

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 registry⁴) and the general population (National Cancer Institute [NCI] Surveillance, Epidemiology, and End Results [SEER] database⁵)
- 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 2018⁶
 - 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 database⁵ and Danish MS registry⁴ 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 ^a	OCR all-exposure population ^a
	IFN β -1a rate per 100 PY (95% CI) ^a	OCR rate per 100 PY (95% CI) ^a	Placebo rate per 100 PY (95% CI) ^a	OCR rate per 100 PY (95% CI) ^a	Jan 2019 rate per 100 PY (95% CI) ^{a,*}	Jan 2019 rate per 100 PY (95% CI) ^{a,*}
Total PY	1,399	1,448	729	1,606	11,025	14,329
Any adverse events ^b	296 (287–305)	290 (281–299)	259 (247–271)	252 (244–260)	214 (211–217)	252 (248–254)
Adverse events leading to treatment discontinuation ^b	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 ^b	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)	11.9 (9.9–13.5)	17.6 (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 (3.8–5.7)	2.9 (2.6–3.3)	3.7 (3.4–4.1)
Injury, poisoning, and procedural complications ^b	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 ^b	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 ^b	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 ^b	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 ^b	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 ^b	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 ^{c,d,e}	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 ^b	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 ^b	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 ^b	0	0	0	0	5	6
Fatalities ^b	0.14 (0.02–0.52)	0.07 (0.0–0.38)	0.41 (0.08–1.20)	0.25 (0.07–0.64)	0.19 (0.12–0.29)	0.16 (0.10–0.24)

^aIncludes patients who received placebo or IFN β -1a during the controlled treatment period of the Phase II studies. ^bIncludes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the Phase II and Phase III studies, plus patients who were originally randomised to comparator (IFN β -1a or placebo) but switched to OCR treatment after the switch to open-label OCR treatment. ^cIncludes 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. ^dData from patients who were originally randomised to comparator (IFN β -1a or placebo) but switched to OCR treatment. ^eMultiple occurrences of the same adverse event (except for malignancies) in one patient are counted multiple times. ^fRate per 100 PY (95% CI) as of January 2019. ^gIncludes adverse events falling into the MedDRA versions 18.1, 18.1 and 21.1. ^hMalignancies are identified using adverse events falling into the standard MedDRA query “Malignant tumours (primary)”. ⁱFrom January 2016, multiple occurrences of the same adverse event in one patient are counted only once. ^jFrom January 2016, for patients with malignancies, exposure in PY was calculated from first treatment to onset of first malignancy. ^kSerious infections are defined using adverse events falling into the MedDRA SOC infections and infestations, and using the event non-serious or serious^h from the adverse event case report form. ^lPotential serious OIs were medically reviewed.

