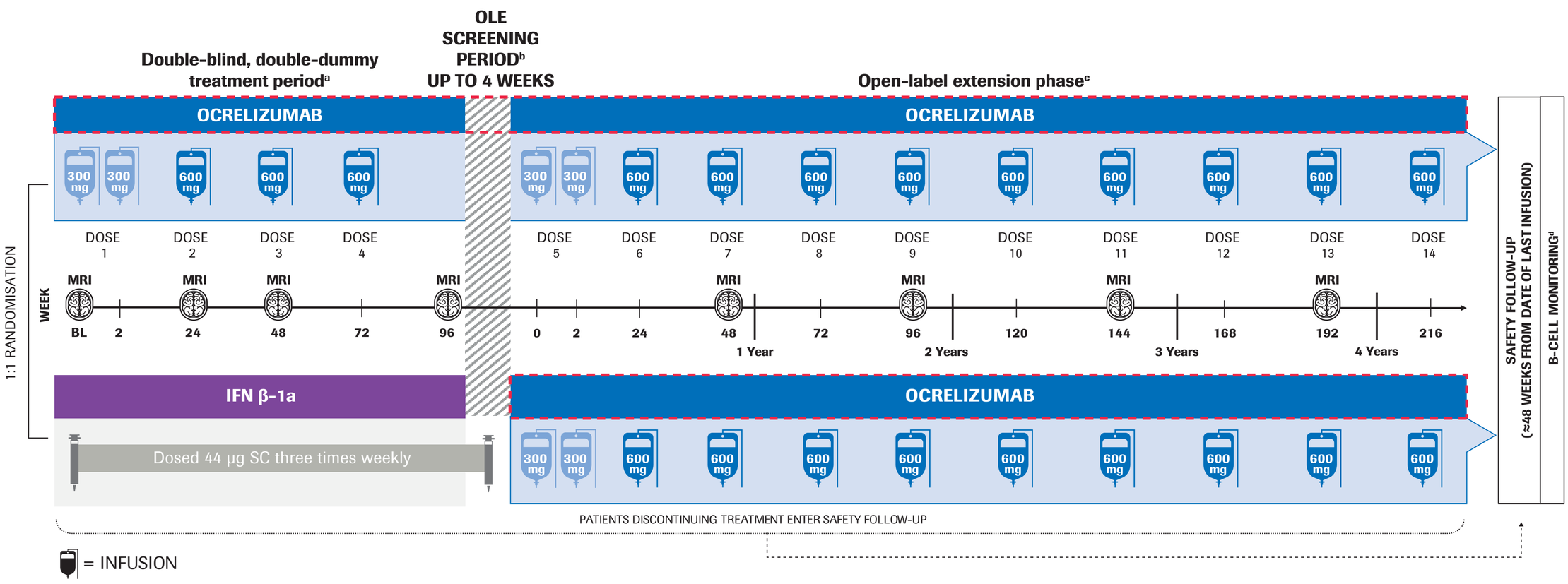
Figure 1. Study designs

Phase II (NCT00676715) study of ocrelizumab in patients with RRMS



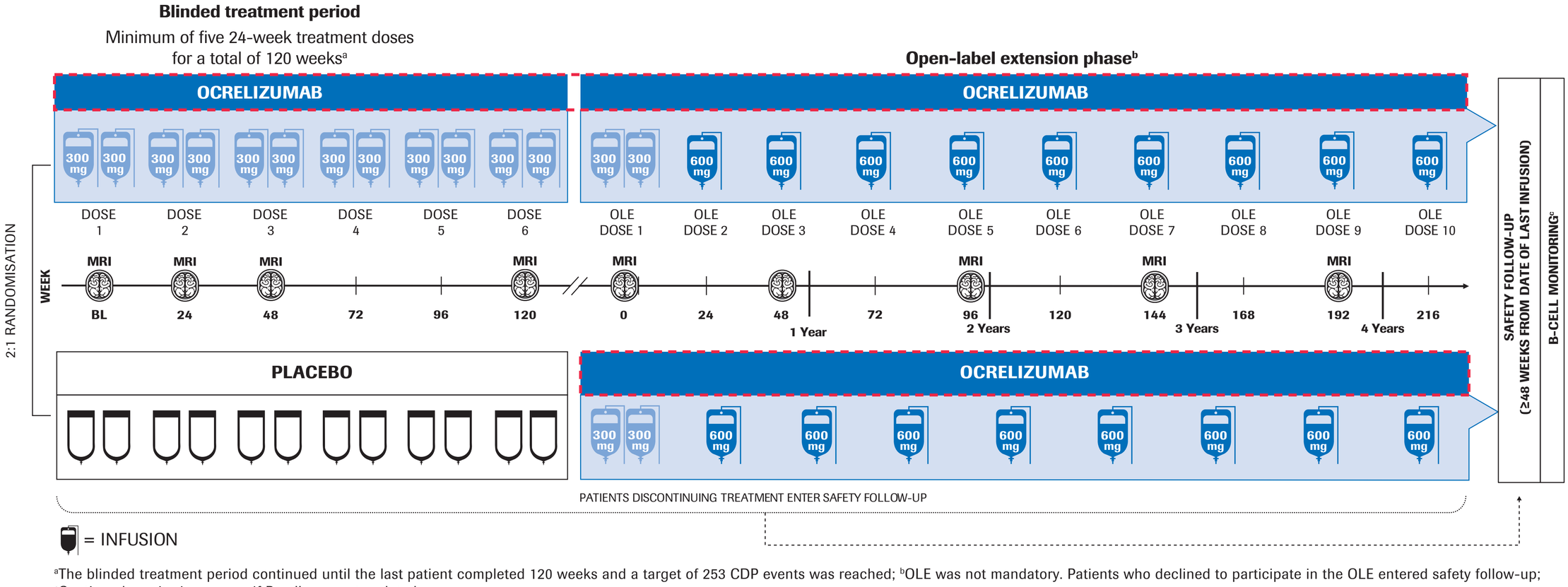
[a]Double-blind treatment for placebo and ocrelizumab arms; rater-blinded treatment for the IM IFN β-1a arm; [b]Variable duration up to 48 weeks; [c]OLE was not mandatory. Patients who declined to participate in the OLE entered safety follow-up; [d]Continued monitoring occurs if B cells are not repleted.

