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Subcutaneous Ocrelizumab in Patients With Multiple Sclerosis: Results of the Phase III OCARINA II Study

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*During completion of the work related to this presentation, O Bortolami was a contractor on the studies listed for F. Hoffmann-La Roche Ltd until December 2023, and is now an employee of IQVIA RDS

NCT05232825

S31.001

Presented at the 76th Annual Meeting of the American Academy of Neurology (AAN); April 13–18, 2024; Denver, CO, USA.

Disclosures

SD Newsome received consultancy fees for scientific advisory boards from Biogen, Genentech, Bristol Myers Squibb, EMD Serono, Greenwich Biosciences, Horizon Therapeutics, Novartis and TG Therapeutics; study lead PI for a Roche clinical trial program; received research funding (paid directly to institution) from Biogen, Lundbeck, Roche, Genentech, National MS Society, The Stiff Person Syndrome Research Foundation, Department of Defense and Patient-Centered Outcomes Research Institute.

E Krzystanek received consultancy fees for scientific advisory boards from Biogen, Merck-Serono, Bayer, Roche, Novartis and the Polish Multiple Sclerosis Society; study lead PI for Roche, TG Therapeutics, Merck, Biogen, Lundbeck and Janssen clinical trial programmes; received compensation for speaking services from Biogen, Bayer, Novartis, UCB, Roche, Merck-Serono, Teva, Lundbeck, Pfizer, Sandoz and Sanofi-Genzyme.

K Selmaj received honoraria for speaking, consulting and serving for advisory boards for Merck, Novartis, Roche, Biogen, Celgene, Bristol Myers Squibb and TG Therapeutics.

L Goldstick received consultancy fees from EMD Serono, Bristol Myers Squibb, Biogen, Sanofi-Genzyme and Roche/Genentech; he has also received research support from Biogen, Roche/Genentech and Sanofi-Genzyme.

C Figueiredo is an employee of and a shareholder in F. Hoffmann-La Roche Ltd.

B Townsend is an employee of and a shareholder in F. Hoffmann-La Roche Ltd.

C Wolf is a partner at Lycalis sprl and reports compensation for his organization for consulting from Bristol Myers Squibb, Celgene, Desitin, Immunic, Merck KGaA, Novartis, Roche, Synthon, Teva and Viatris; and for speaking from Synthon and Viatris.

D Zecevic is an employee of and a shareholder in F. Hoffmann-La Roche Ltd.

C Giacobino is an employee of and a shareholder in F. Hoffmann-La Roche Ltd.

O Bortolami was a contractor for F. Hoffmann-La Roche Ltd until December 2023; his current affiliation is IQVIA RDS

YA Shen is an employee of Genentech, Inc. and a shareholder in F. Hoffmann-La Roche Ltd.

H Kletzl is an employee of and a shareholder in F. Hoffmann-La Roche Ltd.

S Clinch is an employee of and a shareholder in F. Hoffmann-La Roche Ltd.

D Centonze acted as an advisory board member and received honoraria for speaking or consultancy fees from Alexion, Almirall, Amicus, Bayer, Biogen, Bristol Myers Squibb, Celgene, Chiesi, GW Pharmaceuticals, Horizon, Janssen, Lundbeck, Merck-Serono, Novartis, Roche, Sandoz, Sanofi-Genzyme, Viatris and Teva; he is also the Principal Investigator in clinical trials of Biogen, Bristol Myers Squibb, Merck-Serono, Mitsubishi, Novartis, Roche, Sanofi-Genzyme and Actelion; preclinical and clinical research was supported by grants from Bayer Schering, Bristol Myers Squibb, Biogen, Celgene, Lundbeck, Merck-Serono, Novartis, Roche, Sanofi-Genzyme and Teva.

Sponsored by F. Hoffmann-La Roche Ltd, Basel, Switzerland. Writing and editorial assistance for this presentation was provided by Nucleus Global, UK, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland.
Acknowledgments: We would like to thank all patients, their families and the investigators who participated in this study.