Infections and Serious Infections

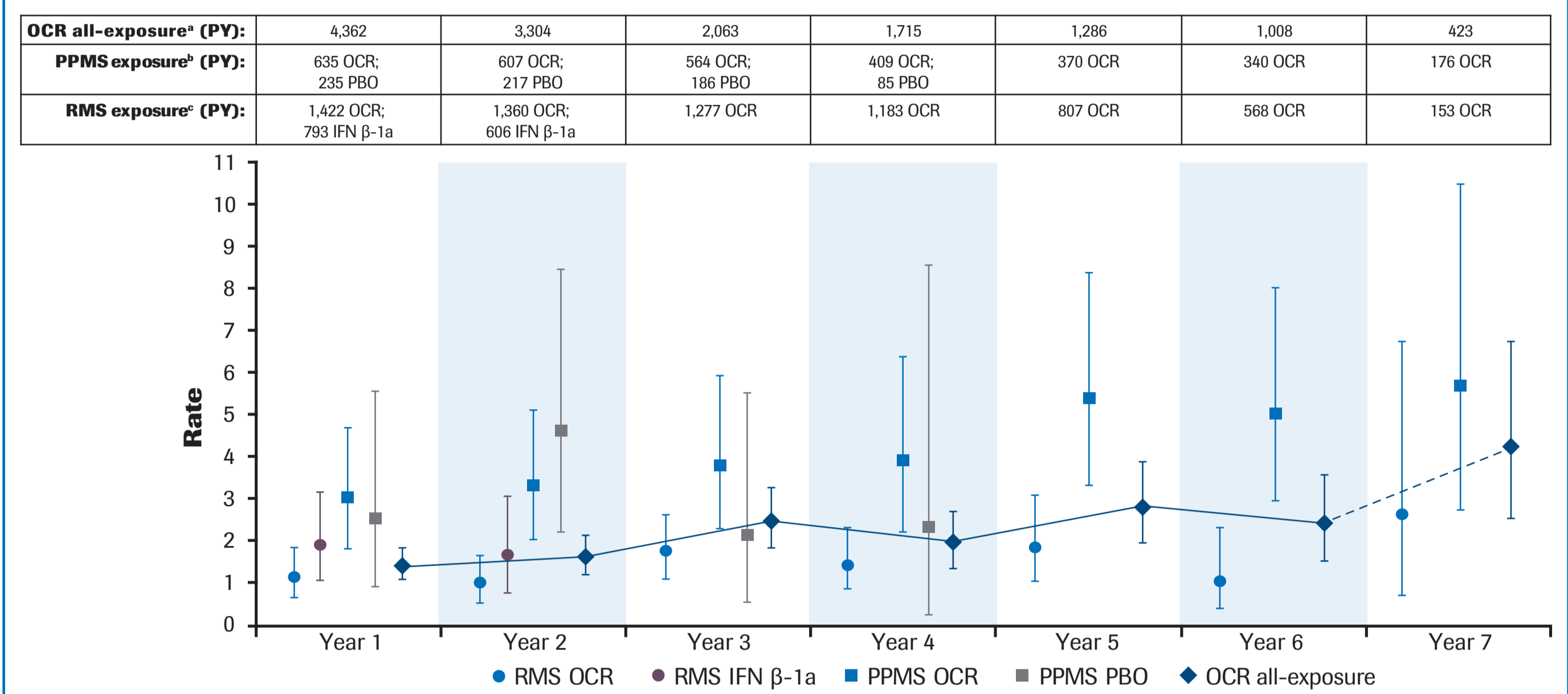
- As of January 2019, the rate of infections was 76.7 (95% CI 75.3–78.2) per 100 PY in the OCR all-exposure population (**Table 2**), consistent with the rate observed at the primary analysis cut-off date
- The most common serious infections were UTIs and pneumonia

DISCLOSURES

SL Hauser serves on the board of trustees for Neurona and on scientific advisory boards for Alektor, Annexon, Bionore, 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, Akkermis, Almiral, Bayer, Biogen, Celgene/Receptos, d-mip, Excerpt, GenSuro SA, Genzyme, Japan Tobacco, Merck, Minoryx, Mitsubishi Pharma, Novartis, Roche, Sanofi-Aventis, Santhera, Teva and Vianex, and royalties for Neurostatus-URB 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. 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, Akkermis, Biogen, Biomed, Celgene, Celine Nanomedicine, EMD Serono, Forward Pharma A/S, GenSuro, MedDay Pharmaceuticals, Novartis, Otsuka, PTC Therapeutics, Roche/Genentech and Sanofi Genzyme; royalties are received for outlicensed monoclonal antibodies through UTHealth from Millipore Corporation.

- 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



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 test 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 the event non-serious or serious^h 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. ^aIncludes 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. ^bIncludes 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. ^cIncludes 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. ^dIFN, 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 (monodermatoma) 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**)

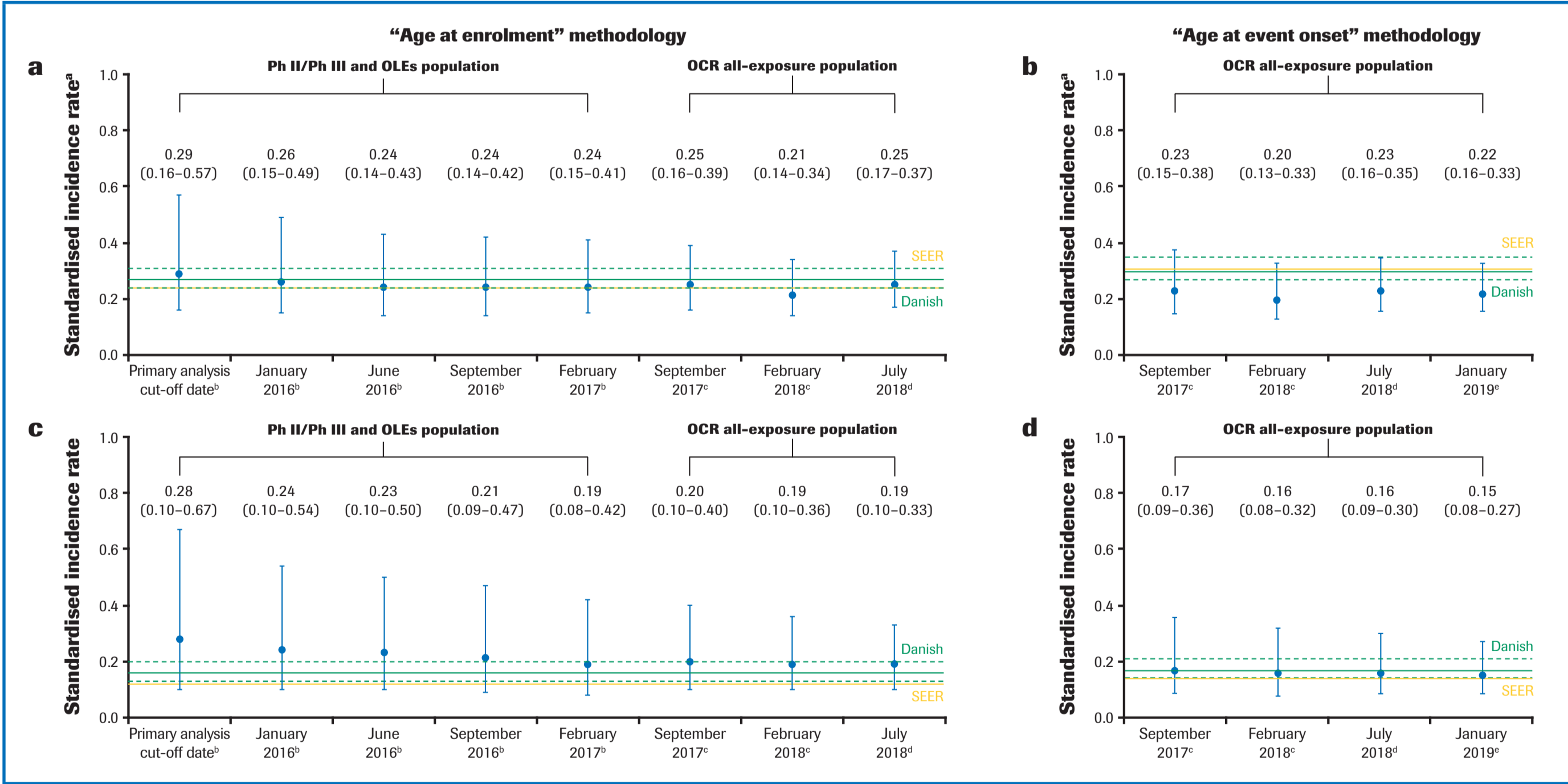
Malignancies and Female Breast Cancer

- 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: 15–84 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 (0.27–0.33). Standardised incidence rate (95% CI) for panel c: SEER: 0.12 (0.12–0.12); Danish MS registry: 0.16 (0.13–0.20). Standardised incidence rate (95% CI) for panel d: SEER: 0.16 (0.16–0.16); Danish MS registry: 0.17 (0.14–0.21). ^aNMSC is not reported in SEER. ^bIncludes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the Phase II and Phase III studies. ^cIncludes 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 OBOE. ^dIncludes 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. ^eIncludes 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.

Table 5. Standardised incidence rates 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. ^aIncludes 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. ^bIncidence rate is calculated based on the age at event onset. ^cNMSC 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

ACKNOWLEDGEMENTS

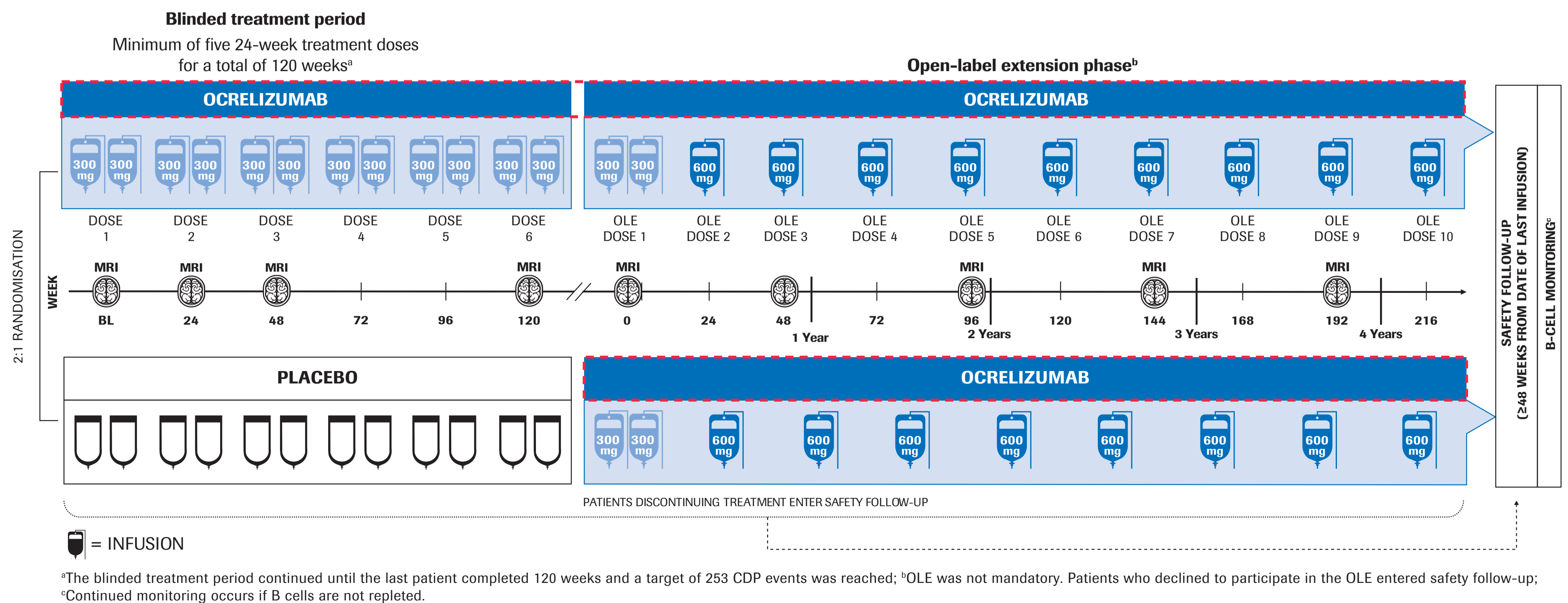
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