Phase III OPERA I (NCT01247324) and OPERA II (NCT01412333) studies of ocrelizumab in patients with RMS



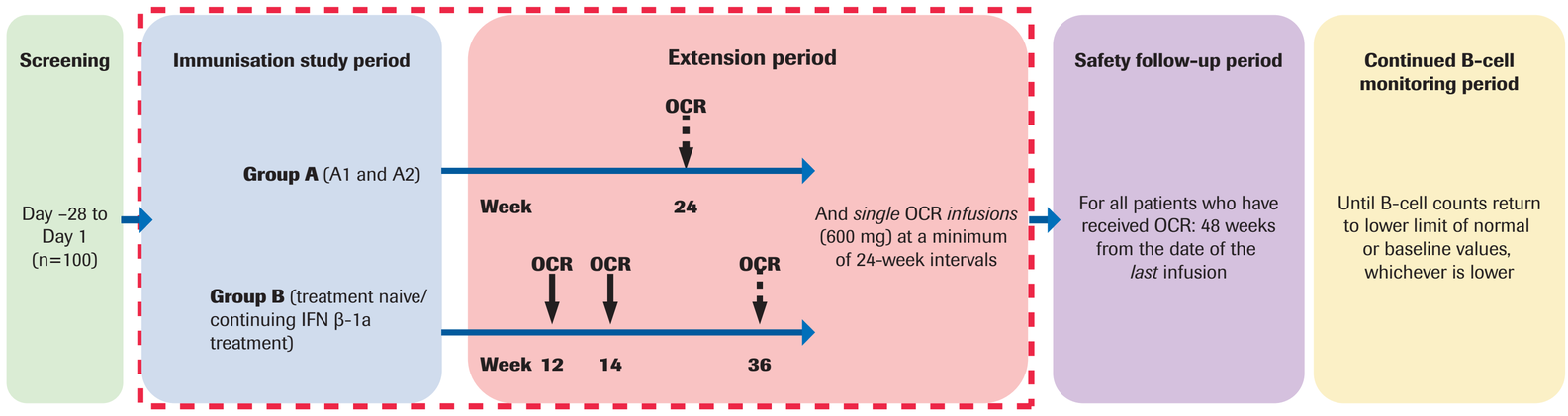
[a]Patients in the ocrelizumab group received placebo injections three times weekly, while patients in the IFN β-1a group received placebo infusions at Days 1 and 15 and Weeks 24, 48 and 72; [b]During OLE screening, patients received IFN β-1a or placebo until first infusion of dose 5; [c]OLE was not mandatory. Patients who declined to participate in the OLE entered safety follow-up; [d]Continued monitoring occurs if B cells are not repleted.

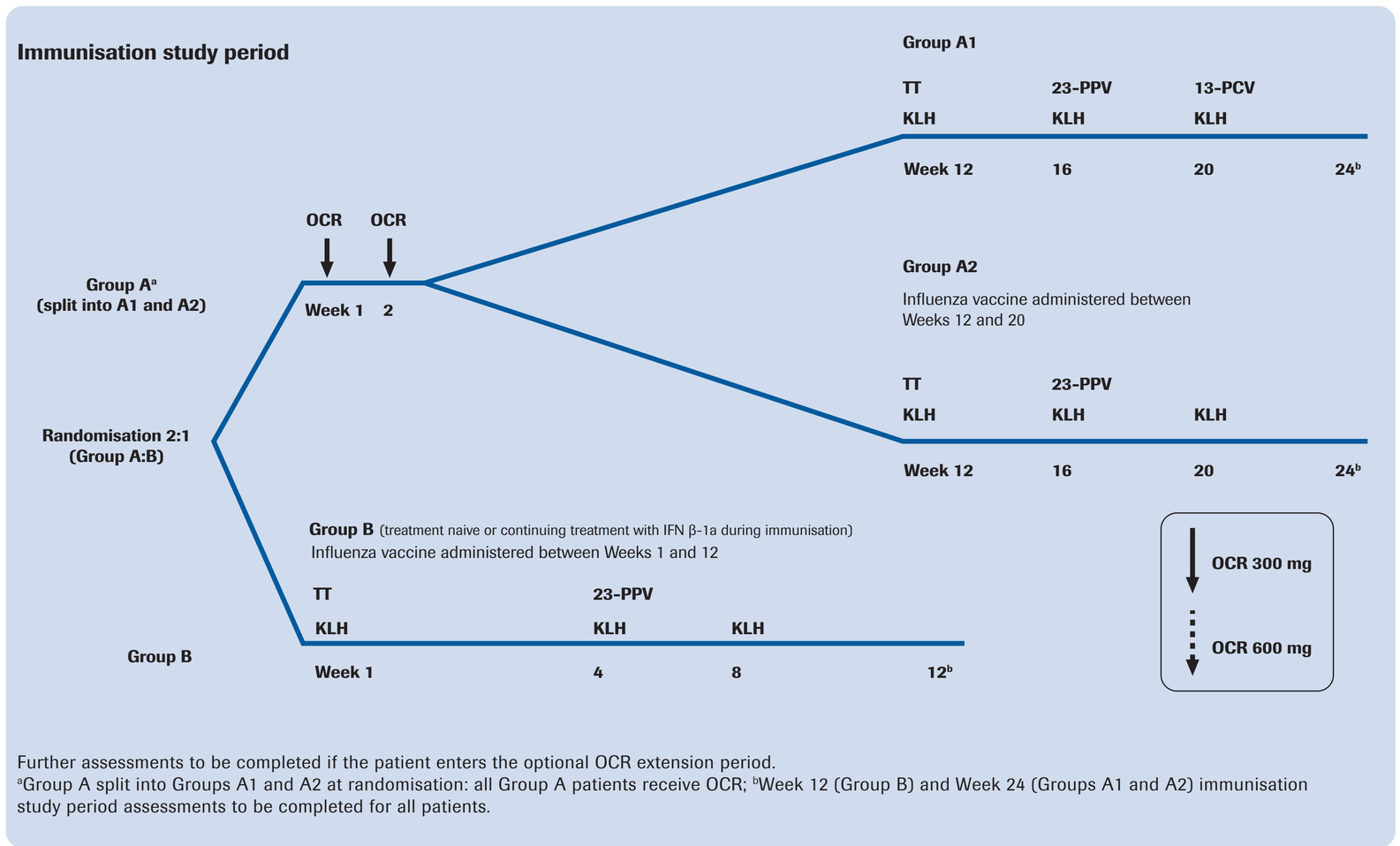
Phase III ORATORIO (NCT01194570) study in patients with PPMS



[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.

