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

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BACKGROUND

- The safety and efficacy of ocrelizumab (OCR) have been characterized 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]
  - Serious AEs, serious infections and malignancies were reported in 7.0%, 1.3% and 0.5% of OCR-treated patients, respectively (vs 8.8%, 2.9% and 0.2% of patients treated with IFN β-1a), during the double-blind treatment period in the pooled Phase III RMS population;[2] in the Phase III PPMS population, these events were reported in 20.4%, 6.2% and 2.3% of OCR-treated patients, respectively (vs 22.2%, 5.9% and 0.8% of patients treated with placebo)[3]
  - Few patients had AE-related treatment withdrawals (approximately 2–4%) with OCR across studies[1–3]
- In the Phase III multiple sclerosis (MS) clinical trial program, 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

OBJECTIVE

- To report ongoing safety evaluations from OCR clinical trials and associated open-label extension (OLE) periods up to September 2017

METHODS

- Details of the MS clinical trial study designs have been previously reported (**Figure 1**)[1–3]
- Safety analyses are based on integrated data for all patients who received OCR in the following MS clinical trials, as of September 2017 (OCR all-exposure population):
  - The Phase II and Phase III MS clinical trials and associated OLE periods, in which they received OCR (Ph II/Ph III and OLEs population)
    - The primary analysis was 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)
  - VELOCE: Effect of OCR on immune responses in patients with RMS
  - CHORDS/CASTING: Study of OCR in patients with RRMS with suboptimal response to disease-modifying treatment (USA/Europe)
  - OBOE (clinical cut-off date: June 2017): Mechanism of action of OCR and B-cell biology in patients with RMS or PPMS
- To account for the different exposure lengths among the controlled and associated open-label periods of the Phase II and Phase III studies, and additional ongoing studies described above, the rate per 100 patient years (PY) is presented for OCR vs comparator (IFN β-1a or placebo)
  - The crude incidence rate of first malignancy (number of first malignancy events per 100 PY) was calculated

For study designs (Figure 1), please scan here

RESULTS

Baseline Patient Characteristics and Treatment Exposure

- As of September 2017, 3,778 patients with MS received OCR in the OCR all-exposure population, resulting in 9,474 PY of exposure (**Table 1**)
  - Data on disease duration were collected on study entry, and remain unchanged

Table 1. Exposure to ocrelizumab (data cut-off: September 2017)

Characteristic	Ph II/Ph III and OLEs population (N=2,304)[a]	OCR all-exposure population (N=3,778)[b]
Total patient years	8,699	9,474
Number of doses, n (%)[c,d]	**Number of patients exposed**	**Number of patients exposed**
≥1	2,304 (100)	3,778 (100)
≥2	2,194 (95.2)	3,271 (86.6)
≥3	2,138 (92.8)	2,373 (62.8)
≥4	2,031 (88.2)	2,078 (55.0)
≥5	1,791 (77.7)	1,791 (47.4)
≥6	1,738 (75.4)	1,738 (46.0)
≥7	1,542 (66.9)	1,542 (40.8)
≥8	1,300 (56.4)	1,300 (34.4)
≥9	1,121 (48.7)	1,121 (29.7)
≥10	1,062 (46.1)	1,062 (28.1)
Mean (SD) number of doses	8.2 (3.6)	5.7 (4.2)
Median number of doses	8.0	4.0
Total cumulative dose, mg		
Mean (SD)	4,846 (2,167)	3,407 (2,485)
Median	4,800	2,400
Range	9–11,800	9–11,800

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 randomized 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 OBOE (as of September 2017; clinical cut-off date for OBOE: June 2017); data from patients who were originally randomized to comparator (IFN β-1a or placebo) are included after the switch to open-label OCR treatment; [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; OCR, ocrelizumab; OLE, open-label extension; SD, standard deviation.

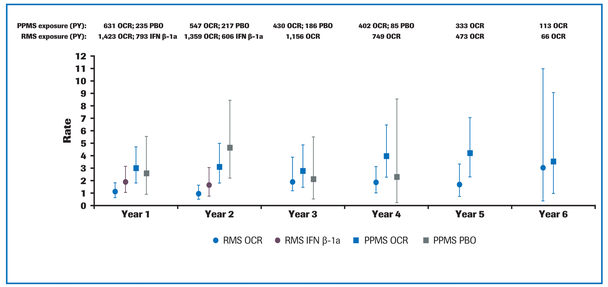
Overall Adverse Events

- As of September 2017, the rate of AEs was 243 (95% CI 240–246) 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 AEs included IRRs, UTIs and upper respiratory tract infections
- Of those patients who received OCR, serious AEs were reported at a rate of 7.29 (95% CI 6.76–7.86) events per 100 PY in the OCR all-exposure population
  - The most common events were classified as infections, coded to the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) term *Infections and Infestations*
- As of September 2017, the rate of AEs leading to treatment withdrawals was 1.09 (95% CI 0.89–1.32) per 100 PY in the OCR all-exposure population
  - The rate of AEs leading to treatment withdrawals remained stable with additional patient exposure

Infections

- As of September 2017, the rate of infections was 73.1 (95% CI 71.4–74.8) 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
  - The rates of other serious infections remained stable compared with the rate observed at the primary analysis cut-off date
- In the OCR all-exposure population, the rate per 100 PY of serious infections as of September 2017 (1.96 [95% CI 1.69–2.27]) was comparable with the rate observed at the primary analysis cut-off date
  - Data for the pooled RMS population showed a change in the rate per 100 PY of serious infections from Year 2 (0.96 [95% CI 0.51–1.64]) to Year 3 (1.90 [95% CI 1.19–2.88]), with no further sustained increase up until Year 6 (3.04 [95% CI 0.37–10.98]) (**Figure 2**)
  - Among patients with PPMS, the rate per 100 PY of serious infections remained stable over time from Year 1 (3.01 [95% CI 1.81–4.71]) to Year 3 (2.79 [95% CI 1.44–4.87]), increased numerically after Year 3, with no further sustained increase up until Year 6 (**Figure 2**)
- As previously reported, two confirmed opportunistic infections had been reported from OCR clinical trials, as of September 2017
  - One non-serious oesophageal candidiasis in a patient with PPMS, which had been reported at the February 2017 data cut-off
    - This patient had concurrent type 2 diabetes mellitus and chronic inhaled corticosteroid use for asthma since February 2014, both of which are risk factors for infections
  - One serious systemic *Pasteurella* infection in a patient with RMS
    - This patient did not present any abnormal laboratory values at the time of the event and preceding the event. The event was resolved within 15 days upon antibiotic treatment, and the patient received the next infusion of OCR without any intervention
- As previously reported, as of September 2017, one confirmed case of progressive multifocal leukoencephalopathy (PML) was reported from a compassionate-use program in an anti-John Cunningham virus antibody-positive patient who was switched to OCR after 36 infusions of natalizumab. Assessment of the available information resulted in the case being reported to regulators as related to natalizumab and not to OCR

Figure 2. Rate per 100 patient years of serious infections during the Phase III studies



Exposure to OCR and comparator (IFN β-1a or placebo) in the Phase III pooled RMS and PPMS populations in total PY. The exposure in Year 5 and Year 6 (placebo-treated patients) was too limited for any meaningful interpretation, thus these data are not included in the plot.
Investigator text for adverse events was encoded using MedDRA versions 18.1 and 19.1.
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.
CI, confidence interval; IFN, interferon; MedDRA, Medical Dictionary for Regulatory Activities; OCR, ocrelizumab; PBO, placebo; PPMS, primary progressive multiple sclerosis; PY, patient years; RMS, relapsing multiple sclerosis; SOC, system organ class.

Table 2. Safety profile observed with ocrelizumab

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,e]	Feb 2017 rate per 100 PY (95% CI)[d,f]	Sep 2017 rate per 100 PY (95% CI)[d,g]	Sep 2017 rate per 100 PY (95% CI)[d,g]
Any adverse event	**296 (287–305)**	**290 (281–299)**	**259 (247–271)**	**252 (244–260)**	**242 (238–246)**	**226 (222–229)**	**220 (217–223)**	**243 (240–246)**
Adverse events leading to study treatment discontinuation	**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)**	**1.09 (0.89–1.32)**
Infections and infestations[h,i]	**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)**	**73.1 (71.4–74.8)**
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)	12.3 (11.4–13.2)	12.7 (12.0–13.6)	12.7 (12.0–13.5)	12.8 (12.1–13.5)
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)	11.4 (10.6–12.3)	11.2 (10.5–12.0)	1.2 (1.0–1.5)	1.2 (1.0–1.4)
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)	10.1 (9.3–10.9)	9.8 (9.1–10.5)	9.4 (8.8–10.1)	9.6 (9.0–10.2)
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)	3.1 (2.8–3.5)
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 (2.7–3.5)
Injury, poisoning and procedural complications[h]	**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)**	**38.8 (37.6–40.1)**
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)	28.4 (27.1–29.8)	23.0 (21.9–24.1)	21.5 (20.5–22.4)	28.4 (27.3–29.5)
Nervous system disorders[j]	**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)**	**24.2 (23.2–25.2)**
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)	7.0 (6.5–7.6)
Musculoskeletal and connective tissue disorders[h]	**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)**	**20.9 (20.0–21.9)**
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)	3.7 (3.3–4.1)
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)	3.0 (2.7–3.4)
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)	2.7 (2.4–3.1)
General disorders and administration site conditions[h]	**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)**	**12.8 (12.1–13.5)**
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)	3.7 (3.3–4.1)
Psychiatric disorders[h]	**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)**	**8.6 (8.0–9.2)**
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)	2.8 (2.4–3.1)
Malignancies[k,l]	**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)**	**0.48 (0.35–0.64)**
Serious adverse events	**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)**	**7.29 (6.76–7.86)**
Serious infections[m]	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)	1.96 (1.69–2.27)
Number of confirmed serious OIs	0	0	0	0	0	0	1	1
Fatalities	**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)**	**0.17 (0.10–0.27)**

[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 randomized 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 OBOE (as of September 2017; clinical cut-off date for OBOE: June 2017); data from patients who were originally randomized 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 2016; [f]Rate per 100 PY (95% CI) as of February 2017; [g]Rate per 100 PY (95% CI) as of September 2017; [h]Includes events occurring in ≥5% of patients; [i]Includes events falling into the MedDRA versions 18.0, 18.1, 19.1 and 20.0 SOC *Infections and Infestations*; [j]Non-serious MS relapses are not considered as an adverse event. If an adverse event reported term was coded to the preferred term "Multiple Sclerosis Relapse", regardless of seriousness, it was considered as an adverse event. When the MS relapse resulted in hospitalization for any reason other than the routine treatment of the relapse, or when the hospitalization was prolonged, the relapse was considered as a serious adverse event; [k]Includes non-melanoma skin cancer as per MedDRA version SMQ Malignant Tumours; [l]Reported as incidence rate per 100 PY of first malignancy; [m]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.
CI, confidence interval; IFN, interferon; MedDRA, Medical Dictionary for Regulatory Activities; MS, multiple sclerosis; OCR, ocrelizumab; OIs, opportunistic infections; OLE, open-label extension; PY, patient years; SMQ, standardized MedDRA query; SOC, system organ class.

Malignancies

- Over time, the crude incidence rate of malignancy per 100 PY in the OCR all-exposure population fluctuated and remained within epidemiological range for patients with MS (Danish MS registry: 0.67 [95% CI 0.63–0.71])
  - As of September 2017, the crude incidence rate of malignancy was 0.48 (95% CI 0.35–0.64) per 100 PY (**Table 2**), consistent with the rate observed at the primary analysis cut-off date
- The crude incidence rate of female breast cancer in the OCR all-exposure population remained stable over time (data not shown)

CONCLUSIONS

- The updated safety profile in the ocrelizumab MS all-exposure population is generally consistent with that seen during the controlled treatment period in the RMS and PPMS populations
- In the ocrelizumab all-exposure population, the pooled RMS population and the PPMS population, rates per 100 PY of serious infections by year fluctuated over time, without any sustained increase
  - No conclusions can be drawn from Year 6 onwards due to the low exposure of the ocrelizumab all-exposure population in this time frame
- As of September 2017, from ocrelizumab clinical trials, one confirmed serious opportunistic infection (systemic *Pasteurella* infection) was reported
- In the updated exposure period to September 2017, the rate of malignancies in ocrelizumab-treated patients remained within the range reported in epidemiological data
- Long-term follow-up and post-marketing requirement studies will monitor safety and specific potential risks in patients with MS receiving ocrelizumab

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DISCLOSURES

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