Background

OCR is **approved for the treatment of PwRMS and PwPPMS** (IV 600 mg every 6 months)[1,2] with **over 10 years of safety and efficacy** experience in clinical trials, and over **300,000 patients treated** in trial and post-marketing settings combined[3–6]

Twice-yearly SC injection of OCR[a] **administered in around 10 minutes,**[b] could deliver the same **clinical benefit** in a **reduced delivery time** and offers **greater flexibility in administration** and **site of patient care**[7–10]

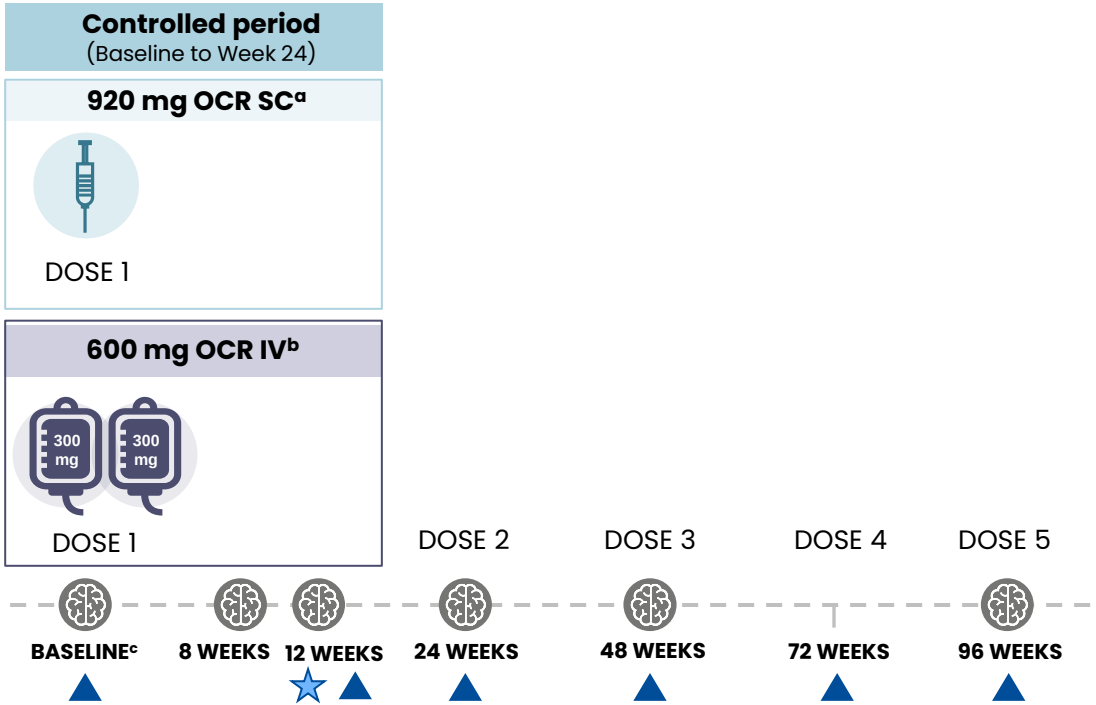
Objectives

OCARINA II (NCT05232825) aims to assess the PK, PD, safety, immunogenicity, radiologic and clinical effects of OCR SC vs OCR IV in PwRMS or PwPPMS

[a]Co-formulated with Halozyme's ENHANZE® rHuPH20, a human hyaluronidase that causes a temporary reduction in the viscosity of the extra-cellular matrix of the hypodermis, thereby allowing injection of a large volume and rapid delivery of SC-administered drugs[11]; [b]OCR SC administration is carried out either manually or using a suitable syringe pump.
IV, intravenous; OCR, ocrelizumab; PD, pharmacodynamic; PK, pharmacokinetic; PwPPMS, people with primary progressive multiple sclerosis; PwRMS, people with relapsing multiple sclerosis; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous.

1. OCREVUS [ocrelizumab] Full Prescribing Information. Genentech, Inc., 2020. 2. OCREVUS [ocrelizumab] Summary of Product Characteristics. Roche Pharma AG, 2020. 3. Hauser SL, *et al. Neurology* 2020;95(13):e1854–e1867. 4. Wolinsky JS, *et al. Lancet Neurol* 2020;19:998–1009. 5. Weber MS, *et al. ECTRIMS-ACTRIMS* 2023;Poster P302. 6. Roche data on file. 7. ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT03972306. Accessed April 12, 2024. 8. ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT05232825. Accessed April 12, 2024. 9. Filippi M, *et al. J Neurol* 2024;271(1):340-354. 10. Overton PM, *et al. Patient Prefer Adherence* 2021;15:811–834. 11. Knowles SP, *et al. Expert Opin Drug Del* 2021;18(11):1673–1685.