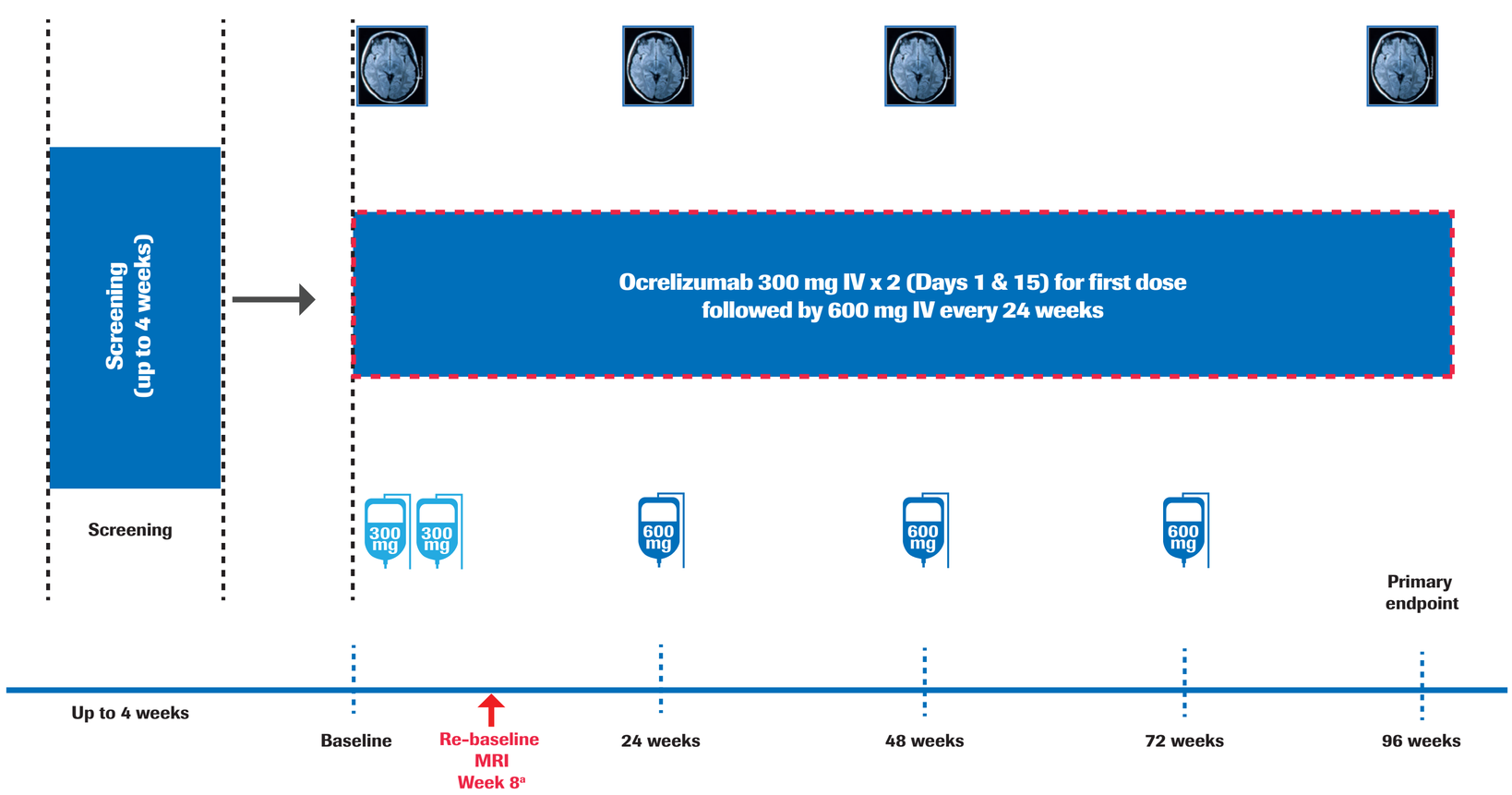
VELOCE (NCT02545868) study in patients with RMS

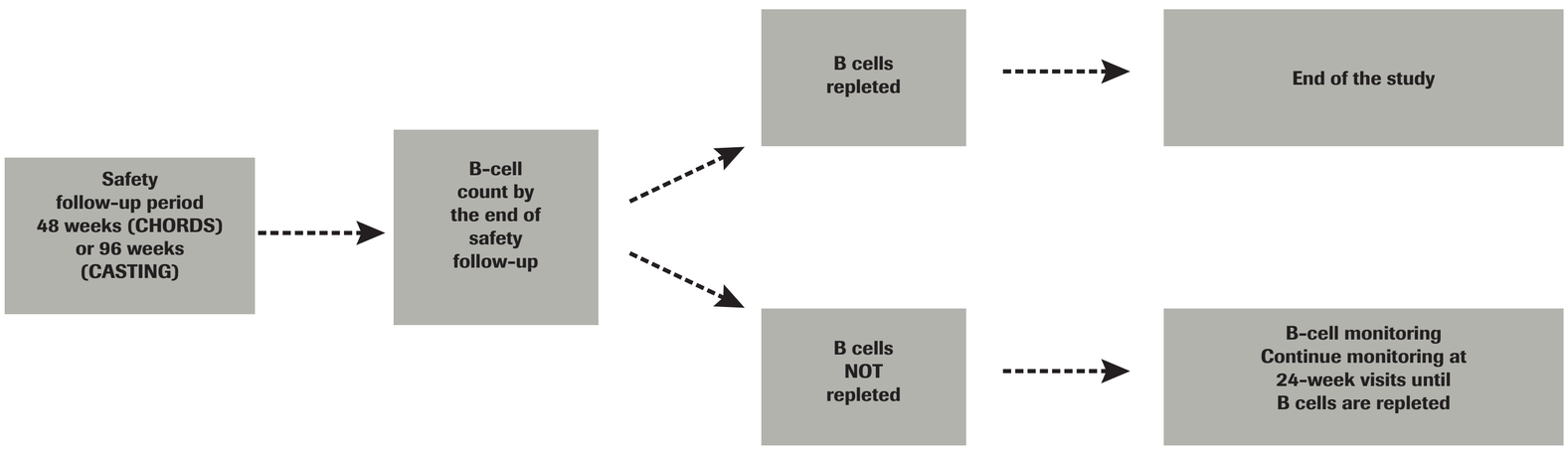




Further assessments to be completed if the patient enters the optional OCR extension period.
[a]Group A split into Groups A1 and A2 at randomisation: all Group A patients receive OCR; [b]Week 12 (Group B) and Week 24 (Groups A1 and A2) immunisation study period assessments to be completed for all patients.

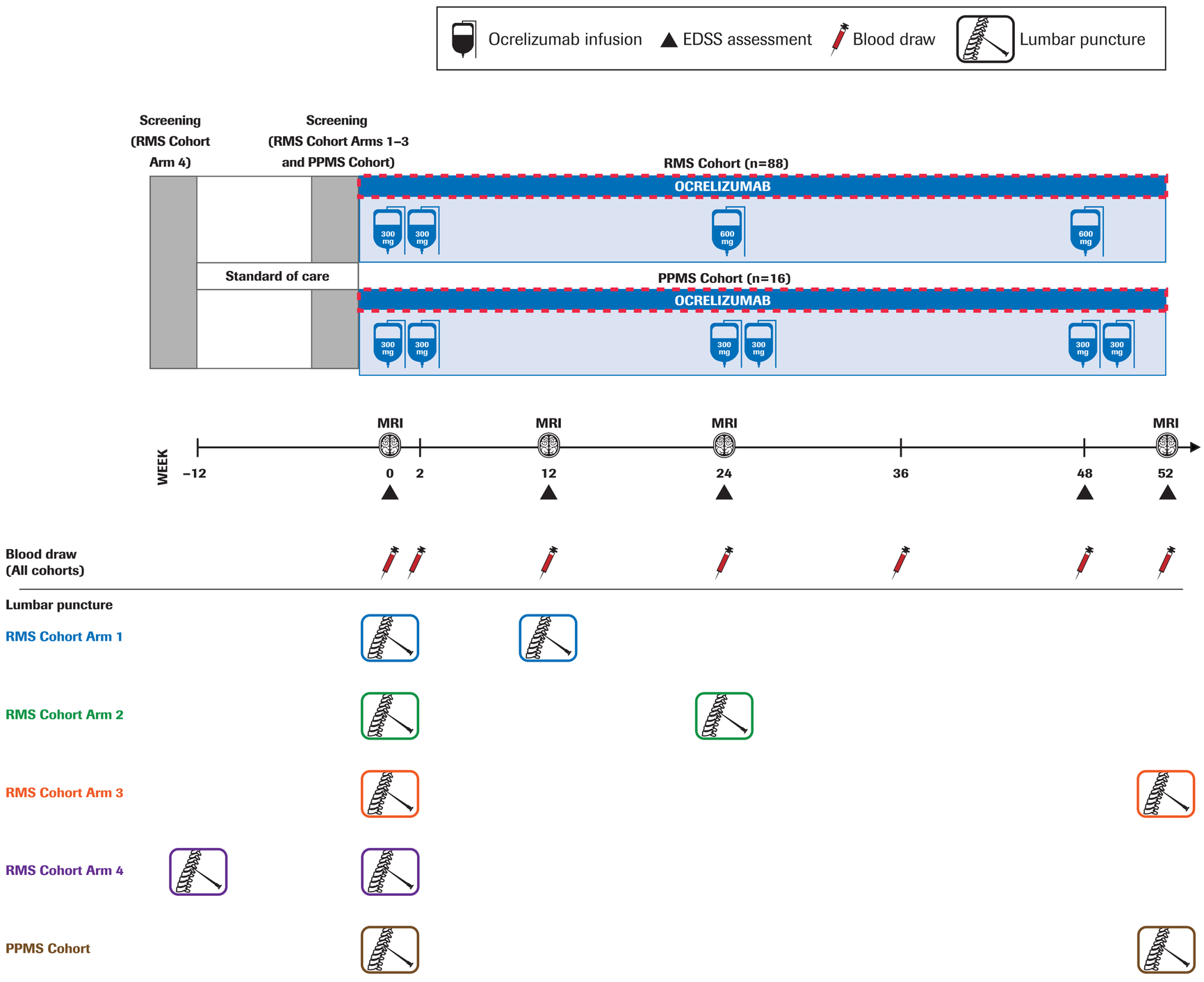
CHORDS (NCT02637856) and CASTING (NCT02861014) studies in patients with RRMS