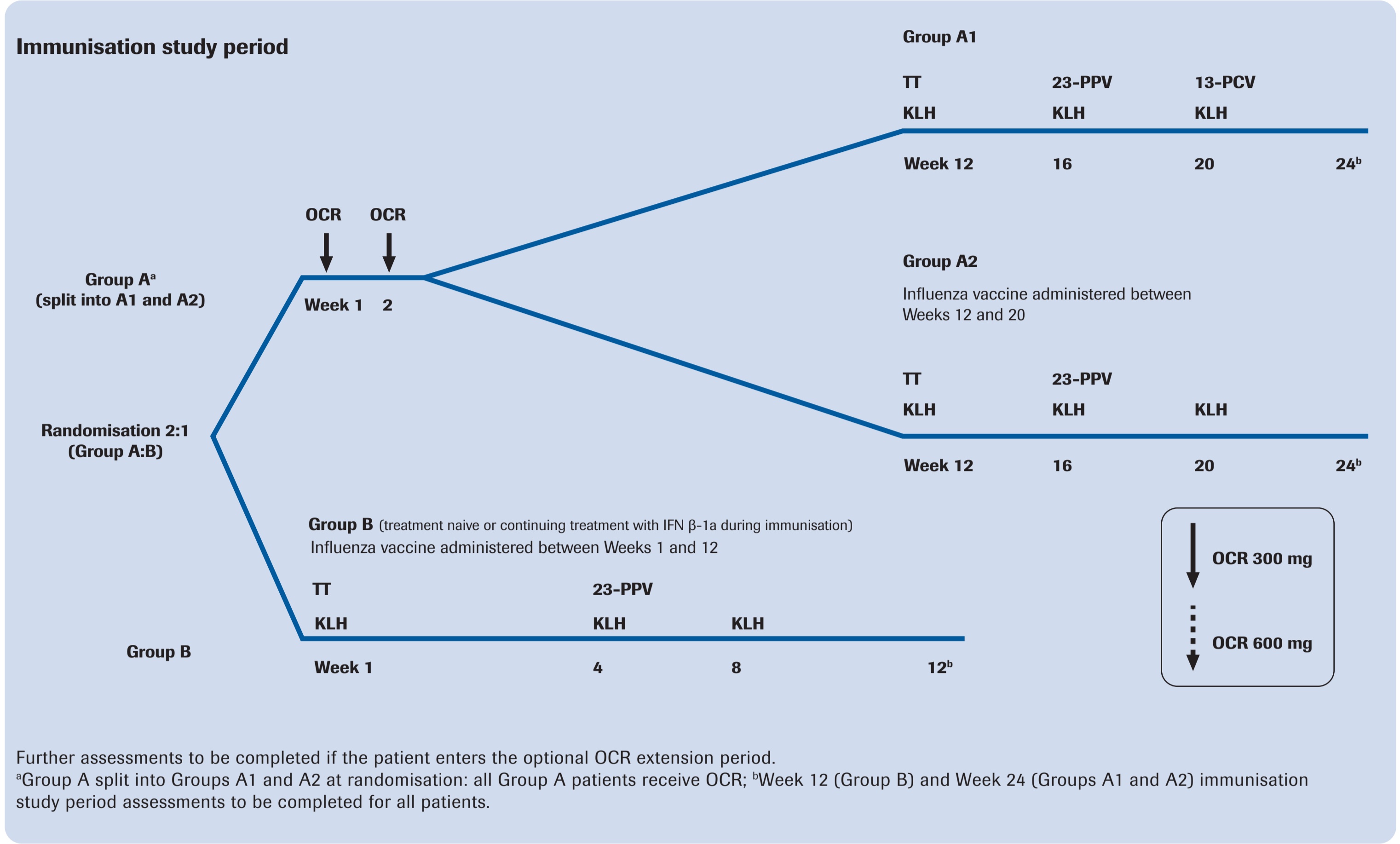
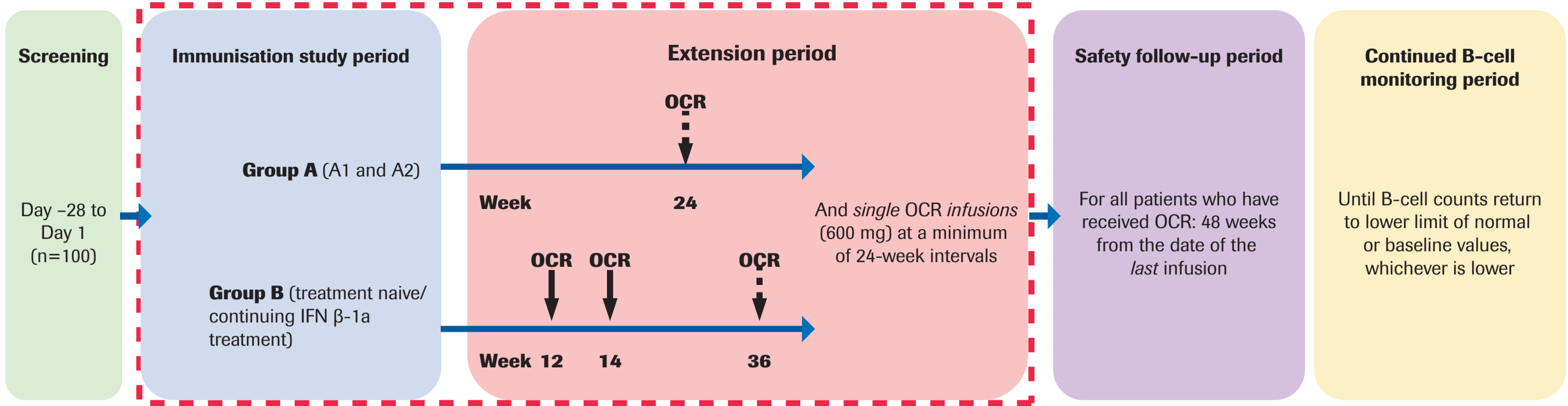
Phase II (NCT00676715) study of ocrelizumab in patients with RRMS

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

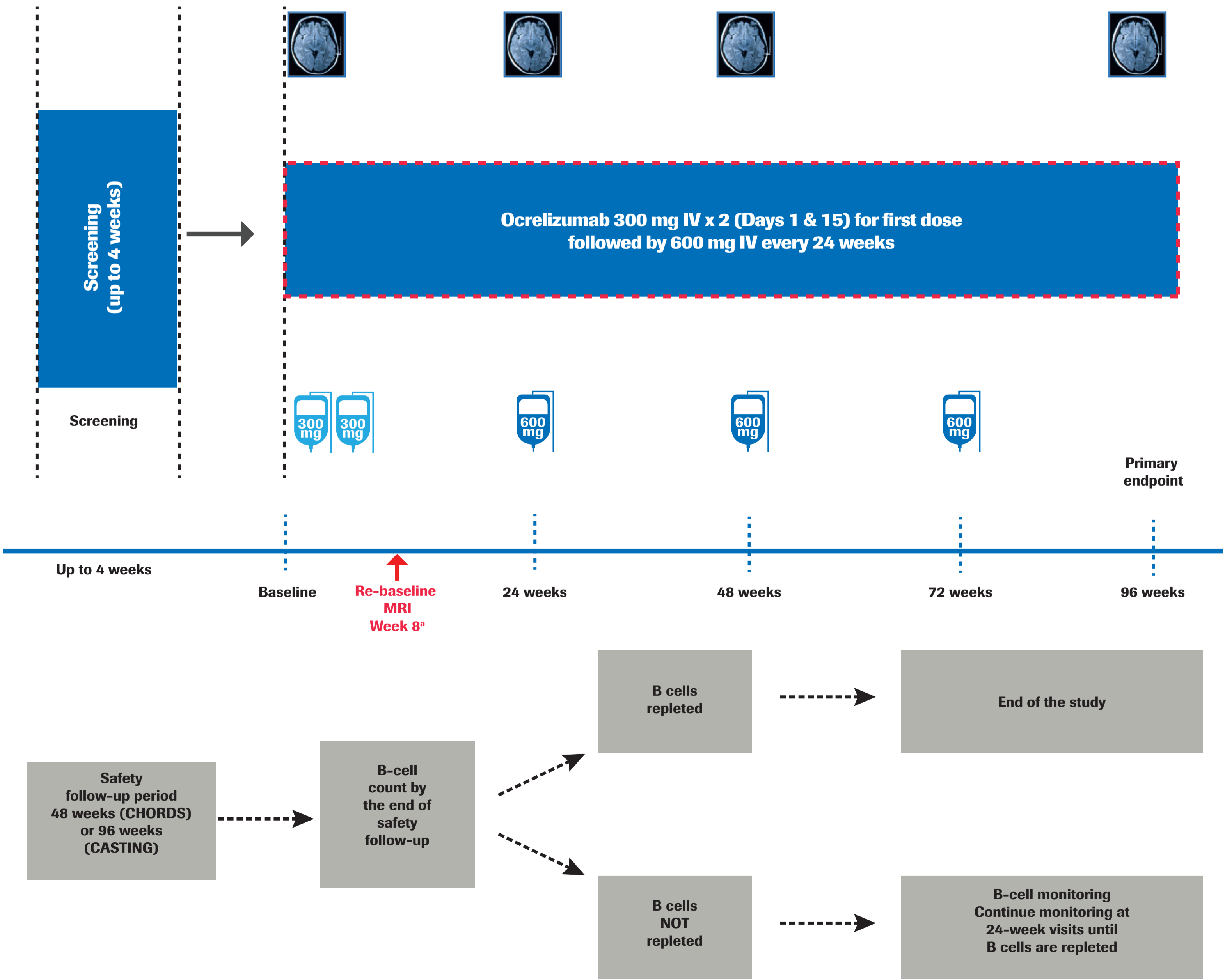


VELOCE (NCT02545868) study in patients with RMS

OCR all-exposure population

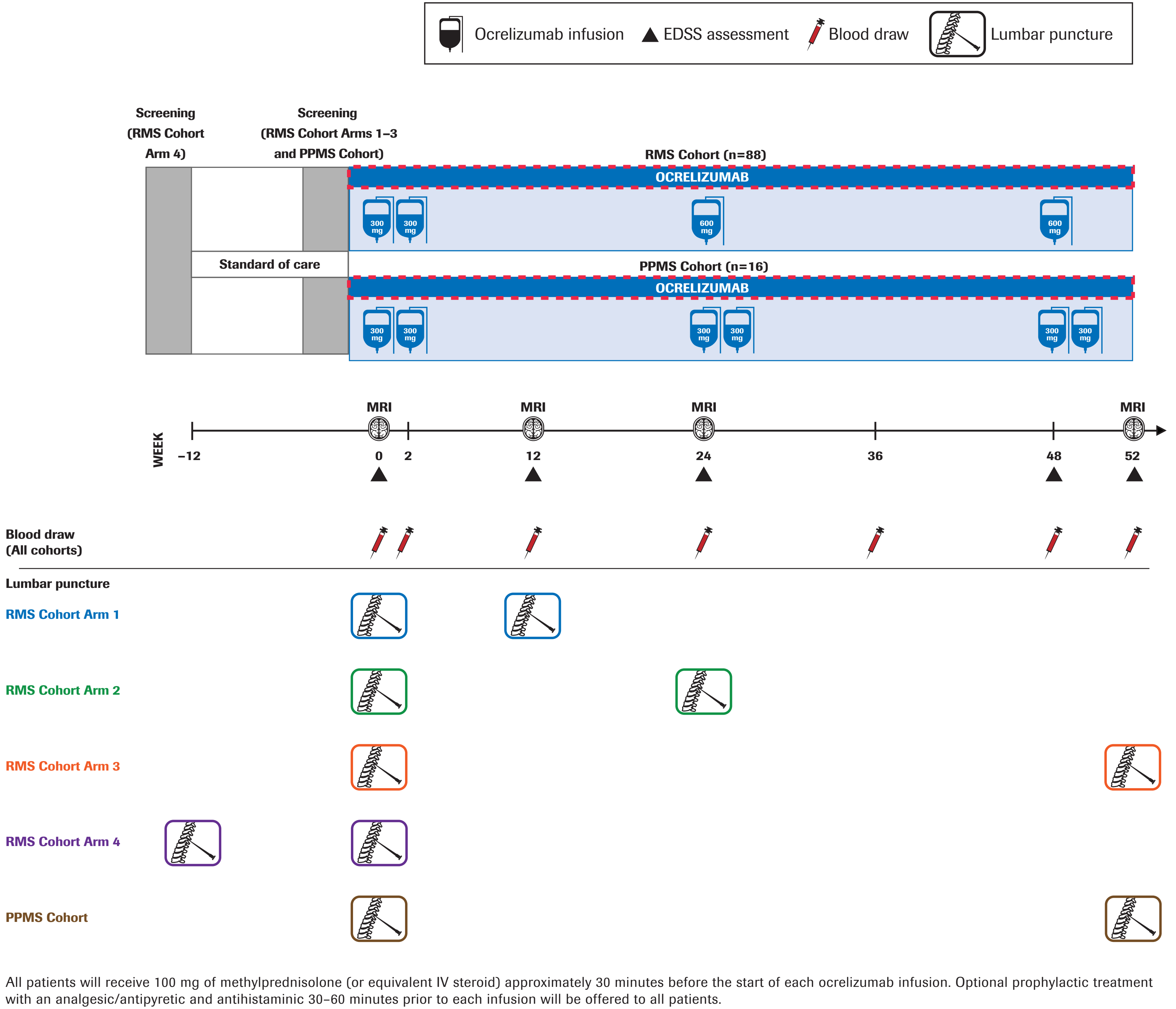


CHORDS (NCT02637856) and CASTING (NCT02861014) studies in patients with RRMS



^aCASTING study only.

OBOE (NCT02688985) study in patients with RMS and PPMS



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

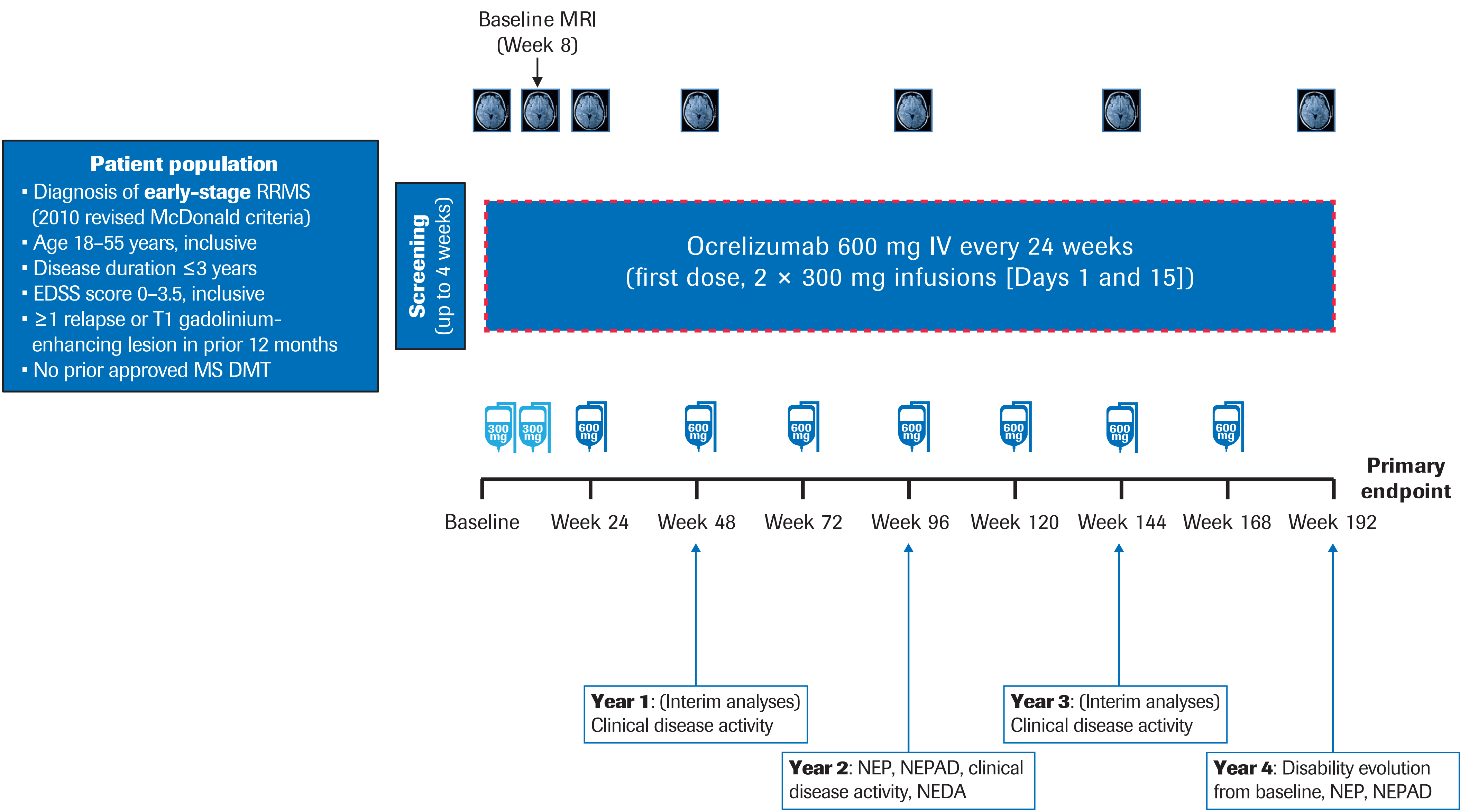


Table 1. Treatment exposure

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.

^aIncludes 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; ^bIncludes 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); ^cIf a patient received any infusion in one dose, it was counted as one dose; ^dMore 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)

^aIncludes patients who received placebo or IFN β-1a during the controlled treatment period of the Phase III studies; ^bIncludes 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; ^cIncludes 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; ^dMultiple occurrences of the same adverse event (except for malignancies^b) in one patient are counted multiple times; ^eIncludes adverse events falling into the MedDRA versions 18.0, 18.1, 19.1, 20.0, 20.1, 21.0 and 21.1; ^fCommon 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; ^gMalignancies are identified using adverse events falling into the standard MedDRA query ‘Malignant tumours (narrow)’; ^hFrom January 2016, multiple occurrences of the same adverse event in one patient are counted only once; ⁱFrom January 2016, for patients with malignancies, exposure in PY was calculated from first treatment to onset of first malignancy; ^jSerious 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; ^kPotential 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
IRR ^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.
^aIncludes 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); ^bPreferred term within MedDRA version 21.1 SOC term Injury, poisoning and procedural complications; ^cMedDRA 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 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.

^aIncludes 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.

^aIncludes 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.