Methods
Study design



Primary analysis
(cut-off date = when last patient completes 12 weeks)

IV SC MRI

Assessments:
- PK
- ADA
- EDSS
- B-cell count (PD)
- Questionnaires

[a]The 920 mg OCR SC dose was established as the recommended dose in the OCARINA I study (NCT03972306); [b]The first dose of OCR IV was administered as two 300 mg IV infusions given 2 weeks apart; [c]The screening phase in patients with RMS and PPMS took place before baseline MRI readings and patients were randomized 1:1 between the two arms.
ADA, antidrug antibody; EDSS, Expanded Disability Status Scale; IV, intravenous; OCR, ocrelizumab; PD, pharmacodynamic; PK, pharmacokinetic; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; SC, subcutaneous.

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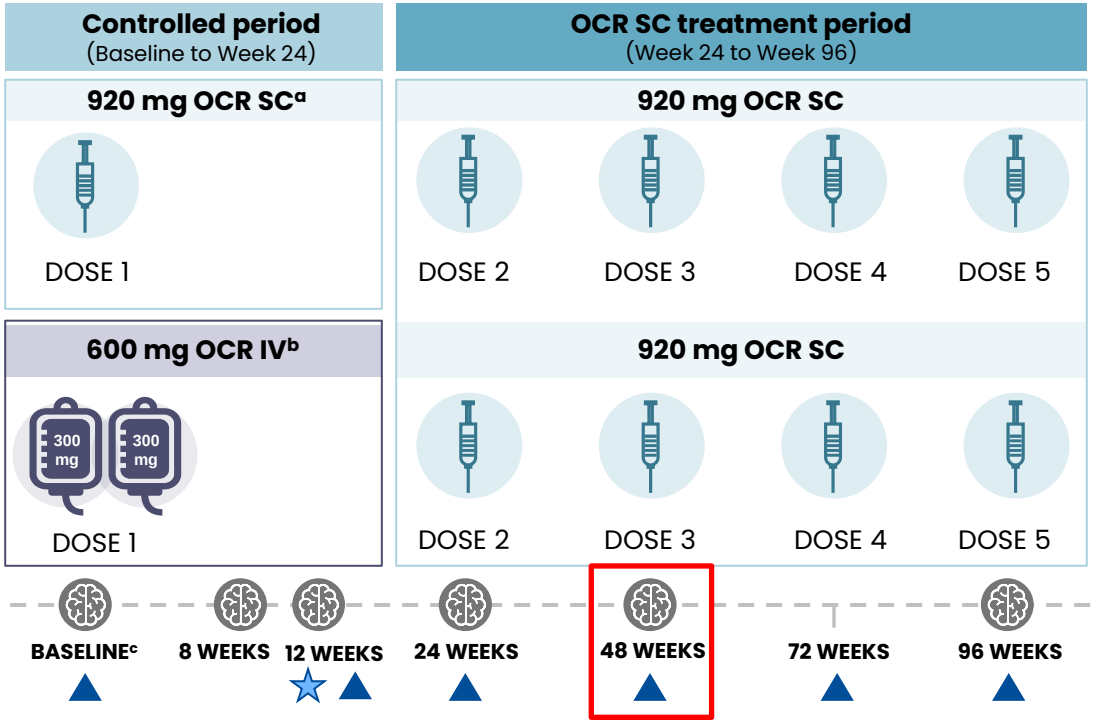
Study design



Safety follow-up phase
(24 weeks after last dose)

Primary analysis ★
(cut-off date = when last patient completes 12 weeks)

IV SC MRI

Assessments:
- PK
- ADA
- EDSS
- B-cell count (PD)
- Questionnaires

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Methods
Patient population and study objectives

PATIENT POPULATION

RMS or PPMS (McDonald 2017)[1]