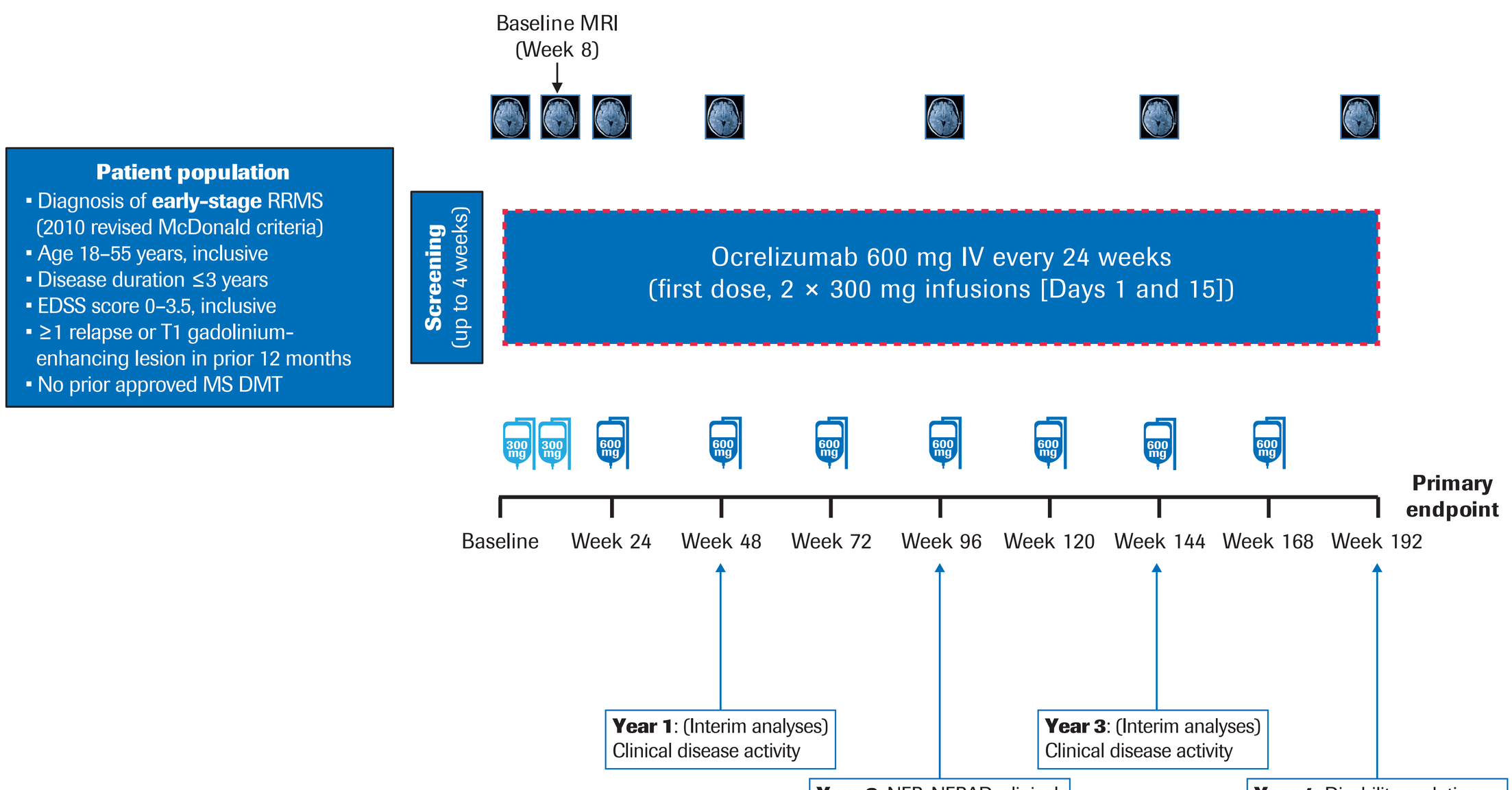
[a]CASTING study only.

OBOE (NCT02688985) study in patients with RMS and PPMS



All patients will receive 100 mg of methylprednisolone (or equivalent IV steroid) approximately 30 minutes before the start of each ocrelizumab infusion. Optional prophylactic treatment with an analgesic/antipyretic and antihistaminic 30–60 minutes prior to each infusion will be offered to all patients.

ENSEMBLE (NCT03085810) study in patients with early-stage RRMS



LIBERTO (NCT03599245) study in patients with MS

BL, baseline; CDP, confirmed disability progression; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; FLAIR, fluid-attenuated inversion recovery; IFN, interferon; IM, intramuscular; IV, intravenous; KLH, keyhole limpet haemocyanin; MRI, magnetic resonance imaging; MS, multiple sclerosis; NEDA, no evidence of disease activity; NEP, no evidence of progression; NEPAD, no evidence of progression or active disease; OCR, ocrelizumab; OLE, open-label extension; PCV, pneumococcal conjugate vaccine; PPMS, primary progressive multiple sclerosis; PPV, pneumococcal polysaccharide vaccine; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SC, subcutaneous; TT, tetanus toxoid.