Age 18–65 years, inclusive

EDSS 0.0–6.5 inclusive

OCR/anti-CD20 naive patients

Any disease duration from onset of MS symptoms except <15 years for patients with EDSS score <2.0 at screening

STUDY OBJECTIVES

★ **PK**	**PK non-inferiority of the SC formulation of OCR in patients with MS on the basis of serum OCR $AUC_{W1–12}$ after SC administration compared with IV infusion up to Week 12**
C_{max}	**Maximum serum concentration of OCR SC**
MRI[a]	**Total number of T1 Gd+ lesions at Weeks 8 and 24, and total number of N/E T2 lesions at Weeks 12 and 24 by MRI**
Relapse[b]	**Annualized PDR rate by Weeks 24 and 48**
Immunogenicity	**Incidence of ADAs to OCR SC and OCR IV, and antibodies to rHuPH20**
PD[c]	**Proportion of patients achieving CD19+ B-cell level ≤5 cells/µL at Weeks 12, 24 and 48**
PRO	**Patient satisfaction and experience in patients receiving OCR SC versus IV**
MRI	**Total number of T1 Gd+ lesions at Week 48 by MRI**
Safety	**Incidence and severity of AEs following OCR administration**

[a]Exploratory radiologic objectives included total T1 Gd+ lesions at Weeks 48 and 96, and N/E T2 lesions at Weeks 8, 48 and 96; [b]Exploratory clinical objectives included annualized PDR rate by Weeks 24, 48 and 96 in patients with RMS, and change in EDSS from baseline at Weeks 48, 72 and 96; [c]Exploratory PD objectives included the proportion of patients achieving CD19+ B-cell level ≤5 cells/µL at Weeks 48 and/or 96.
ADA, antidrug antibody; AE, adverse event; AUC, area under the serum concentration–time curve; C_{max}, maximum serum concentration; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IV, intravenous; MS, multiple sclerosis; N/E, new/enlarging; OCR, ocrelizumab; PD, pharmacodynamic; PDR, protocol-defined relapse; PK, pharmacokinetic; PPMS, primary progressive multiple sclerosis; PRO, patient-reported outcome; rHuPH20, recombinant human hyaluronidase PH20; RMS, relapsing multiple sclerosis; SC, subcutaneous.

1. Thompson AJ, *et al. Lancet Neurol* 2018;17:162–173.

Results
Baseline patient demographics[a] and disposition

		OCR IV/SC (N=118)	OCR SC/SC (N=118)
Age (years), mean ± SD		40.0 ± 11.9	39.9 ± 11.4
Sex, n (%)	**Female**	70 (59.3)	77 (65.3)
	Male	48 (40.7)	41 (34.7)
Weight (kg), mean ± SD		76.1 ± 22.7	75.4 ± 16.6
Time since symptom onset (years), mean ± SD		6.8 ± 7.1	7.7 ± 8.3
MS subtype, n (%)[b]	**RMS**	105 (89.0)	105 (89.0)
	PPMS	12 (10.2)	11 (9.3)
Patients with no T1 Gd+ lesions, n (%)		78/103 (75.7)	82/104 (78.9)
T2 lesion rate, mean ± SD		49.84 (34.56)	44.48 (32.25)
EDSS at baseline, median (range)		3.0 (0.0–6.5)	2.5 (0.0–6.5)
Patients with prior DMT exposure, n (%)[c]		59 (50.0)	65 (55.1)

Randomized patients	**OCR IV/SC (N=118)[d]**	**OCR SC/SC (N=118)**
Ongoing in the OCR SC treatment period	114	115
Discontinued treatment	4	3
Discontinued from the study	3	2

Baseline demographics and disease characteristics in this study were reflective of the broad MS population for which OCR IV is indicated. Overall, the treatment withdrawal rate was low and similar between both arms

[a]The first patient was enrolled on May 3, 2022 and the CCOD was on December 4, 2023 where none of the patients had completed the SFU; [b]Two patients in the SC arm (1.7%) and one patient in the IV arm (0.8%) had aSPMS; [c]The most frequently reported classes of previous DMTs in ≥5% of patients in either arm; OCR SC vs OCR IV, respectively, were immunosuppressants: 38.1% (45 patients) vs 32.2% (38 patients) mostly dimethyl fumarate (16.1% [19 patients] vs 14.4% [17 patients]) and teriflunomide (12.7% [15 patients] vs 12.7% [15 patients]), and immunostimulants: 32.2% (38 patients) vs 27.1% (32 patients) mostly IFN β-1a (17.8% [21 patients] vs 14.4% [17 patients]) and glatiramer acetate (11.9% [14 patients] vs 12.7% [15 patients]); [d]Of the 118 patients randomized to the OCR IV/SC arm, three patients discontinued treatment prior to receiving their first OCR SC dose.
aSPMS, active secondary progressive multiple sclerosis; CCOD, clinical cut-off date; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IFN, interferon; IV, intravenous; MS, multiple sclerosis; OCR, ocrelizumab; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; SC, subcutaneous; SD, standard deviation; SFU, safety follow-up.

Results
Week 12 PK ($AUC_{W1–12}$) and C_{max} analysis

OCR PK SC vs IV[a]

	SC 920 mg[b] (n=116)	IV 600 mg[b] (n=116)	GMR SC vs IV[c] (90% CI)
AUC over the first 12 weeks ($AUC_{W1–12}$)	3,500 µg/mL*day	2,750 µg/mL*day	1.29 (1.23–1.35)
Max concentration (C_{max})	132 µg/mL	137 µg/mL	0.96 (0.92–1.01)

PRIMARY ENDPOINT

Administration of OCR SC 920 mg or OCR IV 600 mg led to similar overall exposure to OCR during the first 12 weeks of the OCARINA II study, demonstrating PK non-inferiority of the OCR SC formulation

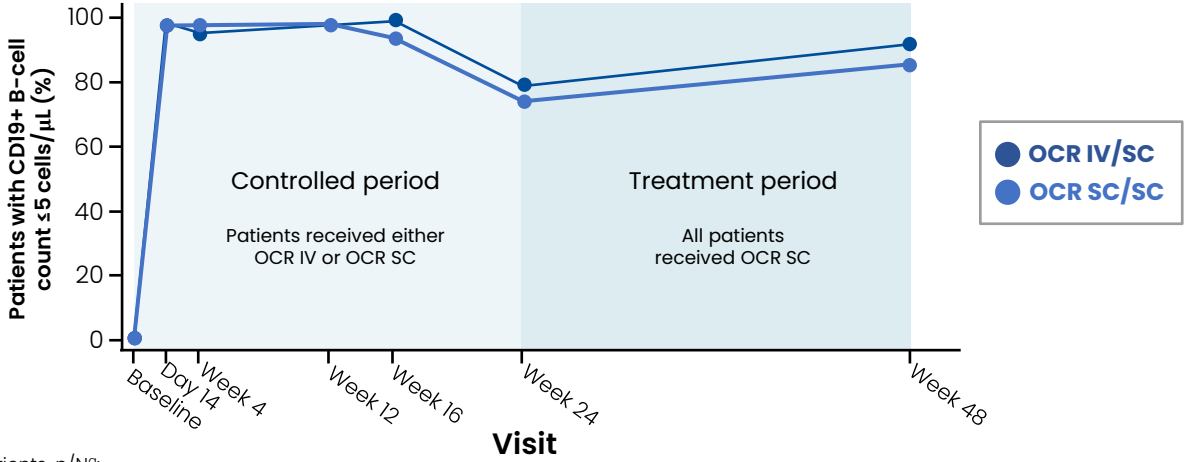
[a]Two patients from the OCR SC/SC arm were excluded from the PK-evaluable analysis set due to an incomplete SC dose and an impossible concentration-time profile. Two patients from the OCR IV/SC arm were excluded from the PK-evaluable analysis set due to a delay in the second IV infusion and a missing second IV infusion; [b]Estimated mean exposure for AUC or C_{max}; [c]GMR and two-sided 90% CI of SC vs IV between baseline and Week 12. Non-inferiority would be established if the lower end of the two-sided 90% CI is >0.8; the non-inferiority limit of 0.8 corresponds to a maximal 20% loss in AUC for the SC administration compared with IV, as recommended in the regulatory guidance documents for demonstration of bioequivalence for PK bridging.[1,2]

AUC, area under the serum concentration–time curve; CI, confidence interval; C_{max}, maximum serum concentration; GMR, geometric mean ratio; IV, intravenous; OCR, ocrelizumab; PK, pharmacokinetic; SC, subcutaneous.