Table 1. Treatment exposure

Characteristic	Ph II/Ph III and OLEs population (N=2,305)[a]	OCR all-exposure population (N=4,611)[b]
Total PY	11,025	14,329
Number of doses, n (%)[c,d]	**Number of patients exposed**	**Number of patients exposed**
≥1	2,305 (100)	4,611 (100)
≥2	2,199 (95.4)	4,360 (94.6)
≥3	2,144 (93.0)	4,071 (88.3)
≥4	2,046 (88.8)	3,503 (76.0)
≥5	1,930 (83.7)	2,458 (53.3)
≥6	1,878 (81.5)	1,971 (42.7)
≥7	1,817 (78.8)	1,844 (40.0)
≥8	1,663 (72.1)	1,663 (36.1)
≥9	1,609 (69.8)	1,609 (34.9)
≥10	1,404 (60.9)	1,404 (30.4)
Number of doses, mean (SD)	10.2 (4.5)	7.0 (4.6)
Number of doses, median	11.0	5.0
Total cumulative dose, mg		
Mean (SD)	5,893 (2,602)	4,051 (2,657)
Median	6,600	3,000
Range	9–13,000	9–13,000

Doses were administered every 6 months.
[a]Includes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the Phase II and Phase III studies; data from patients who were originally randomised to comparator (IFN β-1a or placebo) are included after the switch to open-label OCR treatment; [b]Includes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the Phase II and Phase III studies, plus VELOCE, CHORDS, CASTING (and associated LTE), OBOE and ENSEMBLE (as of January 2019); [c]If a patient received any infusion in one dose, it was counted as one dose; [d]More than four doses equals more than 2 years' exposure, and more than eight doses equals more than 4 years' exposure.
IFN, interferon; LTE, long-term extension; OCR, ocrelizumab; OLE, open-label extension; Ph, Phase; PY, patient years.