1. European Medicines Agency. Guideline on the investigation of bioequivalence. January 2010. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf. Accessed April 12, 2024. 2. Food and Drug Administration. Bioavailability studies submitted in NDAs or INDs – General considerations. April 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bioavailability-studies-submitted-ndas-or-inds-general-considerations. Accessed April 12, 2024.

Results
B-cell depletion

Percentage of patients with CD19+ B-cell count ≤5 cells/µL



Number of patients, n/N[a]:

OCR IV/SC	0/118	112/114	109/114	113/115	112/113	90/114	100/109
OCR SC/SC	0/118	112/115	116/118	113/115	108/115	85/114	97/113

Treatment with OCR led to rapid and sustained B-cell depletion in blood, which was similar in both treatment arms (OCR SC 920 mg and OCR IV 600 mg) up to Week 24, after which all patients received OCR SC 920 mg

[a]The n/N values refer to the number of patients with CD19 count ≤5 cells/µL/number of patients with a valid CD19+ B-cell count result at the visit.
IV, intravenous; OCR, ocrelizumab; SC, subcutaneous.

Results
Ocrelizumab SC all exposure[a] safety profile

Patients with ≥1 event, n (%)	OCR SC 920 mg (N=233)
Adverse events[b]	175 (75.1)
Serious adverse events	6 (2.6)
Infections	89 (38.2)
Injection Reactions[c,d]	120 (51.5)
Local injection reactions	117 (50.2)
Systemic injection reactions	27 (11.6)

Most patients had AEs of Grade 1 or Grade 2 (96.6%); no Grade 4 or Grade 5 AEs were reported

Over a period of 48 weeks, OCR SC was well-tolerated.
No new safety concerns were identified, in addition to the known risks associated with OCR or the new route of administration

[a]Patients who received their first dose of OCR SC were included regardless of which arm they were randomized to; [b]Reported terms of AEs are encoded using MedDRA version 26.1; [c]IRs comprise AEs with the MedDRA PTs injection-related reaction and injection site reaction, which occurred during or within 24 hours after OCR SC administration and which were judged by the investigator to be related to the OCR SC injection; [d]Standard-of-care treatment included mostly analgesics (e.g. paracetamol, oral or topical antihistamines) and were used to treat patients with IRs if needed.
ADA, antidrug antibody; AE, adverse event; COVID-19, coronavirus disease 2019; IR, injection reaction; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; OCR, ocrelizumab; PT, preferred term; rHuPH20, recombinant human hyaluronidase PH20; SAE, serious adverse event; SC, subcutaneous; URTI, upper respiratory tract infection.

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Six patients reported ≥1 SAE:
- Anxiety (n=1)
- Eye pain (n=1)
- Hemorrhagic ovarian cyst (n=1)
- Urinary tract infection (n=1)
- Multiple sclerosis pseudo relapse (n=2)
- Multiple sclerosis relapse (n=1)
- Intentional self-injury (n=1)
- Leukopenia, neutropenia and pyrexia (in the same patient)

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Most common infections were:
- URTI (18/233; 7.7%)
- COVID-19 (14/233; 6.0%)
- Urinary tract infection (10/233; 4.3%)

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All IRs were Grade 1 (76.0%) or Grade 2 (24.0%)
- The majority required no treatment
  - When treatment was administered, the medications were mostly standard of care
- Median duration of IRs was 2 days

Incidence and severity of IRs decreased after the first injection and no IR led to treatment discontinuation; all IRs resolved

Over a period of 48 weeks, OCR SC was well-tolerated.
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Most common symptoms of local IRs were:
- Erythema (81/233; 34.8%)
- Pain (40/233; 17.2%)
- Swelling (22/233; 9.4%)
- Pruritus (13/233; 5.6%)

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Most common symptoms of systemic IRs were:
- Headache (5/233; 2.1%)
- Flushing (3/233; 1.3%)
- Nausea (3/233; 1.3%)