Table 2. Safety profile observed with OCR

Event	OPERA (pooled) controlled treatment period[a]		ORATORIO controlled treatment period[a]		Ph II/Ph III and OLEs population[b]						OCR all-exposure population[c]			
	IFN β-1a rate per 100 PY (95% CI)[d]	OCR rate per 100 PY (95% CI)[d]	Placebo rate per 100 PY (95% CI)[d]	OCR rate per 100 PY (95% CI)[d]	Jan 2016 rate per 100 PY (95% CI)[d]	Feb 2017 rate per 100 PY (95% CI)[d]	Sep 2017 rate per 100 PY (95% CI)[d]	Feb 2018 rate per 100 PY (95% CI)[d]	Jul 2018 rate per 100 PY (95%CI)[d]	Jan 2019 rate per 100 PY (95% CI)[d]	Sep 2017 rate per 100 PY (95%CI)[d]	Feb 2018 rate per 100 PY (95% CI)[d]	Jul 2018 rate per 100 PY (95%CI)[d]	Jan 2019 rate per 100 PY (95% CI)[d]
Total PY	**1,399**	**1,448**	**729**	**1,606**	**5,711**	**7,748**	**8,699**	**9,454**	**10,252**	**11,025**	**9,474**	**10,919**	**12,559**	**14,329**
Any adverse events[e]	**296 (287–305)**	**290 (281–299)**	**259 (247–271)**	**252 (244–260)**	**242 (238–246)**	**226 (222–229)**	**220 (217–223)**	**219 (216–222)**	**217 (214–220)**	**214 (211–217)**	**243 (240–246)**	**242 (239–245)**	**255 (252–258)**	**252 (249–254)**
Adverse events leading to discontinuation[e]	**3.93 (2.96–5.12)**	**2.35 (1.63–3.28)**	**1.10 (0.47–2.16)**	**1.25 (0.76–1.92)**	**1.40 (1.11–1.74)**	**1.24 (1.00–1.51)**	**1.18 (0.97–1.44)**	**1.21 (0.99–1.45)**	**1.18 (0.98–1.41)**	**1.13 (0.94–1.35)**	**1.09 (0.89–1.32)**	**1.06 (0.88–1.27)**	**1.15 (0.97–1.35)**	**1.08 (0.92–1.27)**
Infections and infestations[e]	**67.8 (63.5–72.2)**	**84.5 (79.9–89.4)**	**72.5 (66.5–79.0)**	**70.8 (66.8–75.0)**	**73.6 (71.4–75.9)**	**71.3 (69.5–73.2)**	**70.3 (68.6–72.1)**	**71.5 (69.8–73.2)**	**71.1 (69.4–72.7)**	**71.0 (69.5–72.6)**	**73.1 (71.4–74.8)**	**74.5 (72.9–76.1)**	**77.1 (75.5–78.6)**	**76.7 (75.3–78.2)**
UTI	9.7 (8.1–11.4)	11.6 (9.9–13.5)	17.8 (14.9–21.2)	15.1 (13.2–17.1)	12.3 (11.4–13.2)	12.7 (12.0–13.6)	12.7 (12.0–13.5)	13.0 (12.3–13.7)	13.0 (12.3–13.7)	13.0 (12.3–13.7)	12.8 (12.1–13.5)	12.6 (12.0–13.3)	12.6 (12.0–13.2)	12.4 (11.9–13.0)
Nasopharyngitis[f]	8.3 (6.9–9.9)	13.0 (11.2–15.0)	17.7 (14.8–21.0)	12.8 (11.1–14.6)	11.4 (10.6–12.3)	11.2 (10.5–12.0)	1.2 (1.0–1.5)	11.2 (10.5–11.9)	11.0 (10.4–11.7)	10.8 (10.2–11.5)	1.2 (1.0–1.4)	12.7 (12.0–13.4)	13.5 (12.9–14.2)	13.4 (12.8–14.0)
URTI[f]	9.4 (7.8–11.1)	13.3 (11.5–15.3)	2.9 (1.8–4.4)	5.2 (4.2–6.5)	10.1 (9.3–10.9)	9.8 (9.1–10.5)	9.4 (8.8–10.1)	9.6 (9.0–10.3)	9.6 (9.0–10.2)	9.7 (9.1–10.3)	9.6 (9.0–10.2)	9.8 (9.2–10.4)	10.0 (9.4–10.6)	10.0 (9.5–10.5)
Bronchitis	2.2 (1.5–3.1)	3.5 (2.6–4.6)	2.9 (1.8–4.4)	2.6 (1.9–3.5)	3.4 (2.9–3.9)	3.2 (2.8–3.6)	3.1 (2.8–3.5)	3.2 (2.9–3.6)	3.2 (2.8–3.5)	3.2 (2.9–3.6)	3.1 (2.8–3.5)	3.1 (2.8–3.5)	3.1 (2.8–3.5)	3.1 (2.8–3.4)
Influenza	3.3 (2.4–4.4)	3.1 (2.3–4.2)	3.4 (2.2–5.1)	4.6 (3.6–5.7)	3.1 (2.7–3.6)	3.1 (2.8–3.6)	2.9 (2.6–3.3)	3.1 (2.7–3.4)	3.0 (2.7–3.3)	2.9 (2.6–3.3)	3.1 (2.7–3.5)	3.4 (3.0–3.7)	3.8 (3.4–4.1)	3.7 (3.4–4.1)
Injury, poisoning and procedural complications[e]	**17.1 (15.0–19.4)**	**45.9 (42.4–49.5)**	**36.3 (32.1–41.0)**	**43.5 (40.3–46.8)**	**38.5 (36.9–40.2)**	**33.1 (31.8–34.4)**	**31.5 (30.3–32.7)**	**30.2 (29.1–31.3)**	**29.2 (28.2–30.3)**	**28.2 (27.2–29.2)**	**38.8 (37.6–40.1)**	**37.0 (35.9–38.2)**	**38.7 (37.6–39.8)**	**37.2 (36.2–38.2)**
IRRs	7.9 (6.5–9.5)	34.9 (31.9–38.1)	20.3 (17.2–23.8)	31.0 (28.3–33.9)	28.4 (27.1–29.8)	23.0 (21.9–24.1)	21.5 (20.5–22.4)	20.1 (19.2–21.1)	19.0 (18.1–19.8)	17.9 (17.1–18.7)	28.4 (27.3–29.5)	26.5 (25.6–27.5)	27.5 (26.6–28.5)	26.1 (25.3–26.9)
Nervous system disorders[e]	**34.8 (31.8–38.0)**	**31.6 (28.8–34.7)**	**22.4 (19.1–26.1)**	**22.6 (20.3–25.1)**	**23.7 (22.4–25.0)**	**21.4 (20.4–22.5)**	**20.6 (19.7–21.6)**	**20.1 (19.2–21.0)**	**19.7 (18.8–20.5)**	**19.1 (18.3–19.9)**	**24.2 (23.2–25.2)**	**24.0 (23.1–25.0)**	**25.8 (24.9–26.7)**	**25.5 (24.7–26.3)**
Headache	12.4 (10.6–14.4)	9.5 (8.0–11.3)	6.7 (5.0–8.9)	6.3 (5.1–7.6)	6.4 (5.7–7.1)	5.6 (5.1–6.1)	5.2 (4.8–5.7)	5.0 (4.5–5.4)	4.8 (4.3–5.2)	4.5 (4.2–5.0)	7.0 (6.5–7.6)	7.0 (6.5–7.6)	8.0 (7.5–8.5)	7.9 (7.5–8.4)
Musculoskeletal and connective tissue disorders[e]	**25.0 (22.5–27.8)**	**24.3 (21.8–27.0)**	**31.7 (27.7–36.0)**	**22.8 (20.5–25.3)**	**20.6 (19.5–21.8)**	**19.7 (18.7–20.7)**	**19.3 (18.4–20.3)**	**19.0 (18.1–19.9)**	**18.9 (18.1–19.8)**	**18.7 (17.9–19.5)**	**20.9 (20.0–21.9)**	**20.4 (19.6–21.3)**	**21.6 (20.8–22.4)**	**21.3 (20.5–22.0)**
Back pain	3.1 (2.2–4.1)	4.1 (3.1–5.3)	7.4 (5.6–9.7)	4.8 (3.8–6.0)	3.9 (3.4–4.4)	3.5 (3.1–3.9)	3.4 (3.0–3.8)	3.4 (3.0–3.7)	3.3 (2.9–3.6)	3.2 (2.9–3.6)	3.7 (3.3–4.1)	3.6 (3.3–4.0)	3.7 (3.4–4.1)	3.7 (3.4–4.0)
Arthralgia	3.9 (3.0–5.1)	3.5 (2.6–4.6)	4.3 (2.9–6.0)	3.0 (2.2–4.0)	3.0 (2.6–3.5)	2.9 (2.5–3.3)	2.8 (2.4–3.1)	2.7 (2.4–3.0)	2.6 (2.3–2.9)	2.6 (2.3–2.9)	3.0 (2.7–3.4)	2.9 (2.6–3.2)	3.0 (2.7–3.3)	2.9 (2.6–3.2)
Pain in extremity	2.9 (2.1–4.0)	3.7 (2.7–4.8)	4.7 (3.2–6.5)	2.4 (1.7–3.2)	2.6 (2.2–3.0)	2.4 (2.0–2.7)	2.3 (2.0–2.6)	2.2 (1.9–2.5)	2.2 (1.9–2.5)	2.2 (1.9–2.4)	2.7 (2.4–3.1)	2.5 (2.2–2.8)	2.8 (2.5–3.1)	2.8 (2.5–3.1)
General disorders and administration site conditions[e]	**51.3 (47.6–55.2)**	**17.3 (15.2–19.5)**	**15.6 (12.9–18.8)**	**12.7 (11.0–14.6)**	**12.5 (11.6–13.4)**	**11.1 (10.4–11.9)**	**10.7 (10.0–11.4)**	**10.5 (9.9–11.2)**	**10.4 (9.8–11.1)**	**10.2 (9.6–10.8)**	**12.8 (12.1–13.5)**	**13.0 (12.3–13.7)**	**14.0 (13.3–14.6)**	**13.8 (13.2–14.4)**
Fatigue	5.7 (4.5–7.1)	5.4 (4.3–6.7)	4.4 (3.0–6.2)	1.9 (1.3–2.7)	3.5 (3.0–4.0)	3.2 (2.8–3.6)	3.0 (2.7–3.4)	2.9 (2.6–3.3)	2.8 (2.5–3.2)	2.7 (2.4–3.1)	3.7 (3.3–4.1)	3.8 (3.5–4.2)	4.1 (3.8–4.5)	4.1 (3.7–4.4)
Psychiatric disorders[e]	**14.2 (12.3–16.3)**	**14.4 (12.5–16.5)**	**11.8 (9.4–14.6)**	**7.7 (6.4–9.2)**	**9.5 (8.7–10.3)**	**8.3 (7.7–9.0)**	**7.8 (7.3–8.5)**	**7.6 (7.1–8.2)**	**7.4 (6.9–8.0)**	**7.3 (6.8–7.8)**	**8.6 (8.0–9.2)**	**8.5 (7.9–9.0)**	**8.6 (8.1–9.1)**	**8.5 (8.1–9.0)**
Depression	4.2 (3.2–5.4)	4.9 (3.8–6.2)	5.1 (3.6–7.0)	2.4 (1.7–3.3)	3.2 (2.7–3.7)	2.8 (2.5–3.2)	2.7 (2.4–3.1)	2.6 (2.2–2.9)	2.5 (2.2–2.8)	2.4 (2.1–2.7)	2.8 (2.4–3.1)	2.6 (2.3–3.0)	2.6 (2.3–2.9)	2.5 (2.3–2.8)
Malignancies[e,g,h,i]	**0.14 (0.02–0.52)**	**0.28 (0.08–0.71)**	**0.27 (0.03–0.99)**	**0.93 (0.52–1.54)**	**0.44 (0.29–0.65)**	**0.45 (0.32–0.63)**	**0.51 (0.37–0.68)**	**0.51 (0.38–0.68)**	**0.52 (0.39–0.68)**	**0.51 (0.39–0.67)**	**0.48 (0.35–0.64)**	**0.45 (0.33–0.60)**	**0.47 (0.36–0.61)**	**0.46 (0.35–0.58)**
Serious adverse events[e]	**6.29 (5.05–7.75)**	**5.39 (4.26–6.72)**	**12.07 (9.68–14.87)**	**10.15 (8.65–11.83)**	**6.97 (6.30–7.69)**	**7.18 (6.59–7.80)**	**7.42 (6.85–8.01)**	**7.65 (7.10–8.23)**	**7.93 (7.39–8.49)**	**7.84 (7.32–8.38)**	**7.29 (6.76–7.86)**	**7.23 (6.73–7.75)**	**7.52 (7.05–8.02)**	**7.33 (6.89–7.79)**
Serious infections[j]	1.79 (1.16–2.64)	0.83 (0.43–1.45)	3.02 (1.89–4.57)	2.74 (1.99–3.68)	1.80 (1.47–2.19)	1.86 (1.57–2.19)	2.01 (1.73–2.33)	2.14 (1.85–2.45)	2.21 (1.94–2.52)	2.21 (1.94–2.51)	1.96 (1.69–2.27)	2.00 (1.74–2.28)	2.01 (1.77–2.27)	1.99 (1.77–2.23)
No. of potential serious OIs[k]	0	0	0	0	0	0	1	2	5	5	1	2	6	6
Fatalities[e]	**0.14 (0.02–0.52)**	**0.07 (0–0.38)**	**0.41 (0.08–1.20)**	**0.25 (0.07–0.64)**	**0.14 (0.06–0.28)**	**0.17 (0.09–0.29)**	**0.18 (0.11–0.30)**	**0.18 (0.11–0.29)**	**0.19 (0.11–0.29)**	**0.19 (0.12–0.29)**	**0.17 (0.10–0.27)**	**0.16 (0.09–0.25)**	**0.15 (0.09–0.24)**	**0.16 (0.10–0.24)**