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Post-baseline, none of the evaluable patients had treatment-emergent ADAs to OCR or rHuPH20 in both OCR SC 920 mg and OCR IV 600 mg groups at Week 24

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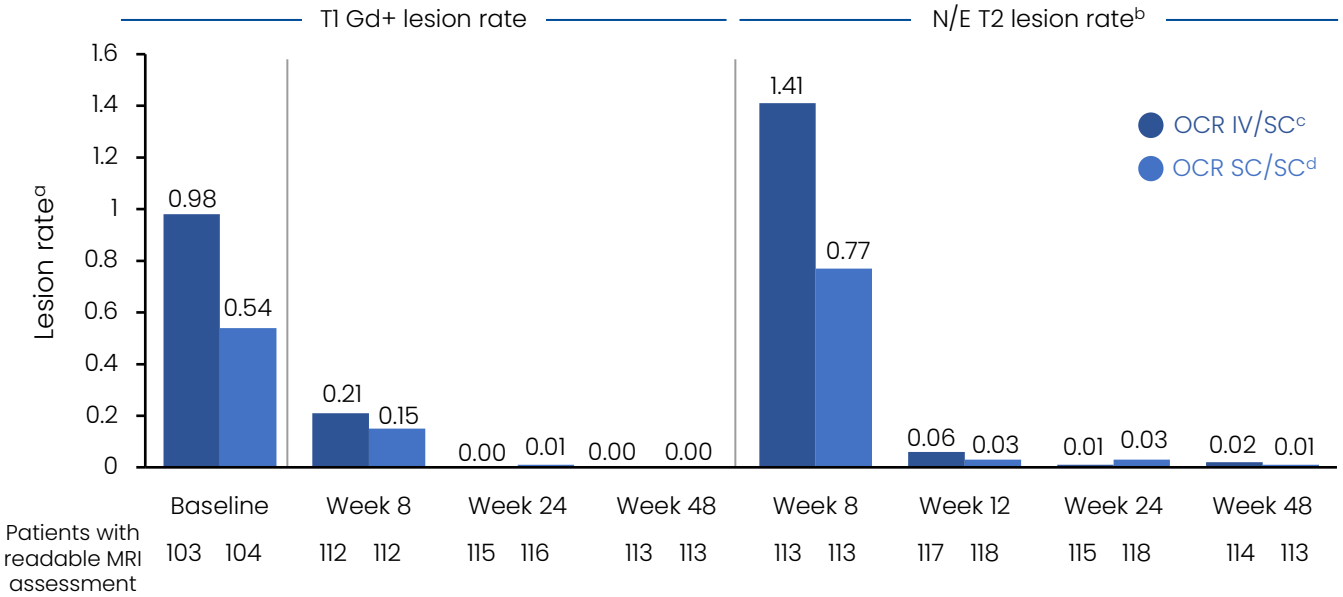
No new safety concerns were identified, in addition to the known risks associated with OCR or the new route of administration

[a]Patients who received their first dose of OCR SC were included regardless of which arm they were randomized to; [b]Reported terms of AEs are encoded using MedDRA version 26.1; [c]IRs comprise AEs with the MedDRA PTs injection-related reaction and injection site reaction, which occurred during or within 24 hours after OCR SC administration and which were judged by the investigator to be related to the OCR SC injection; [d]Standard-of-care treatment included mostly analgesics (e.g. paracetamol, oral or topical antihistamines) and were used to treat patients with IRs if needed.
ADA, antidrug antibody; AE, adverse event; COVID-19, coronavirus disease 2019; IR, injection reaction; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; OCR, ocrelizumab; PT, preferred term; rHuPH20, recombinant human hyaluronidase PH20; SAE, serious adverse event; SC, subcutaneous; URTI, upper respiratory tract infection.