[a]Includes patients who received placebo or IFN β-1a during the controlled treatment period of the Phase III studies; [b]Includes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the Phase II and Phase III studies; data from patients who were originally randomised to comparator (IFN β-1a or placebo) are included after the switch to open-label OCR treatment; [c]Includes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the Phase II and Phase III studies, plus the ongoing Phase IIIb trials VELOCE, CHORDS, CASTING and OBOE (September 2017 and February 2018), and ENSEMBLE (July 2018) and LTE (January 2019); data from patients who were originally randomised to comparator (IFN β-1a or placebo) are included after the switch to open-label OCR treatment; [d]Multiple occurrences of the same adverse event (except for malignancies[h]) in one patient are counted multiple times; [e]Includes adverse events falling into the MedDRA versions 18.0, 18.1, 19.1, 20.0, 20.1, 21.0 and 21.1; [f]Common cold was linked to PT Viral upper respiratory tract infection in September 2017 outputs using MedDRA version 20.0. It was linked to PT Nasopharyngitis in other outputs using other MedDRA versions; [g]Malignancies are identified using adverse events falling into the standard MedDRA query 'Malignant tumours (narrow)'; [h]From January 2016, multiple occurrences of the same adverse event in one patient are counted only once; [i]From January 2016, for patients with malignancies, exposure in PY was calculated from first treatment to onset of first malignancy; [j]Serious infections are defined using adverse events falling into the MedDRA SOC Infections and infestations, and using 'Is the event non-serious or serious?' from the adverse event case report form; [k]Potential serious OIs were medically reviewed.

IFN, interferon; IRR, infusion-related reaction; LTE, long-term extension; MedDRA, Medical Dictionary for Regulatory Authorities; OCR, ocrelizumab; OI, opportunistic infection; OLE, open-label extension; Ph, Phase; PT, preferred term; PY, patient years; SOC, system organ class; URTI, upper respiratory tract infection; UTI, urinary tract infection.

Table 3. Cumulative reasons for discontinuations

	OCR all-exposure population (N=4,611)[a]		
	Number of AEs	AEs per 100 PY	95% CI
AEs leading to treatment discontinuation	**155**	**1.08**	**0.92–1.27**
IRRs[b]	30	0.21	0.14–0.30
Neoplasms benign, malignant and unspecified[c]	28	0.20	0.13–0.28
Infections and infestations[c]	27	0.19	0.12–0.27
SAEs leading to treatment discontinuation	**70**	**0.49**	**0.38–0.62**
IRRs leading to discontinuation at first infusion	**22**	**0.15**	**0.10–0.23**

Investigator text for adverse events was encoded using MedDRA version 21.1. Multiple occurrences of the same adverse event in one patient are counted multiple times.
[a]Includes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the Phase II and Phase III studies, plus VELOCE, CHORDS, CASTING (and associated LTE), OBOE and ENSEMBLE (as of January 2019); [b]Preferred term within MedDRA version 21.1 SOC term Injury, poisoning and procedural complications; [c]MedDRA version 21.1 SOC term.
AE, adverse event; IRR, infusion-related reaction; LTE, long-term extension; MedDRA, Medical Dictionary for Regulatory Activities; OCR, ocrelizumab; OLE; open-label extension; PY, patient years; SAE, serious adverse event; SOC, system organ class.

Table 4. AEs leading to discontinuations

MedDRA SOC MedDRA preferred term	OCR all-exposure population (N=4,611)[a]
Total number of patients with at least one adverse event	**141 (3.1%)**
Total number of events	**155**
Injury, poisoning, and procedural complications	
Total number of patients with at least one adverse event	31 (0.7%)
Total number of events	32
Infusion-related reaction	29 (0.6%)
Lumbar vertebral fracture	1 (<0.1%)
Subdural haematoma	1 (<0.1%)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)[b]	
Total number of patients with at least one adverse event	28 (0.6%)
Total number of events	28
Invasive ductal breast carcinoma[b]	7 (0.2%)
Breast cancer[b]	4 (<0.1%)
Invasive breast carcinoma[b]	1 (<0.1%)
Malignant melanoma	3 (<0.1%)
Adenocarcinoma of colon	1 (<0.1%)
Anaplastic large-cell lymphoma	1 (<0.1%)
Chondrosarcoma	1 (<0.1%)
Endometrial adenocarcinoma	1 (<0.1%)
Endometrial cancer	1 (<0.1%)
Lung neoplasm malignant	1 (<0.1%)
Malignant fibrous histiocytoma	1 (<0.1%)
Metastatic malignant melanoma	1 (<0.1%)
Papillary thyroid cancer	1 (<0.1%)
Prostate cancer	1 (<0.1%)
Renal cell carcinoma	1 (<0.1%)
Squamous cell carcinoma	1 (<0.1%)
Transitional cell carcinoma	1 (<0.1%)
Infections and infestations	
Total number of patients with at least one adverse event	23 (0.5%)
Total number of events	27
Urinary tract infection	3 (<0.1%)
Cellulitis	2 (<0.1%)
Herpes zoster	2 (<0.1%)
Infection	2 (<0.1%)
Acute hepatitis C	1 (<0.1%)
Anal abscess	1 (<0.1%)
Coccidioidomycosis	1 (<0.1%)
Infectious colitis	1 (<0.1%)
Latent tuberculosis	1 (<0.1%)
Mastoiditis	1 (<0.1%)
Nasopharyngitis	1 (<0.1%)
Oesophageal candidiasis	1 (<0.1%)
Oesophageal bacterial	1 (<0.1%)
Oral bacterial infections	1 (<0.1%)
Periodontitis	1 (<0.1%)
Pneumonia	1 (<0.1%)
Pulmonary tuberculoma	1 (<0.1%)
Sepsis	1 (<0.1%)
Septic shock	1 (<0.1%)
Superinfection fungal	1 (<0.1%)
Viral infection	1 (<0.1%)
Psychiatric disorders	
Total number of patients with at least one adverse event	11 (0.2%)
Total number of events	14
Anxiety	2 (<0.1%)
Completed suicide	2 (<0.1%)
Depression	2 (<0.1%)
Delusion	1 (<0.1%)
Hallucination	1 (<0.1%)
Insomnia	1 (<0.1%)
Mental disorder	1 (<0.1%)
Paranoia	1 (<0.1%)
Psychotic disorder	1 (<0.1%)
Suicidal ideation	1 (<0.1%)
Suicide attempt	1 (<0.1%)
Skin and subcutaneous tissue disorders	
Total number of patients with at least one adverse event	10 (0.2%)
Total number of events	11
Rash	2 (<0.1%)
Alopecia	1 (<0.1%)
Decubitus ulcer	1 (<0.1%)
Dermatitis allergic	1 (<0.1%)
Dermatitis bullous	1 (<0.1%)
Erythema nodosum	1 (<0.1%)
Guttate psoriasis	1 (<0.1%)
Interstitial granulomatous dermatitis	1 (<0.1%)
Skin lesion	1 (<0.1%)
Gastrointestinal disorders	
Total number of patients with at least one adverse event	8 (0.2%)
Total number of events	8
Crohn's disease	3 (<0.1%)
Colitis	1 (<0.1%)
Colitis ulcerative	1 (<0.1%)
Diarrhoea	1 (<0.1%)
Enterocolitis	1 (<0.1%)
Gastritis	1 (<0.1%)
General disorders and administration site conditions	
Total number of patients with at least one adverse event	8 (0.2%)
Total number of events	8
Fatigue	2 (<0.1%)
Pyrexia	2 (<0.1%)
Asthenia	1 (<0.1%)
Chest pain	1 (<0.1%)
Chills	1 (<0.1%)
Influenza-like illness	1 (<0.1%)
Nervous system disorders	
Total number of patients with at least one adverse event	5 (0.1%)
Total number of events	6
Multiple sclerosis relapse	2 (<0.1%)
Headache	1 (<0.1%)
Hydrocephalus	1 (<0.1%)
Optic neuritis	1 (<0.1%)
Speech disorder	1 (<0.1%)
Musculoskeletal and connective tissue disorders	
Total number of patients with at least one adverse event	4 (<0.1%)
Total number of events	4
Muscle rigidity	1 (<0.1%)
Osteonecrosis	1 (<0.1%)
Pain in extremity	1 (<0.1%)
Psoriatic arthropathy	1 (<0.1%)
Hepatobiliary disorders	
Total number of patients with at least one adverse event	3 (<0.1%)
Total number of events	3
Hepatitis	1 (<0.1%)
Hepatitis fulminant	1 (<0.1%)
Portal vein thrombosis	1 (<0.1%)
Metabolism and nutrition disorders	
Total number of patients with at least one adverse event	3 (<0.1%)
Total number of events	3
Diabetes mellitus, inadequate control	1 (<0.1%)
Hypoproteinaemia	1 (<0.1%)
Lactic acidosis	1 (<0.1%)
Cardiac disorders	
Total number of patients with at least one adverse event	2 (<0.1%)
Total number of events	2
Aortic valve incompetence	1 (<0.1%)
Congestive cardiomyopathy	1 (<0.1%)
Investigations	
Total number of patients with at least one adverse event	2 (<0.1%)
Total number of events	2
CD4 lymphocytes decreased	1 (<0.1%)
Neutrophil count decreased	1 (<0.1%)
Respiratory, thoracic and mediastinal disorders	
Total number of patients with at least one adverse event	2 (<0.1%)
Total number of events	2
Dysphonia	1 (<0.1%)
Sinus congestion	1 (<0.1%)
Blood and lymphatic system disorders	
Total number of patients with at least one adverse event	1 (<0.1%)
Total number of events	1
Lymphocytosis	1 (<0.1%)
Ear and labyrinth disorders	
Total number of patients with at least one adverse event	1 (<0.1%)
Total number of events	1
Vertigo	1 (<0.1%)
Immune system disorders	
Total number of patients with at least one adverse event	1 (<0.1%)
Total number of events	1
Hypersensitivity	1 (<0.1%)
Pregnancy, puerperium and perinatal conditions	
Total number of patients with at least one adverse event	1 (<0.1%)
Total number of events	1
Abortion spontaneous	1 (<0.1%)
Reproductive system and breast disorders	
Total number of patients with at least one adverse event	1 (<0.1%)
Total number of events	1
Metrorrhagia	1 (<0.1%)

Investigator text for adverse events was encoded using MedDRA version 21.1.
Percentages are based on N. For frequency counts by preferred term, multiple occurrences of the same adverse event in one patient are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same adverse event in one patient are counted separately. Non-serious relapses are excluded.
[a]Includes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the Phase II and Phase III studies, plus VELOCE, CHORDS, CASTING (and associated LTE), ORIOE and ENSEMBLE (as of January 2019); [b]Total number of breast cancer events leading to discontinuation: 12; total number of breast cancer events: 16 (3 cases occurred after treatment discontinuation related to pregnancy or other AEs; 1 patient remains on treatment).
AE, adverse event; LTE, long-term extension; MedDRA, Medical Dictionary for Regulatory Activities; OCR, ocrelizumab; OLE, open-label extension; SOC, system organ class.

Table 6. Yearly incidence rates per 100 patient years of all malignancies

OCR all-exposure population[a]	PY	Number of AEs	AEs per 100 PY (95% CI)
Year 1 (N=4,611)	4,357	12	0.28 (0.14–0.48)
Year 2 (N=3,870)	3,290	15	0.46 (0.26–0.75)
Year 3 (N=2,234)	2,048	14	0.68 (0.37–1.15)
Year 4 (N=1,835)	1,696	10	0.59 (0.28–1.08)
Year 5 (N=1,542)	1,267	7	0.55 (0.22–1.14)
Year 6 (N=1,106)	991	6	0.61 (0.22–1.32)

Investigator text for adverse events was encoded using MedDRA version 21.1. Malignancies are identified using adverse events falling into the standard MedDRA query 'Malignant tumours (narrow)'. For patients with malignancies, PYs are calculated from first treatment to onset of first malignancy event.

[a]Includes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the Phase II and Phase III studies, plus VELOCE, CHORDS, CASTING (and associated LTE), OBOE and ENSEMBLE (as of January 2019).

AE, adverse event; LTE, long-term extension; MedDRA, Medical Dictionary for Regulatory Activities; OCR, ocrelizumab; OLE, open-label extension; PY, patient years.

Table 7. Yearly incidence rates per 100 patient years of female breast cancer

OCR all-exposure population[a]	PY	Number of AEs	AEs per 100 PY (95% CI)
Year 1 (N=2,939)	2,782	1	0.04 (0–0.20)
Year 2 (N=2,474)	2,078	7	0.34 (0.14–0.69)
Year 3 (N=1,369)	1,241	5	0.40 (0.13–0.94)
Year 4 (N=1,106)	1,021	2	0.20 (0.02–0.71)
Year 5 (N=921)	749	1	0.13 (0–0.74)
Year 6 (N=643)	575	0	0 (0–0.64)

Investigator text for adverse events was encoded using MedDRA version 21.1. Breast cancer is identified using adverse events falling into the standard MedDRA query 'Breast malignant tumours (narrow)'. For patients with malignancies, PYs are calculated from first treatment to onset of first malignancy event.

[a]Includes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the Phase II and Phase III studies, plus VELOCE, CHORDS, CASTING (and associated LTE), OBOE and ENSEMBLE (as of January 2019).

AE, adverse event; LTE, long-term extension; MedDRA, Medical Dictionary for Regulatory Activities; OCR, ocrelizumab; OLE, open-label extension; PY, patient years.