Results
Radiologic and clinical effects



Clinical measure at Week 48[e]

97.2%

of patients **were free of relapses** following **OCR SC** administration during the treatment phase or safety follow-up

OCR SC/SC 920 mg
97.2% (n=104/107)

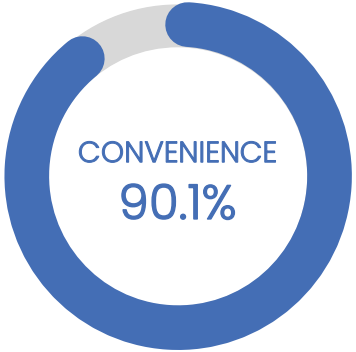
OCR IV/SC 600 mg
98.1% (n=104/106)

Similar to OCR IV, OCR SC 920 mg administration resulted in near-complete suppression of radiologic (MRI) and clinical (relapses) disease activity

[a]The lesion rate is the total number of lesions divided by the number of patients with a readable MRI assessment at the visit; [b]New or enlarging T2 lesion count measurement is performed with respect to the previous scheduled available visit; [c]At baseline for T1 Gd+ lesions, 78/103 (75.7%) patients had no lesions and 11/103 (10.7%) had ≥4 lesions; [d]At baseline for T1 Gd+ lesions, 82/104 (78.8%) patients had no lesions and 5/104 (4.8%) had ≥4 lesions; [e]Two patients (1.9%) in each arm had one relapse and one patient (0.9%) in the OCR SC/SC arm had two relapses at Week 48; unadjusted relapse rate per year was 0.04 and 0.02 in the SC/SC and IV/SC arms, respectively. The unadjusted annualized relapse rate is the total number of relapses for all patients in the considered group divided by the total follow-up time.
Gd+, gadolinium-enhancing; IV, intravenous; N/E, new/enlarging; OCR, ocrelizumab; SC, subcutaneous.

Results
Exploratory patient-reported outcomes (TASQ-SC)[a,b]

The majority of patients were either satisfied or very satisfied with the SC procedure (205/222 patients)



The majority of patients felt that the SC procedure was convenient or very convenient (200/222 patients)

The majority of patients felt that the time taken to get the injection was just right (200/221 patients)

Most of the patients would recommend the SC route of administration to other patients (209/222 patients)

Almost all patients reported a high level of satisfaction for the OCR SC procedure, and this translated into high scores for convenience, time taken and the likelihood of recommending SC administration to another patient

[a]Patients in the OCR SC arm completed the TASQ SC at Day 1, Week 24 and Week 48. Patients in the OCR IV arm completed the TASQ IV at Day 1 and the TASQ SC at Week 24 and Week 48. TASQ SC data at Week 48 are described here and data for earlier time points are described in ECTRIMS 2023.[1] At Week 48, patients initially randomized to OCR SC had received up to a maximum of three OCR injections, while patients initially randomized to OCR IV had received up to a maximum of two OCR injections. The pattern of responses to each item in TASQ SC at Week 48 was generally consistent with that from the earlier time points reported previously; [b]The responses presented here reflect a subset of selected items from the TASQ, which consists of 13 questions in total.
OCR, ocrelizumab; SC, subcutaneous; TASQ, Treatment Administration Satisfaction Questionnaire.
1. Newsome SD, *et al. ECTRIMS* 2023;Poster P370.

Conclusions

- The study achieved its primary objective of demonstrating non-inferiority of ocrelizumab SC 920 mg to ocrelizumab IV 600 mg with respect to $AUC_{W1–12}$
- Administration of ocrelizumab SC 920 mg resulted in near-complete suppression of radiologic (MRI) and clinical (relapses) disease activity as measured up to Week 48
- Ocrelizumab SC led to rapid and sustained B-cell depletion in blood; the initial dose of ocrelizumab SC achieved similar levels of B-cell depletion to the initial dose of ocrelizumab IV up to Week 24
- Ocrelizumab SC was well-tolerated, with no treatment-emergent ADAs to ocrelizumab or antibodies to rHuPH20 at Week 24. Most IRs were mild to moderate and were not treatment-limiting
- The majority of patients were either satisfied or very satisfied with the ocrelizumab 920 mg SC injection procedure

These data indicates that ocrelizumab SC offers comparable clinical benefits to ocrelizumab IV, while providing treatment flexibility along with an additional treatment option for patients and HCPs

ADA, antidrug antibody; AUC, area under the serum concentration–time curve; HCP, healthcare professional; IR, injection reaction; IV, intravenous; MRI, magnetic resonance imaging; PRO, patient-reported outcome; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous.