

ECTRIMS-ACTRIMS MSMilan 2023 Presentations

*Presentations for all Orals/Posters/ePosters at ECTRIMS-ACTRIMS 2023
Milan, Italy | 11–13 October 2023*

ECTRIMS-ACTRIMS 2023 Ocrelizumab Presentations

Short Title/Link	Format	First Author	Full Title
B cells	Poster	A Garcia	Unsupervised Analysis Reveals That Memory IgA B Cells Are Spared by Ocrelizumab Treatment
CHIMES Primary Analysis	Poster	MJ Williams	One-Year Analysis of Efficacy and Safety Data From Black and Hispanic Patients With Relapsing Multiple Sclerosis Receiving Ocrelizumab Treatment in the CHIMES Trial
Combined Efficacy	Poster	N Lewin-Koh	Combining Measures from Clinical Assessments, Imaging and Fluid Biomarkers at 1 Year to Predict Multiple Sclerosis Progression at 2 Years
COVID-19 Vaccinations	Poster	M Tarkowski	Kinetics of T-Cell Reactivity and Antibody Responses to SARS-CoV-2 After Different Rounds of Vaccination in Persons With Multiple Sclerosis Treated With Ocrelizumab
ENSEMBLE Immunological	Poster	T Wirth	Immune Signatures Associated with Ocrelizumab Treatment in Early Relapsing-Remitting Multiple Sclerosis: New Data on T-Cell Function and Pro/Anti-Inflammatory Monocytes of the 12-Month Interim Analysis from the MA30143 Phase IIIb (ENSEMBLE) Substudy
ENSEMBLE Low Disability	Poster	F Patti	Low Disability Accumulation After 4-Year Ocrelizumab Therapy in Treatment-Naive Patients with Early-Stage Relapsing-Remitting Multiple Sclerosis: Data from the Phase IIIb ENSEMBLE Study
General Safety	Poster	SL Hauser	Safety of Ocrelizumab in Multiple Sclerosis: Updated Analysis in Patients with Relapsing and Progressive Multiple Sclerosis
Immune Receptor	Poster	T Schneider-Hohendorf	Analysis of the Adaptive Immune Receptor Repertoire Alongside Treatment with Ocrelizumab
INTONATE	ePoster	J Oh	Utility and Implementation of a Federated Research Infrastructure to Assess Lack of Disease Stability as a Real-World Surrogate of PIRA, by Combining MS Clinical Trial and Real-World Cohort Data (The INTONATE-MS Consortium)

ECTRIMS-ACTRIMS 2023 Ocrelizumab Presentations

Short Title/Link	Format	First Author	Full Title
MSBase Pregnancy	Oral	W Yeh	Disease activity during pregnancy and postpartum in women with relapsing-onset MS receiving ocrelizumab and other modern disease-modifying therapies in a real-world cohort
NfH Biomarker	Poster	Y-A Shen	Cerebrospinal Fluid Neurofilament Heavy Levels Correlate With Spinal Cord Lesions and Disability in Multiple Sclerosis
NTD Persistence	Poster	S Braune	Persistence to Ocrelizumab Compared with Other Disease-Modifying Therapies for Multiple Sclerosis in the German NeuroTransData Registry
OBOE Ig	Poster	MS Weber	Reduction of Intrathecal Immunoglobulin Levels With Ocrelizumab Treatment in Relapsing and Primary Progressive Multiple Sclerosis
OCARINA I Dose Finding Study	Poster	SD Newsome	Subcutaneous Ocrelizumab in Patients with Multiple Sclerosis: Results of the Phase Ib Dose-Finding OCARINA I Study
OCARINA II Primary Results	Poster	SD Newsome	Subcutaneous Ocrelizumab in Patients with Multiple Sclerosis: Results of the Phase III OCARINA II Study
OLE Update	Poster	MS Weber	The Patient Impact of 10 Years of Ocrelizumab Treatment in Multiple Sclerosis: Long-Term Data from the Phase III OPERA and ORATORIO Studies
OPERETTA	Poster	M Valeriani	Ocrelizumab Dose Selection for Treatment of Paediatric Relapsing-Remitting Multiple Sclerosis: Updated Preliminary Pharmacokinetic, Safety and Efficacy Results from the OPERETTA 1 Study
Pregnancy Outcomes	Poster	K Hellwig	Pregnancy and Infant Outcomes in Women Receiving Ocrelizumab for the Treatment of Multiple Sclerosis: Analysis of the Largest Available Outcomes Database
Time to 25FW and cCDW	Poster	L Kappos	Composite Confirmed Disability Worsening is a Useful Clinical Trial Endpoint for Multiple Sclerosis Focusing on Disability Progression

ECTRIMS-ACTRIMS 2023 Fenebrutinib Presentations

Short Title/Link	Format	First Author	Full Title
FEN Microglial	Poster	J Langlois	Fenebrutinib, a Noncovalent, Reversible, Bruton's Tyrosine Kinase Inhibitor, Potently Blocks Neuroinflammation Induced by FcγR Activation in Human Microglial Systems: Implications for MS Treatment
FENopta CSF MRI LBA	Oral	A Bar-Or	Cerebrospinal Fluid and MRI Analyses of Fenebrutinib Treatment in Multiple Sclerosis Reveal Brain Penetration and Early Reduction of New Lesion Activity: Results From the Phase II FENopta Study

ECTRIMS-ACTRIMS 2023 Floodlight Presentations

Short Title/Link	Format	First Author	Full Title
Floodlight Passive Monitoring Analysis	Poster	M Ganzetti	Smartphone-based passive monitoring of gait in people with progressive multiple sclerosis



<https://ter.li/bn6pqa>

Unsupervised Analysis Reveals That Memory IgA B Cells Are Spared by Ocrelizumab Treatment

A Garcia,¹ E Dugast,¹ C Lebrun-Frenay,² E Thouvenot,³ J De Sèze,⁴ E Le Page,⁵ S Vukusic,⁶ A Maurousset,⁷ E Berger,⁸ O Casez,⁹ P Labauge,¹⁰ A Ruet,¹¹ C Raposo,¹² F Le frère,^{13,14} A Nicot,¹ S Wiertelowski,^{1,15} P-A Gourraud,^{1,16} L Berthelot,¹ DA Laplaud^{1,13,15}

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Disclosures

A Garcia, E Dugast, S Shah, J Morille, C Lebrun-Frenay, J De Sèze, P Labauge, F Le Frère, AB Nicot and L Berthelot have nothing to disclose. **E Thouvenot** declares consultancy and board membership from Novartis, BMS, Merck, Actelion and Teva, and grants from Novartis, Biogen and Merck. **E Le Page** declares research support from Teva, and has received honoraria for lectures or consulting from Biogen Idec, Merck-Serono, Novartis, Sanofi-Aventis, Alexion, Roche and Janssen. **S Vukusic** declares board membership, consultancy, grants and payment for lectures from BMS, Biogen, Merck, Novartis, Roche, Sanofi and Janssen. **A Maurousset** declares board membership from Alexion, Merck and Novartis, and expert testimony from Sanofi and Merck. **E Berger** declares board membership from Biogen, Roche and Novartis. **O Casez** declares board membership from BMS, Merck, Novartis and Roche, and payment for manuscript preparation from Biogen, Novartis, Roche and Sanofi. **A Ruet** declares board membership and consultancy from Merck, Novartis and Roche, and grants from Bayer-Healthcare, Biogen, Roche and Sanofi. P-A Gourraud declares consultancy for AstraZeneca, Biogen, Boston Scientific, Cook, Edimark, Ellipses, Elsevier, Methodomics, Merck, Mérieux, Sanofi-Genzyme and WeData. He has no prescription activity, neither drugs nor devices. **S Wiertlewski** declares board membership from Biogen, Novartis and Roche. **C Raposo** is employee of F Hoffmann-La Roche Ltd. **D Laplaud** declares board membership, consultancy and grants from Alexion, Actelion, BMS, Biogen, Merck, Novartis, Roche and Sanofi.

Key Findings

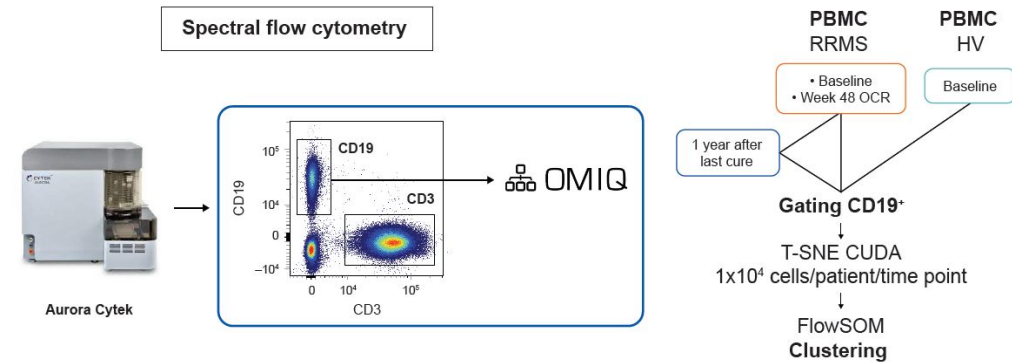


Our study provides novel insights into the effect of the anti-CD20 monoclonal antibody ocrelizumab on the B-cell compartment, showing a change in B-cell proportions with depletion towards enrichment of Immunoglobulin A (IgA)-expressing cells

Methods

- A group of 42 treatment-naive patients with early relapsing-remitting multiple sclerosis, were included from 11 centres participating in an ancillary study of the ENSEMBLE trial (NCT03085810) to evaluate the effectiveness and safety of ocrelizumab (OCR)
- The phenotypic B cell immune profile of cryopreserved peripheral blood mononuclear cells was comprehensively assessed in 18 patients by spectral flow cytometry at baseline and after 24 and 48 weeks of OCR treatment, and descriptively compared with 10 healthy volunteers (matched for age and sex). We also analysed B cell reconstitution 1 year after OCR discontinuation in three patients

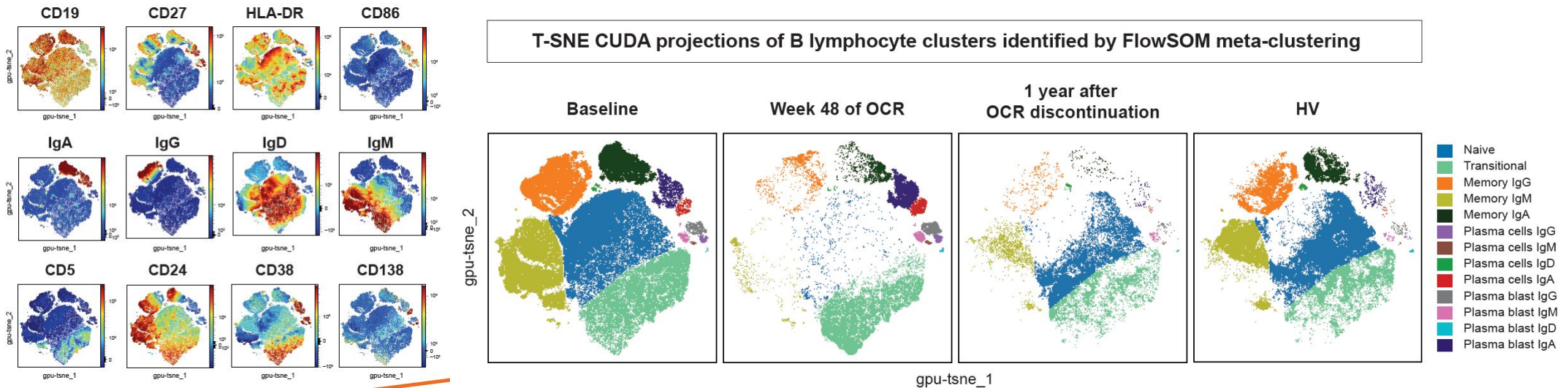
Patient characteristics at baseline	RRMS n=18		
Age, mean (SD), years	29.39 (7.0)	34.33 (3.8)	27.60 (4.0)
Female/male, n (%)	14 (70)/6 (30)	3 (100)/0 (0)	7 (70)/3 (30)



Unsupervised analyses were performed on OMIQ (<https://www.omiq.ai/>).

Results

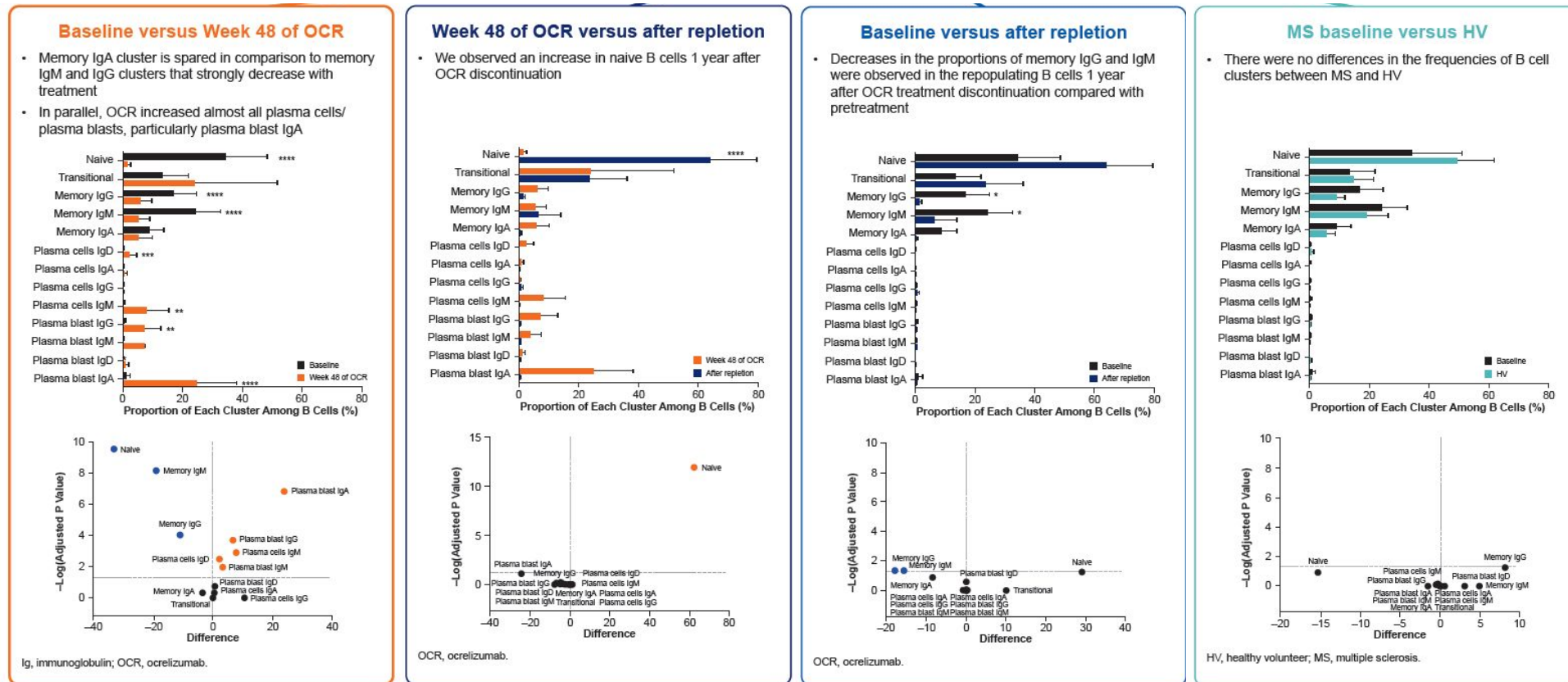
Unsupervised analysis reveals that memory IgA is spared during OCR treatment



We performed a comparative analysis between these different stages

The analysis 1 year after OCR discontinuation is limited to only three patients who stopped treatment during the course of the study

Unsupervised analysis reveals that memory IgA is spared during OCR treatment



Statistical significance determined using the Bonferroni-Dunn method, with alpha = 0.05. Each row was analysed individually, without assuming a consistent SD. Number of t tests: 13.

* p<0.05, ** p<0.01 *** p<0.001, and **** p<0.0001 (mean with SD).

FlowSOM, flow cytometry self-organizing map; HLA-DR, human leukocyte antigen-DR; HV, healthy volunteer; Ig, immunoglobulin; OCR, ocrelizumab;

T-SNE CUDA, t-distributed stochastic neighbor embedding compute unified device architecture.

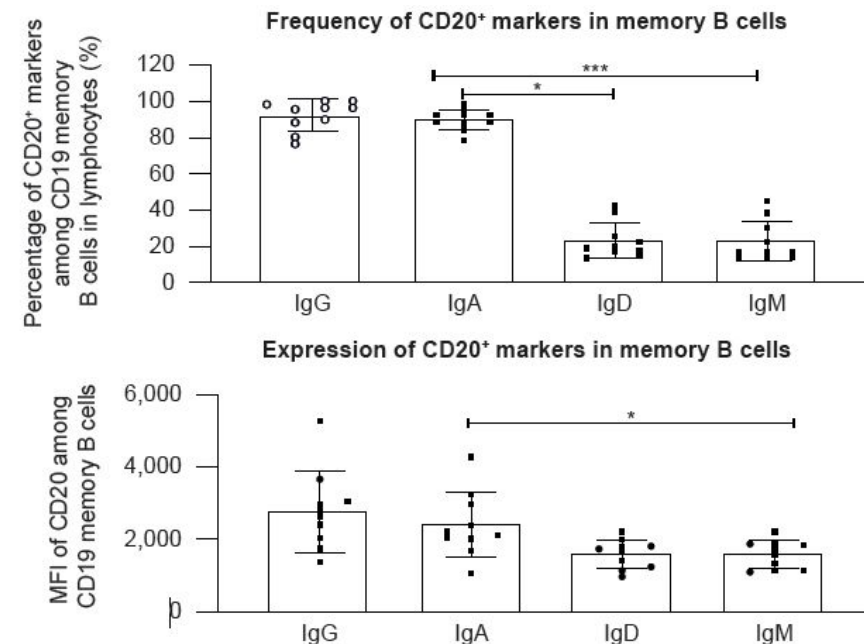
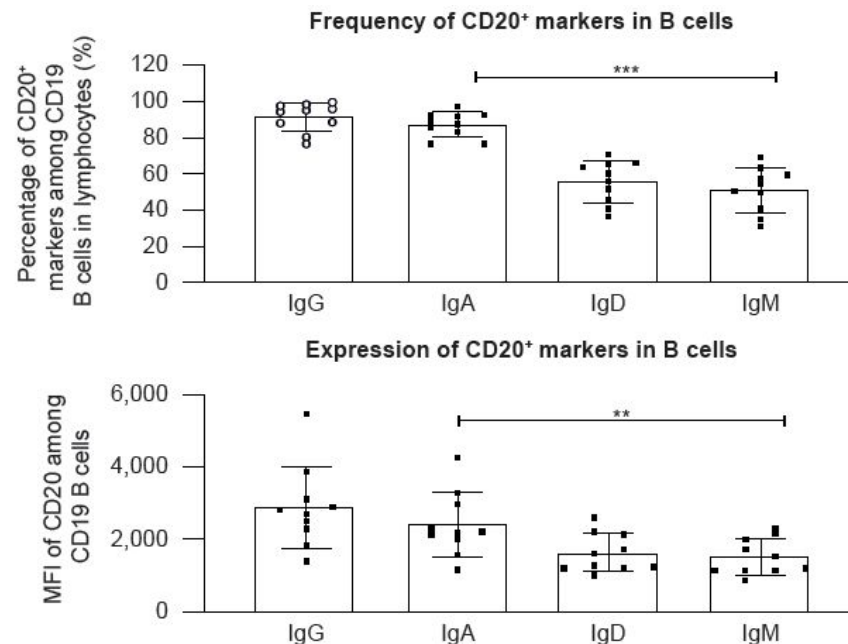
Results

IgA cells do not express the CD20 marker differently from other B cells or memory B cells

- A second cohort was used for this part: CHU Nantes, Agence de Biomedecine (ABM PFS13-003 Collection sclérose en plaques)

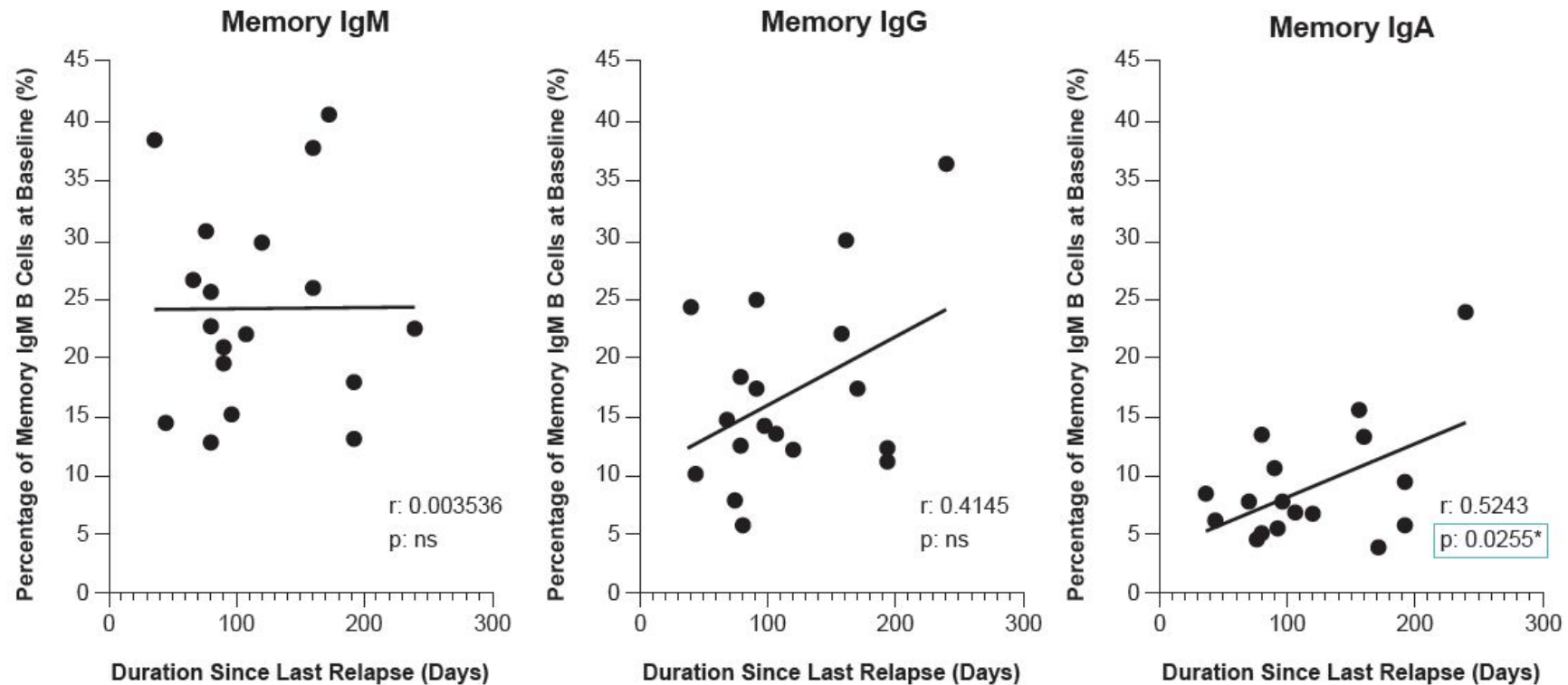
Patient characteristics RRMS n=10
Age, mean (SD), years 39 (5)
Female/male, n (%) 8 (80%)/2 (20%)

Linear regression and Spearman rank test were used. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.



Results

There is correlation between the frequency of memory IgA B cells at baseline and the duration since last relapse



Conclusions



- A regulatory potential of IgA B cells has been demonstrated in a mouse model of multiple sclerosis,¹ and the cells were found in MS lesions²
- In this study we observed that ocrelizumab spared memory IgA cells, which correlated with disease activity, suggesting an implication of these cells in the regulation of MS pathology



<https://ter.li/bmz1mw>

One-Year Analysis of Efficacy and Safety Data From Black and Hispanic Patients With Relapsing Multiple Sclerosis Receiving Ocrelizumab Treatment in the CHIMES Trial

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MJ Williams has received consulting fees from Alexion, Biogen Idec, Bristol Myers Squibb, EMD Serono, Genentech, Inc., Janssen, Novartis, Sanofi Genzyme and TG Therapeutics and serves on speakers bureaus for Biogen, Bristol Myers Squibb, EMD Serono, Janssen, Genentech and TG Therapeutics. **T Vartanian** reports personal compensation for consulting, speaking, or serving on steering committees or advisory boards for Biogen Idec, Novartis, Genentech, Inc., EMD Serono, the National Multiple Sclerosis Society and the National Institutes of Health. **AT Reder** has received consulting fees from Bayer, Biogen, F. Hoffmann-La Roche Ltd, Genentech, Inc., Merck Serono, Novartis and TG Therapeutics; is an editor for MedLink; and has received unrestricted research grant support from Bayer, Biogen, F. Hoffmann-La Roche Ltd, Genentech, Inc., Mallinckrodt, Merck Serono and Novartis. **NL Monson** has received consulting fees from EMD Serono and Genentech, Inc.; is a founder of GenrAb; and holds patent US 8,394,583 B2 on MSPrecise™, a diagnostic tool for predicting conversion to multiple sclerosis. **K Pandey** has served as a consultant for: Biogen, BMS, Genentech/Roche and Sanofi-Genzyme. She has served as a speaker for: Biogen, Genentech/Roche, BMS, Sanofi-Genzyme, Alexion and Horizon Therapeutics. **K Rammohan** has received honoraria from, Biogen, Genentech, Inc., Genzyme, EMD Serono, Novartis and TG Therapeutics and has received research grant support from Biogen, Genentech, EMD Merck Serono, Novartis, Alexion and TG Therapeutics. **B Hendin** has served on advisory and speakers bureau for EMD Serono, Genentech, Genzyme, Novartis, TG Therapeutics, Banner, Horizon, Alexion and Biogen and received research support from Novartis, Genentech, EMD Serono and Genzyme. **DS Sokhi** has received speaker fees from F. Hoffmann-La Roche Ltd. **L Amezcua** reports personal compensation for consulting or serving on steering committees or advisory boards for Biogen Idec, Novartis, Genentech, Inc., and EMD Serono, and has received research support from the National Multiple Sclerosis Society, National Institute of Neurological Disorders and Stroke and Biogen. **E Bernitsas** has received grant support from F. Hoffmann-La Roche Ltd, Genentech, Inc., Sanofi Genzyme, MedImmune, Novartis, EMD Merck Serono, Chugai, Mallinckrodt and TG Therapeutics; is a Chief Editor for the “Brain Sciences” Neuroimaging section; and has received consulting fees/honoraria from Biogen, Merck Serono, Bristol Myers Squibb, Horizon, Janssen Pharmaceuticals and Genentech, Inc. **R Parekh, J Pei, I Abioye, and J Acosta** are employees of Genentech, Inc., and shareholders of F. Hoffmann-La Roche Ltd. **GF Wu** has received honoraria for consulting from Novartis, Sangamo and Genentech, Inc., and research funding from Biogen, EMD Serono and F. Hoffmann-La Roche Ltd.

Background and Objective



Black/African American and Hispanic/Latino people with multiple sclerosis (pwMS) experience greater disease burden and greater eventual MS-related disability than White pwMS¹⁻⁵



Accurate understanding of MS pathophysiology and disease-modifying therapy (DMT) efficacy is precluded by the lack of racial and ethnic diversity in clinical trials^{1,6}



CHIMES (NCT04377555) is a prospective, open-label, single-arm, Phase IV study of ocrelizumab in Black/African American and Hispanic/Latino people with relapsing MS (see **Supplement** for further details)



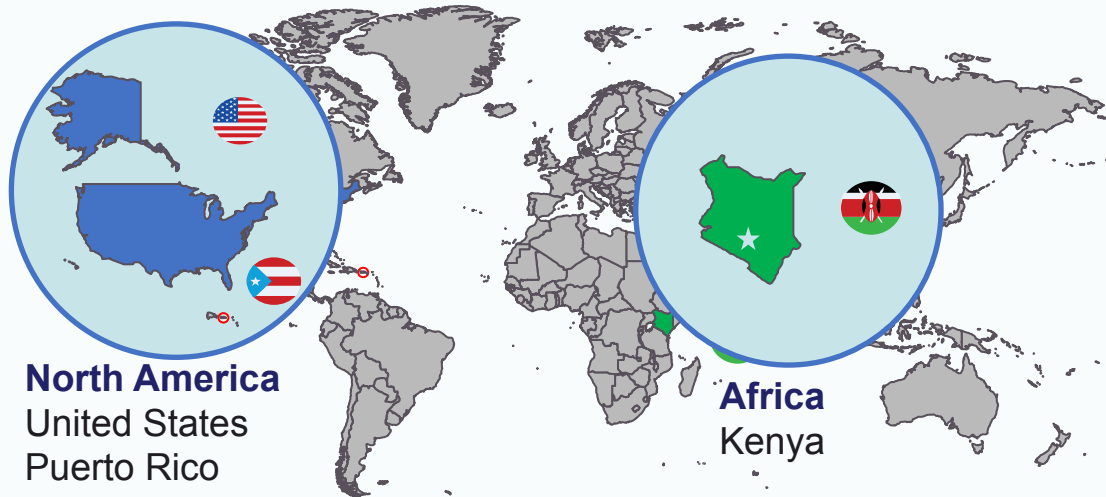
The primary endpoint was no evidence of disease activity (NEDA-3: clinical relapses, confirmed disability progression and MRI activity) at Week 48



To evaluate efficacy and safety during 48 weeks of ocrelizumab treatment in Black/African American and Hispanic/Latino people with relapsing MS

Uniqueness of the CHIMES Study Design

Participants were recruited at **community-based study sites** in the US, Puerto Rico and Kenya



Communication barriers and logistical burdens were addressed to support **inclusive enrollment**



Study materials in multiple languages



Materials reviewed for cultural appropriateness



Flexible scheduling



Compensation for loss of earnings



Ride Health transport



Childcare reimbursement



Travel and meal reimbursement

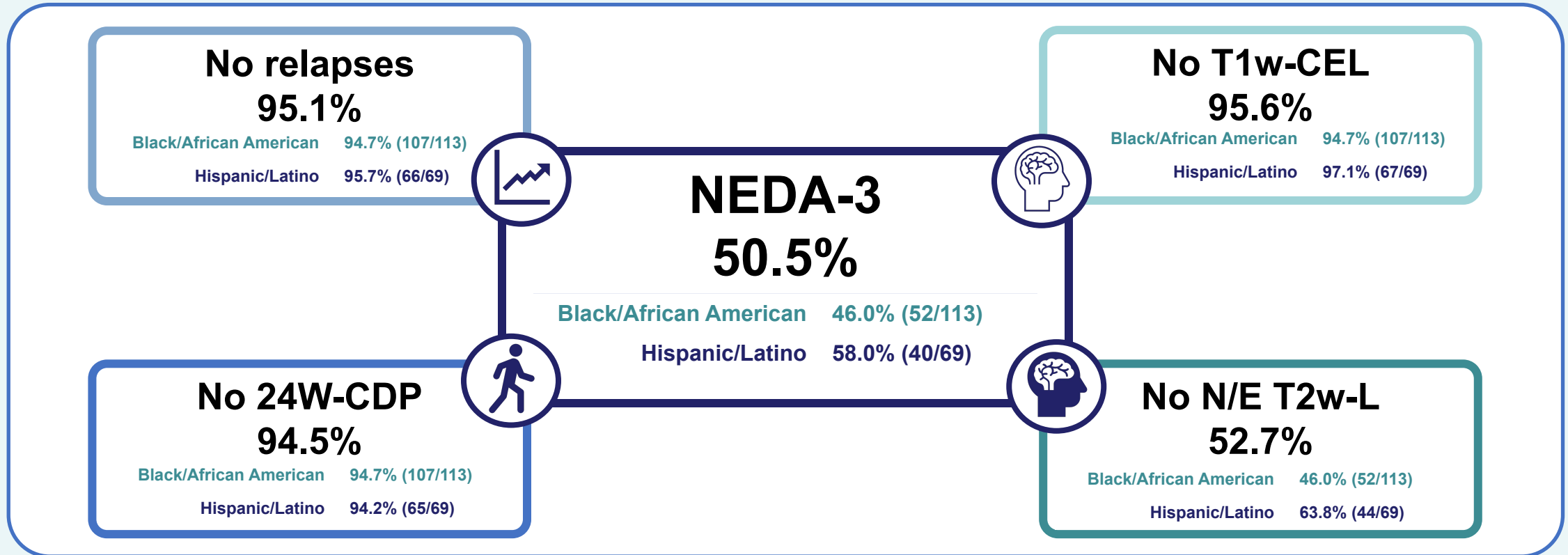
Results

Baseline Demographics and Disease Characteristics

Characteristic	Black/African American n=113	Hispanic/Latino n=69	Total CHIMES N=182
Age, mean (SD), years	36.3 (10.4)	34.2 (10.5)	35.5 (10.5)
Female, n (%)	88 (77.9)	44 (63.8)	132 (72.5)
Ethnicity, n (%)			
Hispanic/Latino	0	69 (100)	69 (37.9)
Not Hispanic/Latino	110 (97.3)	0	110 (60.4)
Unknown	3 (2.7)	0	3 (1.6)
Race, n (%)			
Black/African American	113 (100)	3 (4.3)	116 (63.7)
White	0	63 (98.6)	63 (34.6)
BMI, mean (SD), kg/m ²	31.7 (8.0)	29.9 (6.3)	31.0 (7.4)
Time since symptom onset, mean (SD), years	5.1 (5.7)	4.6 (5.5)	4.9 (5.7)
Time since RMS diagnosis, mean (SD), years	2.9 (4.6)	2.9 (4.4)	2.9 (4.5)
Baseline EDSS (rounded) score, mean (SD)	2.6 (1.4)	2.2 (1.3)	2.4 (1.4)
No. of relapses in the past 24 months, mean (SD)	0.8 (0.6)	0.6 (0.5)	0.7 (0.6)
PwMS receiving previous DMT, n (%)	41 (36.3)	27 (39.1)	68 (37.4)
Time between end of last DMT to initiation of OCR treatment, mean (SD), months	10.2 (18.0)	7.2 (11.0)	9.0 (15.6)
No. of T1 lesions, mean (SD)	2.3 (5.1)	1.2 (2.5)	1.9 (4.3)
No. of T2 lesions, mean (SD)	49.8 (32.9)	48.4 (29.6)	49.3 (31.6)
T2 lesion volume, mean (SD), cm ³	21.4 (20.7)	14.9 (11.9)	18.9 (18.1)

Results

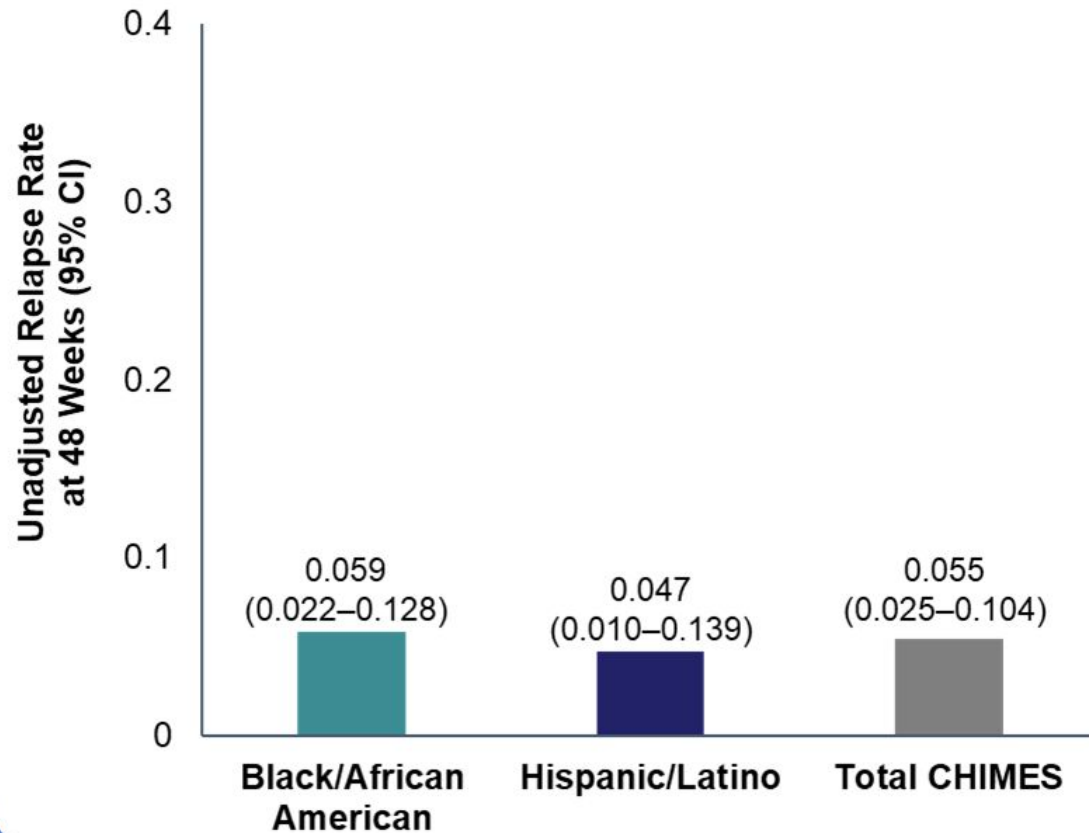
Approximately Half of CHIMES Participants Achieved NEDA at 48 Weeks of Ocrelizumab Treatment



- The majority of CHIMES participants had no relapses, no T1 Gd+ lesions and no disease progression based on 24W-CDP

Results

Ocrelizumab Treatment Resulted in Low Unadjusted Relapse Rates^a in CHIMES Participants



- In the pivotal OPERA I and II trials, 96 weeks of ocrelizumab treatment was associated with an annualised relapse rate (95% CI) of 0.16 (0.12–0.20)⁹

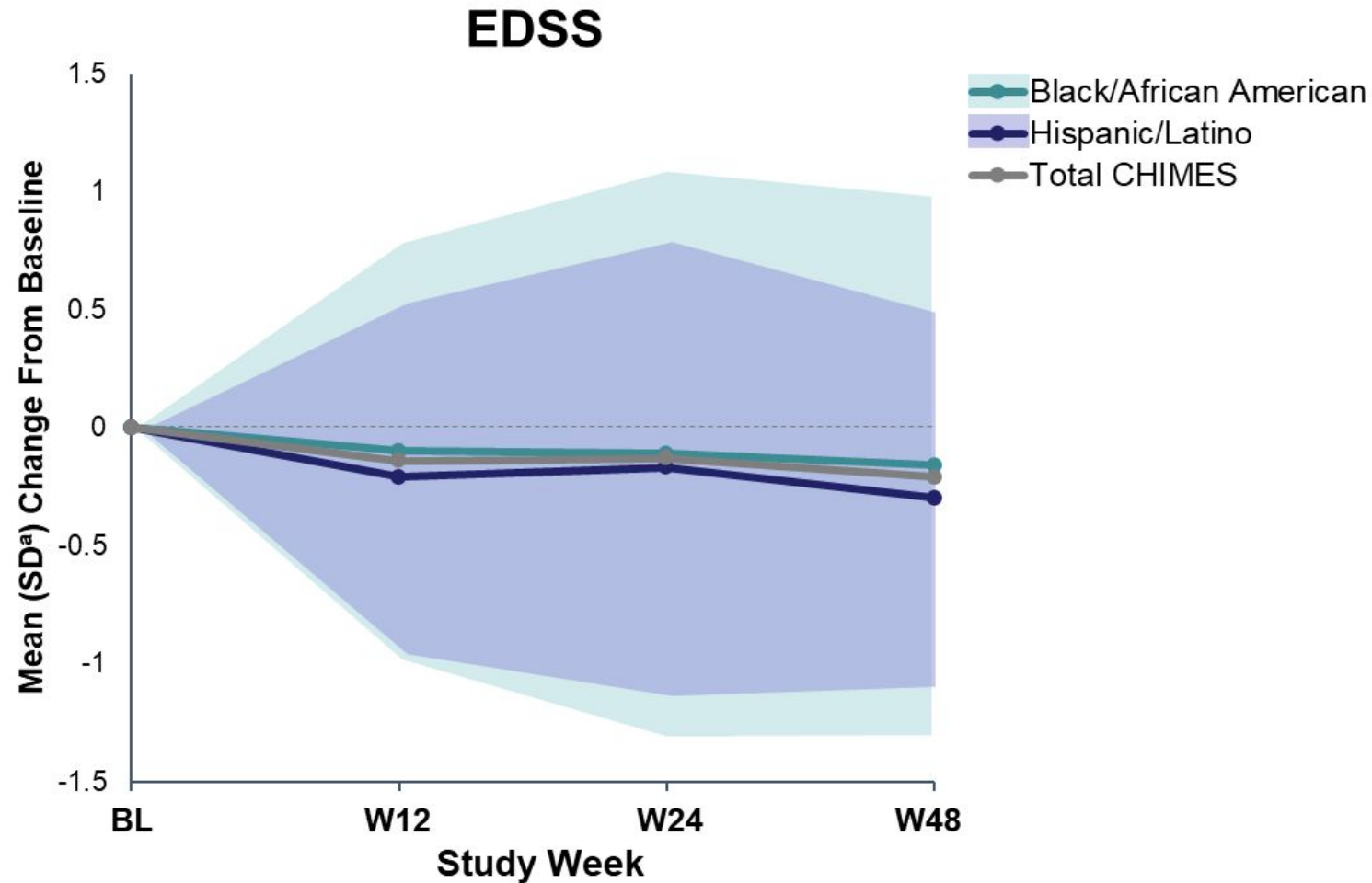
^aThe total number of protocol-defined relapses for all patients divided by the total patient-years of exposure in a year (last assessment for Week 48 or early discontinuation date).

9. Hauser S, et al. *N Engl J Med*. 2017;376(3):221–234.

Results

EDSS Scores Showed Stability From Baseline in CHIMES Participants^a

A



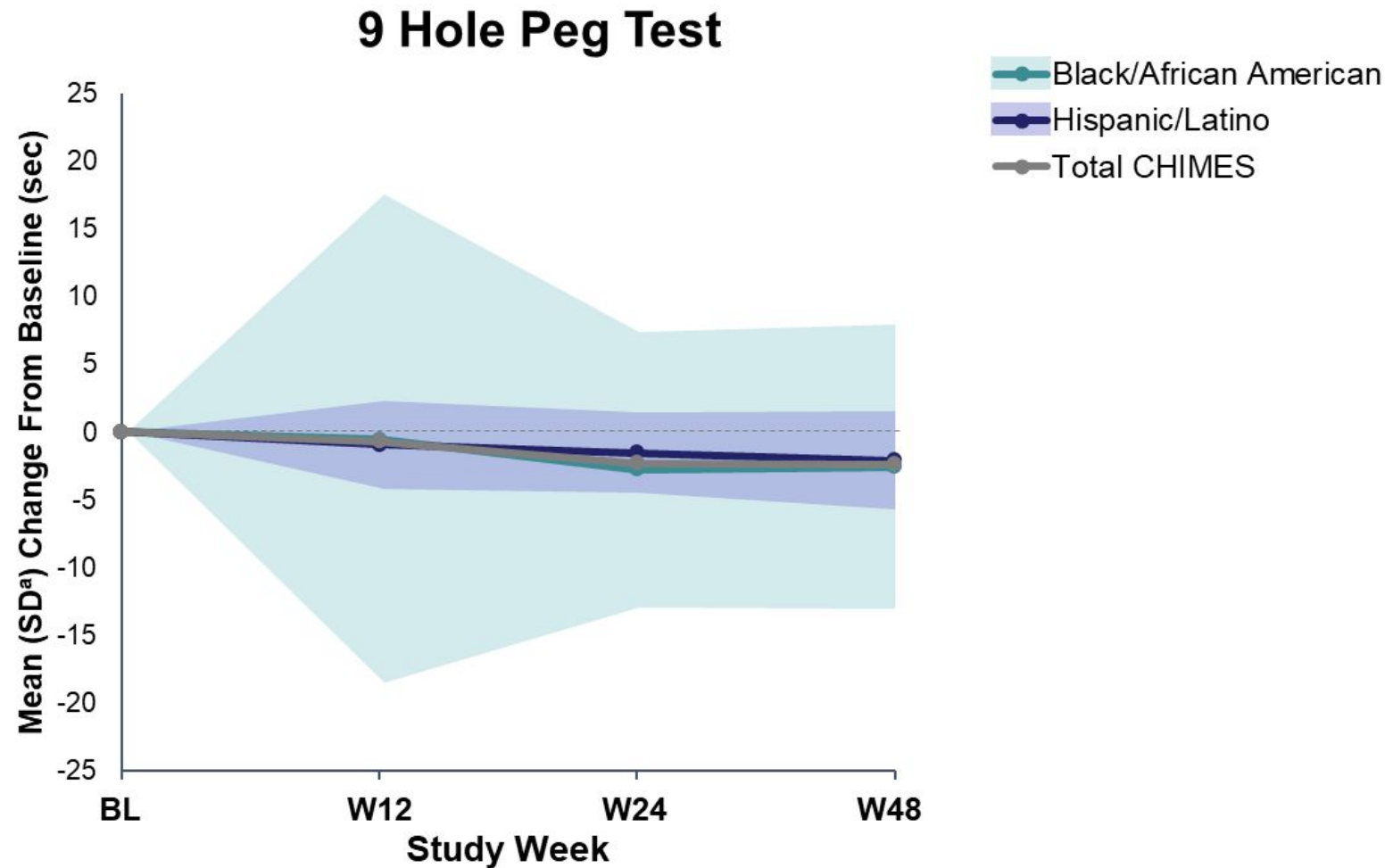
BL, baseline; EDSS, Expanded Disability Status Scale; W, week.

^aLight green and purple shaded areas represent SD for Black/African American and Hispanic/Latino groups, respectively.

Results

9-Hole Peg Tests Showed Stability From Baseline in CHIMES Participants^a

B



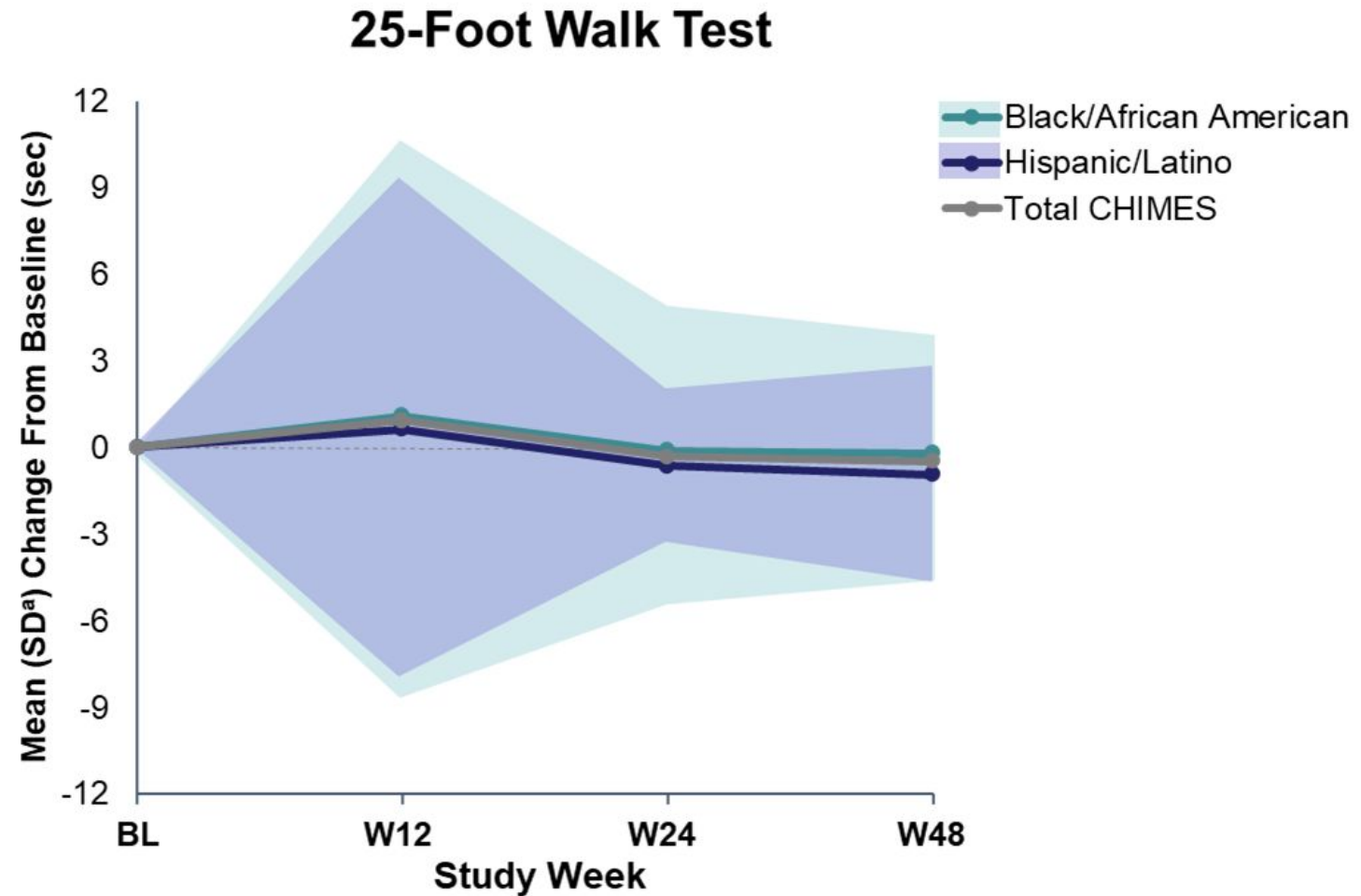
BL, baseline; W, week.

^aLight green and purple shaded areas represent SD for Black/African American and Hispanic/Latino groups, respectively.

Results

25-Foot Walk Tests Showed Stability From Baseline in CHIMES Participants^a

C



BL, baseline; W, week.

^aLight green and purple shaded areas represent SD for Black/African American and Hispanic/Latino groups, respectively.

Results

Safety Summary

Event, n (%)	Black/African American n=113	Hispanic/Latino n=69	Total CHIMES N=182
Any AEs in ≥5% of participants in any group	91 (80.5)	55 (79.7)	146 (80.2)
COVID-19	23 (20.4)	17 (24.6)	40 (22.0)
Headache	14 (12.4)	4 (5.8)	18 (9.9)
Fatigue	5 (4.4)	7 (10.1)	12 (6.6)
Urinary tract infection	10 (8.8)	0	10 (5.5)
Dizziness	3 (2.7)	5 (7.2)	8 (4.4)
Arthralgia	6 (5.3)	0	6 (3.3)
Nausea	6 (5.3)	0	6 (3.3)
Any serious AE^a	7 (6.2)	3 (4.3)	10 (5.5)
Any IRR	28 (24.8)	25 (36.2)	53 (29.1)

- Eleven serious AEs were reported, seven in Black/African American pwMS and four in Hispanic/Latino pwMS
- No IRR was serious

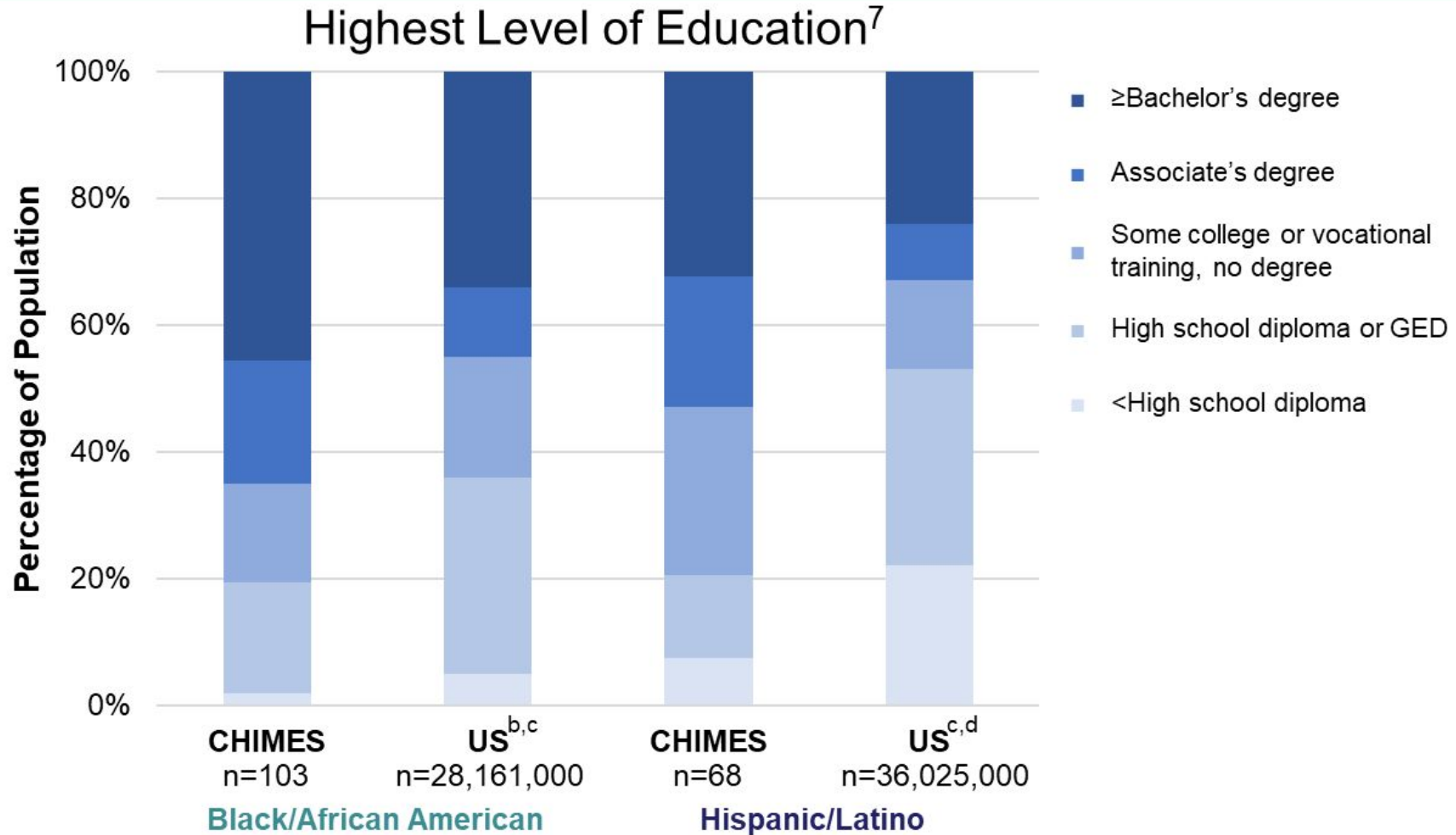
AE, adverse event; IRR, infusion-related reaction; pwMS, people with multiple sclerosis.

^aSerious AEs included COVID-19 (n=2), acute pyelonephritis (n=1), pericarditis (n=1), sinus tachycardia (n=1), acute psychosis (n=1), suicidal ideation (n=1), lower abdominal pain (n=1), papillary thyroid cancer (n=1), endometrial disorder (n=1) and female sterilisation (n=1).

Results

Patterns of Education Level in CHIMES Participants^a Were Different From the Total US Population

A



GED, General Education Development test.

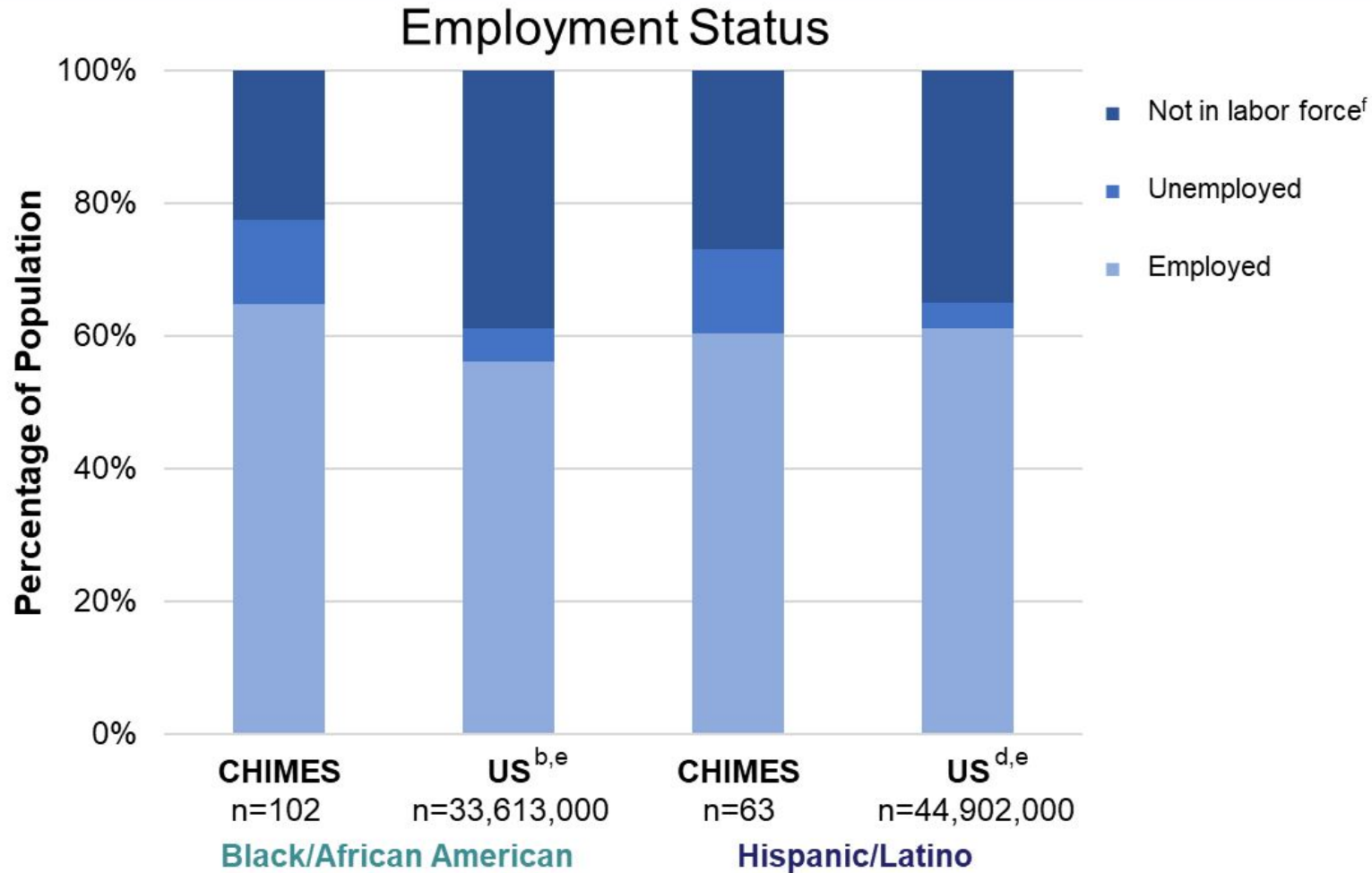
^aKenyan participants were excluded from this analysis; ^bOnly includes individuals who identify solely as Black; ^cSurveyed among those ≥25 years old; ^dIncludes individuals of any race(s).

7. US Bureau of Labor Statistics. Labor Force Characteristics by Race and Ethnicity (2021) Accessed 30 August 2023. <https://www.bls.gov/opub/reports/race-and-ethnicity/2021/>;

Results

Patterns of Employment Status of CHIMES Participants^a Were Similar to the Total US Population

B

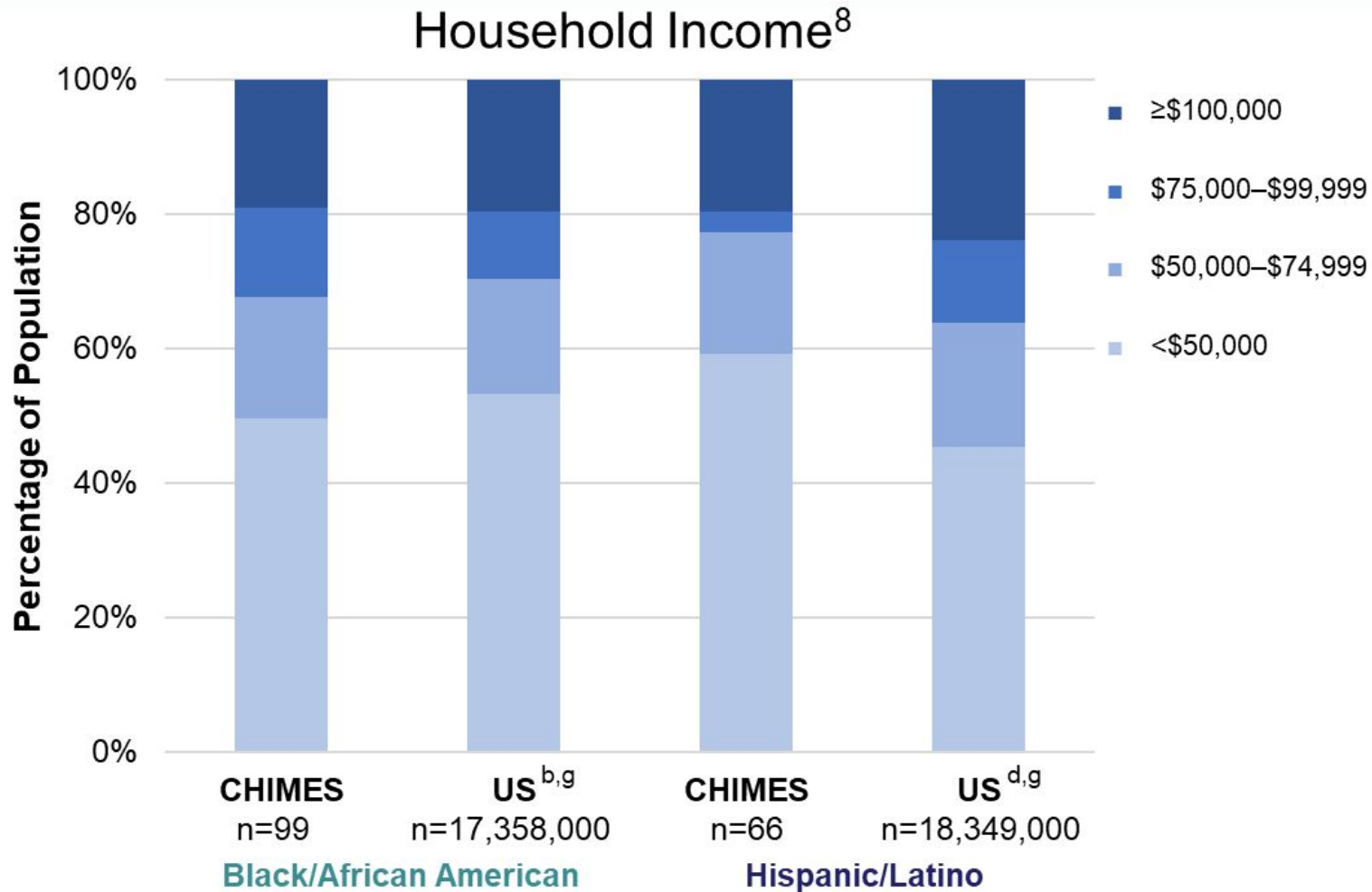


^aKenyan participants were excluded from this analysis; ^bOnly includes individuals who identify solely as Black; ^cSurveyed among those ≥ 16 years old; ^fIncludes those who are retired, homemakers, disabled or not working for other reasons.

Results

Patterns of Household Income of CHIMES Participants^a Were Similar to the Total US Population

C



^aKenyan participants were excluded from this analysis; ^bOnly includes individuals who identify solely as Black. ^gReported as sums of the total income for each person in a household.

8. US Census Bureau. Income and Poverty in the US (2020) Accessed 30 August 2023. <https://www.census.gov/library/publications/2021/demo/p60-273.html>.

Conclusions



- CHIMES is the first and only prospective study addressing the paucity of DMT efficacy data in pwMS among underserved population
- CHIMES is uniquely able to help elucidate cultural or institutional influences on MS disease progression with the inclusion of Kenyan pwMS
- CHIMES participants are representative of patients that neurologists will encounter in their practice
- The overall high efficacy of ocrelizumab observed in CHIMES was in line with efficacy observed in the pivotal OPERA trials⁹
- The safety of ocrelizumab remains favourable as no noticeable differences were observed in CHIMES participants
- Further results and analyses of CHIMES will help fill the knowledge gap in understanding underserved populations

Supplementary Material

Background



Accurate understanding of MS pathophysiology and DMT efficacy is precluded by the lack of racial and ethnic diversity in clinical trials^{1,2}



Black/African American and Hispanic/Latino people with MS experience greater disease burden and greater eventual MS-related disability than White people with MS^{1,3-6}



Ocrelizumab, a humanized anti-CD20 monoclonal antibody, has shown significant and sustained efficacy in people with relapsing or primary progressive MS⁷⁻¹⁰

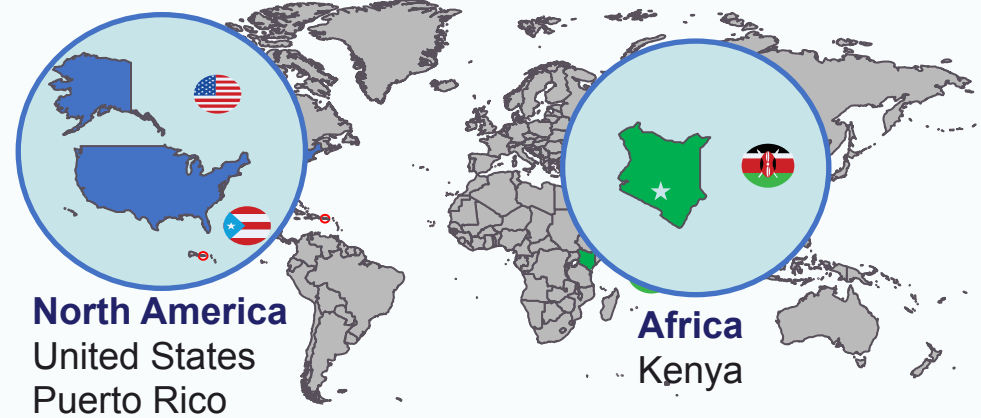
DMT, disease-modifying therapy; MS, multiple sclerosis.

1. Khan O, et al. *Neurol Clin Pract*. 2015;5(2):132-142; 2. Telesford K, et al. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(1):e634; 3. Ventura R, et al. *Mult Scler*. 2017;23(11):1554-1557; 4. Kister I, et al. *Neurol Clin Pract*. 2021;11(4):335-341; 5. Amezcua L, McCauley J. *Mult Scler*. 2020;26(5):561-567; 6. Gray-Roncal K, et al. *Neurol*. 2021;97(9):e881-e889; 7. Hauser S, et al. *N Engl J Med* 2017;376(3):221-234; 8. Hauser S, et al. *Neurol* 2020;95(13); 9. Montalban X, et al. *N Engl J Med* 2017;376(3):209-220; 10. Wolinsky J, et al. *Lancet Neurol*. 2020;19(12):998-1009.

Methods



- CHIMES is a prospective, open-label, single-arm, Phase IV study
- Self-identified Black/African American and Hispanic/Latino people aged 18 to 65 years with RMS and an EDSS score of ≤ 5.5 were recruited at all study sites



Addressing language/communication barriers



Study-related materials were available in multiple languages



Materials were reviewed to ensure understanding and cultural appropriateness

Addressing financial, time and logistic burdens



Flexible scheduling



Compensation for loss of earnings



Ride Health transport



Childcare reimbursement



Travel and meal reimbursement

Results

US-Only CHIMES Baseline Socioeconomic Status

Characteristic, n (%)	Black/African American	Hispanic/Latino	Total CHIMES
Highest level of education	n=103	n=68	N=171
<High school diploma	2 (1.9)	5 (7.4)	7 (4.1)
High school or GED	18 (17.5)	9 (13.2)	27 (15.8)
Technical/vocational program, no degree	6 (5.8)	10 (14.7)	16 (9.4)
<2 years of college	10 (9.7)	8 (11.8)	18 (10.5)
Associate's degree or equivalent	20 (19.4)	14 (20.6)	34 (19.9)
Bachelor's degree	30 (29.1)	12 (17.6)	42 (24.6)
Master's degree or other postgraduate training	16 (15.5)	9 (13.2)	25 (14.6)
Doctoral degree	1 (1.0)	1 (1.5)	2 (1.2)
Employment status	n=102	n=63	N=165
Full time	54 (52.9)	31 (49.2)	85 (51.5)
Part time	12 (11.8)	7 (11.1)	19 (11.5)
Not currently employed	13 (12.7)	8 (12.7)	21 (12.7)
Retired	3 (2.9)	2 (3.2)	5 (3.0)
Homemaker	3 (2.9)	6 (9.5)	9 (5.5)
Disabled	12 (11.8)	6 (9.5)	18 (10.9)
Other	5 (4.9)	3 (4.8)	8 (4.8)
Household income	n=99	n=66	N=165
<\$20,000	20 (20.2)	18 (27.3)	38 (23.1)
\$20,000–\$29,999	9 (9.1)	6 (9.1)	15 (9.1)
\$30,000–\$39,999	15 (15.2)	8 (12.1)	23 (13.9)
\$40,000–\$49,999	5 (5.1)	7 (10.6)	12 (7.3)
\$50,000–\$59,999	14 (14.1)	7 (10.6)	21 (12.7)
\$60,000–\$74,999	4 (4.0)	5 (7.6)	9 (5.5)
\$75,000–\$99,999	13 (13.1)	2 (3.0)	15 (9.1)
>\$100,000	19 (19.2)	13 (19.7)	32 (19.4)

Results

US Socioeconomic Status

Characteristic	Black/African American ^a	Hispanic/Latino ^b
Income¹	n=17,358,000	n=18,349,000
<\$15,000	18.0%	10.6%
\$15,000–\$24,999	11.7%	9.8%
\$25,000–\$34,999	10.3%	10.3%
\$35,000–\$49,999	13.3%	14.7%
\$50,000–\$74,999	17.1%	18.4%
\$75,000–\$99,999	9.9%	12.3%
>\$100,000	19.6%	23.9%
Education²	n=28,161,000	n=36,025,000
>High school	5%	22%
High school graduate, no college	31%	31%
Some college, no degree	19%	14%
Associate's degree	11%	9%
Bachelor's degree and higher	34%	24%
Employment²	n=33,613,000	n=44,902,000
Not in labor force	39.1%	34.5%
Employed	55.7%	61.1%
Unemployed	5.2%	4.4%

^aOnly includes individuals who identify solely as Black. ^bIncludes individuals of any race(s).

1. US Census Bureau. Income and Poverty in the US (2020). Accessed 13 Sep 2023. <https://www.census.gov/library/publications/2021/demo/p60-273.html>;

2. US Bureau of Labor Statistics. Labor Force Characteristics by Race and Ethnicity (2021). Accessed 13 Sep 2023. <https://www.bls.gov/opub/reports/race-and-ethnicity/2021/>.

Results

Baseline Socioeconomic Status in the US-Only CHIMES Population vs the US Population

Characteristic, n (%)	US Black/African American CHIMES Population	US Black/African American Population, (%) ^a	US Hispanic/Latino CHIMES Population	US Hispanic/Latino Population, (%) ^b	All US CHIMES
Highest level of education¹	n=103	n=28,161,000	n=68	n=36,025,000	n=171
<High school diploma	2 (1.9)	(5)	5 (7.4)	(22)	7 (4.1)
High school diploma or GED	18 (17.5)	(31)	9 (13.2)	(31)	27 (15.8)
Some college, no degree	16 (15.5)	(19)	18 (26.5)	(14)	34 (19.9)
Associate's degree	20 (19.4)	(11)	14 (20.6)	(9)	34 (19.9)
≥Bachelor's degree	47 (45.6)	(34)	22 (32.3)	(24)	69 (40.4)
Employment status¹	n=102	n=33,613,000	n=63	n=44,902,000	n=165
Employed	66 (64.7)	(55.7)	38 (60.3)	(61.1)	104 (63.0)
Unemployed	13 (12.7)	(5.2)	8 (12.7)	(4.4)	21 (12.7)
Not in labor force ^c	23 (22.5)	(39.1)	17 (27.0)	(34.5)	40 (24.2)
Household income²	n=99	n=17,358,000	n=66	n=18,349,000	n=165
<\$50,000	49 (49.6)	(53.3)	39 (59.1)	(45.4)	88 (53.4)
\$50,000–\$74,999	18 (18.1)	(17.1)	12 (18.2)	(18.4)	30 (18.2)
\$75,000–\$99,999	13 (13.1)	(9.9)	2 (3.0)	(12.3)	15 (9.1)
>\$100,000	19 (19.2)	(19.7)	13 (19.7)	(23.9)	32 (19.4)

GED, General Education Development test.

^aOnly includes individuals who identify solely as Black. ^bIncludes individuals of any race(s). ^cIncludes those who are retired, homemakers, disabled, or not working for other reasons.

1. US Census Bureau. Income and Poverty in the US (2020) Accessed 30 August 2023. <https://www.census.gov/library/publications/2021/demo/p60-273.html>;

2. US Bureau of Labor Statistics. Labor Force Characteristics by Race and Ethnicity (2021) Accessed 30 August 2023. <https://www.bls.gov/opub/reports/race-and-ethnicity/2021/>.



<https://ter.li/o7obu5>

Combining Measures from Clinical Assessments, Imaging and Fluid Biomarkers at 1 Year to Predict Multiple Sclerosis Progression at 2 Years

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Wednesday, 11 October 2023

Disclosures

N Lewin-Koh is an employee of Genentech, Inc., a member of the Roche Group. **D Clayton** is an employee of Genentech, Inc., a member of the Roche Group, and a shareholder in F. Hoffmann-La Roche Ltd. **C Berge** is an employee of and a shareholder in F. Hoffmann-La Roche Ltd. **F Dahlke** is an employee of Impulze GmbH Zürich and provides consulting services for F. Hoffmann-La Roche Ltd. **HM Schneble** is an employee of and a shareholder in F. Hoffmann-La Roche Ltd. **C Bernasconi** is a contractor for F. Hoffmann-La Roche Ltd.

Background and Study Aims

- MS is typically assessed in clinical trials with clinical evaluations and imaging; fluid biomarkers are often secondary endpoints
- MS Phase III clinical trials require large numbers of subjects and a long duration to identify the efficacy of therapies
- Current Phase II endpoints, which have shorter readout times, are unable to demonstrate benefits over the current standard treatment approaches^a
- A single measure combining information from these assessments for early prediction of long-term progression may improve MS drug development by shortening early-phase trials



- The aim of the study was to evaluate a new combined marker, which can be used to assess the treatment effect and the risk of long-term disease progression in MS Phase II trials at earlier time points than current measures
- The marker should be calibrated such that a change in the marker, due to intervention, greater than δ implies that for the actual endpoint Y, under the same intervention, the change in Y is greater than a threshold, such as a target product profile^b
- Combination markers were assessed based on how well the treatment effect in the combined marker at Week 48 predicts the population level progression summary at Week 96

MS, multiple sclerosis.

^aFor example, new T2 lesions are already inhibited by ocrelizumab (OCR) and other anti-inflammatory treatments. Testing against placebo can show proof-of-concept, but not incremental treatment effects.

^bGenerally, many trials are required to validate such a marker in a meta-analytic framework, as there is only one realisation of the outcomes per trial.

Methods

Derivation of Combined Markers

A subset of patients from the Phase III relapsing multiple sclerosis trials (OPERA I/II) were combined as a training set (n=933), to derive a combined marker from markers of disease worsening^a

The variable selection procedure^b involves calculating four models:¹

1. A survival model of time to CDW on Z (treatment)
2. A survival model of time to CDW on S + Z
3. A survival model of time to CDW on S (marker)
4. A linear model of $h(S)$ on Z, such that $h(s)$ is the linear predictor from model 3

The combined marker is a linear combination of the individual markers, reflecting the linear predictor of the final Cox model

From these four models, proportion of treatment effect (PTE),² likelihood reduction factor (LRF),³ proportion information gained (PIG),⁴ the t-value from the linear model (4) and the z-value from the prognostic model (3), all measures of surrogacy, efficacy or prognostic strength, were calculated and markers ranked for each criterion; best markers were identified based on their mean rank

- PTE is the ratio of the combined marker coefficient with and without the treatment in the model
- LRF and PIG measures the generalised correlation through the likelihood ratio test of the model with and without the marker or the treatment, respectively⁴

CDW, confirmed disability worsening; LRF, likelihood reduction factor; PIG, proportion information gained; PTE, proportion of treatment effect.

^aMarkers included data from clinical assessments, imaging and fluid biomarkers from up to 1 year from baseline.

1. Prentice RL. *Stat Med* 1989;8:431–440. 2. Freedman LS, et al. *Stat Med* 1992;11:167–178. 3. Alonso A, et al. *Biometrics* 2004;60(3):724–728. 4. Qu Y, Case M. *Biometrics* 2007;63(3):958–960.

Methods

Assessment of the Combined Marker via Calibration

Since there is only one pooled dataset, a meta-analytic calibration of the combined marker needs to be done on hypothetical data

A permutation approach was used to generate hypothetical trials with different effect sizes systematically, by ordering the data and switching labels weighting the upper and lower extremes of the combined marker^{a,b} and a subsequent bootstrap procedure was used on each permutation to empirically estimate the variability of the population level parameter

The procedure was performed first permuting the combined marker, and estimating the 24W-CDW HR (forward calibration), then permuting 24W-CDW, and estimating the combined marker difference (reverse calibration)
– A positive slope indicates the potential for finding a threshold

A validation of the combined marker was performed on an independent test dataset of patients (n=382) with PPMS treated with OCR vs placebo (ORATORIO; NCT01194570)

CDW, confirmed disability worsening; HR, hazard ratio; OCR, ocrelizumab; PPMS, primary progressive multiple sclerosis; W, week.

^aPlease see Supplementary Materials for further information; ^bThis approach is similar to that of the Monte-Carlo simulation approach to get the individual (causal) threshold effect.⁵

5. Van der Elst, et al. *Pharm Stat* 2021;20(6):1216–1231.

Results

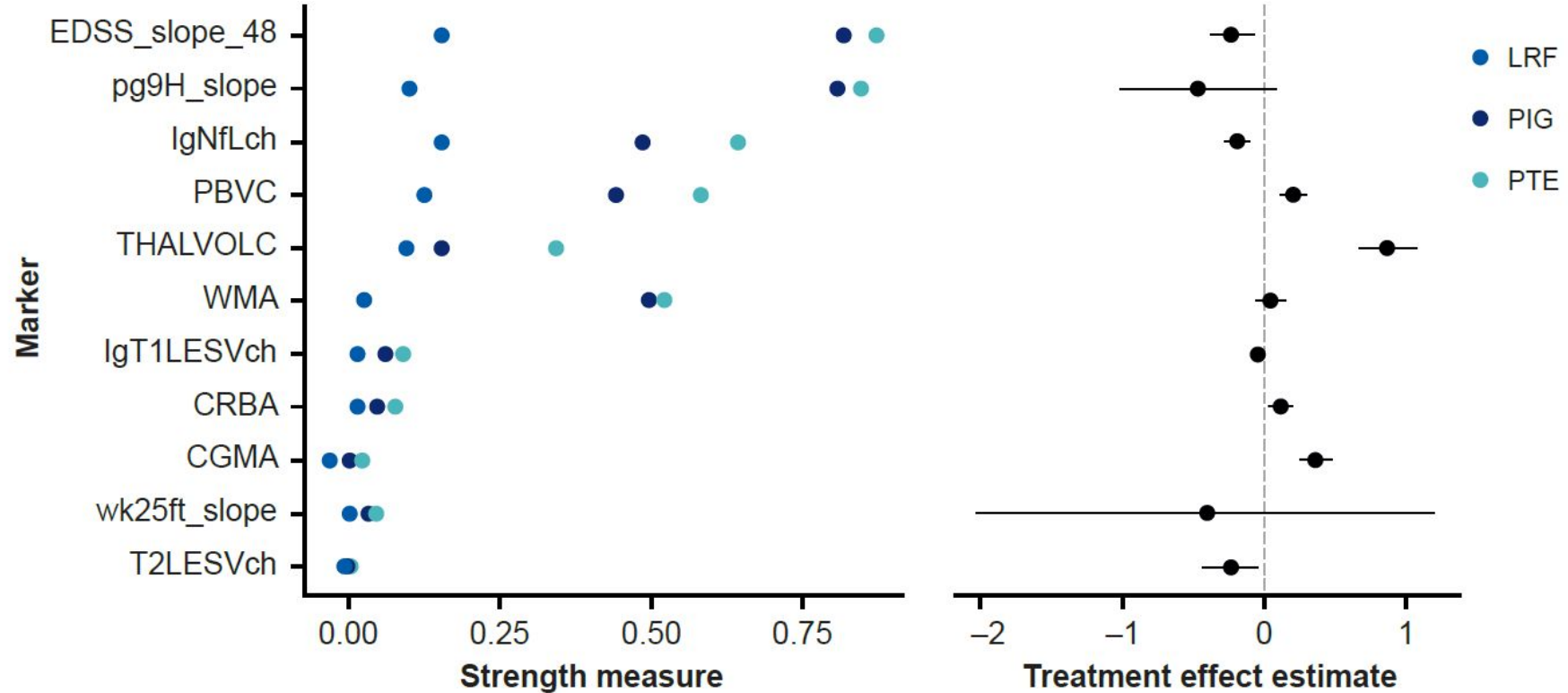
Initial List of Potential Markers^a

Variable name	Description	Transformation
EDSS (clinical)	Expanded Disability Status Scale	Regression slope (per patient)
wk25ft (clinical)	Timed 25-Foot Walk Test	Regression slope (per patient)
pg9H (clinical)	Nine-Hole Peg Test	Regression slope (per patient)
IgNfL (fluid biomarker)	Serum neurofilament light chain protein	Change from baseline of log (NfL)
CGMA (MRI)	Cortical grey matter atrophy	None
PBVC (MRI)	Percent brain volume change	None
T2LESV (MRI)	T2 lesion volume	Change from baseline
THALVOLC (MRI)	Thalamic volume change	None
WMA (MRI)	White matter atrophy	None
CRBA (MRI)	Cerebellar atrophy	None
IgT1LESV (MRI)	Non-enhancing T1 lesion volume	Change from baseline of log (T1LESV)

^aMarkers were chosen based on assumed prognostic value for progression.

Results

Selecting Restricted Set of Individual Markers^a



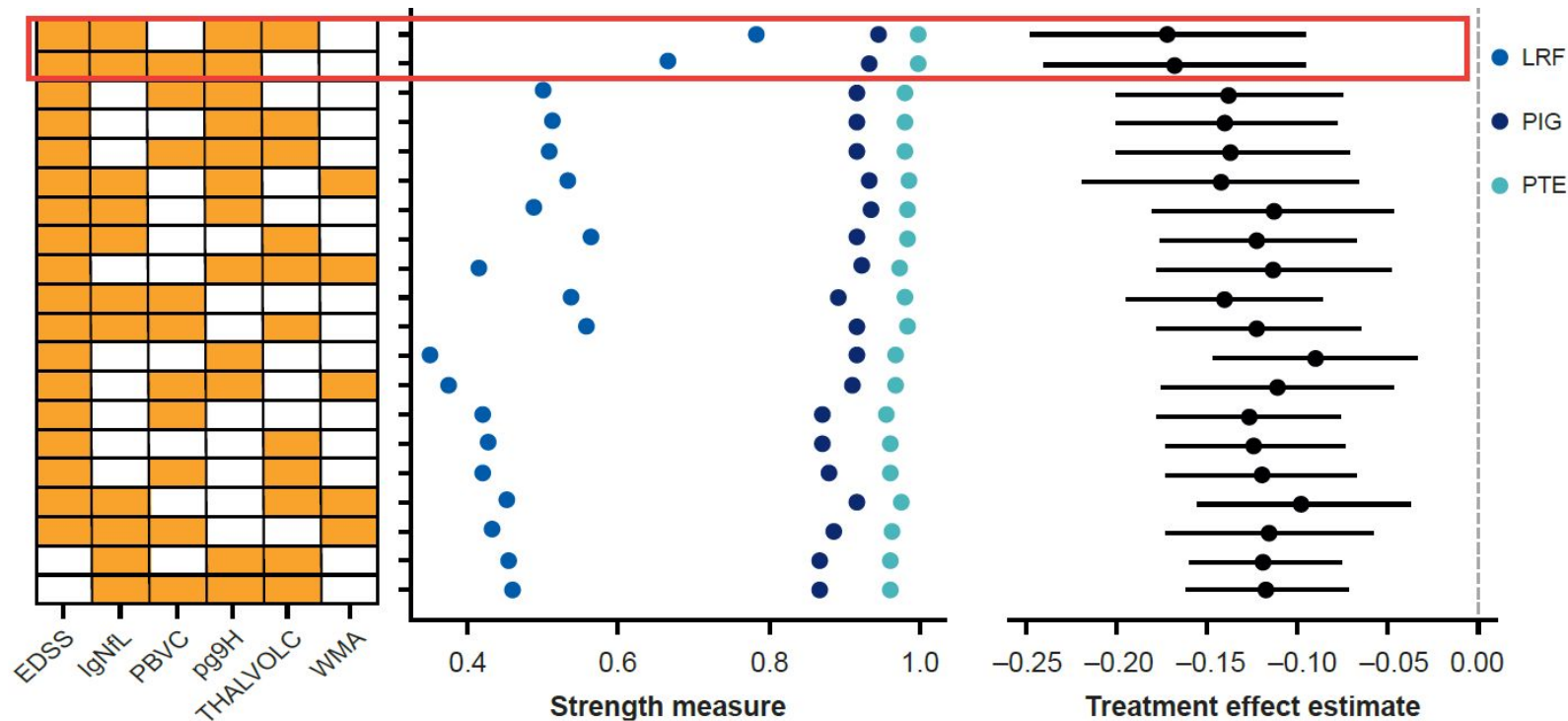
Based on average rankings from the Prentice criterion model, changes in whole brain volume, NfL levels, EDSS scores, Nine-Hole Peg Test scores and thalamic volume were selected for further investigation^b

EDSS, Expanded Disability Status Scale; LRF, likelihood reduction factor; NfL, neurofilament light chain; PIG, proportion information gained; PTE, proportion of treatment effect.

^aPlease refer to the prior table for definitions of the markers. Markers are ordered by their mean rank, based on PTE, PIG, LRF, t-value from a combined marker effect model and the z-value from a prognostic model; ^bMarkers were selected based on having the highest standardised treatment effect, and effectively absorbing the treatment effect.

Results

Selecting the Combined Markers^a



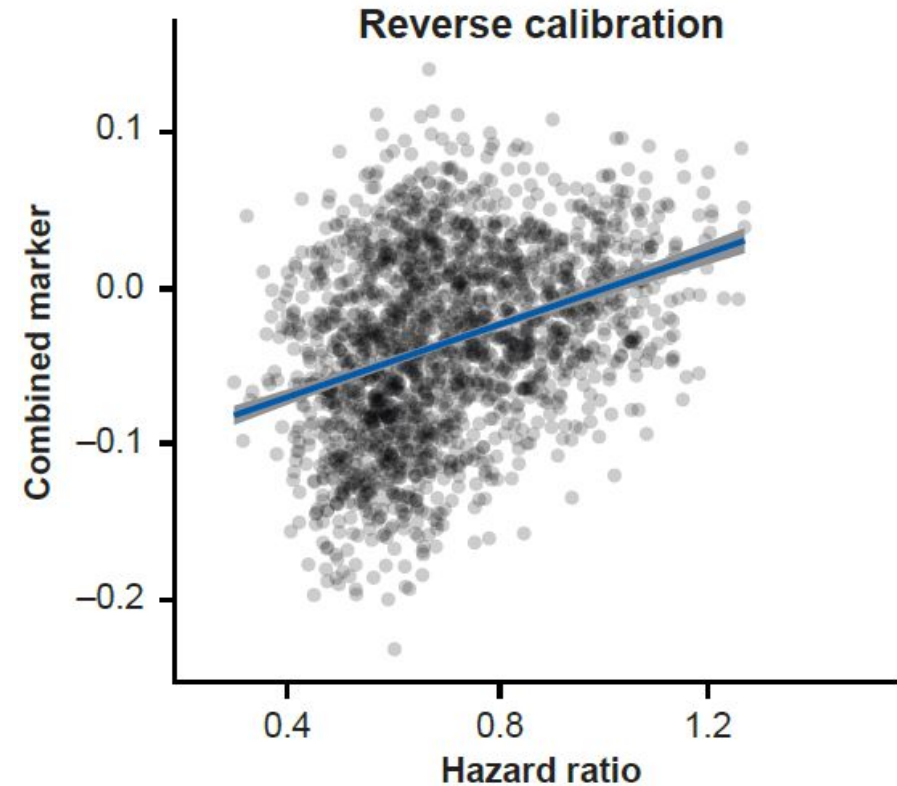
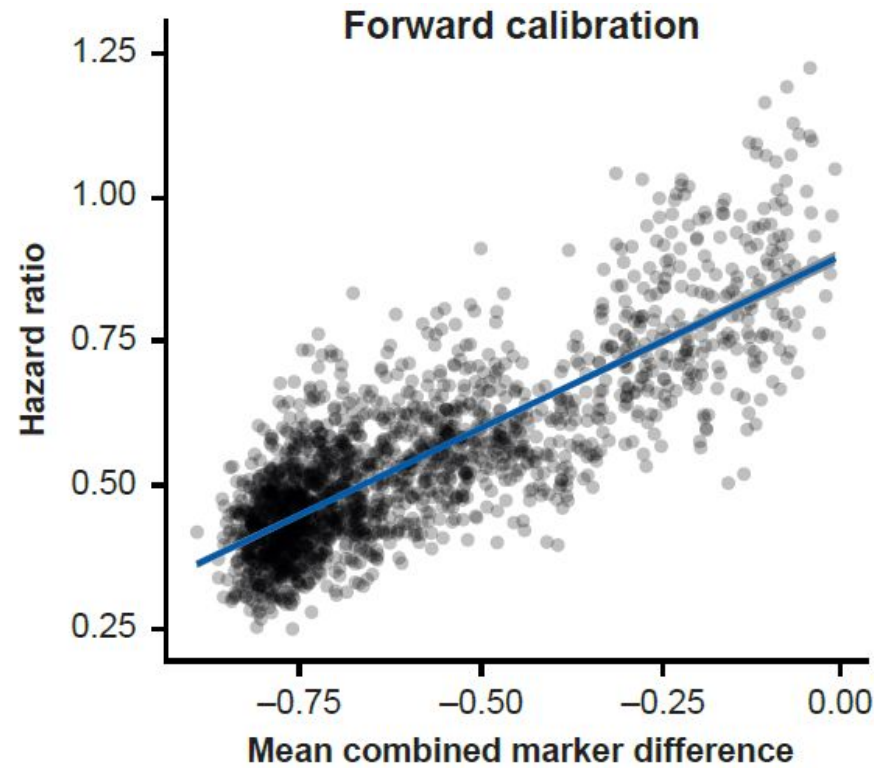
- The top two models were very close in terms of mean rank, differing only by using thalamic volume or whole brain volume
- Due to a high correlation between thalamic volume and whole brain volume changes (0.66), THALVOLC was removed, and PBVC was chosen for the final model^{b,c}
- The final model used for developing the combined marker model utilised EDSS, IgNfL, PBVC and pg9H
- At Week 48, only a weak correlation was observed between the four individual markers^d

EDSS, Expanded Disability Status Scale; IgNfL, Serum neurofilament light chain protein; LRF, likelihood reduction factor; PBVC, percent brain volume change; pg9H, Nine-Hole Peg Test; PIG, proportion information gained; PTE, proportion of treatment effect; THALVOLC, thalamic volume change; WMA, white matter atrophy.

^aPlease refer to the prior table for definitions of the markers; combined markers are ordered by their mean rank, based on PTE, PIG, LRF, t-value from a combined marker effect model and z-value from a prognostic model; ^bMarkers were selected based on having the highest standardised treatment effect, effectively absorbing the treatment effect; ^cPBVC was chosen over THALVOLC to allow for the incorporation of other brain regions in the model; ^dPlease refer to the Supplementary Materials for more information

Results

Calibration of the Chosen Marker Set with HRs^a



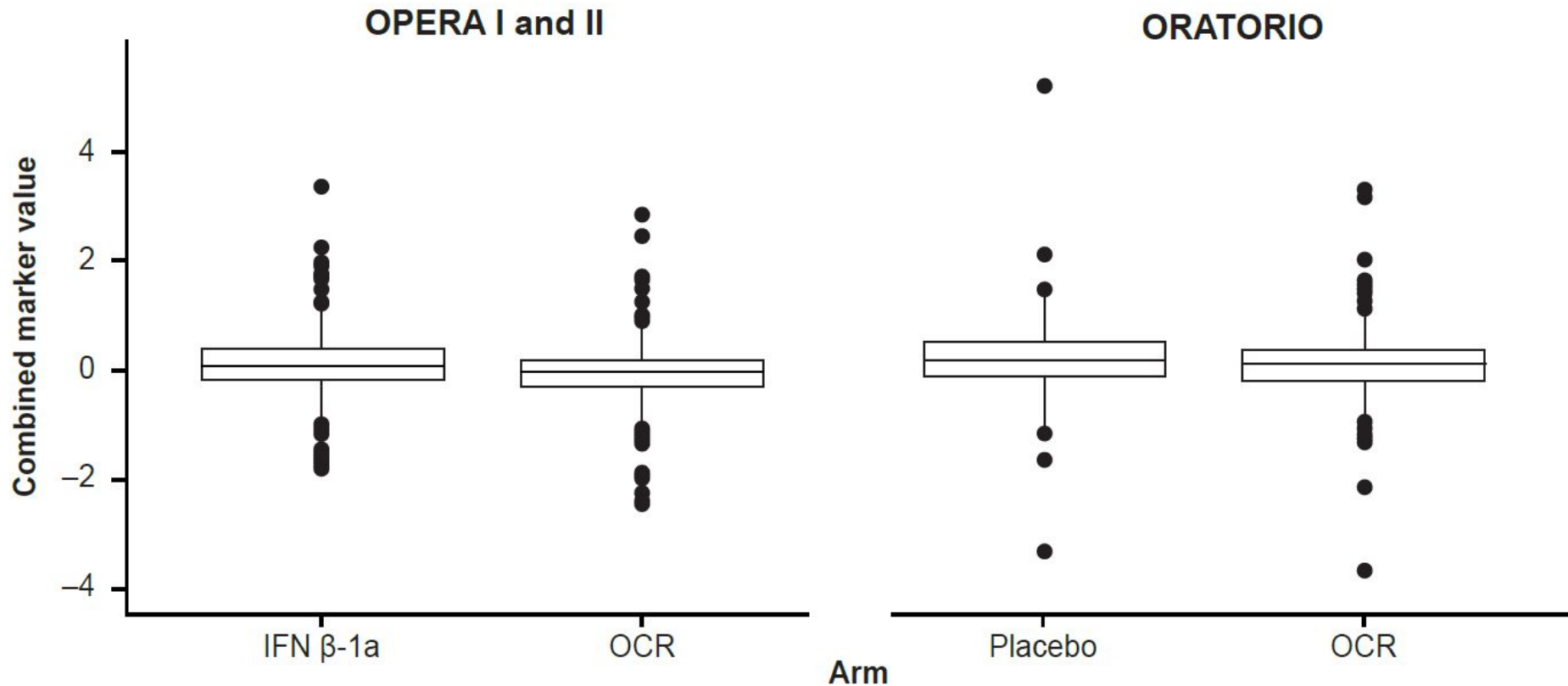
The effect size in the 1-year combined marker model was proportional to the 2-year HR with slopes of 0.6 ($r^2=0.46$) and 1.1 ($r^2=0.12$) in the forward and reverse calibration, respectively^b

24W-CDW, 24-week confirmed disability worsening; HR, hazard ratio.

^aThe HR is a single numbers summary of the difference between two survival distributions and only captures average differences; ^bCalibration curves of the mean combined marker difference vs 24W-CDW HR showed a positive slope in both directions, 0.75 ($r^2=0.46$) in the forward direction and 0.089 ($r^2=0.12$) in reverse.

Results

Checking the Combined Markers in a New Dataset



The combined marker model demonstrated a significant difference between IFN β -1a and OCR among patients from OPERA at Week 48. Similar findings were observed among patients with PPMS from the ORATORIO study^a

IFN, interferon; OCR, ocrelizumab; PPMS, primary progressive multiple sclerosis.

^aThe population in ORATORIO is PPMS; therefore, this study does not provide a direct comparison with the OPERA population used to derive this model.

Conclusions



- **Combining early readouts from multiple modalities into a single measure to predict the 24W-CDW HR at later time points holds promise and can be useful in early-phase MS trials**
- Here, it was shown that multiple markers can be combined to produce a stronger predictive measure of disease worsening in MS clinical trials
- The combined endpoint effect sizes correspond to changes in 24W-CDW HRs, indicating a relationship between endpoints in both training and test sets; the within-trial forward and reverse calibrations suggest that the combined marker model is generalisable to future trials
- This is further supported by the observed treatment effect in ORATORIO, which was independent of the training data (OPERA I and II) and in a different MS population, primary progressive MS (PPMS)

Future Directions



- Work is underway to validate the approach in a meta-analytic setting with multiple MS trials
- Furthermore, evaluation of alternative approaches for ranking marker candidates; as well as assessing whether additional candidate markers could be incorporated
 - Resampling to better estimate model selection error
 - Model relationship of early marker to final endpoint embedded in a single model
- Assessing and accounting for missing data
 - Missing data increase with the number of markers: $n=1,520$ in the combined trials, but only data on 944 patients for all four markers
- There are patients censored prior to marker readout at Week 48

Supplementary Material

Methods

Measures of the Strength of Surrogacy

Combined markers were used to create the new endpoint model for this study, to avoid the historical context associated with the term, surrogate; however, the procedures used were based on evaluating surrogate elements.

Let S be the surrogate and Z be an intervention, in relation to an outcome Y . We can fit the following models:

$$(1) Y_i = \alpha + \gamma_1 Z_i + \epsilon_i$$

and

$$(2) Y_i = \alpha + \nu S_i + \gamma_2 Z_i + \epsilon_i$$

The ratio $\frac{\gamma_2}{\gamma_1}$ is the PTE, accounting for the amount of the treatment effect subsumed by the surrogate in (2). PTE is not very robust and can sometimes be negative.

Methods

Measures of the Strength of Surrogacy

Two measures based on information theory have been developed that mitigate some of the problems with PTE.^{1,2} Both measure the strength of association of models involving the intervention and the surrogate.

Measure 1: The LRF (LRF_A),¹ measures the generalised correlation through the LRT of the surrogate treatment model, with and without the surrogate:

$$LRF_A(S, Z: Z) = 1 - \exp\{-LRT((S, Z: Z))/n\}$$

Measure 2: The PIG,² is also derived from a slightly different formulation of the LRF (LRF_{QC}), which in this case measures the generalised correlation through the LRT of the surrogate model, with and without the treatment:

$$LRF_{QC}(S, Z: S) = 1 - \exp\{-LRT((S, Z: S))/n\} \text{ and } PIG \approx 1 - LRF_{QC}(S, Z: S)$$

The difference between PIG and LRF_A , is that PIG gives more weight to the prognostic value of the surrogate, whereas LRF_{QC} gives more weight to the treatment effect absorbed by the surrogate.

Results

Algorithms for Forward and Reverse Calibration

The idea behind the permutation approach used for forward and reverse calibration is that in a meta-analysis there would be a large number of trials with similar populations and different effect sizes. Both Y and S would be measured in all trials in relation to a trial-specific intervention, Z_T . In this case since there is only one trial (OPERA), synthetic trials with varying treatment effects were generated. Two steps are used:

1. Use controlled permutations of the data to vary the effect size
1. Bootstrap from each permutation to empirically estimate the variability of the population level parameter

This is similar to the Monte-Carlo simulation approach,³ used to get the individual (causal) threshold effect. While simple in theory, in practise it is more complicated because the forward and backward procedures are different. In the forward direction, there is only the effect size of the surrogate to consider, and the HR can be calculated from the selected samples in the permutation bootstrap. In the reverse direction censoring of the time to disability progression, administrative censoring and intercurrent events need to be considered to vary the effect size of the original endpoint, Y .

Results

Forward Calibration – Mean Difference to HR

For the forward calibration, the effect size in the surrogate is varied to evaluate the HR. Large mean differences in S should translate to the HR. To protect against 'bad' bootstrap samples, such as a low count of events in one arm, the fractional weighted bootstrap is used. This ensures effective estimates of the HRs are obtained in the resampling procedure. This algorithm does not account for intercurrent events. The following algorithm was used:

- Calculate the maximum permutation:
 - Sort the data on the marker
 - Label the $n^+/2$ highest values for standard of care and the $n^-/2$ lowest values
- From the maximum permutation, start permuting labels from quantile thresholds to reduce the effect from the maximum
- From each permutation, K bootstrap samples
- Calculate the mean difference and HR from each K bootstrap samples

Results

Calibration – HR to Surrogate

Reverse calibration:

- Separate the events as per the following categories: 1) actual progression events, 2) administratively censored and 3) intercurrent event censored patients
- Permute the labels of the events in specified fractions to vary the effect size
 - The proportions in each group that are administratively censored are compensated to maintain balance
 - Intercurrent events are held equal
- From each permutation a number of bootstrap samples are drawn
- This represents varying the HR and looking at the surrogate, it is important to also vary the surrogate and examine the impact on the HR



<https://ter.li/rqw4ql>



Kinetics of T-Cell Reactivity and Antibody Responses to SARS-CoV-2 After Different Rounds of Vaccination in Persons With Multiple Sclerosis Treated With Ocrelizumab

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C Raposo,⁴ MA Rocca,^{3,5} L Moiola,³ M Filippi,^{3,5} A Riva,^{1,6} R Furlan^{2,5}

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Thursday, 12 October 2023

Disclosures

M Tarkowski, A Mandelli, A Gabrieli, A Finardi and **A Riva** have nothing to disclose. **C Zanetta** received compensation for speaking activities, and/or consulting services, from Alexion, Biogen, Bristol Myers Squibb, Janssen, Merck, Novartis, F. Hoffmann-La Roche Ltd and Sanofi. **R Pedotti** is an employee of F. Hoffmann-La Roche Ltd. **C Raposo** is an employee of F. Hoffmann-La Roche Ltd. **MA Rocca** received consulting fees from Biogen, Bristol Myers Squibb, Eli Lilly, Janssen, F. Hoffmann-La Roche Ltd; and speaker honoraria from AstraZaneca, Biogen, Bristol Myers Squibb, Bromatech, Celgene, Genzyme, Horizon Therapeutics Italy, Merck Serono SpA, Novartis, F. Hoffmann-La Roche Ltd, Sanofi and Teva. She receives research support from the MS Society of Canada, the Italian Ministry of Health, the Italian Ministry of University and Research, and Fondazione Italiana Sclerosi Multipla. She is Associate Editor for Multiple Sclerosis and Related Disorders. **L Moiola** has received honoraria for speaking activities and for participating in advisory boards from Biogen, Merck, Sanofi, Novartis, F. Hoffmann-La Roche Ltd, Celgene, Alexion, Almirall. **M Filippi** is Editor-in-Chief of the Journal of Neurology, Associate Editor of Human Brain Mapping, Neurological Sciences, and Radiology; received compensation for consulting services from Alexion, Almirall, Biogen, Merck, Novartis, F. Hoffmann-La Roche Ltd, Sanofi; speaking activities from Bayer, Biogen, Celgene, Chiesi Italia SpA, Eli Lilly, Genzyme, Janssen, Merck-Serono, Neopharmed Gentili, Novartis, Novo Nordisk, Roche, Sanofi, Takeda, and TEVA; participation in Advisory Boards for Alexion, Biogen, Bristol-Myers Squibb, Merck, Novartis, F. Hoffmann-La Roche Ltd, Sanofi, Sanofi-Aventis, Sanofi-Genzyme, Takeda; scientific direction of educational events for Biogen, Merck, Roche, Celgene, Bristol-Myers Squibb, Lilly, Novartis, Sanofi-Genzyme; he receives research support from Biogen Idec, Merck-Serono, Novartis, Roche, the Italian Ministry of Health, the Italian Ministry of University and Research, and Fondazione Italiana Sclerosi Multipla. **R Furlan** has received speaker fees from F. Hoffmann-La Roche Ltd, BMS, Merck, Alexion, Novartis, Biogen, Sanofi, Horizon.

Study Aim and Background



The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has constituted a major challenge for people with multiple sclerosis (PwMS) taking immune-suppressive therapies, who may not be able to generate adequate immune responses against viral infection or following vaccination¹



Several studies have reported on the effect of the anti-CD20 therapy, ocrelizumab,^{2,3} which mainly depletes B cells, but only a few such studies evaluated the evolution of immune responses over different rounds of vaccination using different antigens^{4,5}



The aim of this study was to define the kinetics of T-cell reactivity and of antibody levels in PwMS treated with ocrelizumab and vaccinated up to four times against SARS-CoV-2

PwMS, people with multiple sclerosis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

1. Hughes R, et al. *Mult Scler Relat Disord* 2021;49:102725; 2. Gadani SP, et al. *EBioMedicine* 2021;73:103636; 3. Brill L, et al. *JAMA Neurol* 2021;78:1510–1514;

4. Apostolidis SA, et al. *Nat Med* 2021;27:1990–2001; 5. Woopen C, et al. *Vaccines* 2023;11:1464.

Methods

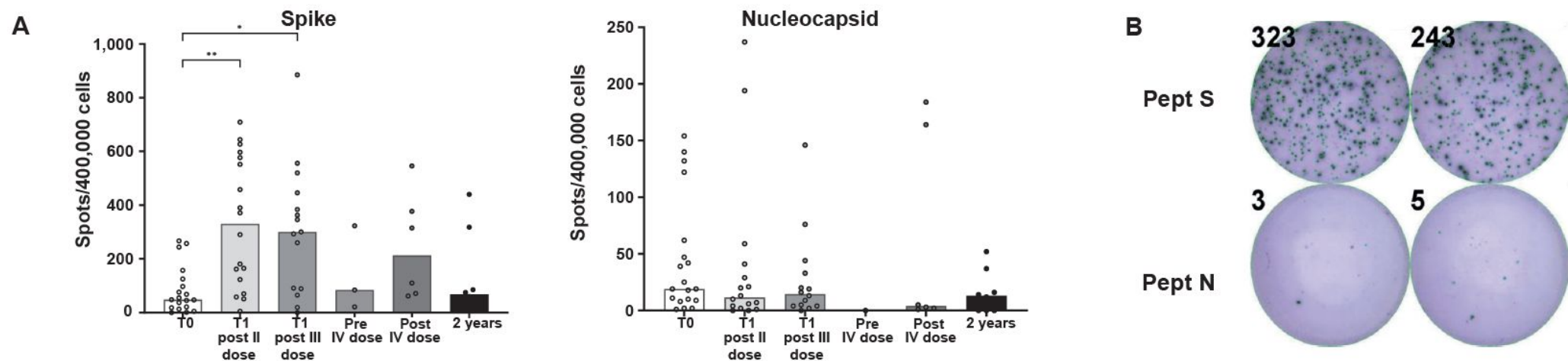


- We sampled the blood of PwMS treated with ocrelizumab at different time points: samples were collected before vaccination (T0), 1 month after the second (T1 post II dose), 1 month after the third (T1 post III dose) and 1 month after the fourth (post IV dose) shot of anti-SARS-CoV-2 vaccine.
- Samples were also collected 2 years after the first dose of vaccination. We used enzyme-linked immunosorbent spot (ELISpot) and fluorescence-activated cell sorting (FACS) to determine T-cell reactivity, and Luminex® xMAP® technology to measure anti-SARS-CoV-2 antibody levels using the Merck MILLIPLEX® platform.

Results

T-cell response to anti-SARS-CoV-2 vaccination

Figure 1. SARS-CoV-2-specific T-cell response assessed by ELISpot assay



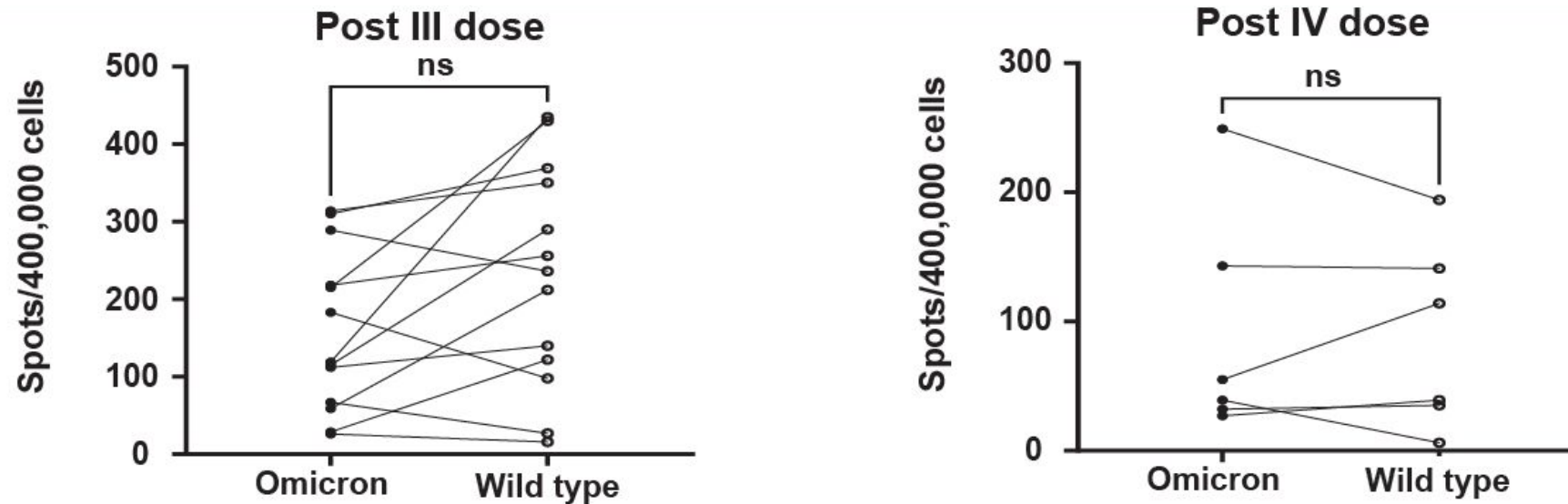
ELISpot, enzyme-linked immunosorbent spot; N, nucleocapsid; Pept, peptides; S, spike; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

(A) Analysis of Interferon-gamma (IFN- γ)-producing cells responding to SARS-CoV-2 peptides (S and N proteins) after different shots of vaccination. T-cell response was measured as the number of IFN- γ spots/400,000 cells. Stimulation with an irrelevant peptide was used for background subtraction. Dots represent mean values from duplicate wells of each donor. Data were analysed by fitting a mixed model and using Dunnett's multiple comparison test. * $p < 0.05$, ** $p < 0.01$. (B) Representative images of ELISpot wells stimulated with spike (S) and nucleocapsid (N) peptides (pept).

Results

T-cell response to anti-SARS-CoV-2 vaccination

Figure 2. T cells reactive to the spike protein of the BA.1, BA.2, BA.4/BA.5 variant of the SARS-CoV-2 B.1.1.529 lineage (Omicron variant)



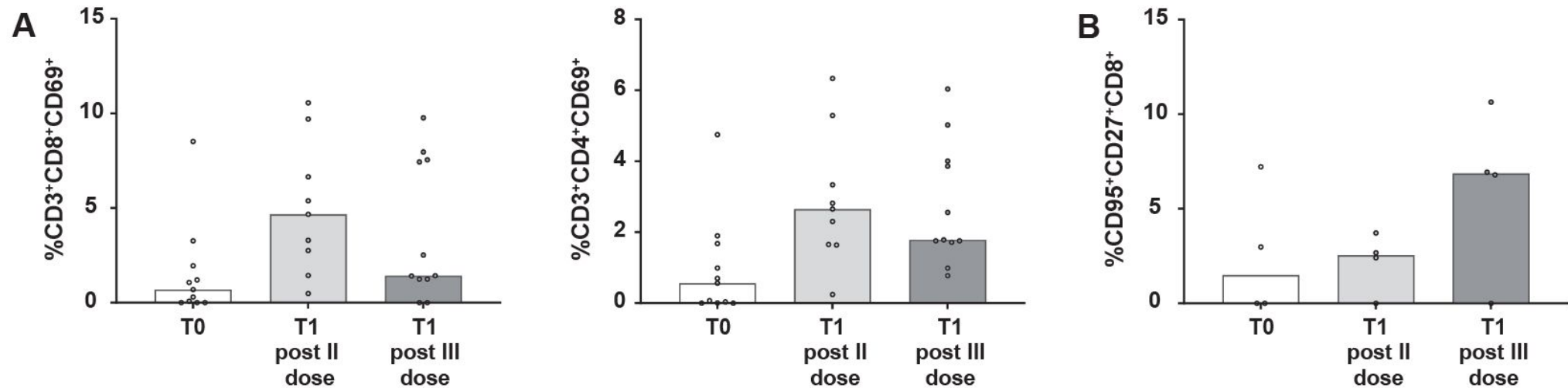
ns, not significant; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

The PepTivator Mutation Pools cover selectively the mutated regions in the surface or spike glycoprotein ("S") of the respective variant, whereas Wild Type Reference Pools cover the homologous domains of the Wuhan sequence.

Results

T-cell response to anti-SARS-CoV-2 vaccination

Figure 3. Longitudinal flow cytometry analysis of spike-specific T cell induced by vaccination



SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

(A) Percentage of CD8⁺ (left) and CD4⁺ (right) T cells showing upregulation of activation marker CD69 following overnight stimulation with a pool of overlapping peptides covering the spike protein.

(B) Percentage of spike-specific CD8⁺ T stem memory cells (CD95⁺CD27⁺ naive CD8⁺ T cells).

Results

Antibody response to anti-SARS-CoV-2 vaccination

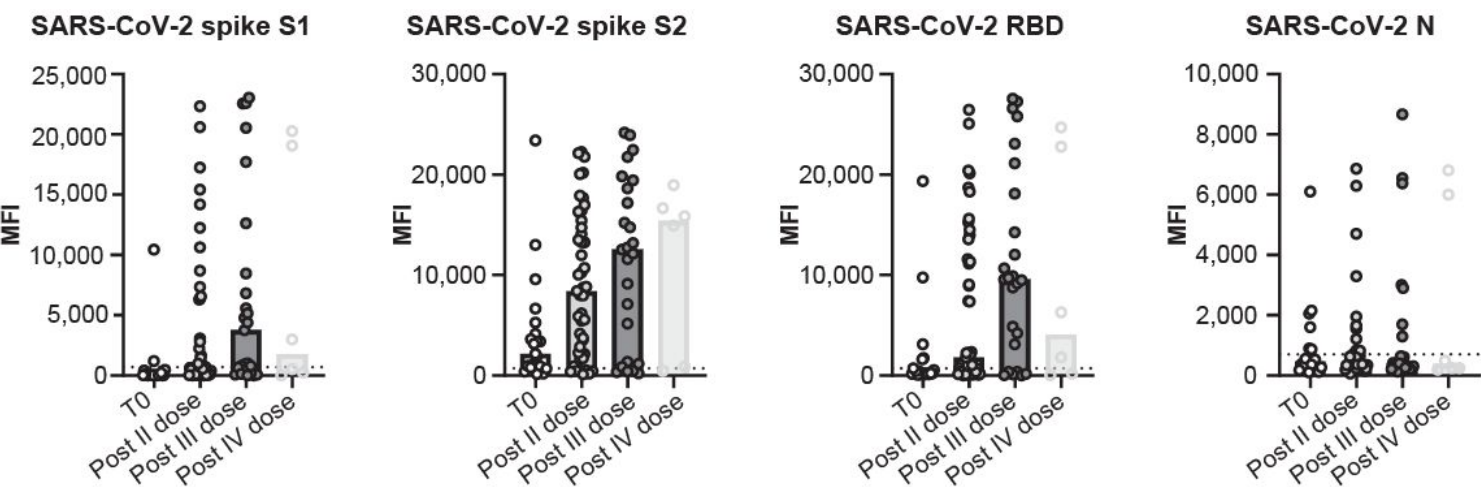
Table 1. Donor characteristics

Participants, N	245
Sex (female; male), n (%)	148 (60.4); 97 (39.6)
Age, years, median (range)	43 (22–73)
Diagnosis (RRMS; SPMS; PPMS), n	186; 7; 52
Last EDSS before infection, median (range)	3 (0–8.5)
Time on current treatment, months, median (range)	45.5 (3–89)
Time between last infusion and vaccination completion, days, median (range)	645 (252–1,490)
Participants infected with SARS-CoV-2, n (%)	155 (63.3)
One infection; two infections; three infections, n	118; 32; 5
Participants with breakthrough infections, n (%)	136 (55.5)
One infection, two infections; three infections, n	107; 26; 3

Results

Antibody response to anti-SARS-CoV-2 vaccination

Figure 4. Simultaneous analysis of SARS-CoV-2 spike S1, SARS-CoV-2 spike S2, SARS-CoV-2 receptor-binding domain (RBD) and SARS-CoV-2 N in PwMS treated with ocrelizumab



	T0	Post II dose	Post III dose	Post IV dose
Samples, n	21	47	25	6
Positive S1, n (%)	2 (9.5)	23 (48.9)	17 (68.0)	3 (50.0)
Positive S2, n (%)	17 (80.9)	40 (85.1)	21 (84.0)	5 (83.3)
Positive RBD, n (%)	6 (28.6)	30 (63.8)	19 (76.0)	4 (66.6)
Positive N, n (%)	6 (28.6)	13 (27.6)	7 (28.0)	2 (33.3)

N, nucleocapsid; PwMS, people with multiple sclerosis; RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. Plasma samples from vaccinated PwMS were tested using the 4 plex kit MILLIPLEX® SARS-CoV-2 Antigen Panel 1 IgG. Data are shown as Median Fluorescent Intensity (MFI). A working cut-off for a positive result was established using MFI data from a known negative sample population (MFI=700, dotted line).

Conclusions



- PwMS treated with ocrelizumab were already known to mount an efficient T-cell memory response upon vaccination against SARS-CoV-2, and to benefit from vaccination
- Data shown here suggest that several rounds of vaccination also induce the formation of virus-specific B-cell memory with delayed kinetics
- This may inform vaccination strategies for persons taking B-cell–depleting therapies



<https://ter.li/xn7dah>

Immune Signatures Associated with Ocrelizumab Treatment in Early Relapsing-Remitting Multiple Sclerosis: New Data on T-Cell Function and Pro/Anti-Inflammatory Monocytes of the 12-Month Interim Analysis from the MA30143 Phase IIb (ENSEMBLE) Substudy

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P1460

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Disclosures

T Wirth reports no conflict of interest related to the current study. **A Schulte-Mecklenbeck** reports no conflict of interest related to the current study. **O Steinberg** reports no conflict of interest related to the current study. **C Raposo** is an employee of and shareholder in F. Hoffmann-La Roche Ltd. **C Groß** received speaker honoraria from MyLan and DIU Dresden International University GmbH; and travel expenses for attending meetings from Biogen, Euroimmun, MyLan and Novartis Pharma. Her research is funded by the German Research Foundation (DFG), the German Ministry for Education and Research (BMBF), the European Union (Horizon2020), the IZKF Münster, Biogen, Roche and Novartis. **H Wiendl** received honoraria for acting as a member of scientific advisory boards for Janssen, Merck and Novartis; as well as speaker honoraria and travel support from Alexion, Amicus Therapeutics, Biogen, Biologix, Bristol Myers Squibb, Cognomed, F. Hoffmann-La Roche Ltd, Gemeinnützige Hertie-Stiftung, Medison, Merck, Novartis, Roche Pharma AG, Genzyme, Teva and WebMD Global. He acted as a paid consultant for Biogen, Bristol Myers Squibb, EMD Serono, Idorsia, Immunic, Novartis, Roche, Sanofi, the Swiss Multiple Sclerosis Society and UCB. His research is funded by the German Ministry for Education and Research (BMBF), German Research Foundation (DFG), Deutsche Myasthenie Gesellschaft e.V., Alexion, Amicus Therapeutics, Argenx, Biogen, CSL Behring, F. Hoffmann-La Roche Ltd, Genzyme, Merck KgaA, Novartis Pharma, Roche Pharma and UCB Biopharma. **L Klotz** received compensation for serving on scientific advisory boards for Alexion, Genzyme, Janssen, Merck-Serono, Novartis and Roche. She received speaker honoraria and travel support from Bayer, Biogen, Genzyme, Grifols, Merck-Serono, Novartis, Roche, Santhera and Teva. She receives research support from the German Research Foundation (DFG), the German Ministry for Education and Research (BMBF), the IZKF Münster, IMF Münster, Biogen, Novartis and Merck-Serono.

Background and Objective



Ocrelizumab (OCR) is an approved treatment for relapsing multiple sclerosis (RMS) and primary progressive MS (PPMS) that targets CD20-expressing B cells^{1,2}



The impact of OCR on peripheral blood immune cell subset composition beyond B cells is not fully elucidated



In the ENSEMBLE study (NCT03085810), the effects of OCR are studied in **treatment-naïve patients with early-stage relapsing-remitting MS (RRMS)**



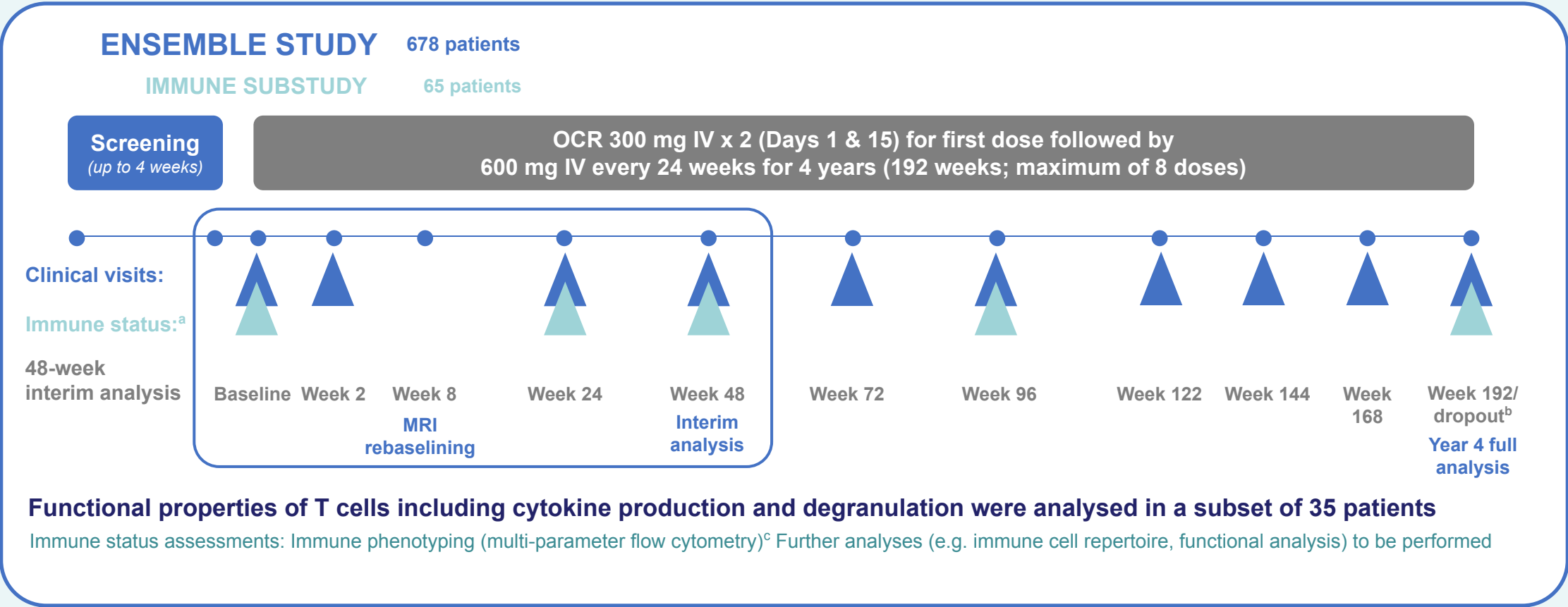
We aim to assess blood immunological effects, T-cell function and monocyte-associated inflammatory marker expression in patients treated with OCR from the ENSEMBLE study



We present here the interim results after two cycles of OCR treatment, at 48 weeks, in the immune substudy of ENSEMBLE

Methods

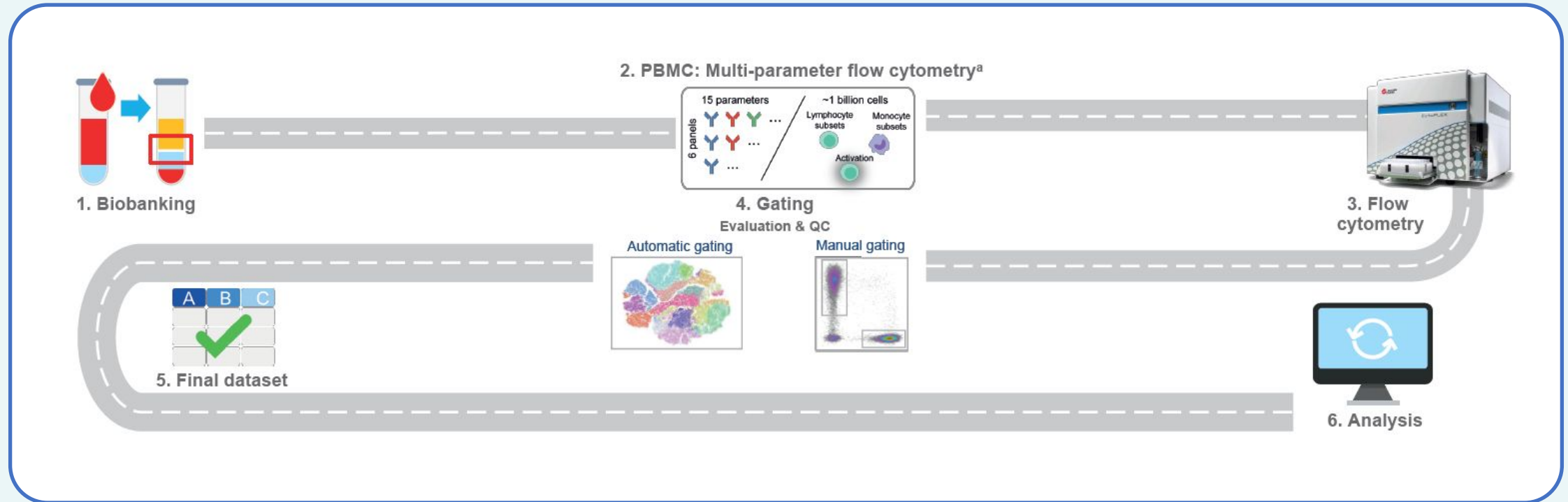
Immune Substudy Design



IV, intravenous; OCR, Ocrelizumab.
^aBlood samples are collected *a priori*; ^bFor dropouts, a measurement 24 months after discontinuation will be performed to assess immune status during repletion; ^cMedian cell counts (cells/ μ l) and percentage of cell populations were evaluated using Kruskal–Wallis test followed by Dunn’s test with Bonferroni correction.

Methods

Immunological Study Workflow



PBMC, peripheral blood mononuclear cells; QC, quality check.

^aMarkers used for flow cytometry can be found in the Supplementary Materials.

Results

Baseline Demographics and Disease Characteristics

Variable	ITT Population (N=678)
Age, mean (SD), years	32.4 (9.1)
Age category, n (%)	
≤40 / >40 years	539 (79.5) / 139 (20.5)
Sex, n (%)	
Male / female	240 (35.4) / 438 (64.6)
Race, n (%)	
White	555 (81.9)
Unknown	88 (13.0)
Time since MS symptom onset, mean (SD), years	1.10 (0.84)
Time since RRMS diagnosis, mean (SD), years	0.36 (0.40)
EDSS score at baseline,^a mean (SD)	1.71 (0.95)
EDSS score at baseline category,^a n (%)	
<2.5 / ≥2.5 years	508 (74.9) / 170 (25.1)
Number of relapses in the year prior to enrolment, n (%)	
0	38 (5.6)
1	438 (64.6)
2	166 (24.5)
3	27 (4.0)
≥4	9 (1.3)



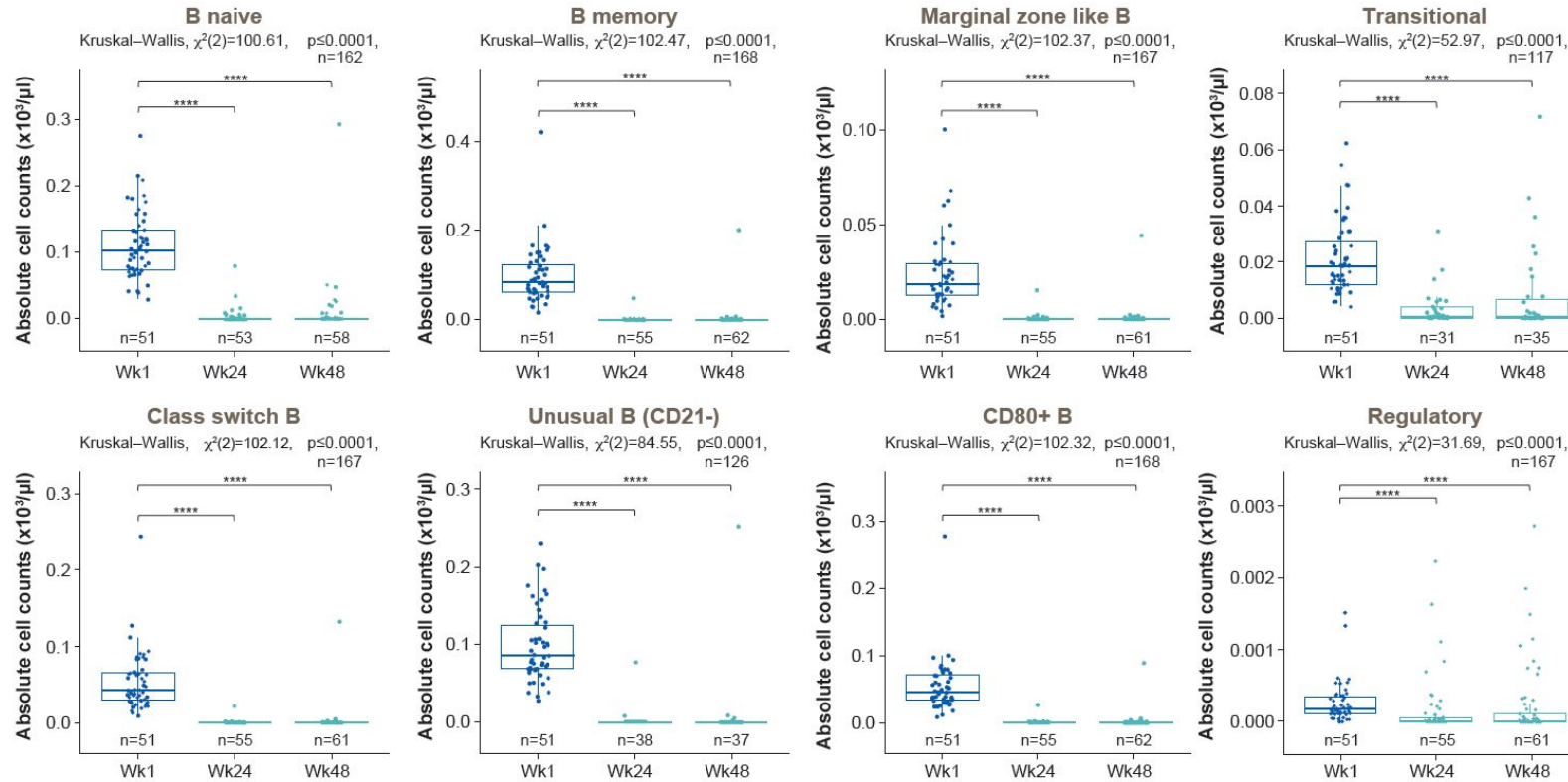
Baseline demographics and disease characteristics of the ENSEMBLE population were consistent with early-stage RRMS disease

EDSS, Expanded Disability Status Scale; ITT, intention-to-treat; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation.

^aBaseline EDSS is defined as the average of the EDSS scores at screening and baseline visit. If one of the EDSS scores from screening or baseline visits was missing, the other was used for baseline EDSS.

Results

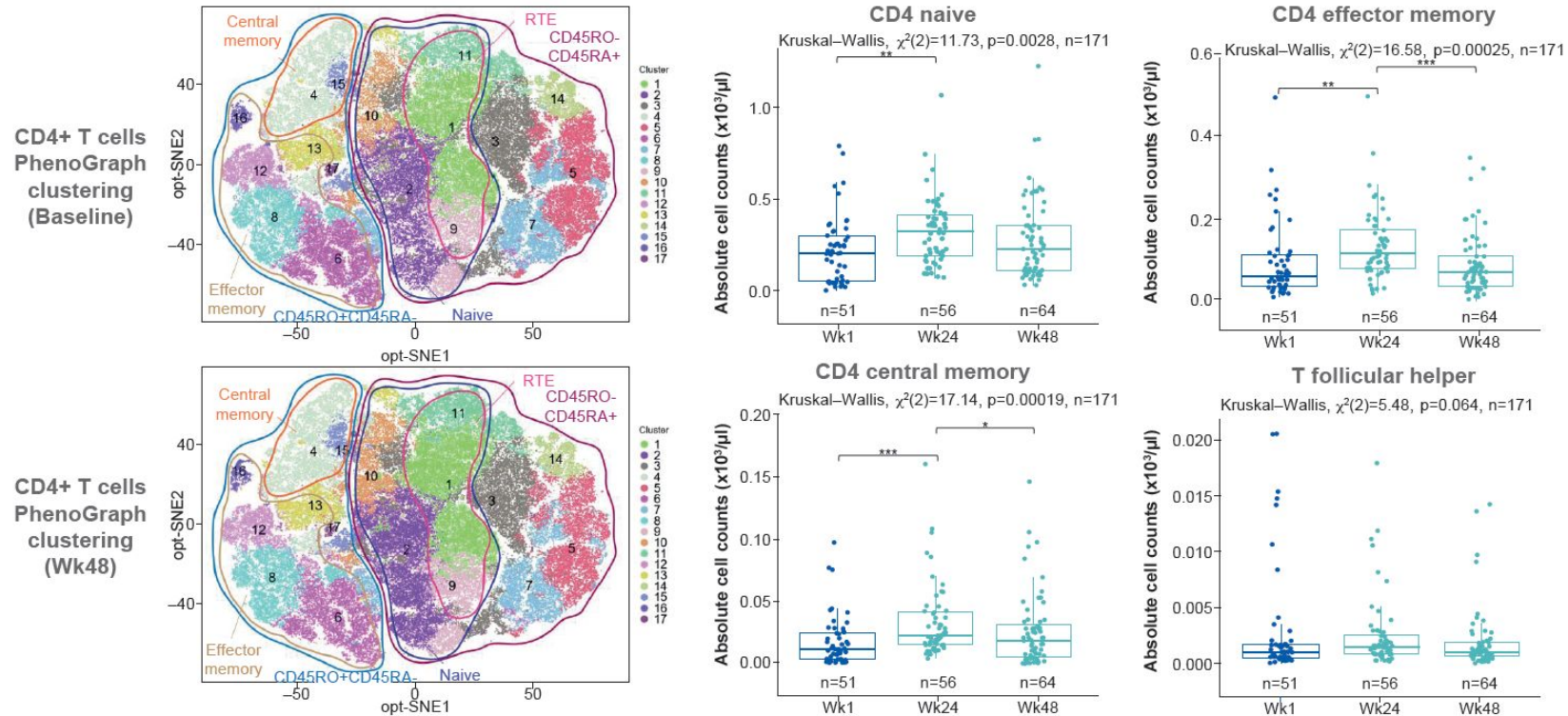
B-Cell Levels were Significantly Depleted Following OCR Treatment



B-cell depletion is reflected in an overall significant reduction in multiple B-cell markers, indicating a reduction in B-cell counts of all analysed subsets after 48 weeks of OCR treatment

Results

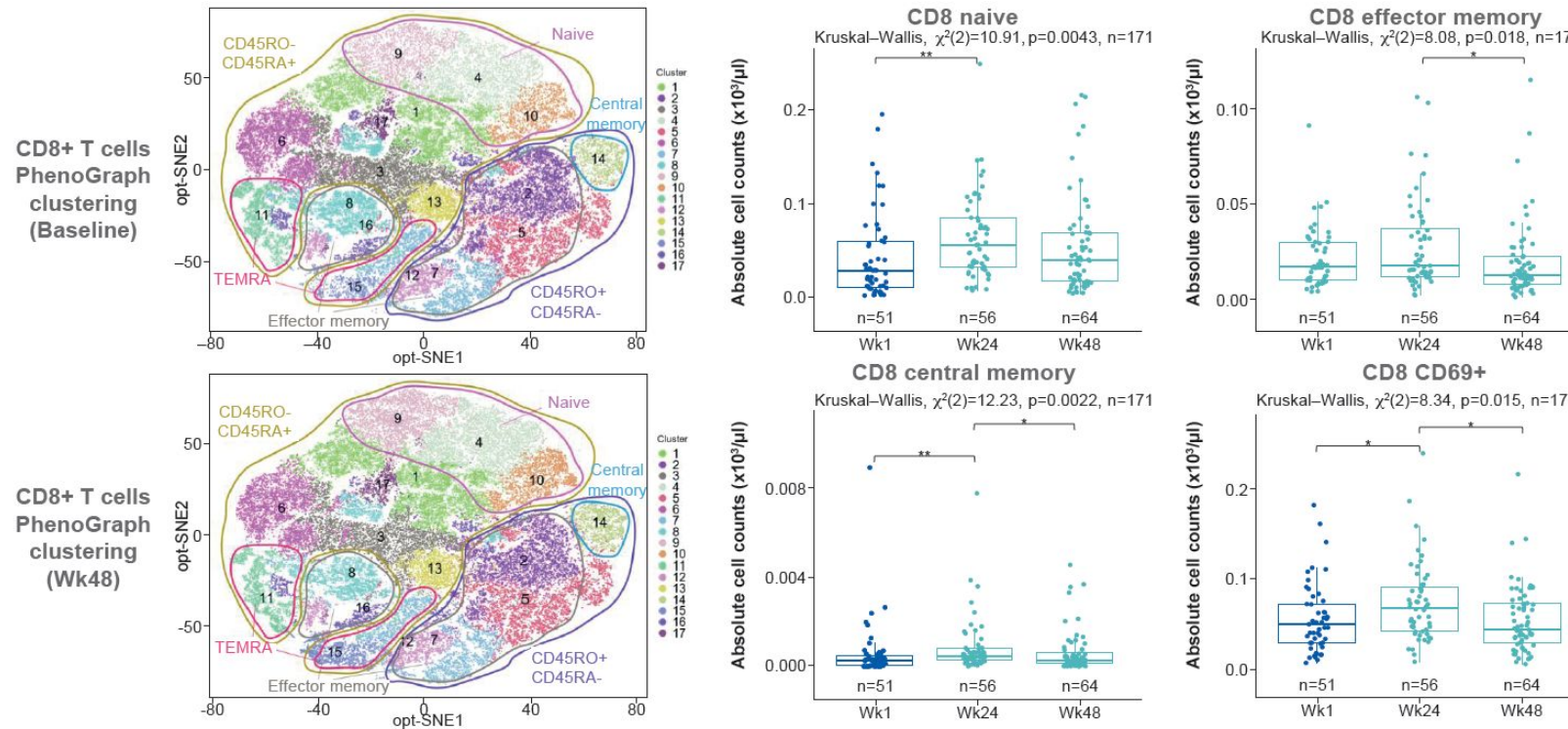
Unbiased Analysis Reveals No Major Effect on CD4+ T-Cell Subsets After 48 Weeks of OCR Treatment



An initial transient increase in most analysed CD4+ T-cell subsets was observed, with all subsets returning to baseline levels at Week 48

Results

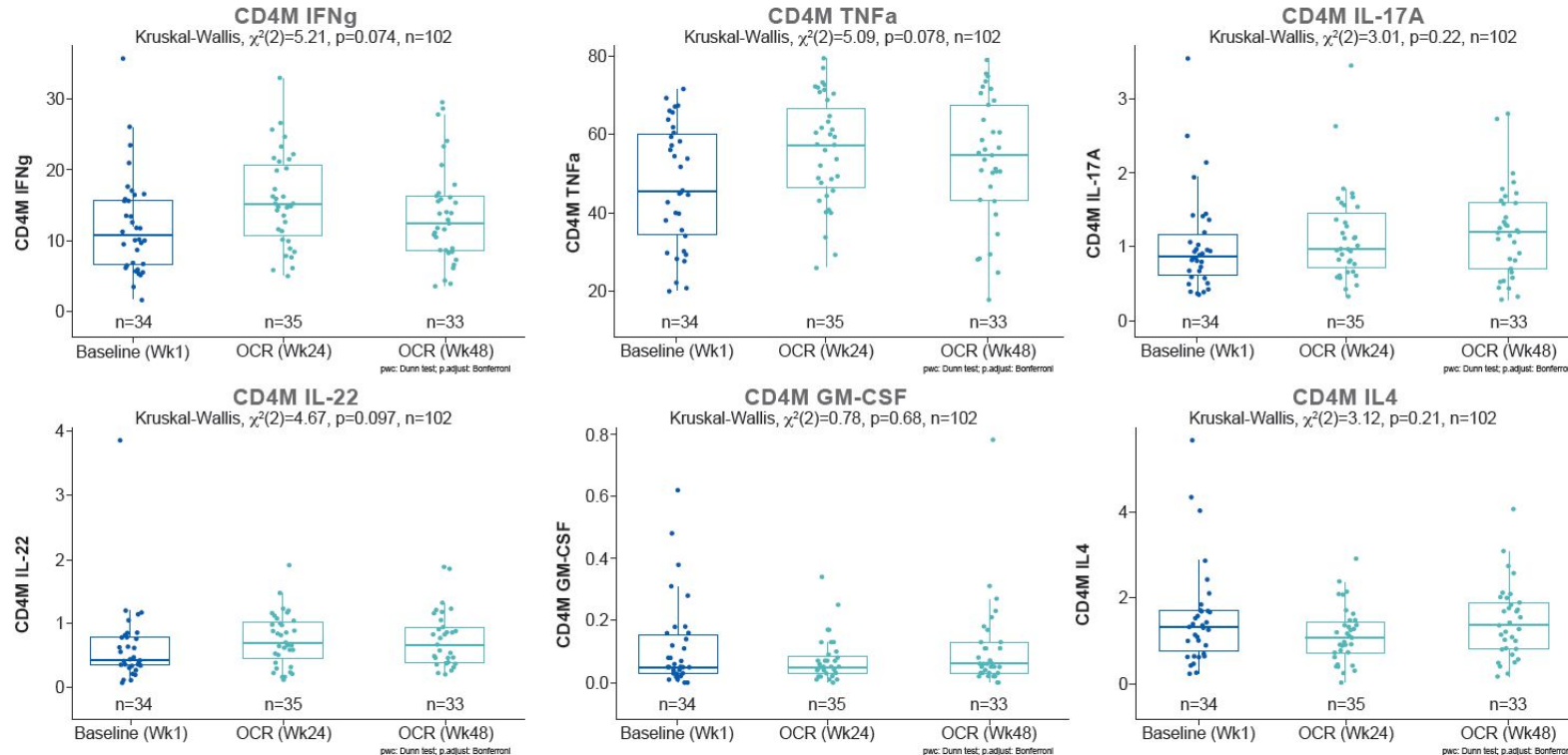
Unbiased Analysis Reveals no Major Effect on CD8+ T-Cell Subsets After 48 Weeks of OCR Treatment



Similarly, an initial transient increase in most analysed CD8+ T-cell subsets was observed, with all subsets returning to baseline levels at Week 48

Results

CD4 Memory T-Cell Cytokine Levels Remain Stable After 48 Weeks of OCR Treatment^a



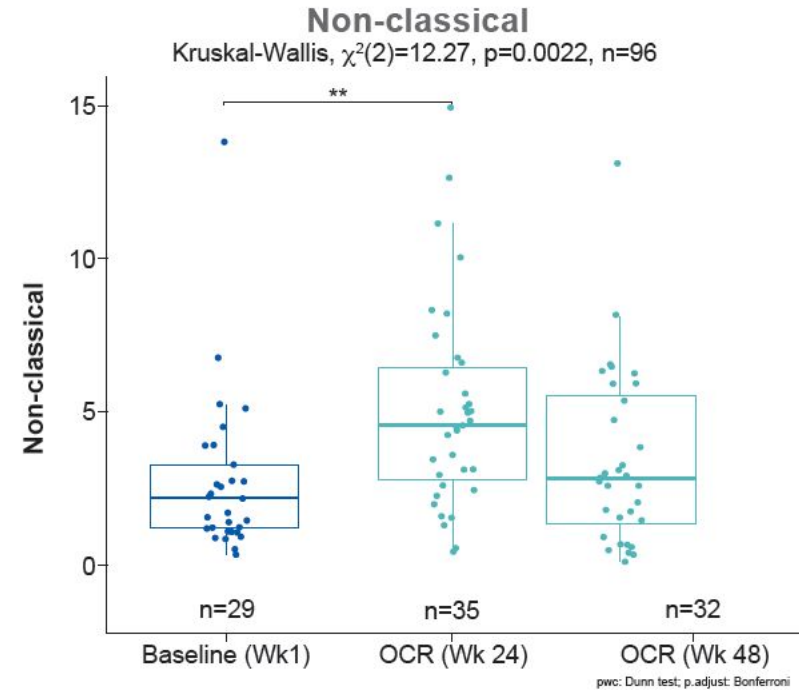
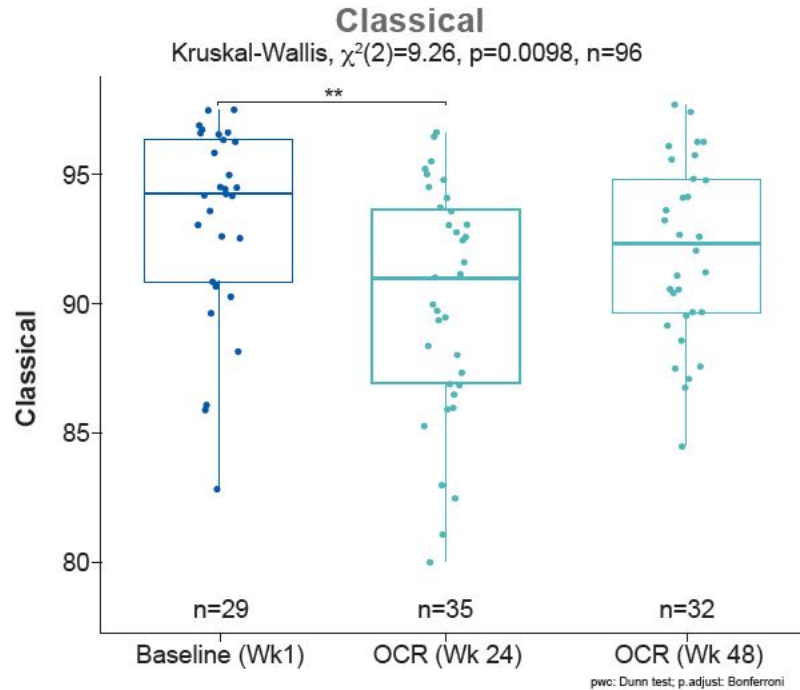
No effects on cytokine (IFN- γ , TNF- α , GM-CSF, IL-22, IL-17, IL-4) production were observed from CD4 T cells after 48-week OCR treatment

GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; OCR, ocrelizumab; pwc, pairwise comparison; TNF, tumour necrosis factor; Wk, Week.

^aT-cell cytokine levels are presented as % of CD4 memory. Box and Whisker plots: pwc, Dunn test; p.adjust, Bonferroni.

Results

Monocyte Compartments Normalise After 48 Weeks of OCR Treatment^a



Classical monocyte counts decreased, and non-classical (CD14^{low}CD16^{high}) monocytes increased transiently after 24 weeks OCR treatment, reverting to normal levels at Week 48

OCR, ocrelizumab; Wk, Week.

^aMonocyte levels are presented as % of HLA-DR+ LinX(CD3/CD19/CD56)-. Box and Whisker plots: pwc, Dunn test; p.adjust, Bonferroni. ** $p<0.01$.

Conclusions



- As expected, a depletion in the levels of all investigated B-cell subsets was observed following treatment with ocrelizumab in early-stage RRMS
- In contrast, we did not observe significant changes of CD4 or CD8 T-cell subsets or their cytokine profiles over 1 year of treatment
- Symmetry of classical/non-classical monocyte compartments was restored after 48 weeks
- Of note, a similar study (Laplaud, P258) in the same ENSEMBLE population found a preservation of differentiated B-cell clusters, particularly plasmablast immunoglobulin A (IgA), at Week 48
- Later time points will be reported to investigate the long-term impact of ocrelizumab treatment on peripheral blood immune cell subsets



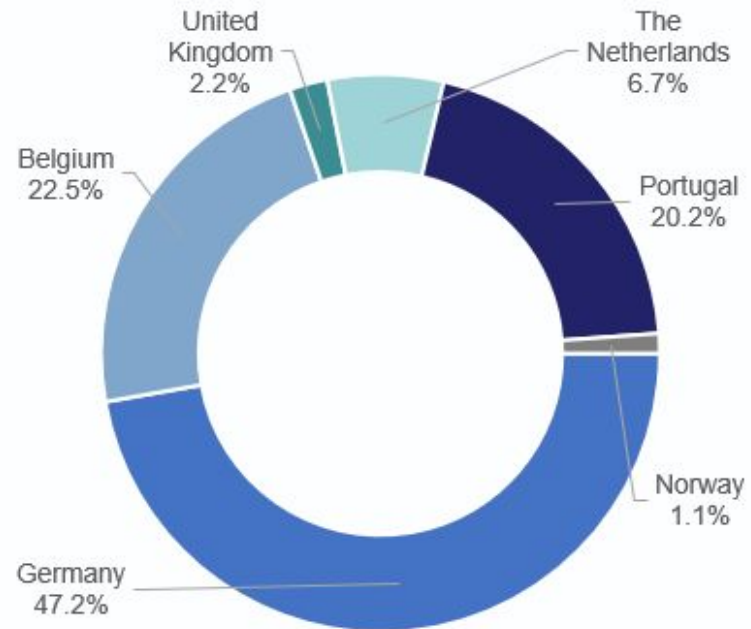
After 1 year of treatment with ocrelizumab, with exception of a significant depletion of B-cell subsets, the investigated innate and adaptive immune cell populations were preserved

Supplementary Materials

Methods

Immune Sub-study Design

SAMPLE ORIGIN



Methods

Overview of Flow Cytometry Panel Design

	Marker/channel												
Panel	FL1	FL2	FL3	FL4	FL5	FL6	FL7	FL8	FL9	FL10	FL11	FL12	FL13
Basic	CD1c	CD69	HLA-DR	Vα24-Jα18-	CD56	CD4	CD19	CD16	CD8	CD14		CD3	
B cell	anti-IgD	CD80	CD24	CD38	CD27	CD23	CD19	CD20	CD21	Anti-IgM			
T cell	CD45RA	CD57	CD31	CD45RO	CD56	CD226 (DNAM-1)	CD28	CD3	CD8	CD4	CD197 (CCR7)	CD27	CD62L
T helper1	CD183 (CXCR3)	PD-1	CD56	CD194 (CCR4)	CD196 (CCR6)	CD185 (CXCR5)	CD8	CD3	ICOS	CD146	CD45RO	CD27	CD4
Treg	Helios	FoxP3	CD56	CD31	TIGIT	CD226 (DNAM-1)	CD127	CD3	CD39	CD8	CD45RO	CD25	CD4
DC	CD25	IL-15Ra	HLA-DR	CD86	CD1c	Lineage (CD3, CD19, CD56)	CD11c	CD141	CD303	CD14			

Methods

Gating Strategy for Conventional Gating of Immune Cell Subsets

Main compartment		
Population	Defining marker	Compartment
Lymphocytes	CD45+FSClowSSClowCD14-	PBMC
Monocytes	CD45+FSCintSSCintCD14+HLA-DR+	PBMC
T cells	CD3+CD56-	Lymphocytes
B cells	CD19+CD20+	Lymphocytes
NK cells	CD3-CD56+	Lymphocytes
B-cell compartment		
Population	Defining marker	Compartment
B class switch memory	CD27+IgM-IgD-	B cells
Marginal zone like B	CD27+IgM+IgD+	B cells
B IgM only	CD27+IgM+IgD-	B cells
B unusual	IgM+IgD+CD38-CD21-	B cells
B transitional	IgM+IgD+CD38+CD24+CD21+	B cells
B regulatory	CD27+CD38+CD24+	B cells
CD4 T-cell compartment		
Population	Defining marker	Compartment
CD4 naive	CD27+CD197+CD62L+	CD4 CD45RO-CD45RA+ T cells
CD4 CM	CD27+CD197+CD62L+	CD4 memory T cells
CD4 EM	CD27-CD197-CD62L-	CD4 memory T cells
Tfh	CXCR5+PD1+ICOS+	CD4 memory T cells
RTE	CD31+	CD4 naive
CD8 T-cell compartment		
Population	Defining marker	Compartment
CD8 naive	CD27+CD197+CD62L+	CD8 CD45RO-CD45RA+ T cells
CD8 CM	CD27+CD197+CD62L+	CD8 memory T cells
CD8 EM	CD27-CD197-CD62L-	CD8 memory T cells
TEMRA	CD27-CD197-CD62L-	CD8 CD45RO-CD45RA+ T cells

CM, central memory; EM, effector memory; HLA-DR, major histocompatibility complex II cell surface receptor; Ig, immunoglobulin; NK, natural killer; PBMC, peripheral blood mononuclear cells; RTE, recent thymic emigrants; TEMRA, effector memory cells re-expressing CD45RA; Tfh, T follicular helper.

Methods

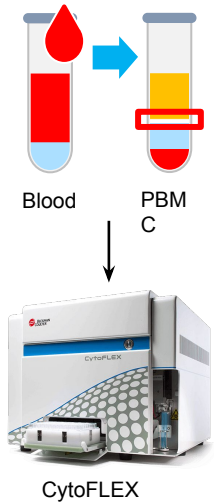
Unsupervised Cluster Analysis (t-SNE/PhenoGraph) Workflow

- | | | |
|---------------------------------|----|--|
| Preprocessing | 1. | Quality control and data cleaning (FlowAI/PeacoQC) |
| | 2. | Linearisation by ArcSin transformation (Scaling) |
| | 3. | Gating on cells of interest (e.g. T cells) |
| | 4. | Downsampling |
| Dimensionality reduction | 5. | Dimensionality reduction using t-SNE |
| Unsupervised clustering | 6. | Cluster identification with PhenoGraph |
| Validation | 7. | Verification and evaluation of the results (gating and exploring the embedding) |
| | 8. | Cluster assignment to immunological compartments (clustered heatmaps/backgating) |
| Interpretation | 9. | Group comparison/statistical differential analysis |

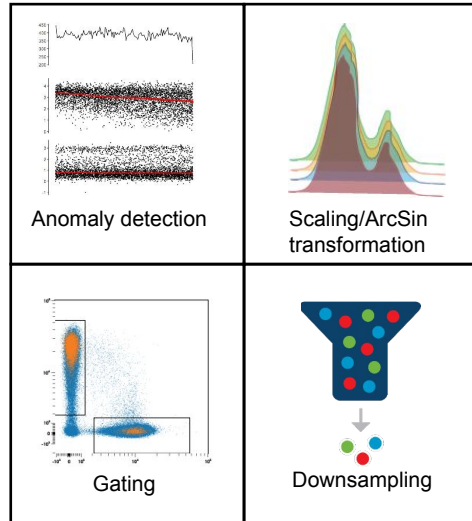
Methods

Unsupervised Cluster Analysis (t-SNE/PhenoGraph) Workflow

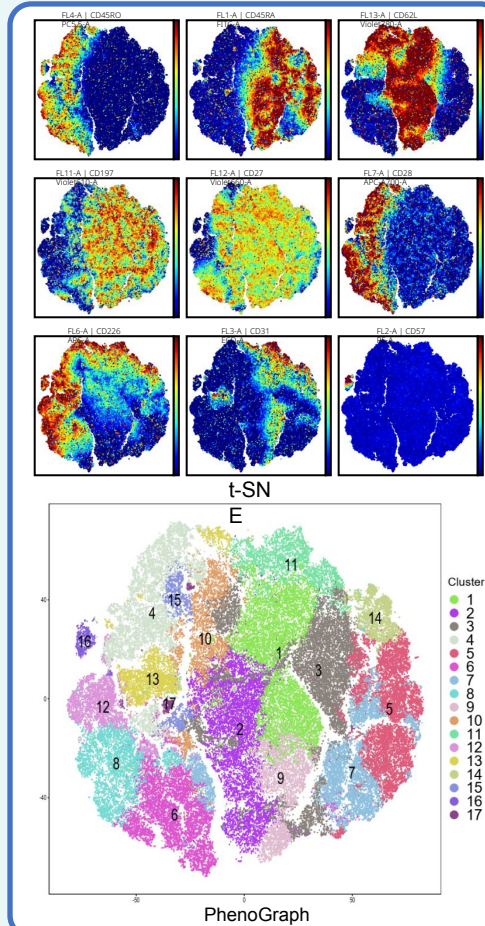
Data acquisition



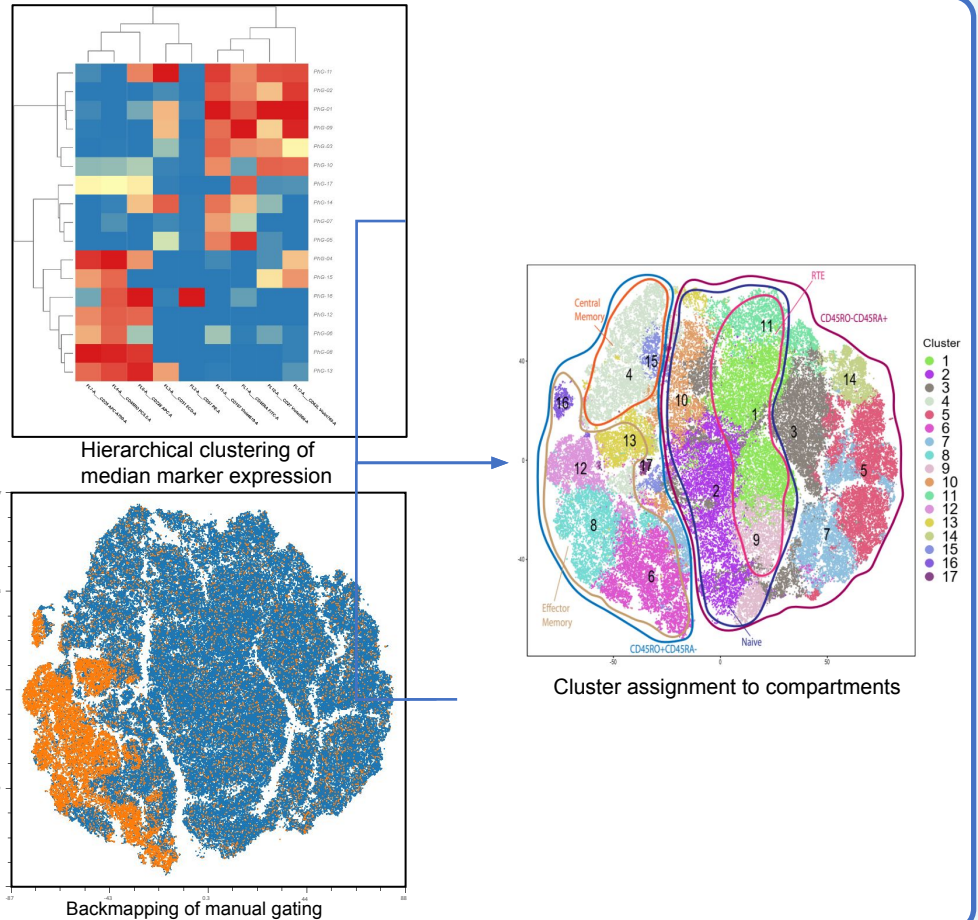
Pre-processing



Dimensionality reduction and clustering



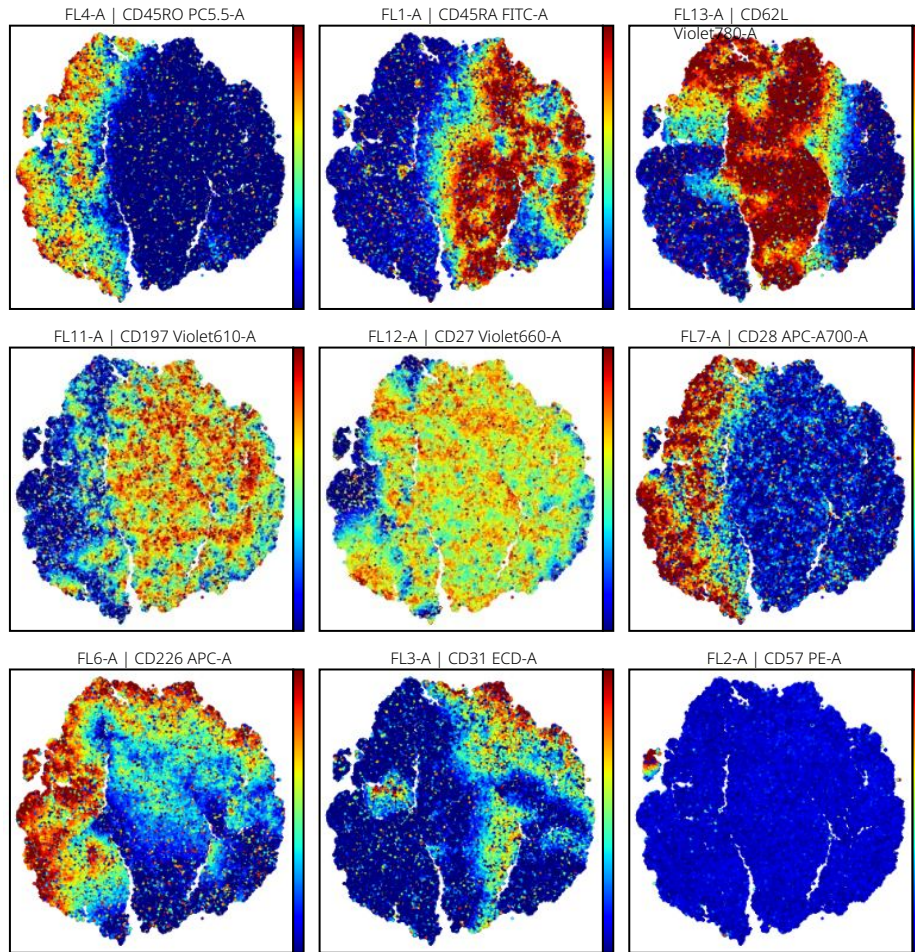
Cluster assignment to immunological compartments (clustered heatmaps/backgating)



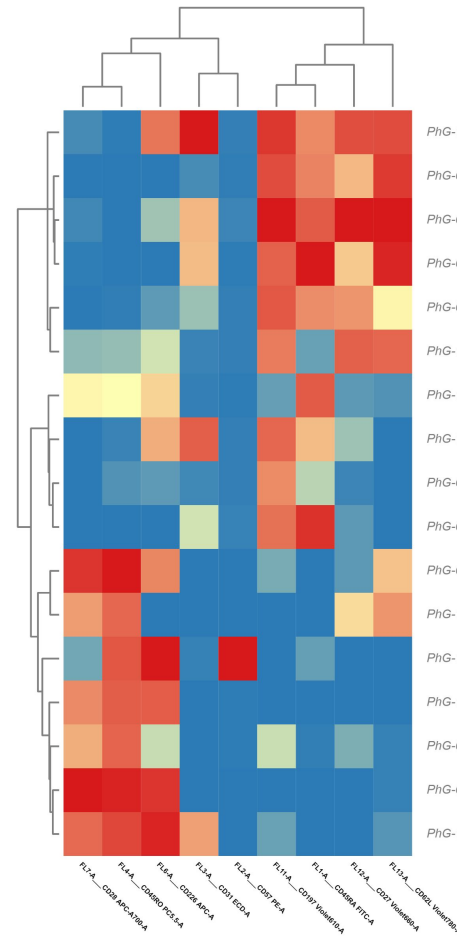
Methods

Individual Cluster Identities of CD4+ T Cells

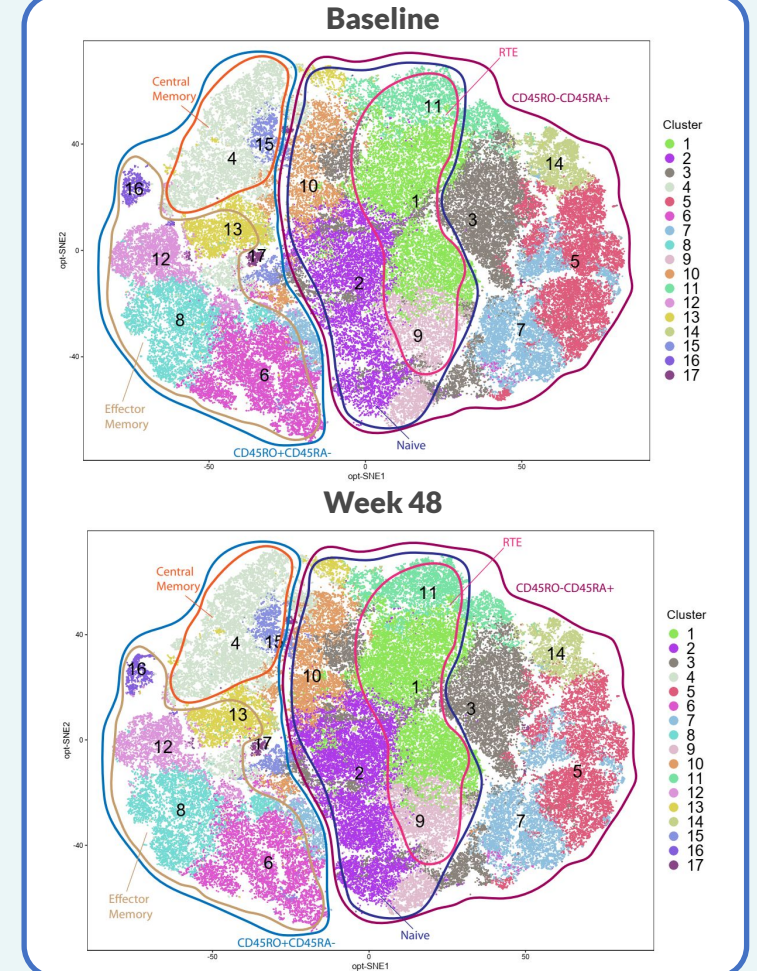
Single marker expression
opt-SNE plots



Median marker expression
clustered heatmap



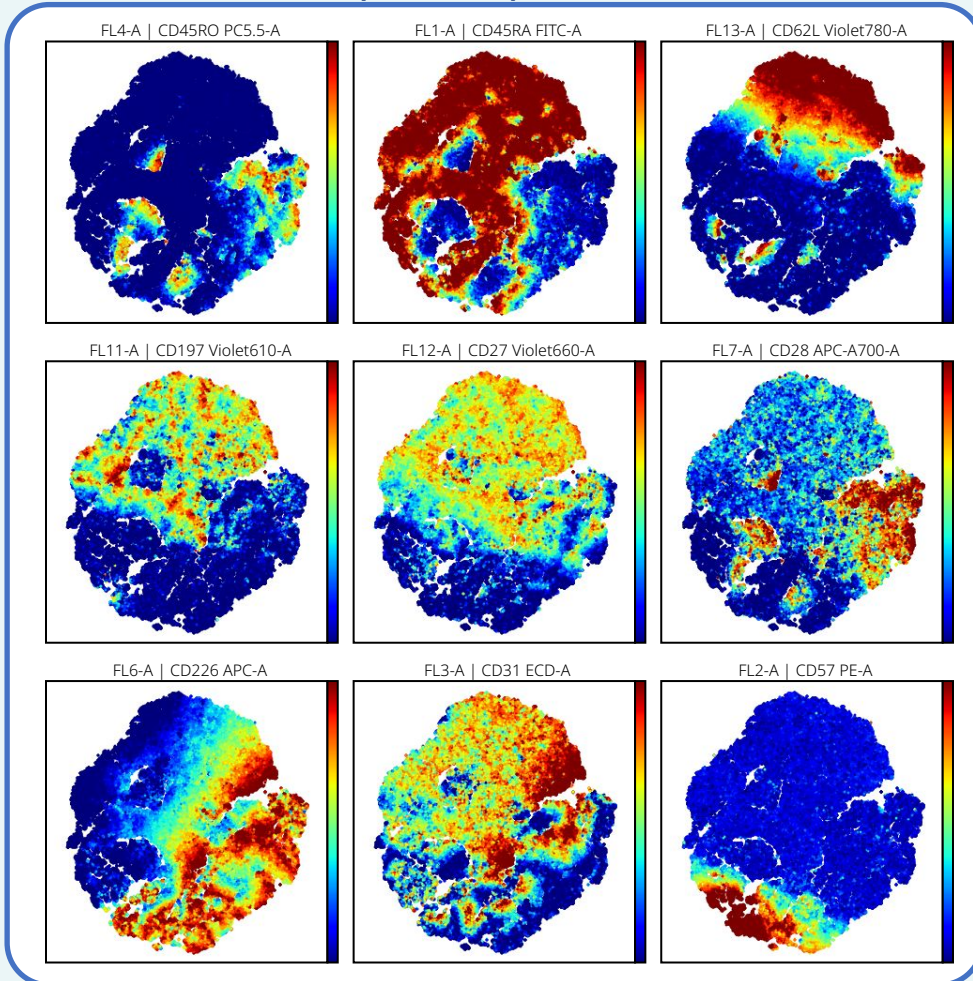
CD4+ T cells
PhenoGraph clustering



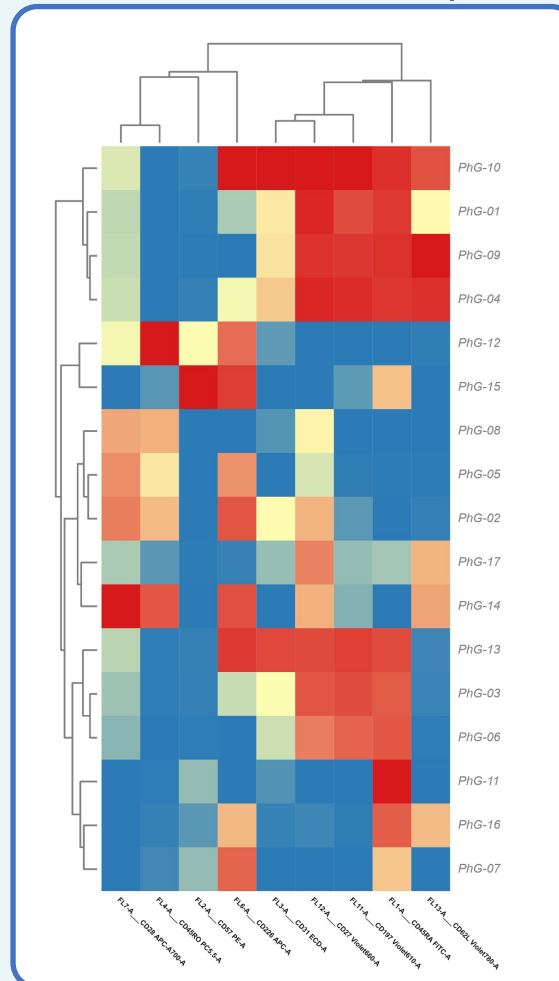
Methods

Individual Cluster Identities of CD8+ T Cells

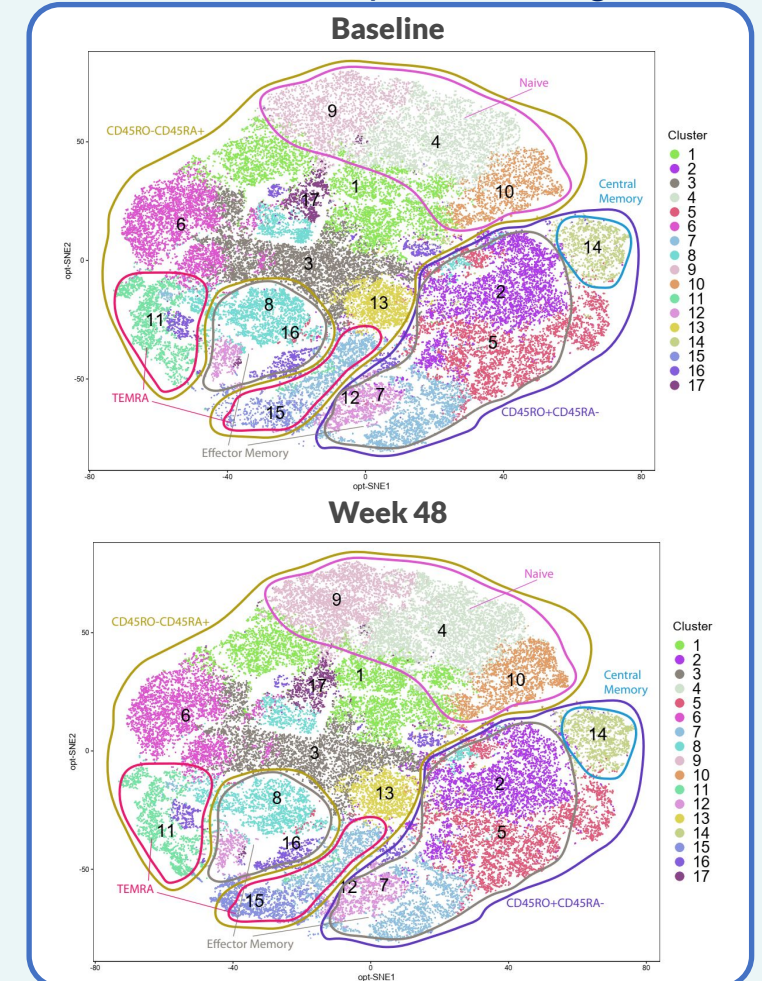
Single marker expression
opt-SNE plots



Median marker expression
clustered heatmap

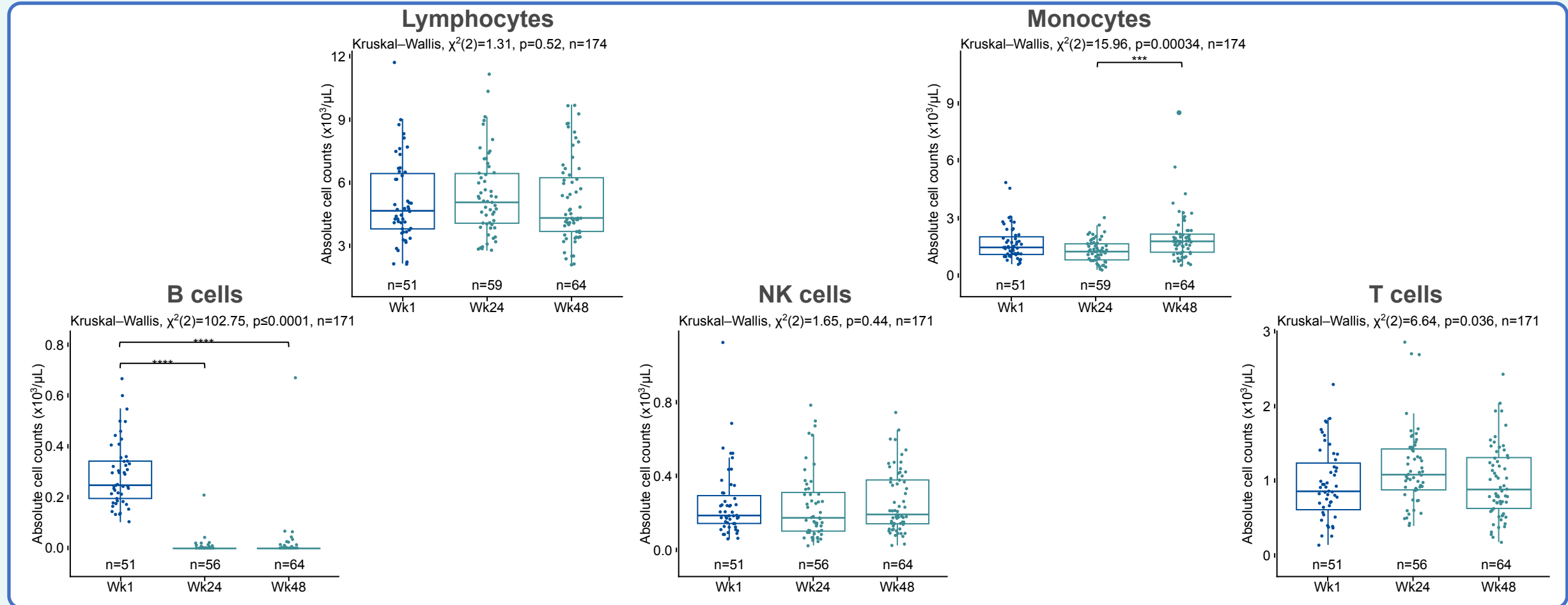


CD8+ T cells
PhenoGraph clustering



Results

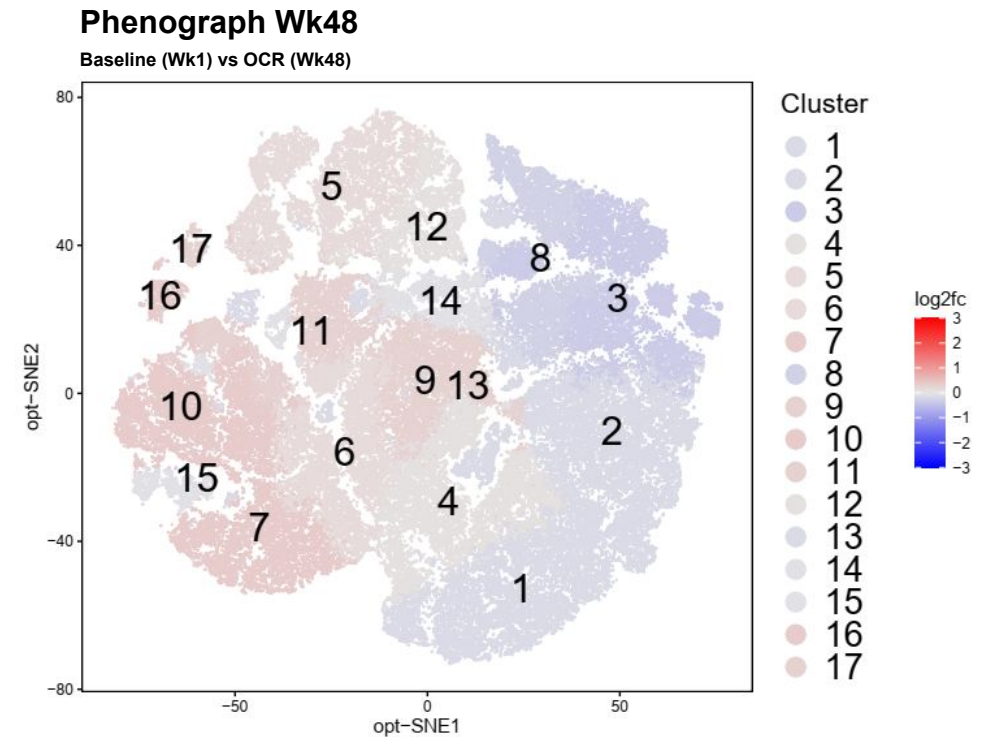
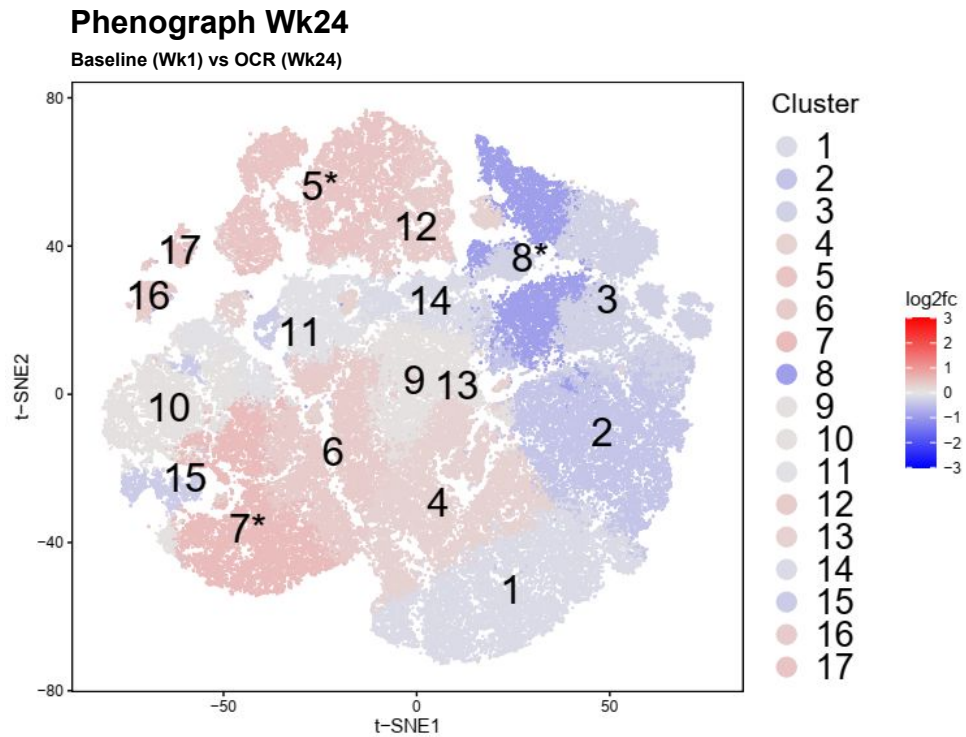
Most Major Blood Immune Cell Populations Exhibit No Change After 48 Weeks of OCR Treatment



As expected, following OCR treatment, B-cell levels significantly decreased after 24 and 48 weeks
No persistent changes in the other immune cell populations were observed

Results

High-Dimensional Analysis of CD4 Memory Cytokine Production (1/2)



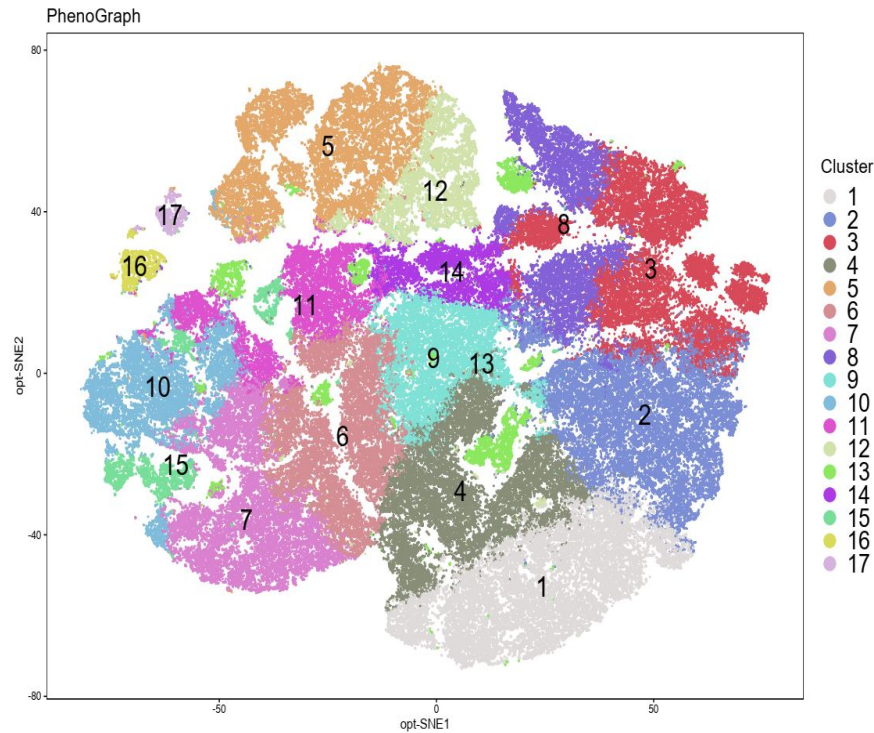
opt-SNE, optimised parameters for T-distributed stochastic neighbour embedding; PBMC, peripheral blood mononuclear cells; T-SNE, T-distributed stochastic neighbour embedding; Wk, Week.

Statistical significance of changes after Wk24 and Wk48 compared to Baseline were assessed by Dunn's test with FDR-correction for multiple comparisons as depicted by asterisks on clusters *p<0.05.

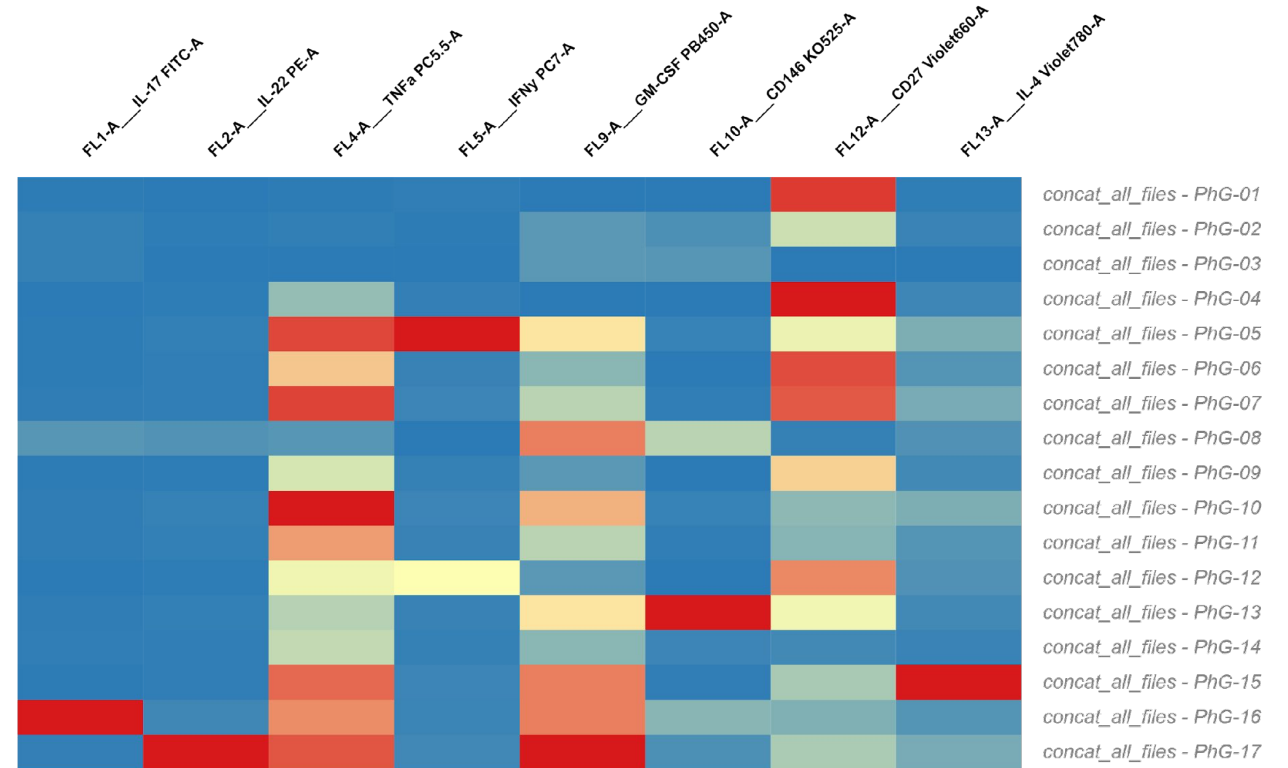
t-SNE representations obtained from concatenated PBMC samples (n=35 vs 35) stimulated with lymphocyte activation cocktail (PMA/Ionomycin) gated on CD4 memory cells.

Results

High-Dimensional Analysis of CD4 Memory Cytokine Production (2/2)



Heatmap of PhenoGraph Cluster Median Marker Expression



OCR, ocrelizumab; opt-SNE, optimised parameters for T-distributed stochastic neighbour embedding; PMA, phorbol myristate acetate; PBMC, peripheral blood mononuclear cells;

T-SNE, T-distributed stochastic neighbour embedding; Wk, Week.

t-SNE representations obtained from concatenated PBMC samples (n=35 vs 35) stimulated with lymphocyte activation cocktail (PMA/Ionomycin) gated on CD4 memory cells. Unsupervised clustering by PhenoGraph identified cell clusters as indicated by numbers. The colour of the cluster signifies the log2 fold changes of cluster abundance in up- (red) or downregulation (blue) of the respective timepoints (Wk24 / Wk48) after OCR treatment compared with Baseline (Wk1).



<https://ter.li/wuna96>

Low Disability Accumulation After 4-Year Ocrelizumab Therapy in Treatment-Naive Patients with Early-Stage Relapsing-Remitting Multiple Sclerosis: Data from the Phase IIb ENSEMBLE Study

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Disclosures

F Patti has received personal compensation for speaking activities and serving on the advisory board by Almirall, Bayer, Biogen, Celgene, Merck, Novartis, Roche, Sanofi-Genzyme and Teva. He also received research grants by Biogen, Merck, FISM (Fondazione Italiana Sclerosi Multipla), RELOAD Onlus Association and University of Catania. **R Bermel** has served as a consultant for AstraZeneca, Biogen, EMD Serono/Merck, Genzyme/Sanofi, Genentech/Roche, LabCorp, Eli Lilly, Novartis, TG Therapeutics and Viela Bio/Horizon. He receives research support from Biogen, Genentech and Novartis, and shares rights to intellectual property underlying the Multiple Sclerosis Performance Test, currently licensed to Qr8 Health and Biogen. **B Brochet** or his institution has received honoraria for consulting, speaking at scientific symposia or serving on advisory boards from Biogen Idec, Bristol Myers Squibb, Merck-Serono, Novartis, Roche and Sanofi-Genzyme. **T Berger** has participated in meetings sponsored by and received honoraria (lectures, advisory boards, consultations) from pharmaceutical companies marketing treatments for multiple sclerosis: Almirall, Bayer, Biogen, Biologix, Bionorica, Bristol Myers Squibb/Celgene, GW/Jazz Pharma, Horizon, Janssen-Cilag, MedDay, Merck, Novartis, Octapharma, Roche, Sandoz, Sanofi-Genzyme, TG Therapeutics, Teva-Ratiopharm and UCB. His institution has received financial support in the last 12 months by unrestricted research grants (Biogen, Bristol Myers Squibb/Celgene, Merck, Novartis, Roche and Sanofi-Genzyme) and for participation in clinical trials in multiple sclerosis sponsored by Alexion, Biogen, Bristol Myers Squibb/Celgene, Merck, Novartis, Octapharma, Roche, Sanofi-Genzyme and Teva. **WM Carroll** has received honoraria for serving on steering committees and advisory boards, and for speaking at scientific meetings from Bayer, Biogen Idec, Merck, Novartis, Roche and Sanofi-Genzyme. **MS Freedman** has received research or educational grants from Sanofi-Genzyme Canada; honoraria/consultancy fees from Alexion, Atara Biotherapeutics, Bayer HealthCare, Beigene, Bristol Myers Squibb (Celgene), EMD Inc., F. Hoffmann-La Roche Ltd, Janssen (J&J), Merck-Serono, Novartis, Sanofi-Genzyme and Teva Canada Innovation; is a member of a company advisory board, board of directors or other similar group for Alexion, Atara Biotherapeutics, Bayer HealthCare, Beigene, Bristol Myers Squibb (Celgene), Celestra, F. Hoffmann-La Roche Ltd, Janssen (J&J), McKesson, Merck-Serono, Novartis and Sanofi-Genzyme; and has participated in a company-sponsored speaker's bureau for Sanofi-Genzyme and EMD Serono. **T Holmøy** has received honoraria/consultancy fees from Biogen Idec, Merck, Novartis, Roche, Bristol Myers Squibb, Santen and Sanofi-Genzyme. **R Karabudak** received honoraria for consulting, lectures and advisory boards from Sanofi-Genzyme, Roche, Novartis, Merck-Serono, Gen İlaç TR and Teva. **J Killestein** has carried out contracted research for F. Hoffmann-La Roche Ltd, Biogen, Teva, Merck, Novartis and Sanofi-Genzyme. **C Nos** has received funding for registration for scientific meeting from Novartis. **L Vanopdenbosch** has received compensation for lectures and consultancy from Biogen, F. Hoffmann-La Roche Ltd, Novartis, Merck-Serono and Sanofi-Genzyme. **T Vollmer** has received compensation for consultancy from Biogen Idec, Genentech/F. Hoffmann-La Roche Ltd and Novartis; and has received research support from Rocky Mountain Multiple Sclerosis Center, Celgene, Biogen Idec, Anokion, Genentech/F. Hoffmann-La Roche Ltd, GW Pharma and TG Therapeutics. **T Kuenzel** is an employee of F. Hoffmann-La Roche Ltd. **K Kadner** is an employee of F. Hoffmann-La Roche Ltd. **I Kulyk** is an employee of F. Hoffmann-La Roche Ltd. **HP Hartung** has received honoraria for consulting, serving on steering committees and speaking at scientific symposia with approval by the Rector of Heinrich-Heine University Düsseldorf from Bayer, Biogen, Bristol Myers Squibb/Celgene, F. Hoffmann-La Roche Ltd, GeNeuro SA, Genzyme, MedImmune, Merck-Serono, Novartis, Octapharma, Sanofi-Genzyme, Teva, TG Therapeutics and Viela Bio.

Background and Objective



As MS is a progressive disease from the onset, initial and sustained treatment with high-efficacy therapies is important to optimise patient function²



OCR, an anti-CD20 monoclonal antibody approved for the treatment of RMS and PPMS,^{3,4} now has a decade of safety and efficacy experience in the context of clinical trials, and over 300,000 patients in clinical trials and the post-marketing setting combined⁵



As a high-efficacy therapy, OCR reduces disease activity and the risk of long-term disability progression in patients with RMS;^{6–8} however, data are lacking on first-line OCR use in early RMS; based on the need for efficacious treatments for early stages of MS, trials with other high-efficacy therapies are being investigated^{9,10}



ENSEMBLE (NCT03085810) was a prospective, 4-year, multicentre, open-label, single-arm Phase IIIb study investigating OCR as a therapy for very early-stage RRMS



To demonstrate the effect of OCR as a first-line therapy on measures of disability progression in patients with recently diagnosed RRMS over 4 years

MS, multiple sclerosis; OCR, ocrelizumab; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

2. Ontaneda D, et al. *Lancet Neurol* 2019;18:973–980; 3. OCREVUS [ocrelizumab] Full Prescribing Information. Genentech, Inc., 2023; 4. OCREVUS [ocrelizumab] Summary of Product Characteristics.

Roche Pharma AG, 2020; 5. Roche data on file; 6. Hauser SL, et al. *N Engl J Med* 2017;376:221–234; 7. Hauser SL, et al. *Neurology* 2020;95:e1854–e1867; 8. Cerqueira J, et al. *ECTRIMS* 2022;Poster 723;

9. ClinicalTrials.gov. <https://clinicaltrials.gov/study/NCT03535298>. Accessed 3 August 2023; 10. ClinicalTrials.gov. <https://clinicaltrials.gov/study/NCT03500328>. Accessed 3 August 2023.

Methods^a



Patients with very early-stage RRMS^b received first-line OCR 600 mg IV every 24 weeks for 4 years^c



The following endpoints related to disability progression were assessed:

- NEP (cCDP); a composite measure of 24W-CDP,^d 24W-T25FW and 24W-9HPT
- 24/48W-CDP^d
- 24/48W-CDI^e
- Mean change in EDSS from baseline^f
- Safety measures

9HPT, 9-Hole Peg Test; cCDP, composite confirmed disability progression; CDI, confirmed disability improvement; EDSS, Expanded Disability Status Scale; IV, intravenous; NEP, no evidence of progression; OCR, ocrelizumab; RRMS, relapsing-remitting multiple sclerosis; T25FW, Timed 25-Foot Walk; W, week.

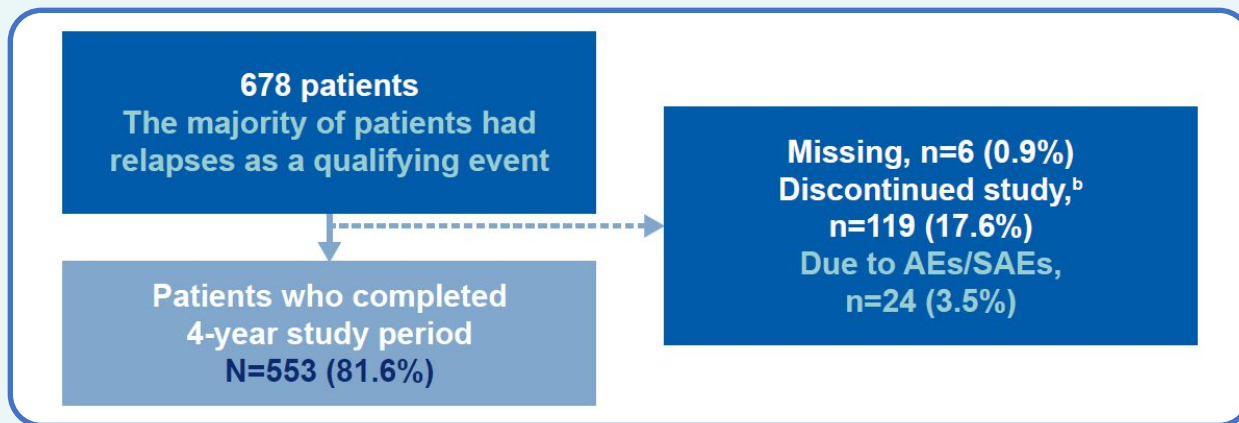
^aFor further information on the study methods, see Supplementary Materials; ^bRecruitment criteria: RRMS diagnosis (McDonald 2010),¹¹ age 18–55 years inclusive, disease duration ≤3 years, EDSS 0.0–3.5 inclusive, one or more relapses or MRI activity in prior 12 months, and treatment-naïve. The majority of patients qualified for the ENSEMBLE study based on relapses. For further information, see Supplementary Materials; ^cFirst OCR dose consisted of OCR 300 mg IV x2 on Days 1 and 15; ^dCDP was defined as an increase of ≥1.0 points from baseline EDSS score or increase of ≥1.5 points if baseline EDSS score was <1.0, each confirmed at 24/48 weeks; ^eCDI was defined as a reduction of ≥1.0 points in EDSS score when baseline EDSS score was ≥2 but ≤5.5, and a decrease of 0.5 points when baseline EDSS score >5.5, each confirmed at 24/48 weeks; ^fBaseline EDSS is defined as the average of the EDSS scores at screening and baseline visit. If one of the EDSS scores from screening or baseline visits was missing, the other was used for baseline EDSS.

11. Polman CH, et al. *Ann Neurol* 2011;69:292–302.

Results

Patient Disposition, and Baseline Demographics and Disease Characteristics

KEY PATIENT DISPOSITION^a



KEY BASELINE CHARACTERISTICS^a

Variable	ITT population (N=678)
Age, mean (SD)	32.4 (9.1)
Mean duration since MS symptom onset, year (SD) ^c	1.10 (0.84)
Mean duration since RRMS diagnosis, year (SD)	0.36 (0.40)
Mean EDSS at baseline ^d (SD)	1.71 (0.95)



Baseline demographics and disease characteristics were consistent with a very young, early-stage RRMS population

A relatively high retention rate (81.6%) was observed across the study, with few patients withdrawing due to AEs

AE, adverse event; EDSS, Expanded Disability Status Scale; ITT, intention-to-treat; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SAE, serious adverse event; SD, standard deviation.

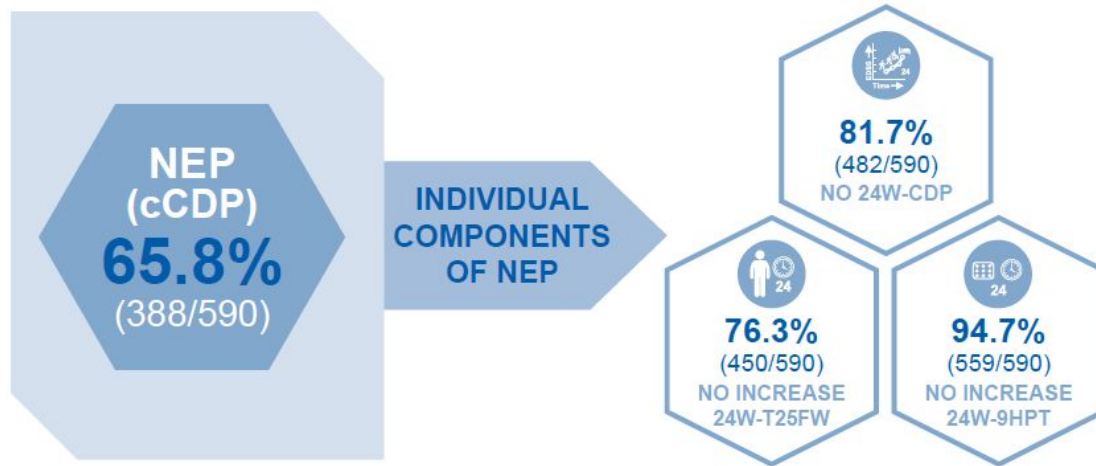
^aPatient disposition and further patient demographics and baseline characteristics are available in the Supplementary Materials; ^bFor detailed discontinuation data, see Supplementary Materials. ^cn=673;

^dBaseline EDSS is defined as the average of the EDSS scores at screening and baseline visit. If one of the EDSS scores from screening or baseline visit was missing, the other was used for baseline EDSS.

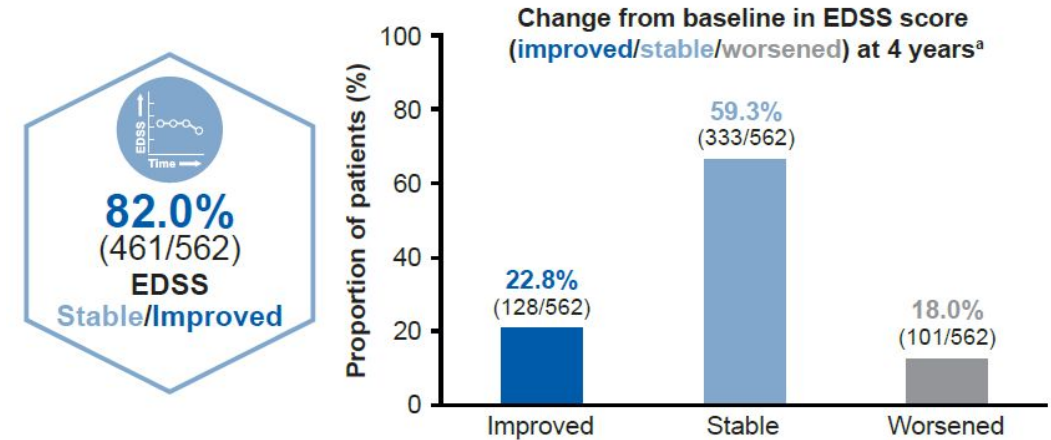
Results

4-Year NEP (cCDP) and EDSS

4-Year NEP (cCDP)



EDSS



After 4 years, almost two-thirds (65.8%) of patients treated with first-line OCR showed complete control of their disease as measured by NEP (cCDP)



The majority of patients treated with first-line OCR (82.0%) maintained stable or improving EDSS scores over 4 years

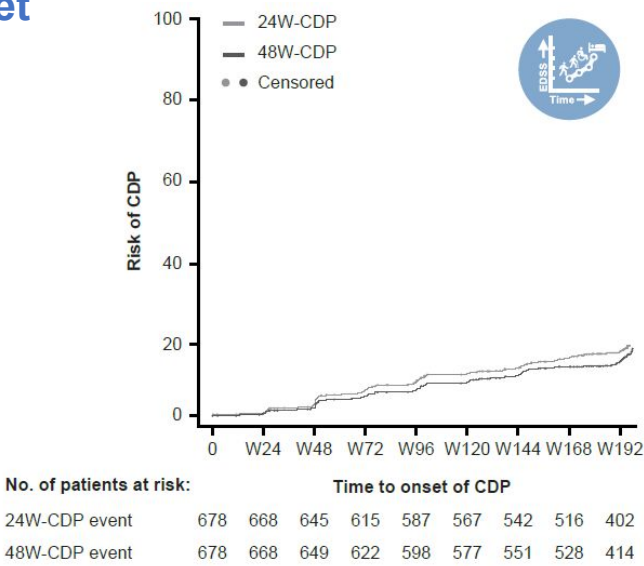
9HPT, 9-Hole Peg Test; cCDP, composite confirmed disability progression; CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; NEP, no evidence of progression; OCR, ocrelizumab; T25FW, Timed 25-Foot Walk; W, week.

^aAbsolute change from baseline in EDSS score: Improved, <-0.5 ; stable, ≤ 0.5 and ≥ -0.5 ; worsened, >0.5 . Patients with missing EDSS scores were excluded. EDSS scores from baseline over 4 years are available in the Supplementary Materials.

Results

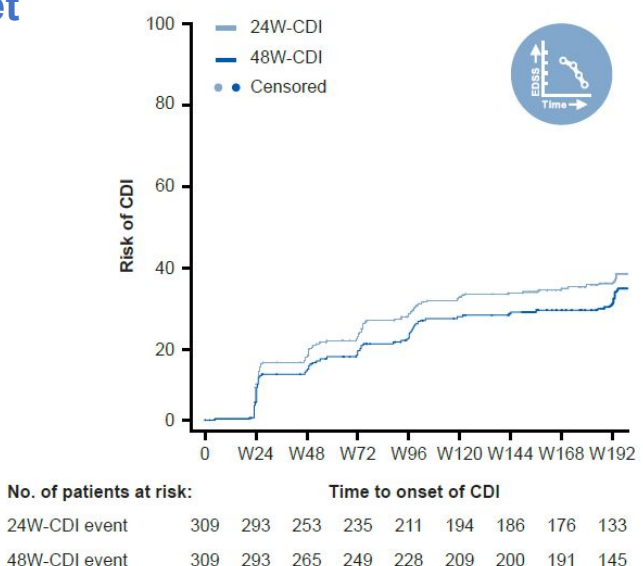
Time to Onset of 24W- and 48W-CDP and CDI

Time to Onset of 24W- and 48W-CDP



The possibility of no 24W-CDP and no 48W-CDP at 4 years was 84.1% and 85.0%, respectively

Time to Onset of 24W- and 48W-CDI



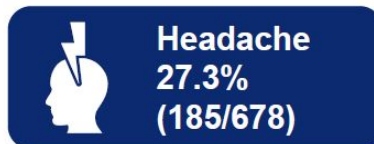
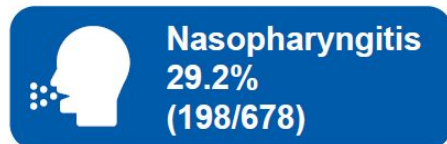
The possibility of achieving 24W-CDI and 48W-CDI at 4 years was 35.9% and 31.7%, respectively

Results

Safety Overview^a

ADVERSE EVENTS

- AEs were reported in 647/678 patients (95.4%)
- The most common AEs^b (occurring in >20% patients):

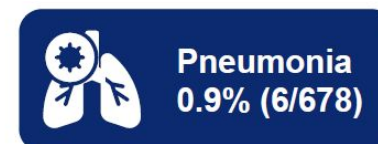
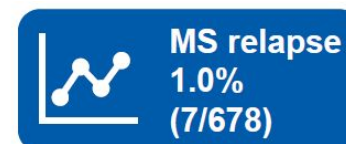
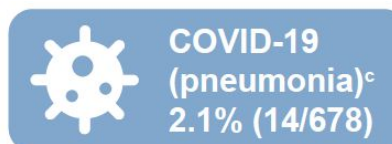


Of the 51.8% IRRs (n=351)

- Thirteen were Grade 3
- None were Grade 4 or above

SERIOUS ADVERSE EVENTS

- SAEs were reported in 105/678 patients (15.5%)
- The most common SAEs (occurring in >0.5% patients):



- Serious IRRs were reported in 0.4% of patients^d



Safety results were consistent with the known OCR profile, with no new safety signals

AE, adverse event; IRR, infusion-related reaction; MS, multiple sclerosis; OCR, ocrelizumab; SAE, serious adverse event.

^aPlease refer to the OCR General Safety poster (Hauser, P326; <https://ter.li/drk6ao>) for full safety updates; ^bAEs defined by preferred terms; ^cThere were nine patients who had COVID-19 infections as well as a further five patients with COVID-19 pneumonia; ^dThe three serious IRRs were: 1) Pruritus and stridor, Grade 3, resolved, drug withdrawn; 2) diarrhoea, dry mouth, palpitations, nausea, tachycardia, Grade 3, resolved, dose not changed; 3) cough, eye pain, laryngeal discomfort, tachycardia, Grade 3, resolved, dose not changed. One of the three patients were randomised to shorter infusion.

Conclusions



- **The positive benefit–risk profile observed in ENSEMBLE supports the use of ocrelizumab as a first-line therapy in newly diagnosed patients with early RRMS to control long-term disability progression**
- Most patients showed complete control of their disability progression as measured by NEP (cCDP)
- Patients had low levels of disability accumulation, with most patients showing stable or improved EDSS scores, and a third having disability improvement
- Safety results were consistent with the known ocrelizumab safety profile, with no new safety signals
- The high progression-free rate in ENSEMBLE was consistent with that seen in treatment-naïve patients with early RMS from the OPERA open-label extension substudy (79% 24-week CDP-free over 9 years with continuous ocrelizumab)¹

Supplementary Material

Methods

PATIENT POPULATION

RRMS diagnosis (McDonald 2010)¹

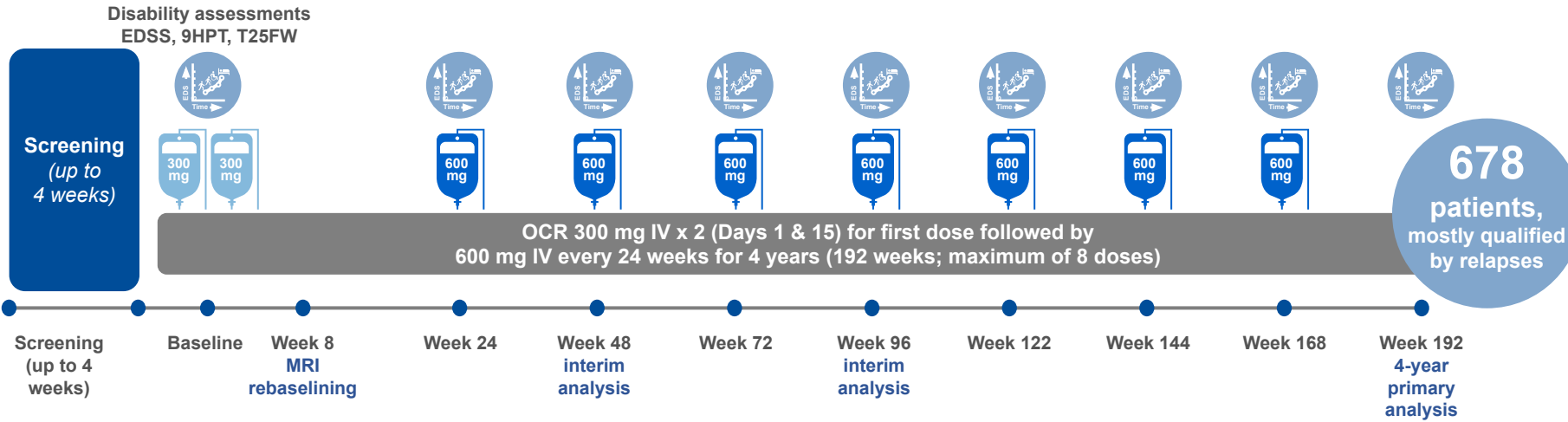
Age 18–55 years, inclusive

Disease duration ≤3 years (early-stage MS)

EDSS^a 0.0–3.5 inclusive

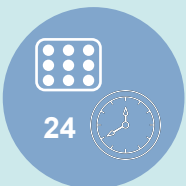
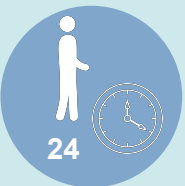
One or more relapses or MRI activity in prior 12 months

Treatment naive



DISABILITY PROGRESSION-RELATED ENDPOINTS

- NEP (cCDP), a composite measure of the absence of:



24/48W-CDP^b



24/48W-CDI^c



Mean change in EDSS from baseline



Safety

T25FW, Timed 25-Foot Walk; W, week.

^aBaseline EDSS is defined as the average of the EDSS scores at screening and baseline visit. If one of the EDSS scores from screening or baseline visits was missing, the other was used for baseline EDSS.

^bCDP was defined as an increase of ≥1.0 point from baseline EDSS score or increase of ≥1.5 points if baseline EDSS score was <1.0, each confirmed at 24/48 weeks.

^cCDI was defined as a reduction of ≥1.0 point in EDSS score when baseline EDSS score was ≥2 but ≤5.5, and a decrease of 0.5 point when baseline EDSS score >5.5, each confirmed at 24/48 weeks.

9HPT, 9-Hole Peg Test; cCDP, composite CDP; CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; IV, intravenous; MS, multiple sclerosis; NEDA, no evidence of disease activity; OCR, ocrelizumab; RRMS, relapsing-remitting multiple sclerosis;

1. Polman CH, et al. Ann Neurol 2011;69:292–302.

Results

Patient disposition, and baseline demographics and disease characteristics

Missing, n=6 (0.9%)
Discontinued study, n=119 (17.6%)

- Adverse event, 18 (2.7%)
- Death, 6 (0.9%)
- Withdrawal by participant, 44 (6.5%)
- Physician decision, 11 (1.6%)
- Lost to follow-up, 9 (1.3%)
- Lack of efficacy, 4 (0.6%)
- Pregnancy, 2 (0.3%)
- Commercial OCR available, 2 (0.3%)
- Study terminated by sponsor, 1 (0.1%)
- Other, 22 (3.2%)

Patients who underwent treatment with OCR 600 mg (ITT population) N=678 (100.0%)

Patients who completed 4-year study period N=553 (81.6%)

Variable	ITT population (N=678)
Mean age, year (SD)	32.4 (9.1)
Sex, n (%)	
Male/female	240 (35.4) / 438 (64.6)
Race, n (%)	
White	555 (81.9)
Unknown	88 (13.0)
Mean duration since MS symptom onset, year (SD)	1.10 (0.84)
Mean duration since RRMS diagnosis, year (SD)	0.36 (0.40)
Mean EDSS at baseline ^a (SD)	1.71 (0.95)
EDSS at baseline category, ^a n (%)	
<2.5 / ≥2.5	508 (74.9) / 170 (25.1)
Number of relapses in the year prior to enrolment, n (%)	
0	38 (5.6)
1	438 (64.6)
2	166 (24.5)
3	27 (4.0)
≥4	9 (1.3)

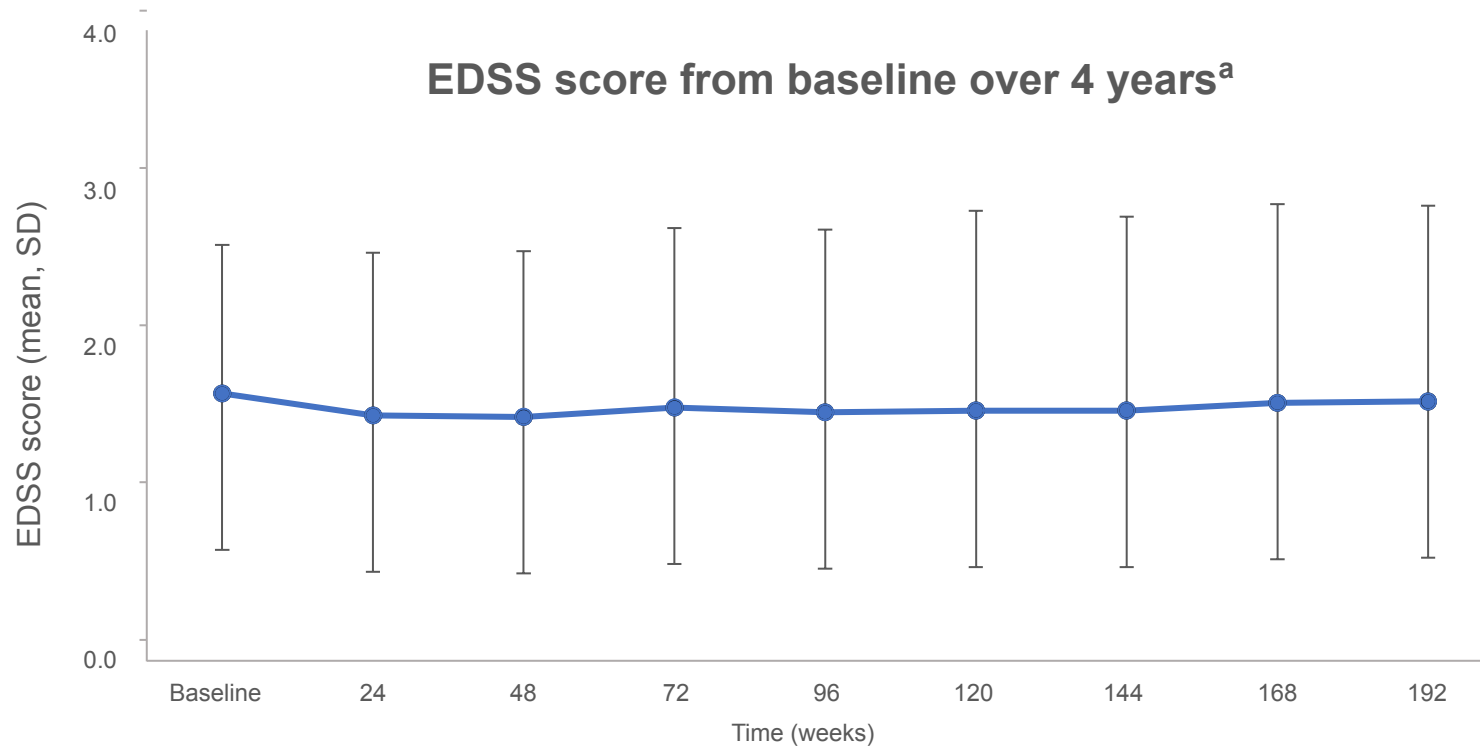


Baseline demographics and disease characteristics were consistent with a young, early-stage RRMS population

A relatively high retention rate was observed across the study

Results

EDSS – Change from baseline; absolute values



Patients treated with first-line OCR maintained stable EDSS scores over 4 years, with no overall accrual of disability compared with baseline



<https://ter.li/drk6ao>

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

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¹UCSF Weill Institute for Neurosciences, University of California San Francisco, San Francisco, CA, USA; ²Research Center for Clinical Neuroimmunology and Neuroscience, University Hospital Basel, University of Basel, Basel, Switzerland; ³Department of Neurology-Neuroimmunology, Multiple Sclerosis Centre of Catalonia, Vall d'Hebron University Hospital, Barcelona, Spain; ⁴F. Hoffmann-La Roche Ltd, Basel, Switzerland; ⁵Genentech, Inc., South San Francisco, CA, USA; ⁶IQVIA Solutions, Inc., Courbevoie, France; ⁷Department of Neurology, McGovern Medical School, The University of Texas Health Science Center at Houston (UTHealth), Houston, TX, USA

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Wednesday, 11 October 2023

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F. Hoffmann-La Roche Ltd, Sanofi, Santhera, Shionogi and TG Therapeutics); speaker fees (Bayer HealthCare, Biogen, Merck, Novartis, F. Hoffmann-La Roche Ltd and Sanofi); support of educational activities (Allergan, Bayer HealthCare, Biogen, CSL Behring, Desitin, Sanofi-Genzyme, Merck, Novartis, F. Hoffmann-La Roche Ltd, Pfizer, Sanofi, Shire and Teva); license fees for Neurostatus products; and grants (Bayer HealthCare, Biogen, European Union, Innosuisse, Merck, Novartis, F. Hoffmann-La Roche Ltd, Swiss MS Society and Swiss National Research Foundation). **X Montalban** has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with AbbVie, Actelion, Alexion, Biogen, Bristol Myers Squibb/Celgene, EMD Serono, F. Hoffmann-La Roche Ltd, Immunic, Janssen, MedDay, Merck, Mylan, NervGen, Novartis, Sandoz, SanofiGenzyme, Teva, TG Therapeutics, ExeMed, MSIF and NMSS. **C Chognot** is a shareholder and employee of F. Hoffmann-La Roche Ltd. **N Pasquarelli** is a shareholder and employee of F. Hoffmann-La Roche Ltd. **K Kadner** is an employee of F. Hoffmann-La Roche Ltd.

B El Azzouzi is an employee of F. Hoffmann-La Roche Ltd. **A Pradhan** is an employee of Genentech, Inc. **E Incera** has received consulting fees from F. Hoffmann-La Roche Ltd for statistical assistance, and is an employee of IQVIA Solutions, Inc. **JS Wolinsky** has received personal compensation for consulting, serving on a scientific advisory board, speaking or other activities with Cleveland Clinic Foundation, EMD Serono,

Immunogene, Novartis, F. Hoffmann-La Roche Ltd, Genentech, Sandoz and Zenas BioPharma; royalties are received for out-licensed monoclonal antibodies through UHealth from Millipore Corporation.

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Study Aim



To examine safety outcomes of patients continuously treated with OCR in clinical trials over a 10-year period (up to November 2022)

Results



As of November 2022, 6,155 patients with MS received OCR across 13 clinical trials (all-exposure population), amounting to 28,269 PY of exposure

Approximately 60% of patients (3,677) received at least 8 doses (~4 years of treatment)



As of March 2023, over 300,000 patients with MS (amounting to >750,000 PY of exposure) had started OCR in the post-marketing setting

Results

Over 10 Years of Continuous OCR Treatment, the Overall Safety Profile Remained Consistent

Adverse event Rate per 100 PY (95% CI)	OPERA (RMS)			All RMS ^c	ORATORIO (PPMS)			All PMS ^d	All OCR trials
	CTP ^a (Jul 2015)		CTP + OLE ^b (Nov 2022)	Nov 2022	CTP ^a (Jul 2015)		CTP + OLE ^b (Nov 2022)	Nov 2022	OCR all-exposure population ^e
	IFN β-1a	OCR	OCR	OCR	Placebo	OCR	OCR	OCR	
Total no. of patients	826	825	1,448	4,558	239	486	644	1,597	6,155
Total PY	1,399	1,448	10,798	21,080	729	1,606	4,669	7,190	28,269
Any AEs	296 (287–305)	290 (281–299)	194 (191–196)	227 (225–229)	259 (247–271)	252 (244–260)	223 (219–228)	215 (212–219)	224 (222–226)
AEs leading to withdrawal	3.9 (3.0–5.1)	2.4 (1.6–3.3)	1.3 (1.1–1.5)	1.0 (0.9–1.2)	1.1 (0.5–2.2)	1.2 (0.8–1.9)	1.1 (0.8–1.4)	1.0 (0.8–1.3)	1.0 (0.9–1.2)
Serious AEs	6.3 (5.1–7.8)	5.4 (4.3–6.7)	6.2 (5.8–6.7)	5.7 (5.4–6.0)	12.1 (9.7–14.9)	10.2 (8.7–11.8)	12.7 (11.7–13.8)	10.9 (10.1–11.7)	7.0 (6.7–7.3)
Infections and infestations	67.8 (63.5–72.2)	84.5 (79.9–89.4)	65.9 (64.4–67.4)	66.2 (65.1–67.3)	72.5 (66.5–79.0)	70.8 (66.8–75.0)	70.0 (67.8–72.6)	61.6 (59.8–63.4)	65.1 (64.1–66.0)
Serious infections ^f	1.8 (1.2–2.6)	0.8 (0.4–1.5)	1.7 (1.5–2.0)	1.5 (1.3–1.7)	3.0 (1.9–4.6)	2.7 (2.0–3.7)	4.4 (3.8–5.0)	3.7 (3.3–4.2)	2.1 (1.9–2.2)
IRRs	7.9 (6.5–9.5)	34.9 (31.9–38.1)	11.2 (10.5–11.8)	23.2 (22.6–23.9)	20.3 (17.2–23.8)	31.0 (28.3–33.9)	16.6 (15.5–17.8)	16.8 (15.9–17.8)	21.6 (21.1–22.2)
Malignancies ^{g,h}	0.1 (0.0–0.5)	0.3 (0.1–0.7)	0.4 (0.3–0.6)	0.4 (0.3–0.4)	0.3 (0.0–1.0)	0.9 (0.5–1.5)	1.0 (0.7–1.3)	0.9 (0.7–1.2)	0.5 (0.4–0.6)
Deaths	0.1 (0.0–0.5)	0.1 (0.0–0.4)	0.1 (0.0–0.2)	0.1 (0.1–0.2)	0.4 (0.1–1.2)	0.3 (0.1–0.6)	0.5 (0.3–0.7)	0.4 (0.3–0.6)	0.2 (0.1–0.2)

AE, adverse event; CI, confidence interval; CTP, controlled treatment period; IFN, interferon; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; OCR, ocrelizumab; OLE, open-label extension; PMS, progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; PY, patient years; RMS, relapsing multiple sclerosis; SOC, System Organ Class.

COVID-19 related AEs were excluded from this analysis, but patients continued to contribute to the incidence of all other AEs (see Supplementary Material for COVID-19 analysis). AEs were classified according to MedDRA versions 18.0, 18.1, 22.1 and 24.1. Multiple occurrences of the same AE in one patient are counted multiple times, except for malignancies.

^aData as of April–July 2015; ^bIncludes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase III studies, including patients originally randomised to comparator (IFN β-1a or placebo) who switched to open-label OCR treatment (data as of November 2022); ^cIncludes patients with RMS who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, CHIMES and OLERO (data as of November 2022); ^dIncludes patients with PMS who received any dose of OCR during the CTP and associated OLE periods of OBOE, CONSONANCE and OLERO (data as of November 2022); ^eIncludes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, CONSONANCE, CHIMES and OLERO including patients originally randomised to comparator (IFN β-1a or placebo) who switched to open-label OCR treatment (data as of November 2022); ^fSerious infections are defined using AEs falling into the MedDRA SOC 'Infections and Infestations', and using 'Is the event nonserious or serious?' from the AE case report form; ^gMalignancies are identified using AEs falling into the standard MedDRA query 'Malignant tumours (narrow)'; ^hFor malignancies, incidence rates are reported and exposure in PY was calculated from first treatment to onset of first malignancy.

Results

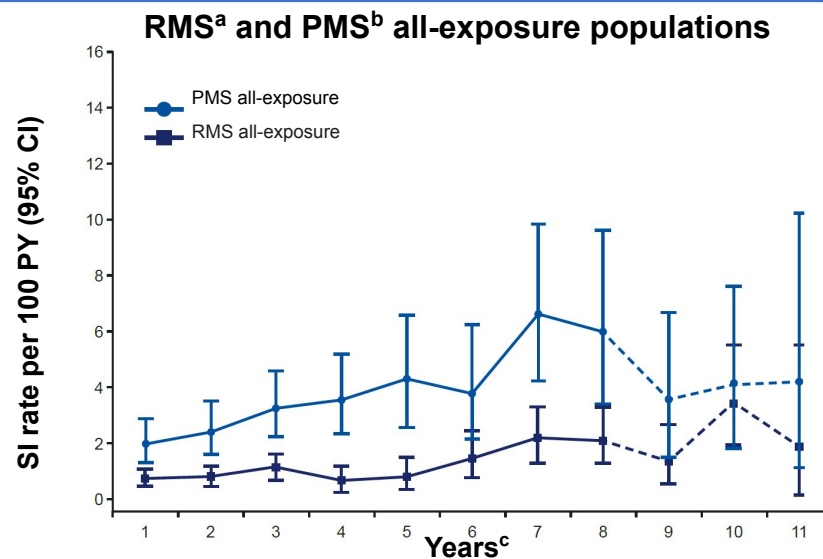
Over 10 Years of Continuous OCR Treatment, the Overall Safety Profile Remained Consistent



- Cumulative AE and SAE incidence rates remained consistent with the rates observed during the CTP
- The cumulative standardised incidence rates of (a) all malignancies and (b) female breast cancer remained within the range reported in real-world registries^{1,2} (see Supplementary Material)
- Withdrawal due to AEs was infrequent and did not increase over time

Results

SI Rates Remained Stable with Non-Significant Year-on-Year Variation and Within the Range Reported in Real-World Registries^{3,4}



Exposure (PY)	4,496	4,132	3,169	2,590	1,648	1,239	1,161	1,081	738	529	177
	1,524	1,289	1,157	886	519	457	405	302	282	250	112
Event rate (per 100 PY)	1.1	1.2	1.5	1.1	1.3	1.7	2.6	2.5	1.8	3.8	2.3
	2.4	2.8	3.6	4.0	4.6	4.2	6.9	6.3	3.9	4.4	4.5
Number of SIs	50	51	48	28	21	23	30	27	13	20	4
	36	36	42	35	24	19	28	19	11	11	5
N	4,558	4,360	3,435	2,979	1,881	1,351	1,198	1,131	910	611	332
	1,597	1,387	1,199	1,109	583	478	433	322	295	268	200

- In the RMS and PMS all-exposure populations, UTI and pneumonia were the most commonly reported SIs; this is consistent with incidence rates and patterns observed in real-world studies^{4–6}

CI, confidence interval; CTP, controlled-treatment period; OCR, ocrelizumab; PMS, progressive multiple sclerosis; PY, patient years; RMS, relapsing multiple sclerosis; SI, serious infection; UTI, urinary tract infection. COVID-19 related AEs were excluded from this analysis, but patients continued to contribute to the incidence of all other AEs (see Supplementary Material for COVID-19 analysis). ^aIncludes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, CHIMES and OLERO (data as of November 2022); ^bIncludes patients who received any dose of OCR during the CTP and associated OLE periods of OBOE, CONSONANCE and OLERO (data as of November 2022); ^cThe exposure in PY during Years 8–11 is limited for meaningful interpretation, so these data are presented in the plots with dotted lines

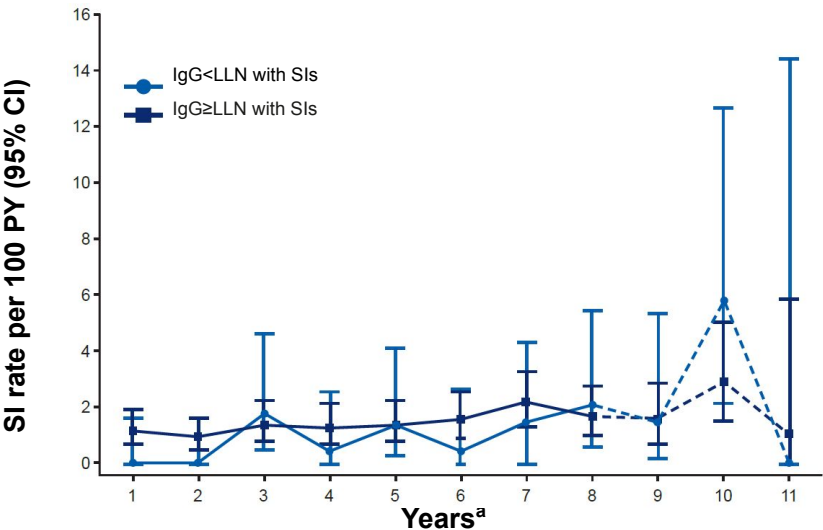
3. Wijnands JMA, et al. *J Neurol Neurosurg Psychiatry* 2018;89:1050–1056; 4. Knapp R, et al. *Mult Scler Relat Disord* 2022;68:104245; 5. Wijnands JMA, et al. *Mult Scler* 2017;23:1506–1516;

6. Persson et al. *Mult Scler Relat Disord* 2020;41(1):101982.

Results

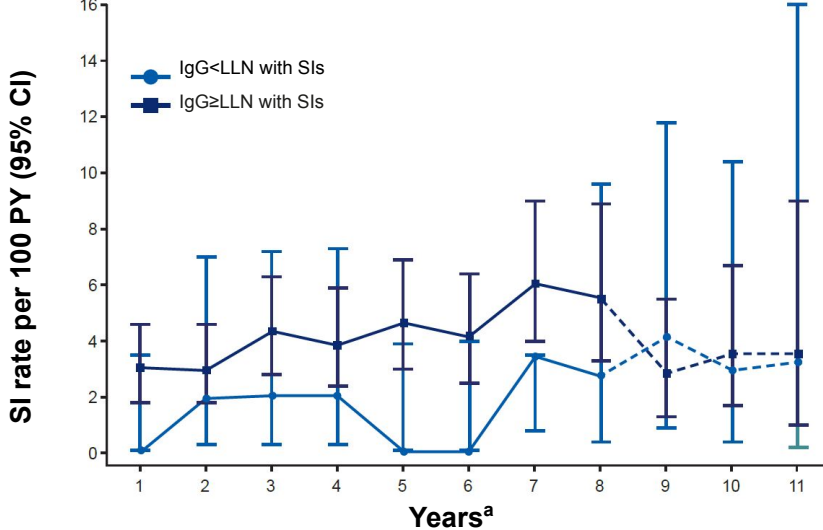
In Both RMS and PPMS Populations, Longer Exposure to OCR Did Not Lead to an Increased Risk of SIs Regardless of IgG Status (Normal Levels or Levels Below the LLN)

RMS (OPERA I, II and OLERO)



Exposure (PY) IgG<LLN with SI	224	223	222	219	215	212	204	188	135	103	26
Exposure (PY) IgG≥LLN with SI	1,420	1,358	1,275	1,214	1,160	1,119	1,064	987	649	444	95
IgG<LLN number of SIs	0	0	4	1	3	1	3	4	2	6	0
IgG≥LLN number of SIs	17	13	18	16	16	18	23	17	10	13	1

PPMS (ORATORIO and OLERO)



Exposure (PY) IgG<LLN with SI	104	102	99	98	95	93	86	74	73	68	31
Exposure (PY) IgG≥LLN with SI	634	609	574	538	496	456	405	302	282	250	112
IgG<LLN number of SIs	0	2	2	2	0	0	3	2	3	2	1
IgG≥LLN number of SIs	19	18	25	21	23	19	25	17	8	9	4

- The type, severity, latency and duration of SIs observed during episodes of IgG<LLN were consistent with the overall SIs observed in patients treated with OCR

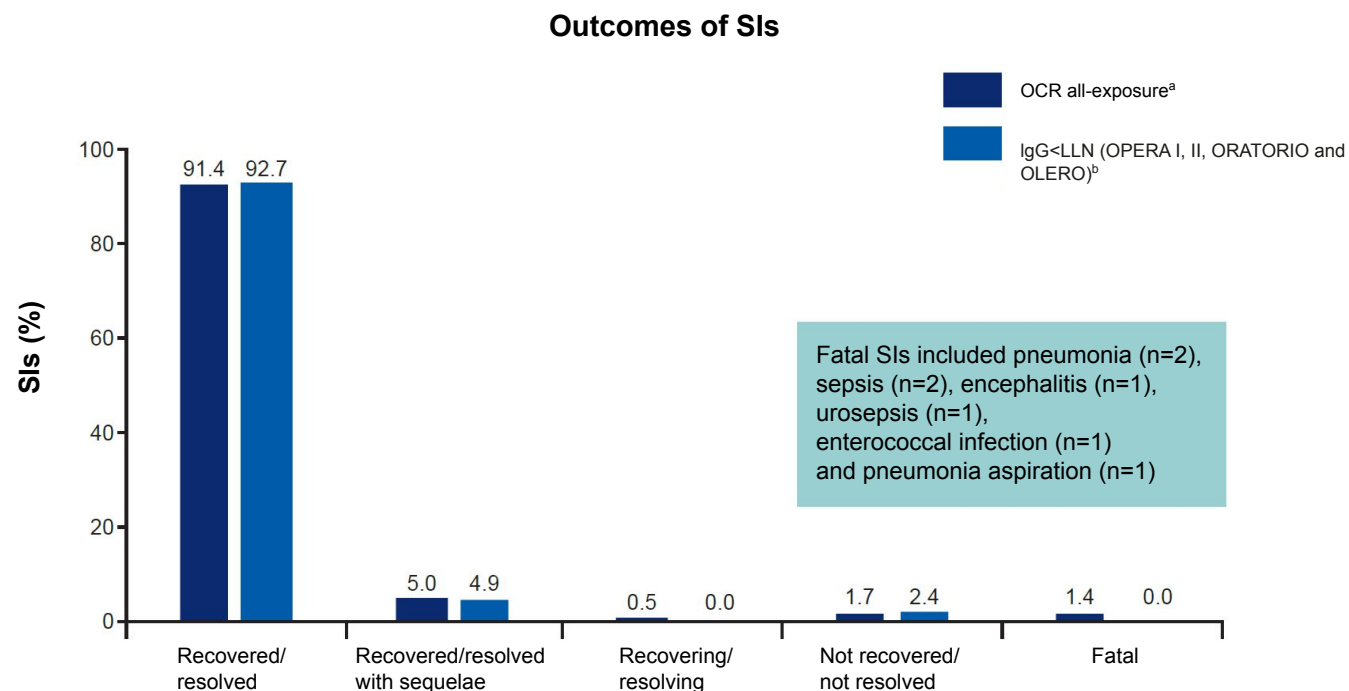
CI, confidence interval; CTP, controlled-treatment period; IgG, immunoglobulin G; LLN, lower limit of normal; OCR, ocrelizumab; PPMS, primary progressive multiple sclerosis; PY, patient years; RMS, relapsing multiple sclerosis; SI, serious infection.

COVID-19 related AEs were excluded from this analysis, but patients continued to contribute to the incidence of all other AEs (see Supplementary Material for COVID-19 analysis).

^aThe exposure in PY during Years 8–11 is limited for meaningful interpretation, so these data are presented in the plots with dotted lines.

Results

The Majority of SIs Were of Grade 3 Intensity, >90% Had Resolved (Regardless of IgG Status) and Were Not Treatment Limiting



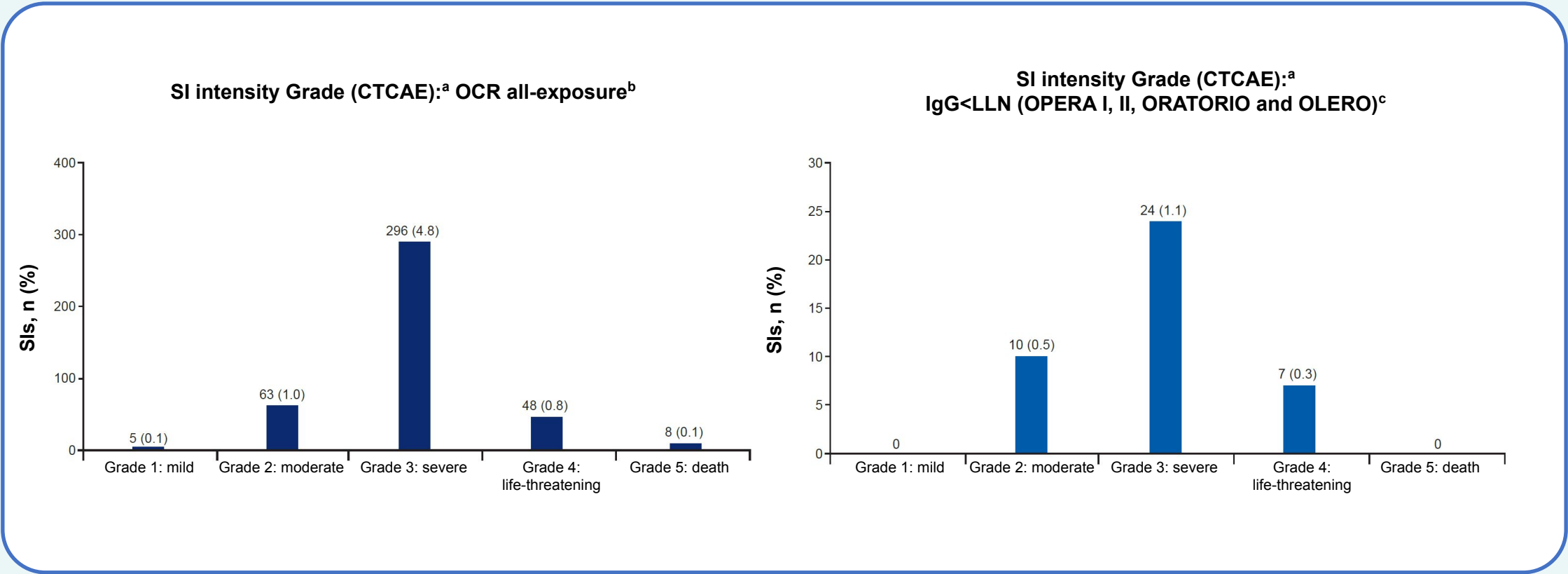
IgG, immunoglobulin G; LLN: Lower limit of normal [LLN=5.65 (g/L)]; OCR, ocrelizumab; SI, serious infection.

COVID-19 related AEs were excluded from this analysis, but patients continued to contribute to the incidence of all other AEs (see Supplementary Material for COVID-19 analysis).

^aIncludes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, CONSONANCE, CHIMES and OLERO (total N=6,155 patients); ^bSingle-drop method (total N=2,092); percentages are calculated using the number of patients that experienced any number of SIs (counting multiple occurrences once), by the number of patients.

Results

The Majority of SIs Were of Grade 3 Intensity, >90% Had Resolved (Regardless of IgG Status) and Were Not Treatment Limiting (cont.)



ADL, activities of daily living; CTCAE, Common Terminology Criteria for Adverse Events; IgG, immunoglobulin G; LLN: Lower limit of normal [LLN=5.65 (g/L)]; OCR, ocrelizumab; SI, serious infection. COVID-19 related AEs were excluded from this analysis, but patients continued to contribute to the incidence of all other AEs (see Supplementary Material for COVID-19 analysis).
^aGrade 1 (mild): Asymptomatic or mild symptoms/clinical or diagnostic observation only/intervention not indicated; Grade 2 (moderate): Minimal, local or noninvasive intervention indicated/limiting age-appropriate instrumental ADL; Grade 3 (severe): Severe or medically insignificant but not immediately life-threatening/hospitalisation or prolongation of hospitalisation indicated/disabling/limiting self-care ADL; Grade 4 (life-threatening): Life-threatening consequences/urgent intervention required; Grade 5 (death): Death related to AE (not applicable for all AEs); percentages are calculated using the number of patients that experienced any number of SIs (counting multiple occurrences once), by the number of patients; ^bIncludes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, CONSONANCE, CHIMES and OLERO (total N=6,155 patients); ^cSingle-drop method (total N=2,092).

Conclusions



- Over a 10-year follow-up period in clinical trials, OCR continues to exhibit a stable and favourable safety profile
- AE rates in all RMS and PMS populations remained consistent with the rates observed during the CTP
- Rates of SIs remained low and stable over time in both RMS and PMS populations irrespective of IgG levels
- AEs leading to treatment withdrawal remained infrequent and were not driven by serious infections

Supplementary Materials

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Methods

Safety Analyses

Safety analyses were based on integrated data for all patients who received OCR in the following MS clinical trials



OPERA OLE (comprising the DBP and OLE periods of pooled OPERA I/II studies)^a



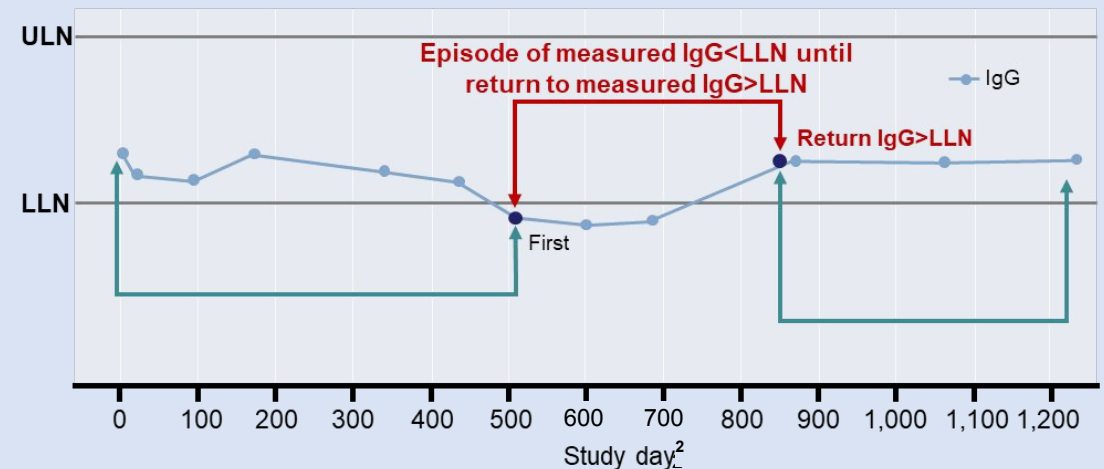
ORATORIO OLE (comprising the ORATORIO DBP and OLE period)^a



OCR all exposure

(Phase II and Phase III MS clinical trials DBP and associated OLE periods, plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO,^b CONSONANCE, CHIMES and OLERO)

- The number of post-marketing OCR-treated patients was based on the estimated number of vials sold and US claims data
- AEs were classified according to the MedDRA, and the rates of **AEs were expressed per 100 PY**
- The **single-drop method (figure)** was used to examine the rate of SIs during the period of IgG below the LLN compared with the rate of SIs during the period of $\text{IgG} \geq \text{LLN}$ ¹



AE, adverse event; CTP, controlled-treatment period; DBP, double-blind period; ECP, extended-controlled period; IgG, immunoglobulin G; MedDRA, Medical Dictionary for Regulatory Activities; LLN, lower limit of normal; MS, multiple sclerosis; OCR, ocrelizumab; OLE, open-label extension; PY, patient years; SI, serious infections; ULN, upper limit of normal.

^aUpon completion of the CTP, patients were eligible to receive OCR in OLEs. In ORATORIO, following completion of the DBP, patients could enter the OLE, via an ECP; bLIBERTO is the long-term extension study to CASTING and ENSEMBLE.

1. Cerqueira JJ, et al. Neurol 2023 (pre-submission); 2. Cerqueira JJ, et al. Neurol 2023;Supplement (pre-submission).

- Age- and sex-standardised incidence rates of all malignancies (excluding NMSC) and age-standardised incidence rates of female breast cancer, were compared with rates from real-world epidemiological sources, both MS specific (Danish MS Registry)¹ and for the general population (NCI SEER database)²
- The standardised incidence ratios, calculated as the observed/expected number of events, were determined for all malignancies (excluding NMSC) and female breast cancer, using SEER and Danish MS Registry data as reference populations

Methods

Overview of Phase II/III/IIIb Studies and Patient Exposure

i

As of November 2022, 6,155 patients with MS had received OCR across 13 clinical trials (amounting to 28,269 PY of exposure)

As of March 2023, over 300,000 patients with MS had started OCR globally in the post-marketing setting

Phase III
N=1,448
PY=10,798

Phase III
CTP + OLE
N=644
PY=4,669

OCR
all exposure
N=6,155
PY=28,269

Phase II in **RRMS**¹ OLE

OPERA I/II in **RMS**² OLE

ORATORIO in **PPMS**³ OLE

Phase IIIb study in **RMS**: VELOCE

Phase IIIb study in **RRMS**: CHORDS/CASTING

Phase IIIb study in **RMS & PPMS**: OBOE

Phase IIIb study in early **RRMS**: ENSEMBLE

Phase IIIb study in PMS (**PPMS & SPMS**): CONSONANCE

Phase IIIb study in **RRMS**: LIBERTO^a

Phase IV study in **RMS**: CHIMES

Jul 2008 Mar–Sep 2011 Jan 2016 Feb 2017 Sep 2017 Feb 2018 Jul 2018 Jan 2019 Jan 2020 Nov 2020 Nov 2021 Nov 2022

CTP, controlled-treatment period; MS, multiple sclerosis; OCR, ocrelizumab; OLE, open-label extension; PMS, progressive MS; PPMS, primary progressive MS; PY, patient years; RMS, relapsing MS; RRMS, relapsing-remitting MS.

^aLIBERTO is the long-term extension study to CASTING and ENSEMBLE.

1. Kappos L, et al. Lancet 2011;378:1779–1787; 2. Hauser SL, et al. N Engl J Med 2017;376:221–234; 3. Montalban X, et al. N Engl J Med 2017;376:209–220.

Methods

Overview of Study Designs

Study name	Population (start date)	Naive/pretreated (%) ^a	Design	Treatment	Number of patients	Overall PY (Nov 2022)	Duration of main study	Entering OLE? ^b	Objective of study	Primary endpoint	Current status
Phase II (NCT00676715)	RRMS (2008)	Naive and pretreated (41.3%)	Controlled	OCR 2,000 mg every 6M ^{c,d}	55	1,458	96 weeks	Yes	Evaluate the efficacy and safety of two dose regimens of OCR	Total number of T1 Gd-enhancing lesions observed on brain MRI scans at Weeks 12, 16, 20 and 24	Active, not recruiting
				OCR 600 mg every 6M ^e	55						
				Placebo every 6M ^f	54						
				IFN β-1a 30 µg once weekly ^f	54						
OPERA I (NCT01247324)	RMS (2011)	Naive and pretreated (27.4%)	Controlled	OCR 600 mg every 6M ^e	410	5,537	96 weeks	Yes	Evaluate the efficacy and safety of OCR in comparison to IFN β-1a	ARR at Week 96	Completed
				IFN β-1a 44 µg three times weekly	411						
OPERA II (NCT01412333)	RMS (2011)	Naive and pretreated (25.9%)	Controlled	OCR 600 mg every 6M ^e	417	5,262	96 weeks	Yes	Evaluate the efficacy and safety of OCR in comparison to IFN β-1a	ARR at Week 96	Completed
				IFN β-1a 44 µg three times weekly	418						
ORATORIO (NCT01194570)	PPMS (2011)	Naive and pretreated (11.6%)	Controlled	OCR 600 mg every 6M ^g	488	4,669	120 weeks	Yes	Evaluate the efficacy and safety of OCR in comparison to placebo	Percentage of patients with CDP sustained for at least 12 weeks	Completed
				Placebo every 6M	244						

Methods

Overview of Study Designs (cont.)

Study name	Population (start date)	Naive/pretreated (%) ^a	Design	Treatment	Number of patients	Overall PY (Nov 2022)	Duration of main study	Entering OLE? ^b	Objective of study	Primary endpoint	Current status
VELOCE (NCT02545868)	RMS (2015)	Naive and pretreated (41.2%)	Controlled	OCR 2,000 mg every 6M ^e	68	472	24 weeks	Yes	Evaluate the immune response to vaccines after administration of OCR	Percentage of patients with a positive response 8 weeks post-tetanus vaccine	Completed
				IFN β-1a or no DMT	34						
CHORDS (NCT02637856)	RRMS (2016)	Pretreated (100%)	Single arm	OCR 600 mg every 6M ^e	611	1,116	96 weeks	No ^h	Evaluate the efficacy and safety of OCR in patients with a suboptimal response to a DMT in the USA/Canada	Percentage of patients free from any protocol-defined event during 96-week period, including occurrence of at least one of the following: a protocol-defined relapse, a T1 Gd-enhancing lesion, a new and/or enlarging T2 lesion, or CDP at 24 weeks	Completed
CASTING (NCT02861014)	RRMS (2016)	Pretreated (100%)	Single arm	OCR 600 mg every 6M ^e	681	516	96 weeks	Yes	Evaluate the efficacy and safety of OCR in patients with a suboptimal response to a DMT in Europe	Percentage of patients with NEDA (as per protocol-defined events) during 96-week period	Completed

Methods

Overview of Study Designs (cont.)

Study name	Population (start date)	Naive/pretreated (%) ^a	Design	Treatment	Number of patients	Overall PY (Nov 2022)	Duration of main study	Entering OLE? ^b	Objective of study	Primary endpoint	Current status
OBOE (NCT02688985)	RMS (2016)	Naive and pretreated (37.5%)	Single arm	OCR 600 mg every 6M ^e	88	492	52 weeks	Yes	Explore the mechanism of action of OCR and B-cell biology	Change in NfL levels in the CSF from baseline to post-treatment with OCR; changes in the numbers of CD19 ⁺ B cells and CD3 ⁺ T cells in the CSF from baseline to post-treatment with OCR	Completed
	PPMS (2016)			OCR 600 mg every 6M ^g	16						
ENSEMBLE (NCT03085810)	Early-stage RRMS (2017)	Naive (100%)	Single arm	OCR 600 mg every 6M ^e	1,233 ⁱ	2,181	192 weeks	Yes	Evaluate the efficacy and safety of OCR	A set of endpoints addressing different facets of MS: clinical assessments conducted every 24 weeks; MRI conducted at Weeks 8 (rebaselining), 24, 48, 96, 144 and 192	Completed
LIBERTO (NCT03599245)	MS (2018)	Pretreated (100%)	Single arm	OCR 600 mg every 6M ^e	1,500 ⁱ	3,949	144 weeks	Yes	Long-term extension study to CASTING and ENSEMBLE to evaluate the efficacy and safety of OCR	Effectiveness of OCR in patients with MS assessed by progression of disease up to 2 years	Active, not recruiting

Methods

Overview of Study Designs (cont.)

Study name	Population (start date)	Naive/pretreated (%) ^a	Design	Treatment	Number of patients	Overall PY (Nov 2022)	Duration of main study	Entering OLE? ^b	Objective of study	Primary endpoint	Current status
CONSONANCE (NCT03523858)	PMS (PPMS and SPMS) (2018)	Pretreated (100%)	Single arm	OCR 600 mg every 6M ^j	633	2,393	192 weeks	Yes	Open-label study to evaluate the effectiveness and safety of OCR in patients with PMS	Percentage of patients with NEP and NEPAD from baseline to Week 96, Week 96 to Week 192, and baseline to Week 192	Active, not recruiting
OLERO (NCT05269004)	RMS and PPMS (2022)	Pretreated (100%)	Single arm	OCR 600 mg every 6M ^j	~1,300	0	192 weeks	Yes	Open-label study to evaluate the effectiveness and safety of OCR in patients with MS who were previously enrolled in Phase III studies	Incidence and severity of adverse events, with severity determined according to the NCI CTCAE from baseline to Week 192	Recruiting
CHIMES (NCT04377555)	RMS (2022)	Naive or initiating 1st or 2nd switch from treatment with certain DMTs	Single arm	OCR 600 mg every 6M ^j	182	225	48 weeks (optional 168 weeks extension)		Open-label study to assess disease activity biomarkers of neuronal damage in minority patients with RMS	Proportion of participants free of any protocol-defined events (relapse, progression, a T1 Gd-enhancing lesion, a new and/or enlarging T2 lesion) from baseline to Week 48	Active, not recruiting

6M, 6 months; ARR, annualised relapse rate; CDP, confirmed disability progression; CSF, cerebrospinal fluid; CTCAE, Common Terminology Criteria for Adverse Events; DMT, disease-modifying therapy; Gd, gadolinium; IFN, interferon; NCI, National Cancer Institute; NEDA, no evidence of disease activity; NEP, no evidence of progression; NEPAD, no evidence of progression and no active disease; NfL, neurofilament light; OCR, ocrelizumab; OLE, open-label extension; PMS, progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; PY, patient years; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

^aPercentage refers to the number of pretreated patients; ^bPatients in the OLE received 600 mg OCR every 6M; ^cThe first OCR dose was given as 2 x 1,000-mg infusions with 14-day interval; ^dAt Week 24, OCR 2,000 mg was reduced to 1,000 mg; ^eThe first OCR dose was given as 2 x 300-mg infusions with 14-day interval; ^fAt Week 24, patients in the placebo and IFN β -1a groups received OCR 600 mg; ^gAll doses of OCR were given as 2 x 300-mg infusions; ^hOptional infusion at Week 96 (dose 5; not included in safety analysis); eligible patients could participate in the CHORDS extension substudy, where they received a 600-mg infusion of OCR over a reduced infusion time of approximately 2 hours; ⁱEstimated enrolment; ^jAn initial dose of 2 x 300-mg infusions separated by 14 days (on Days 1 and 15), and then 600 mg at every subsequent dose every 24 weeks for the remainder of the study treatment period (approximately 192 weeks).

Results

Treatment Exposure



In the OCR all-exposure population, approximately 60% of patients (3,677) received ≥ 8 doses

	RMS all-exposure population (n=4,558) ^a	PMS all-exposure population (n=1,597) ^b	OCR all-exposure (N=6,155) ^c
Age at start of treatment, median (range), years	35.0 (18–65)	49.0 (19–66)	39.0 (18–66)
Total patient years	21,080	7,190	28,269
Number of doses, n (%) ^d	Number of patients	Number of patients	Number of patients
≥ 1	4,558 (100)	1,597 (100)	6,155 (100)
≥ 2	4,425 (97.1)	1,542 (96.6)	5,967 (96.9)
≥ 3	4,317 (94.7)	1,412 (88.4)	5,729 (93.1)
≥ 4	4,074 (89.4)	1,274 (79.8)	5,348 (86.9)
≥ 5	3,260 (71.5)	1,162 (72.8)	4,422 (71.8)
≥ 6	2,950 (64.7)	1,102 (69.0)	4,052 (65.8)
≥ 7	2,841 (62.3)	1,047 (65.6)	3,888 (63.2)
≥ 8	2,721 (59.7)	956 (59.9)	3,677 (59.7)
≥ 9	1,815 (39.8)	508 (31.8)	2,323 (37.7)
≥ 10	1,641 (36.0)	493 (30.9)	2,134 (34.7)
≥ 11	1,475 (32.4)	460 (28.8)	1,935 (31.4)
≥ 12	1,230 (27.0)	445 (27.9)	1,675 (27.2)
Number of doses, mean (SD)	9.7 (6.5)	9.5 (6.8)	9.6 (6.5)
Number of doses, median	8.0	8.0	8.0
Total cumulative dose, mg			
Mean (SD)	5,825.9 (3,892.4)	5,650.8 (4,057.7)	5,780.5 (3,936.3)
Median	4,800	4,800	4,800
Range	9–18,200	19–15,600	9–18,200

CTP, controlled-treatment period; IFN, interferon; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; SD, standard deviation.

Data cut-off: November 2022. Doses were administered every 6 months.

^aIncludes patients with RMS who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, CHIMES and OLERO (data as of November 2022); ^bIncludes patients with PMS who received any dose of OCR during the CTP and associated OLE periods of ORATORIO, OBOE, CONSONANCE and OLERO; ^cIncludes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, CHIMES, CONSONANCE and OLERO, including patients originally randomised to comparator (IFN β -1a or PBO) who switched to open-label OCR treatment; ^dIf a patient received any infusion in one dose, it was counted as one dose.

Results

With and Without COVID-19 Over 10 Years of Continuous OCR Treatment, the Overall Safety Profile Remained Consistent

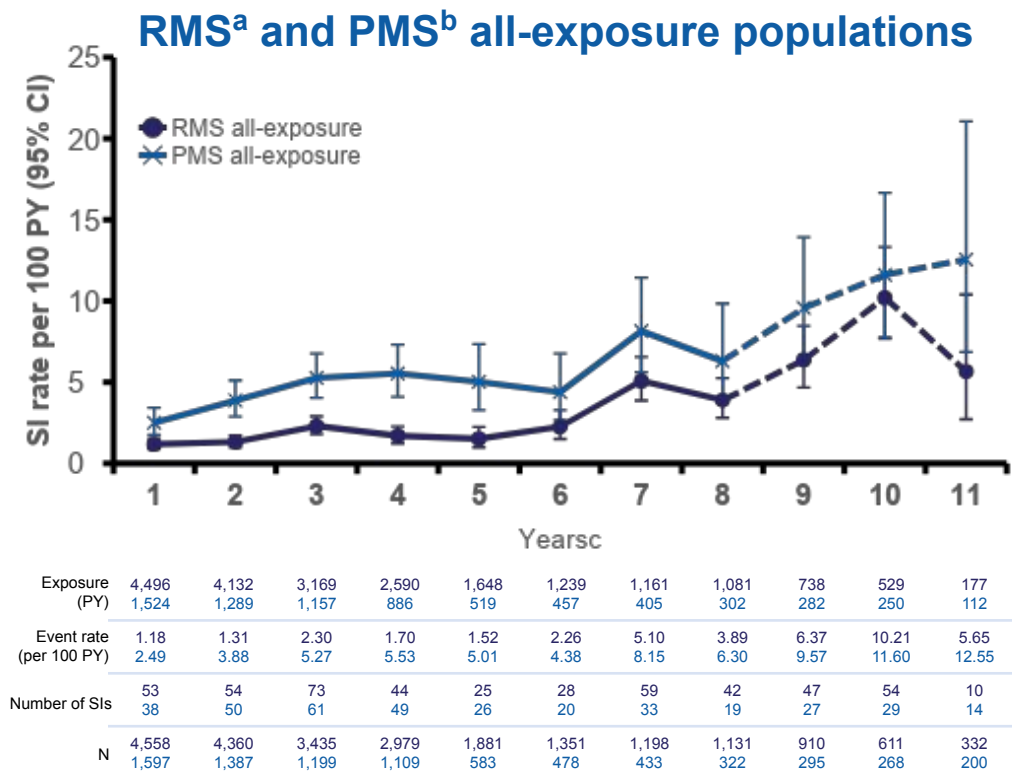
Adverse event Rate per 100 PY (95% CI)	OPERA (RMS)				All RMS ^c		ORATORIO (PPMS)				All PMS ^d		All OCR trials	
	CTP ^a (Jul 2015)		CTP + OLE ^b (Nov 2022)		Nov 2022		CTP ^a (Jul 2015)		CTP + OLE ^b (Nov 2022)		Nov 2022		OCR all-exposure population ^e	OCR all-exposure population ^e (Ex-COVID-19)
	IFN β-1a	OCR	OCR	OCR (Ex-COVID-19)	OCR	OCR (Ex-COVID-19)	Placebo	OCR	OCR	OCR (Ex-COVID-19)	OCR	OCR (Ex-COVID-19)		
Total no. of patients	826	825	1,448	1,448	4,558	4,558	239	486	644	644	1,597	1,597	6,155	6,155
Total PY	1,399	1,448	10,798	10,798	21,080	21,080	729	1,606	4,669	4,669	7,190	7,190	28,269	28,269
Any AEs	296 (287–305)	290 (281–299)	199 (196.6–201.9)	194 (191–196)	233 (231–235)	227 (225–229)	259 (247–271)	252 (244–260)	227 (224–233)	223 (219–228)	223 (219–226)	215 (212–219)	230 (229–232)	224 (222–226)
AEs leading to withdrawal	3.9 (3.0–5.1)	2.4 (1.6–3.3)	1.3 (1.1–1.6)	1.3 (1.1–1.5)	1.1 (1.0–1.2)	1.0 (0.9–1.2)	1.1 (0.5–2.2)	1.2 (0.8–1.9)	1.1 (0.8–1.4)	1.1 (0.8–1.4)	1.1 (0.9–1.3)	1.0 (0.8–1.3)	1.1 (1.0–1.2)	1.0 (0.9–1.2)
Serious AEs	6.3 (5.1–7.8)	5.4 (4.3–6.7)	7.3 (6.8–7.8)	6.2 (5.8–6.7)	6.5 (6.2–6.9)	5.7 (5.4–6.0)	12.1 (9.7–14.9)	10.2 (8.7–11.8)	13.8 (12.8–14.9)	12.7 (11.7–13.8)	12.3 (11.5–13.1)	10.9 (10.1–11.7)	8.0 (7.6–8.3)	7.0 (6.7–7.3)
Infections and infestations	67.8 (63.5–72.2)	84.5 (79.9–89.4)	71.2 (69.6–72.0)	65.9 (64.4–67.4)	72.1 (70.9–73.2)	66.2 (65.1–67.3)	72.5 (66.5–79.0)	70.8 (66.8–75.0)	74.0 (71.6–76.5)	70.0 (67.8–72.6)	68.9 (66.9–70.8)	61.6 (59.8–63.4)	71.2 (70.3–72.2)	65.1 (64.1–66.0)
Serious infections ^f	1.8 (1.2–2.6)	0.8 (0.4–1.5)	2.8 (2.5–3.1)	1.7 (1.5–2.0)	2.3 (2.1–2.6)	1.5 (1.3–1.7)	3.0 (1.9–4.6)	2.7 (2.0–3.7)	5.5 (4.8–6.2)	4.4 (3.8–5.0)	5.1 (4.6–5.6)	3.7 (3.3–4.2)	3.0 (2.8–3.3)	2.1 (1.9–2.2)
IRRs	7.9 (6.5–9.5)	34.9 (31.9–38.1)	11.2 (10.5–11.8)	11.2 (10.5–11.8)	23.2 (22.6–23.9)	23.2 (22.6–23.9)	20.3 (17.2–23.8)	31.0 (28.3–33.9)	16.6 (15.5–17.8)	16.6 (15.5–17.8)	16.8 (15.9–17.8)	16.8 (15.9–17.8)	21.6 (21.1–22.2)	21.6 (21.1–22.2)
Malignancies ^{g,h}	0.1 (0.0–0.5)	0.3 (0.1–0.7)	0.4 (0.3–0.6)	0.4 (0.3–0.6)	0.4 (0.3–0.4)	0.4 (0.3–0.4)	0.3 (0.0–1.0)	0.9 (0.5–1.5)	1.0 (0.7–1.3)	1.0 (0.7–1.3)	0.9 (0.7–1.2)	0.9 (0.7–1.2)	0.5 (0.4–0.6)	0.5 (0.4–0.6)
Deaths	0.1 (0.0–0.5)	0.1 (0.0–0.4)	0.3 (0.2–0.4)	0.1 (0.0–0.2)	0.26 (0.2–0.3)	0.1 (0.1–0.2)	0.4 (0.1–1.2)	0.3 (0.1–0.6)	0.6 (0.4–0.9)	0.5 (0.3–0.7)	0.6 (0.4–0.8)	0.4 (0.3–0.6)	0.3 (0.3–0.4)	0.2 (0.1–0.2)

AE, adverse event; CI, confidence interval; COVID-19, coronavirus disease 2019; CTP, controlled treatment period; IFN, interferon; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; OCR, ocrelizumab; OLE, open-label extension; PMS, progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; PY, patient years; RMS, relapsing multiple sclerosis; SOC, System Organ Class.

AEs were classified according to MedDRA versions 18.0, 18.1, 22.1 and 24.1. Multiple occurrences of the same AE in one patient are counted multiple times, except for malignancies. ^aData as of April–July 2015; ^bIncludes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase III studies, including patients originally randomised to comparator (IFN β-1a or placebo) who switched to open-label OCR treatment (data as of November 2022); ^cIncludes patients with RMS who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, CHIMES and OLERO (data as of November 2022); ^dIncludes patients with PMS who received any dose of OCR during the CTP and associated OLE periods of OBOE, ORATORIO, CONSONANCE and OLERO (data as of November 2022); ^eIncludes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, CONSONANCE, CHIMES and OLERO including patients originally randomised to comparator (IFN β-1a or placebo) who switched to open-label OCR treatment (data as of November 2022); ^fSerious infections are defined using AEs falling into the MedDRA SOC 'Infections and Infestations', and using 'Is the event nonserious or serious?' from the AE case report form; ^gMalignancies are identified using AEs falling into the standard MedDRA query 'Malignant tumours (narrow)'; ^hFor malignancies, incidence rates are reported and exposure in PY was calculated from first treatment to onset of first malignancy.

Results

With COVID-19, SI Rates Remained Stable with Non-Significant Year-on-Year Variation and Within the Range Reported in Real-World Registries^{1,2}



UTIs and pneumonia were the most commonly reported SIs; this is consistent with incidence rates and patterns observed in real-world studies²⁻⁴

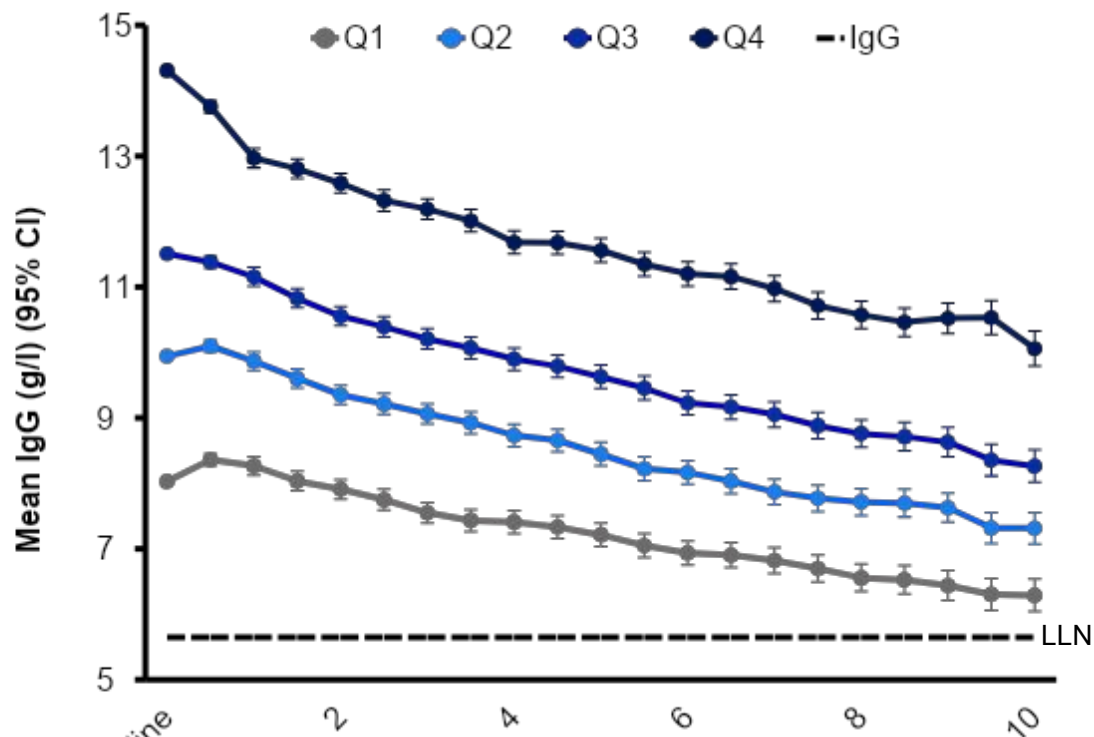
CI, confidence interval; COVID-19, coronavirus disease 2019; CTP, controlled-treatment period; OCR, ocrelizumab; PMS, progressive multiple sclerosis; PY, patient years; RMS, relapsing multiple sclerosis; SI, serious infection; UTI, urinary tract infection. COVID-19 related AEs were excluded from this analysis, but patients continued to contribute to the incidence of all other AEs (see Supplementary Material for COVID-19 analysis). ^aIncludes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, CHIMES and OLERO (data as of November 2022); ^bIncludes patients who received any dose of OCR during the CTP and associated OLE periods of ORATORIO, OBOE, CONSONANCE and OLERO (data as of November 2022); ^cThe exposure in PY during Years 8–11 is limited for meaningful interpretation, so these data are presented in the plots with dotted lines.

1. Wijnands JMA, et al. *Mult Scler* 2017;23:1506–1516. 2. Knapp R, et al. *Mult Scler Relat Disord* 2022;68:104245. 3. Wijnands JMA, et al. *Mult Scler* 2017;23:1506–1516. 4. Persson et al. *Mult Scler Relat Disord* 2020;41(1):101982.

Results

Over a Period of 10 Years, Trajectories in IgG Reach a Plateau in Patients with MS Receiving OCR

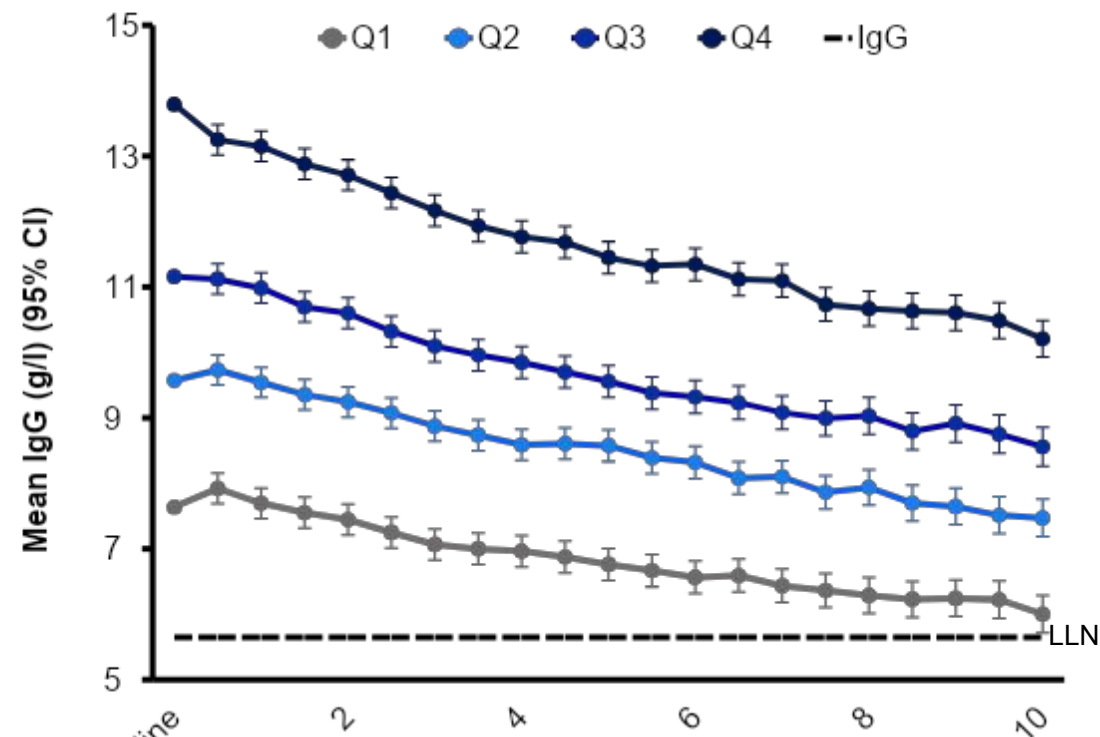
RMS (OPERA)



Number of patients:

Q1 363 363 357 347 333 323 314 300 292 286 281 275 267 262 256 247 237 207 164 147 133
 Q2 369 369 361 355 343 333 324 318 310 306 300 296 294 288 280 272 266 242 181 149 137
 Q3 361 361 358 355 348 337 326 319 312 301 294 288 279 275 265 259 251 222 166 135 120
 Q4 344 344 341 340 331 324 312 303 299 296 286 281 276 274 268 261 255 217 143 103 90

PMS (ORATORIO)



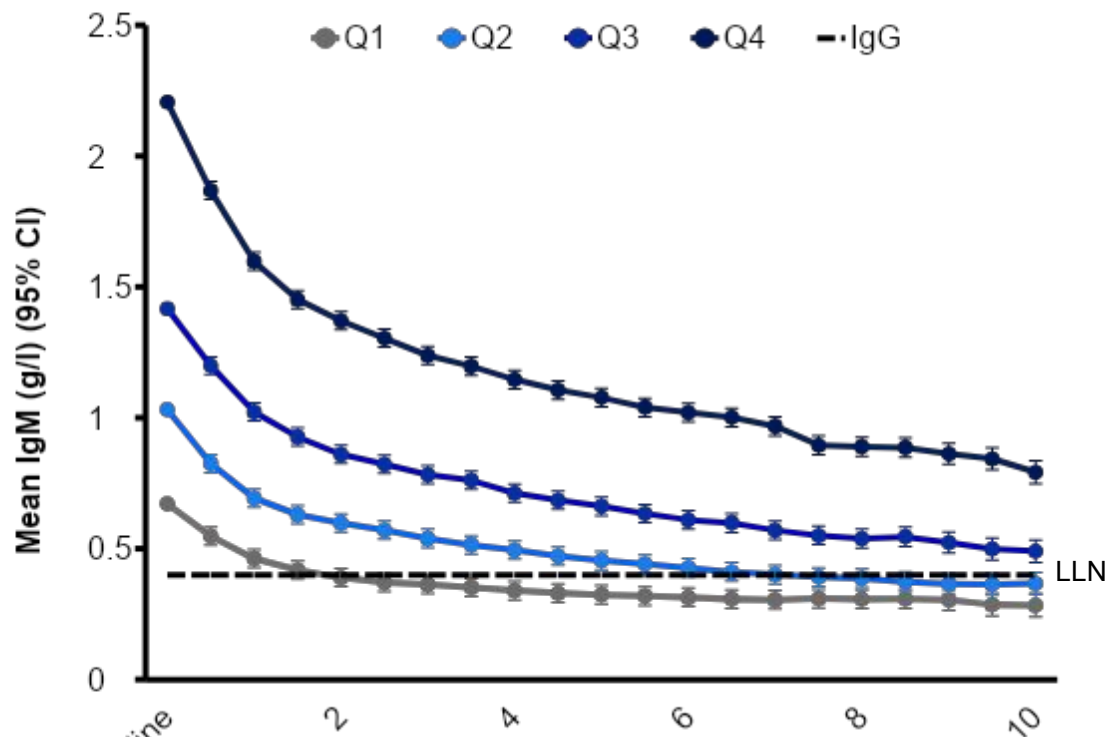
Number of patients:

Q1 157 157 155 153 151 146 140 136 135 129 125 118 115 106 100 95 76 75 71 66 64
 Q2 162 162 161 160 152 149 145 142 136 128 122 118 117 114 110 94 75 72 70 67 64
 Q3 158 156 156 153 149 144 136 136 127 124 122 117 111 106 100 86 68 68 65 61 55
 Q4 155 155 154 153 151 148 145 140 134 132 126 123 117 113 111 101 85 81 78 74 70

Results

Over a Period of 10 Years, Declining Trajectories in IgM Reach a Plateau in Patients with MS Receiving OCR

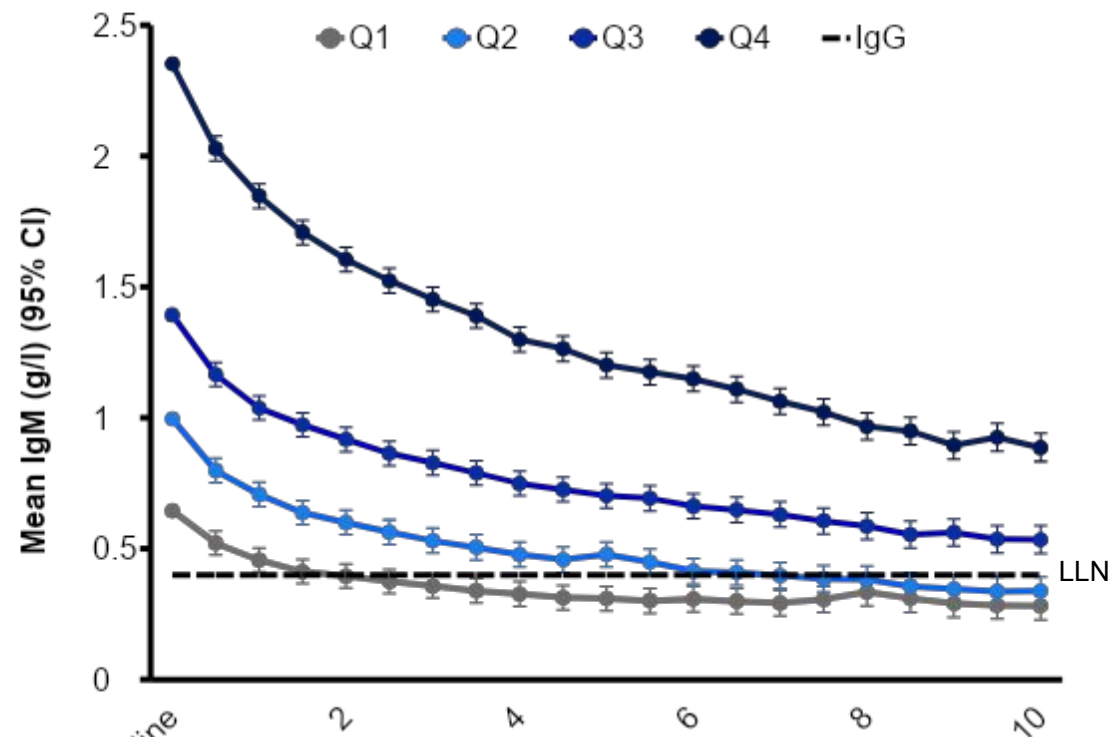
RMS (OPERA)



Number of patients:

Q1	359	351	356	350	336	329	318	308	301	298	295	289	283	280	272	260	251	220	154	126	107
Q2	355	353	351	346	342	333	327	313	307	301	293	290	285	282	272	267	260	226	171	142	128
Q3	363	358	360	355	344	334	317	311	306	300	291	285	279	272	269	262	254	222	164	133	127
Q4	353	345	349	345	332	320	313	307	298	289	281	275	268	264	255	249	243	219	164	132	117

PMS (ORATORIO)



Number of patients:

Q1	162	153	160	159	154	150	144	143	136	133	126	123	118	110	103	87	69	69	65	63	59
Q2	154	151	154	151	148	144	138	132	127	120	117	114	111	109	106	97	81	79	72	67	62
Q3	160	151	159	157	152	148	140	137	134	131	128	120	117	116	112	96	77	75	75	69	66
Q4	154	147	153	152	149	145	144	142	135	129	124	119	114	104	100	96	77	73	72	69	66

Results

After 10 Years of Treatment, IgG and IgM Levels Remained Normal for Most Patients and Were Overall Not Treatment Limiting

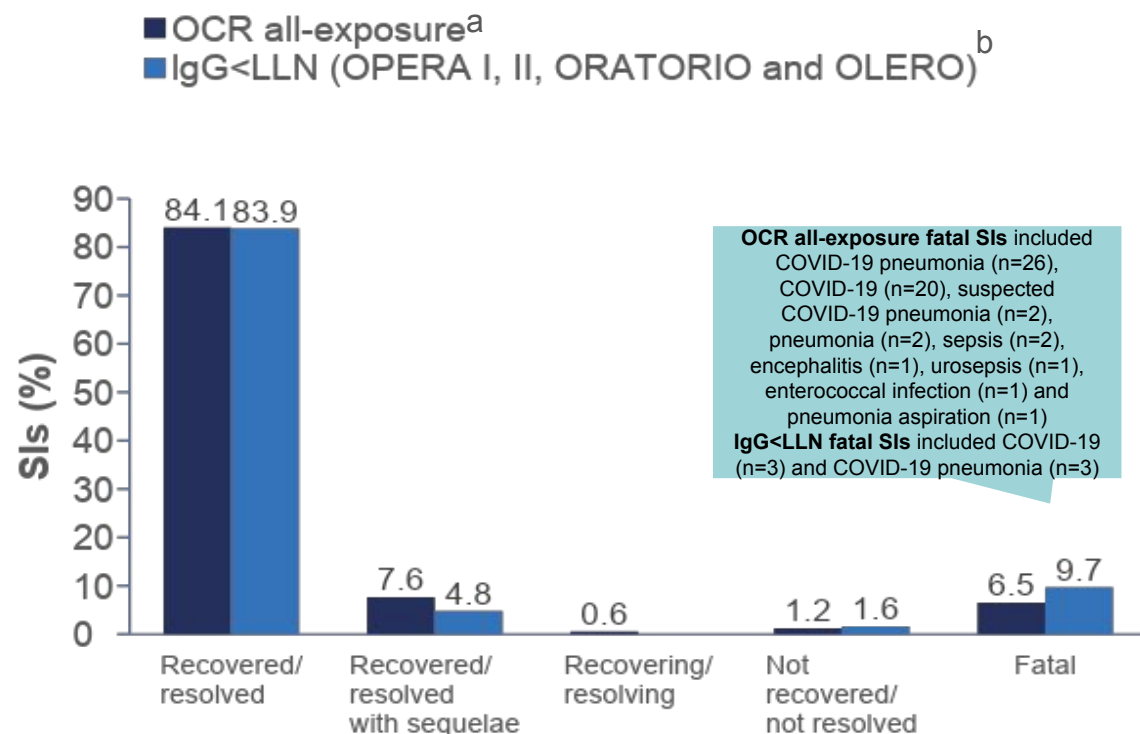


- After 12 years of continuous treatment, IgG levels remained normal for >85% of patients. For 46% of patients with IgG<LLN periods of hypogammaglobulinemia were transient, returning to normal after three infusion cycles while still on treatment
- Over a period of up to 12 years, discontinuations due to low IgG or due to SIs associated with low IgG were observed in n=20/2092 patients. Twelve patients (0.6%) discontinued due to SIs during periods of low IgM (<0.4 g/L)

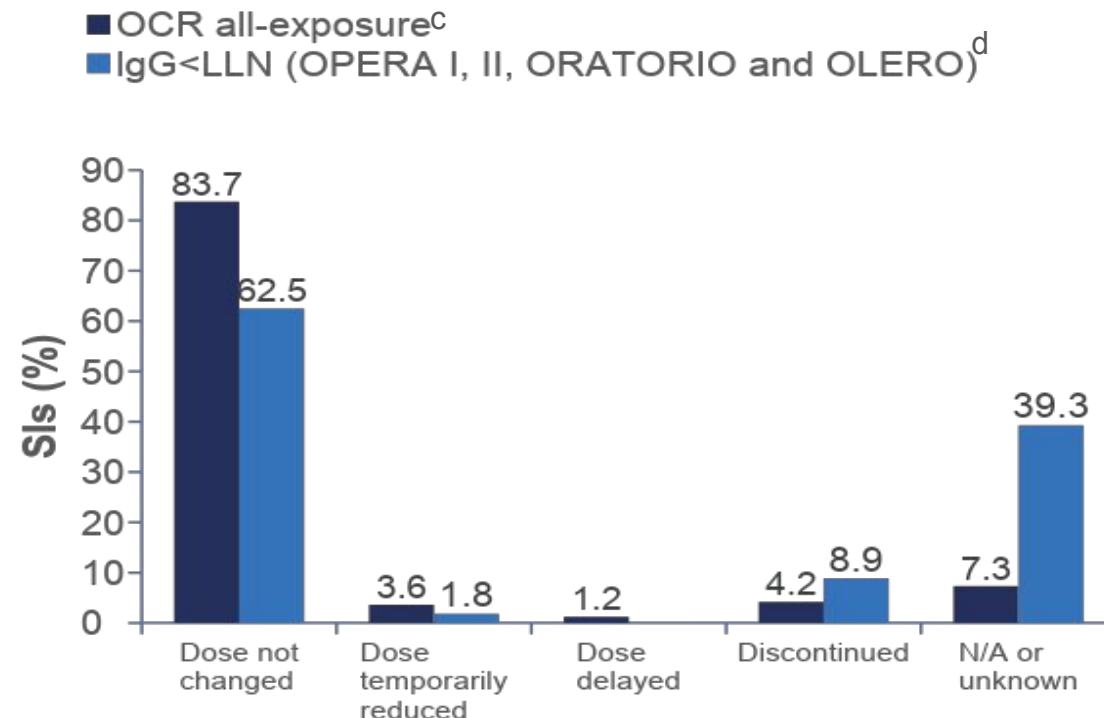
Results

Irrespective of IgG Levels, the Majority of Serious Infections Had Resolved and Were Not Treatment Limiting

Outcomes of SIs



Action taken with OCR



COVID-19, coronavirus disease 2019; IgG, immunoglobulin G; LLN, lower limit of normal [LLN=5.65 (g/L)]; OCR, ocrelizumab; SI, serious infection.

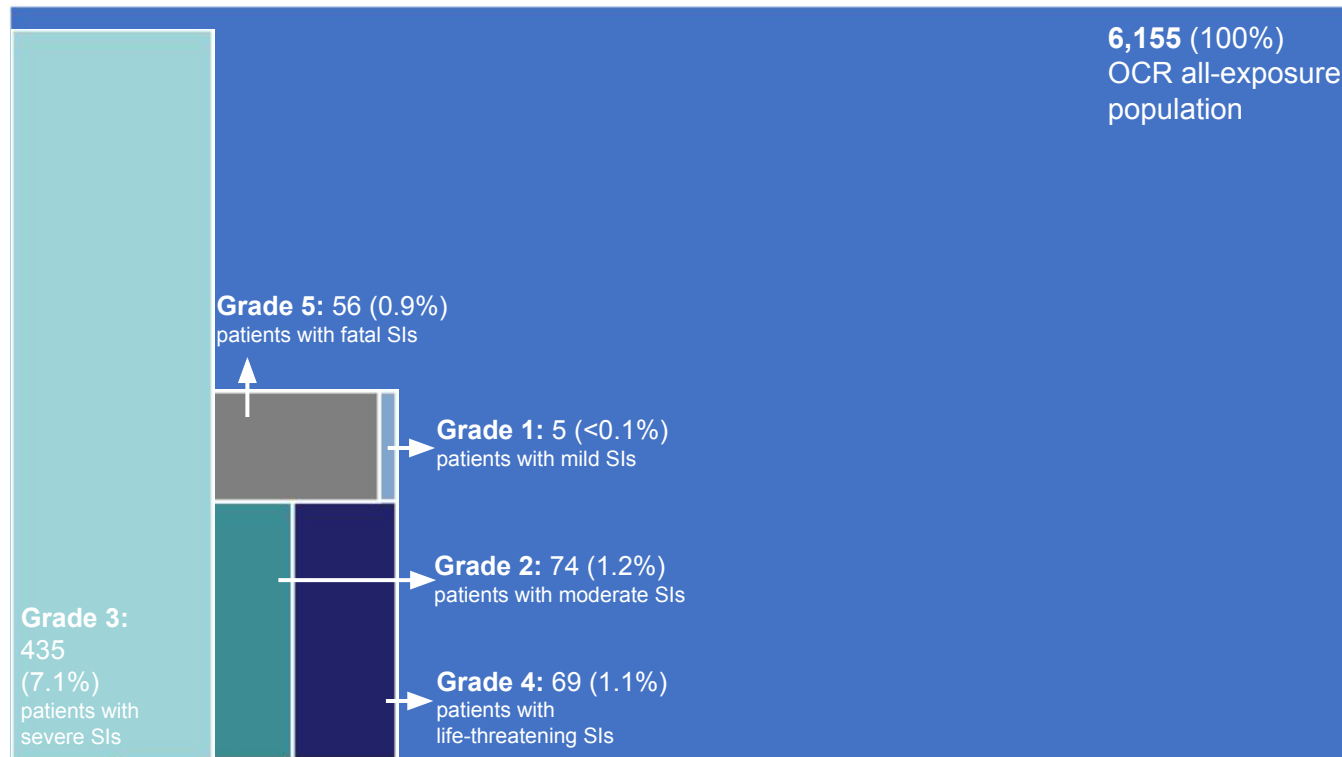
Percentages are calculated using the number of patients that experienced any number of SIs (counting multiple occurrences once), by the number of patients.

^aIncludes patients with at least one adverse event and associated OLE periods of the Phase II and Phase III studies plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, CONSONANCE, CHIMES and OLERO (total n=858 patients); ^bSingle-drop method which includes patients with at least one adverse event (total n=62); ^cIncludes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, CONSONANCE, CHIMES and OLERO (total n=802 patients, excludes 56 fatal cases from the analysis patients); ^dSingle-drop method (total n=56 patients, excludes 6 fatal cases from the analysis).

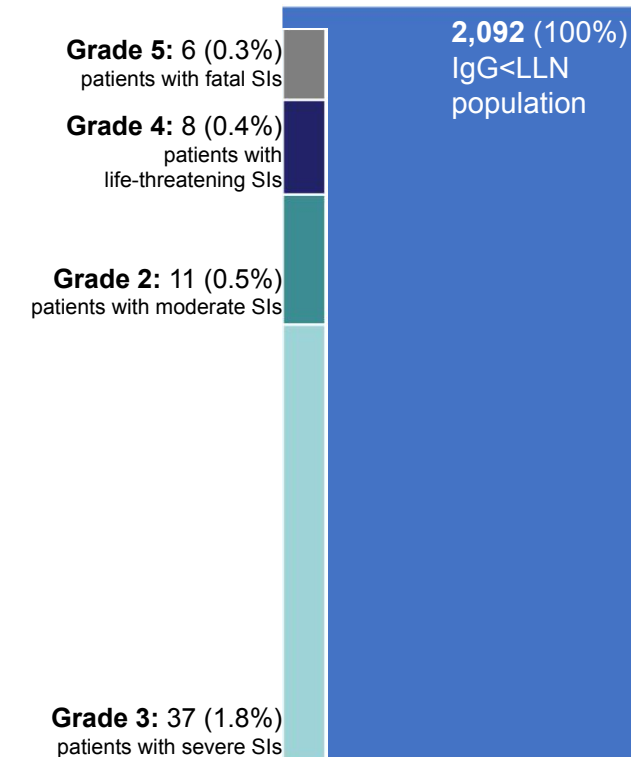
Results

With COVID-19, the Majority of Serious Infections Were of Grade 3 Intensity

SI intensity Grade (CTCAE):^a
OCR all-exposure^b



SI intensity Grade (CTCAE):^a
IgG<LLN (OPERA I, II, ORATORIO and OLERO)^c



ADL, activities of daily living; COVID-19, coronavirus disease 2019; CTCAE, Common Terminology Criteria for Adverse Events; IgG, immunoglobulin G; LLN, lower limit of normal [LLN=5.65 (g/L)]; OCR, ocrelizumab; SI, serious infection.

^aGrade 1 (mild): Asymptomatic or mild symptoms/clinical or diagnostic observation only/intervention not indicated; Grade 2 (moderate): Minimal, local or noninvasive intervention indicated/limiting age-appropriate instrumental ADL; Grade 3 (severe): Severe or medically insignificant but not immediately life-threatening/hospitalisation or prolongation of hospitalisation indicated/disabling/limiting self-care ADL; Grade 4 (life-threatening): Life-threatening consequences/urgent intervention required; Grade 5 (death): Death related to AE (not applicable for all AEs); percentages are calculated using the number of patients that experienced any number of SIs (counting multiple occurrences once), by the number of patients; ^bIncludes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, CONSONANCE, CHIMES and OLERO (total N=6,155 patients); ^cSingle-drop method (total N=2,092).

Results

Potential Serious OIs Over 10 Years in the OCR All-exposure Population Remained Infrequent

- At the November 2022 CCOD, in the MS all-exposure population, the rate per 100 PY of potential serious OIs was low, at a rate of 0.03 per 100 PY (95% CI 0.01–0.06)
- No cases of fever of unknown origin, cryptococcosis, aspergillosis, listeriosis, toxoplasmosis or cytomegalovirus infection had been reported up to November 2022
- As of May 2023, no cases of PML had been reported in the context of clinical trials
- There are 14 confirmed cases of PML in more than 302,199 ocrelizumab-treated patients
 - Of these, 11 cases were carry-over PML, attributed to prior exposure to DMTs causally associated with PML and one non-carry-over case was confounded by advanced age and lymphopenia
 - In the remaining two non-carry-over cases, there was a potential causal association with ocrelizumab
 - The review of the confirmed PML cases reported to date provides only weak evidence of a causal association between ocrelizumab and PML and results in reporting rate of 1 in 100,000 exposed patients

Results

IRRs, Neoplasms and Infections Were the Most Common AEs Leading to Discontinuation in the OCR All-exposure Population^a

MedDRA SOC MedDRA preferred term	Number of patients
Overall total number of patients	306
Neoplasms benign, malignant and unspecified (including cysts and polyps)	62
Invasive ductal breast carcinoma	10
Breast cancer	10
Malignant melanoma	5
Prostate cancer	3
Invasive breast carcinoma	2
Lung adenocarcinoma	2
Lung neoplasm malignant	2
Papillary thyroid cancer	2
Squamous cell carcinoma	2
Adenocarcinoma of colon	1
Anaplastic large-cell lymphoma	1
Basal cell carcinoma	1
Carcinoma <i>in situ</i> of penis	1
Cervix carcinoma Stage II	1
Chondrosarcoma	1
Endometrial adenocarcinoma	1
Endometrial cancer	1
Hypergammaglobulinaemia (benign, monoclonal)	1
Lobular breast carcinoma <i>in situ</i>	1
Malignant fibrous histiocytoma	1
Meningioma	1
Metastatic malignant melanoma	1
Nodular melanoma	1
Non-small cell lung cancer	1
Pancreatic carcinoma metastatic	1
Renal cell carcinoma	1
Renal cancer	1
Transitional cell carcinoma	1
Breast cancer <i>in situ</i>	1
Breast neoplasm	1
Intraductal papillary breast neoplasm	1
Invasive lobular breast carcinoma	1
Testis cancer	1

MedDRA SOC MedDRA preferred term	Number of patients
Injury, poisoning and procedural complications	35
IRR	34
Subdural haematoma	1
Infections and infestations	65
Urinary tract infection	9
COVID-19	8
COVID-19 pneumonia	7
Pneumonia	3
Sepsis	3
Bronchitis	2
Chorioretinitis	2
Encephalitis	2
Herpes zoster	2
Infection ^b	2
Periodontitis	2
Vaginal infection	2
Acute hepatitis C	1
Anal abscess	1
Aspergilloma	1
Bacterial vaginosis	1
Cellulitis	1
Chronic sinusitis	1
<i>Clostridium difficile</i> colitis	1
Coccidioidomycosis	1
Large intestine infection	1
Latent tuberculosis	1
Mastoiditis	1
Nasopharyngitis	1
Oesophageal candidiasis	1
Pneumonia bacterial	1
Post procedural infection	1
Pulmonary tuberculoma	1
Pulmonary tuberculosis	1
Septic shock	1
Viral infection	1
Endocarditis	1
Intervertebral discitis	1

Please see Supplemental Materials slide 36 for footnotes and abbreviations related to this table.

Results

IRRs, Neoplasms and Infections Were the Most Common AEs Leading to Discontinuation in the OCR All-exposure Population^a (cont.)

MedDRA SOC MedDRA preferred term	Number of patients
Psychiatric disorders	16
Depression	3
Anxiety	2
Completed suicide	2
Delusion	1
Depressive symptom	1
Hallucination	1
Insomnia	1
Mental disorder	1
Paranoia	1
Psychiatric disorder	1
Suicidal ideation	1
Suicide attempt	1
Skin and subcutaneous tissue disorders	15
Rash	3
Alopecia	2
Acne	1
Decubitus ulcer	1
Dermatitis allergic	1
Drug eruption	1
Erythema nodosum	1
Guttate psoriasis	1
Interstitial granulomatous dermatitis	1
Pruritis allergic	1
Psoriasis	1
Skin lesion	1
Gastrointestinal disorders	16
Crohn's disease	6
Colitis	2
Diarrhoea	2
Colitis ulcerative	1
Enteritis	1
Enterocolitis	1
Gastritis	1
Gastrointestinal inflammation	1
Small intestine obstruction	1

MedDRA SOC MedDRA preferred term	Number of patients
General disorders and administration site conditions	12
Fatigue	2
Pyrexia	2
Asthenia	1
Chest pain	1
Chills	1
Death	1
Disease progression	1
Influenza-like illness	1
Oedema peripheral	1
Systemic inflammatory response	1
Nervous system disorders	17
Paraesthesia	3
Multiple sclerosis relapse	2
Amyotrophic lateral sclerosis	1
Ataxia	1
Cognitive disorder	1
Headache	1
Hydrocephalus	1
Migraine	1
Motor dysfunction	1
Neurological symptom	1
Optic neuritis	1
Partial seizures with secondary generalisation	1
Secondary progressive multiple sclerosis	1
Speech disorder developmental	1
Musculoskeletal and connective tissue disorders	10
Muscular weakness	2
Arthralgia	1
Muscle rigidity	1
Myalgia	1
Osteonecrosis	1
Pain in extremity	1
Psoriatic arthropathy	1
Rheumatoid arthritis	1
Seronegative arthritis	1

Results

IRRs, Neoplasms and Infections Were the Most Common AEs Leading to Discontinuation in the OCR All-exposure Population^a (cont.)

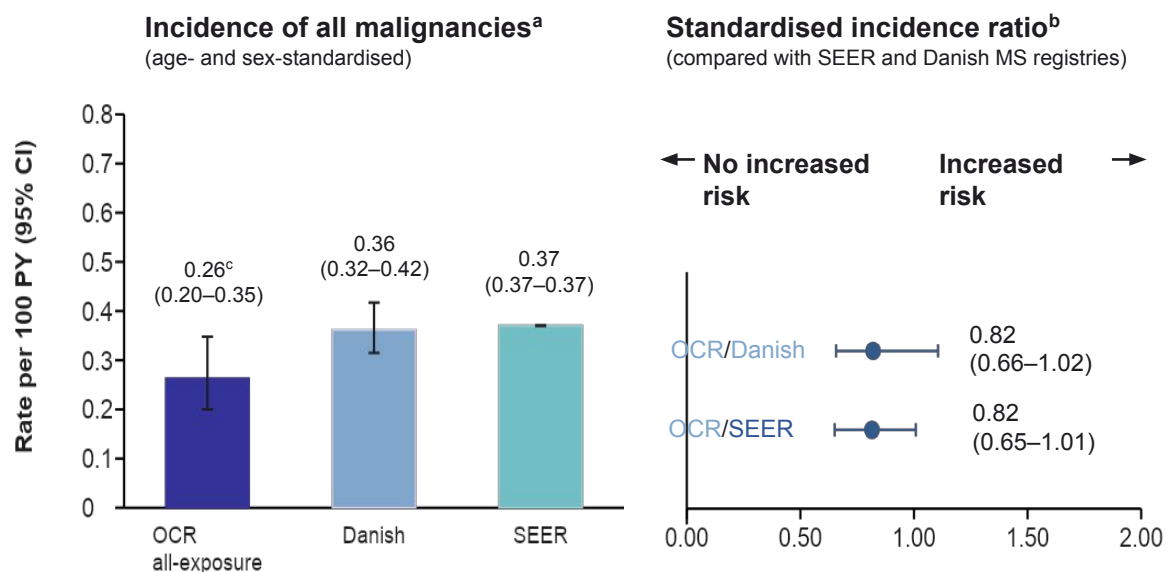
MedDRA SOC MedDRA preferred term	Number of patients
Investigations	16
Neutrophil count decreased	2
Blood creatine increased	1
Blood immunoglobulin G decreased	1
Capillary permeability increased	1
CD19 lymphocytes decreased	1
CD4 lymphocytes abnormal	1
CD4 lymphocytes decreased	1
Electrocardiogram QT prolonged	1
Gamma-glutamyltransferase increased	1
Hepatitis B virus test positive	1
Liver function test abnormal	1
Liver function test increased	1
Mycobacterium tuberculosis complex test positive	1
Transaminases increased	1
White blood cell count increased	1
Cardiac disorders	5
Aortic valve incompetence	1
Cardiac arrest	1
Congestive cardiomyopathy	1
Myocardial infarction	1
Pericarditis	1
Hepatobiliary disorders	3
Hepatitis	1
Hepatitis fulminant	1
Portal vein thrombosis	1
Metabolism and nutrition disorders	3
Diabetes mellitus inadequate control	1
Hypoproteinaemia	1
Lactic acidosis	1
Blood and lymphatic system disorders	3
Lymphocytosis	1
Lymphopenia	1
Neutropenia	1

MedDRA SOC MedDRA preferred term	Number of patients
Immune system disorders	9
Hypogammaglobulinaemia	4
Haemophagocytic lymphohistiocytosis	1
Hypersensitivity	1
Immune reconstitution inflammatory syndrome	1
Immunodeficiency	1
Sarcoidosis	1
Reproductive system and breast disorders	3
Benign prostatic hyperplasia	1
Cervical dysplasia	1
Intermenstrual bleeding	1
Respiratory, thoracic and mediastinal disorders	7
Pulmonary embolism	2
Acute respiratory failure	1
Dysphonia	1
Organising pneumonia	1
Sinus congestion	1
Tracheal stenosis	1
Eye disorders	4
Giant papillary conjunctivitis	1
Retinal degeneration	1
Serious retinopathy	1
Vitreous floaters	1
Renal and urinary disorders	2
Bladder perforation	1
Cystitis interstitial	1
Vascular disorders	1
Accelerated hypertension	1
Ear and labyrinth disorders	1
Vertigo	1
Surgical and medical procedures	1
Vertigo	1

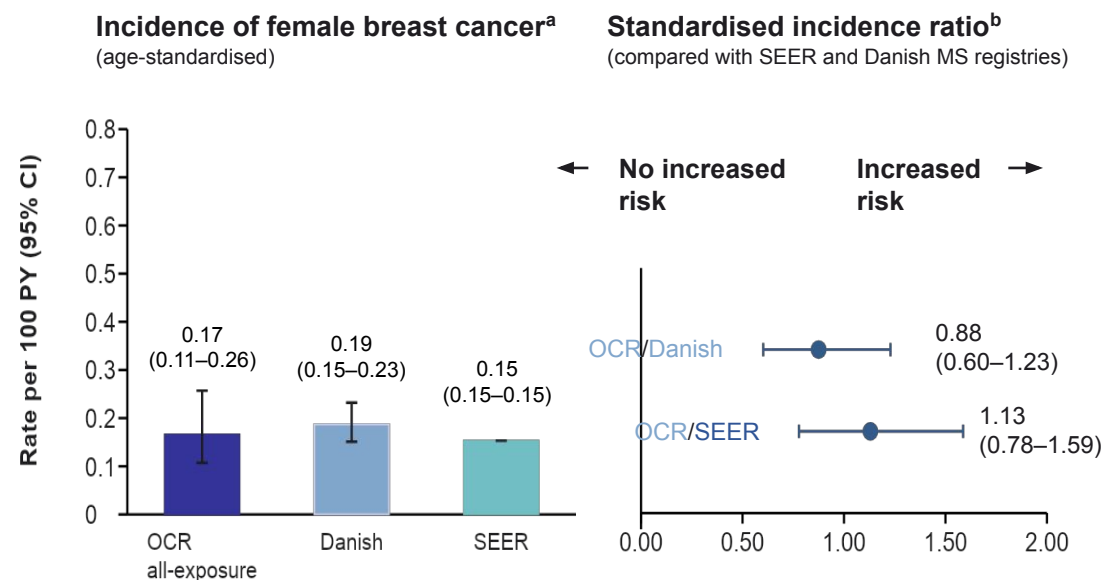
Results

Over 10 Years, the Cumulative Standardised Incidence Rates of (A) All Malignancies and (B) Female Breast Cancer Remained Within the Range Reported in Real-World Registries^{1,2}

A. Incidence of all malignancies (Age- and sex-standardised)



B. Incidence of female breast cancer (Age-standardised)



CI, confidence interval; MS, multiple sclerosis; NMSC, nonmelanoma skin cancer; OCR, ocrelizumab; PY, patient years; SEER, Surveillance, Epidemiology and End Results; SIR, standardised incidence ratio.

^aThe standardised incidence rates were reported to allow comparison with the SEER database and the Danish MS Registry, using the direct standardisation method. Standardised incidence rates were derived by applying age–sex specific rates to the 2,000 USA standard population, with restriction to the age range of the MS clinical trials (15–59 years); ^bThe SIR, calculated as observed/expected number of events, was determined for all malignancies (excluding NMSC) and female breast cancer, using the SEER database and the Danish MS Registry as reference populations; ^cIt excludes NMSC for comparison with SEER rates, as NMSC is not reported in SEER.

1. National Institutes of Health (NIH). Surveillance, Epidemiology and End Results Program. Available from: <https://seer.cancer.gov>; 2. Nørgaard M, et al. *Mult Scler Relat Disord* 2019;28:81–85.

Results

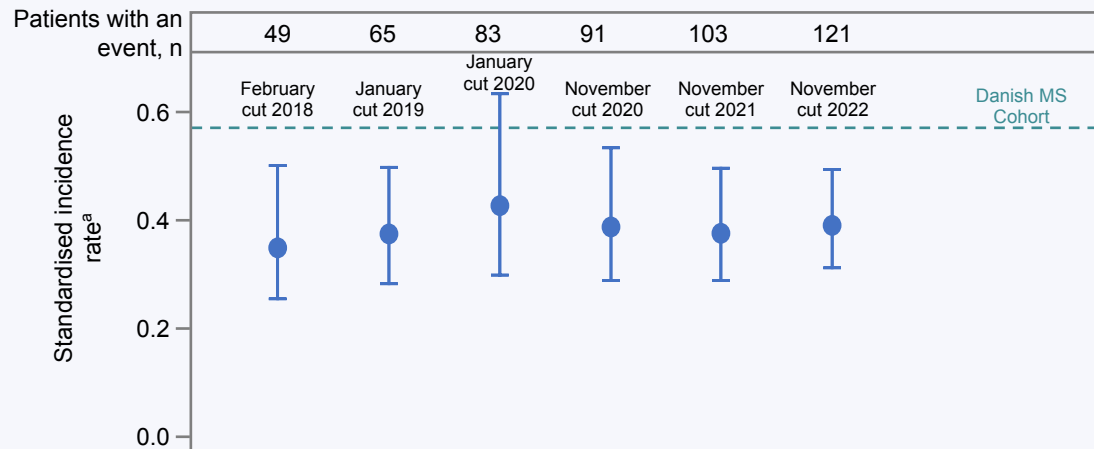
Cumulative Standardised Incidence Rates of All Malignancies and Female Breast Cancer Remained Stable Over Time and Within the Ranges Reported in Registries

i

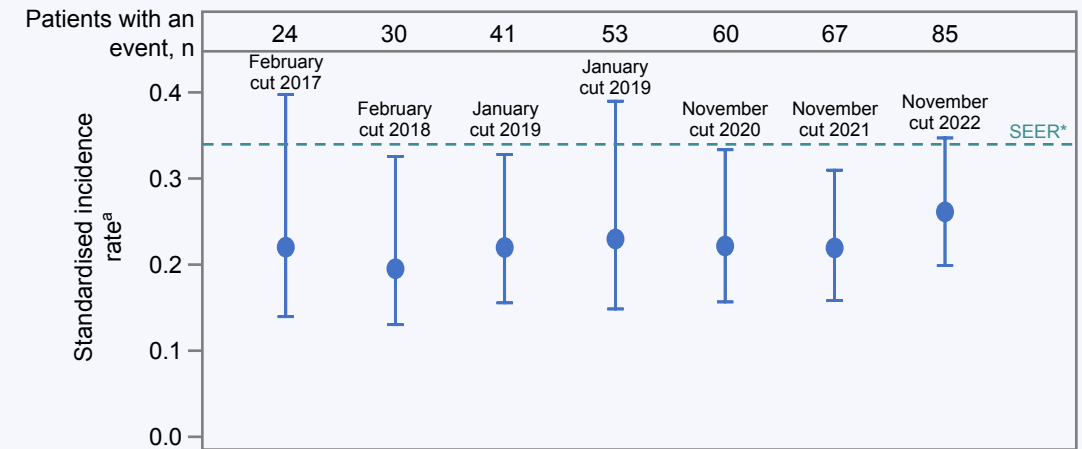
The **cumulative standardised incidence rates of all malignancies and female breast cancer among** OCR-treated patients remained stable over time and within the ranges reported in epidemiological data^{1,2}

Yearly crude incidence rates of all malignancies including NMSC, and female breast cancer in the OCR-all exposure population remained stable over time

All malignancies: Age and sex standardised^b



Female breast cancer: Age standardised^b



NMSC, nonmelanoma skin cancer; MS, multiple sclerosis; OCR, ocrelizumab; SEER, Surveillance, Epidemiology and End Results.

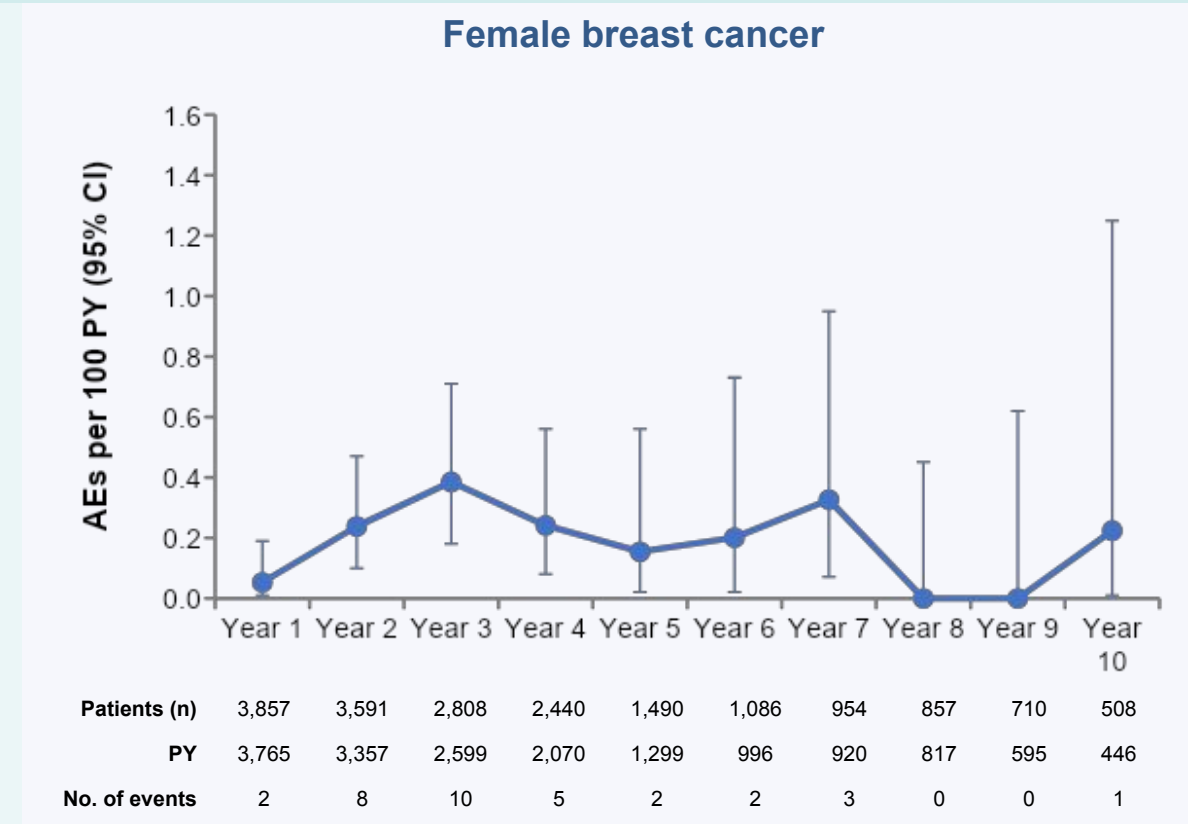
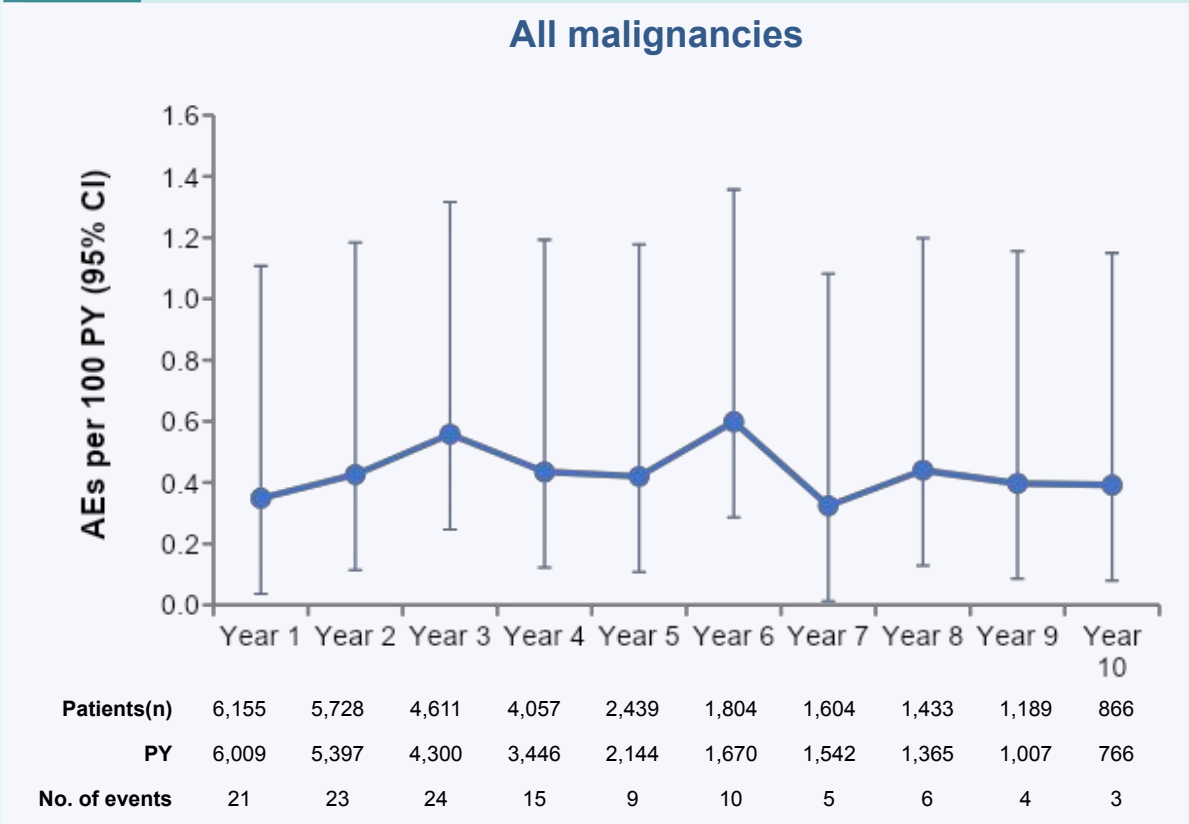
Please see Supplemental Materials slide 36 in this deck for additional slide footnotes and references.

1. Wijnands JMA, et al. J Neurol Neurosurg Psychiatry 2018;89:1050–1056; 2. National Institutes of Health (NIH). Available at: <https://seer.cancer.gov>.

Results

Over 10 Years of Treatment, Longer Exposure to OCR Did Not Lead to an Increase in the Yearly Incidence Rate

i Yearly crude incidence rates of all malignancies including NMSC, and female breast cancer in the OCR all-exposure population remained stable over time^a



Supplemental Materials

Presentation Footnotes

Supplemental slide 30–32 (most common AEs leading to discontinuation in the OCR all-exposure population)

Investigator text for AEs was encoded using MedDRA version 25.1. Multiple occurrences of the same AE in one patient were counted multiple times.

^aIncludes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies, including patients originally randomised to comparator (IFN β -1a or PBO) who switched to open-label OCR treatment, plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, CONSONANCE, LIBERTO, CHIMES and OLERO.

AE, adverse event; CTP, controlled-treatment period; COVID-19, coronavirus disease 2019; IFN, interferon; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; SOC, system organ class; WBC, white blood cell.

Supplemental slide 34 (cumulative standardised incidence rates of all malignancies and female breast cancer)

Data cut-off: November 2022. The incidence rate of first malignancy (number of first malignancy events per 100 PY) was calculated. Standardised incidence rates of malignancies were calculated using the age of the patient at study baseline (“age at enrolment”; age range: 15–59 years) up to February 2017; from September 2017 onwards, rates were calculated based on the age of the patient at the onset of malignancy (“age at event onset”; age range: 15–64 years). The “age at event onset” is a more accurate method that reflects the fact that patients become older throughout the course of the studies.

^aNMSC is not reported in SEER; ^bIncludes patients who received any dose of OCR during the controlled-treatment, ECP and associated OLE periods of the Phase II and Phase III studies, including patients originally randomised to comparator (IFN β -1a or placebo) who switched to open-label OCR treatment.

ECP; extended-controlled period; IFN, interferon; NMSC, nonmelanoma skin cancer; OCR, ocrelizumab; OLE, open-label extension; PY, patient years; SEER, Surveillance, Epidemiology and End Results; SIR, standardised incidence ratio.

Supplemental slide 35 (yearly crude incidence rates of all malignancies and female breast cancer)

Data cut-off: November 2022. Studies are ongoing.

^aIncludes patients who received any dose of OCR during the CTP and associated OLE periods of the Phase II and Phase III studies, plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO, CONSONANCE and OLERO, including patients originally randomised to comparator (IFN β -1a or placebo) who switched to open-label OCR treatment.

AE, adverse event; CI, confidence interval; CTP, controlled-treatment period; IFN, interferon; NMSC, nonmelanoma skin cancer; OCR, ocrelizumab; OLE, open-label extension; PY, patient years.



<https://ter.li/6bn46g>

Analysis of the Adaptive Immune Receptor Repertoire Alongside Treatment with Ocrelizumab

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B Tackenberg,^{3,4} C Raposo,³ CC Gross,¹ L Klotz,¹ H Wiendl,¹ N Schwab¹

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Thursday, 12 October 2023

Disclosures

T Schneider-Hohendorf received research support from Novartis and travel support from Biogen. **F Rubelt** is an employee of F. Hoffmann-La Roche Ltd. **H Mirebrahim** is an employee of F. Hoffmann-La Roche Ltd. **H Asgharian** is an employee of F. Hoffmann-La Roche Ltd. **C Wünsch** reports no conflicts of interest. **A Schulte-Mecklenbeck** reports no conflicts of interest. **L Lohmann** reports no conflicts of interest. **B Tackenberg** is an employee of F. Hoffmann-La Roche Ltd. **C Raposo** is an employee of F. Hoffmann-La Roche Ltd. **CC Gross** received grants from Biogen, F. Hoffmann-La Roche Ltd and Novartis Pharma; and consultancy fees from MyLan and DIU Dresden International University GmbH. **L Klotz** received fees from Alexion, Bayer, Biogen, Celgene, Sanofi, Horizon, Grifols, Merck-Serono, Novartis, F. Hoffmann-La Roche Ltd, Santhera and Teva; and research grants from Biogen, Immunic AG, Novartis and Merck-Serono. **H Wiendl** received consultancy fees for Abbvie, Alexion, Argenx, Biogen, Bristol Myers Squibb/Celgene, EMD Serono, F. Hoffmann-La Roche Ltd, Fondazione Cariplo, Genzyme, Gossamer Bio, Idorsia, Immunic, Immunovant, Janssen, Lundbeck, Merck, Neurodiem, NexGen, Novartis, PSI CRO, Roche Pharma AG, Sanofi, Swiss Multiple Sclerosis Society, Teva, UCB Biopharma, WebMD Global and Worldwide Clinical Trials; and research grants from Deutsche Myasthenie Gesellschaft e.V., Alexion, Amicus Therapeutics Inc., Argenx, Biogen, CSL Behring, F. Hoffmann-La Roche Ltd, Genzyme, Merck, Novartis Pharma, Roche Pharma AG and UCB Biopharma outside of the submitted work. **N Schwab** received grants from Biogen and F. Hoffmann-La Roche Ltd.

Introduction

- Specific presence of plasma cells in CSF, intrathecal production of antibodies and efficacy of B-cell-depleting therapies suggest involvement of B cells in MS pathophysiology
- Depletion of circulating B cells by ocrelizumab therapy does not immediately decrease antibody levels and could affect B and plasma cells residing in tissues differently
- Treatment with OCR also depletes circulating, CD20-expressing T cells¹
- Some MS patients experience signs of progression during OCR therapy, and it was suggested that MS progression could be associated with accumulation of plasma cells and/or CD20⁺ T cells in the CNS tissue
- It is unknown to which extent re-emerging B cells after depletion are reconstituted from the naïve reservoir within lymphoid tissues, or repopulate from memory reservoirs within lymphoid or non-lymphoid tissues

Aim

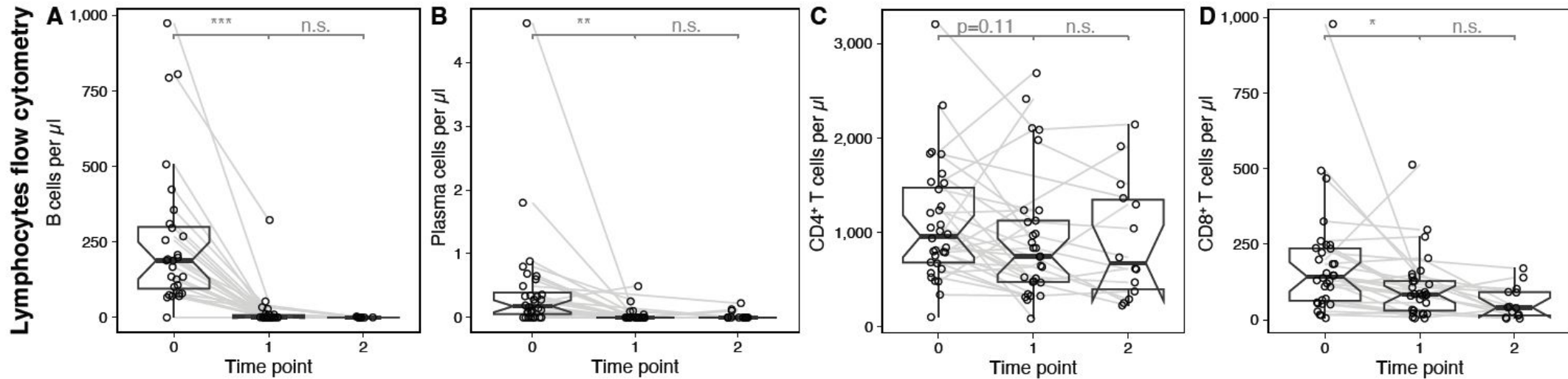
- To evaluate whether treatment of MS patients with OCR modulates the TCR repertoire due to depletion of CD20⁺ T cells
- To investigate how treatment of MS patients with OCR modulates the BCR repertoire with special regard to reconstruction from the naive reservoir and repopulation from non-depleted memory cells

Methods

- The studied **real-world cohort** consisted of:
 - Twenty-nine patients with relapsing-remitting MS (76% female, mean age: 40.3 years, mean EDSS: 2.8) and 11 with primary progressive MS (47% female, mean age: 50.1 years, mean EDSS: 4.6) before (M00), 6 months (M06) and 12 months (M12) after the start of treatment with OCR
 - Fifteen patients with MS with two time points, 6 months apart, both during long-term NAT therapy (>18 months, NAT)
 - Eleven healthy controls before the 1st (M00) and after the 2nd mRNA vaccination against SARS-CoV-2 (M06) (HD)
- 1x10⁷ cryopreserved peripheral blood mononuclear cells per sample were sequenced with the ImmunoPETE assay (Roche), which simultaneously assesses the immunoglobulin heavy chain of BCRs, the β -chain of $\alpha\beta$ TCRs and the δ -chain of $\gamma\delta$ TCRs, together with unique molecular identifiers enabling determination of cell identities²
- Processing and analysis of BCR sequencing data was performed with the Immcantation framework³

Results

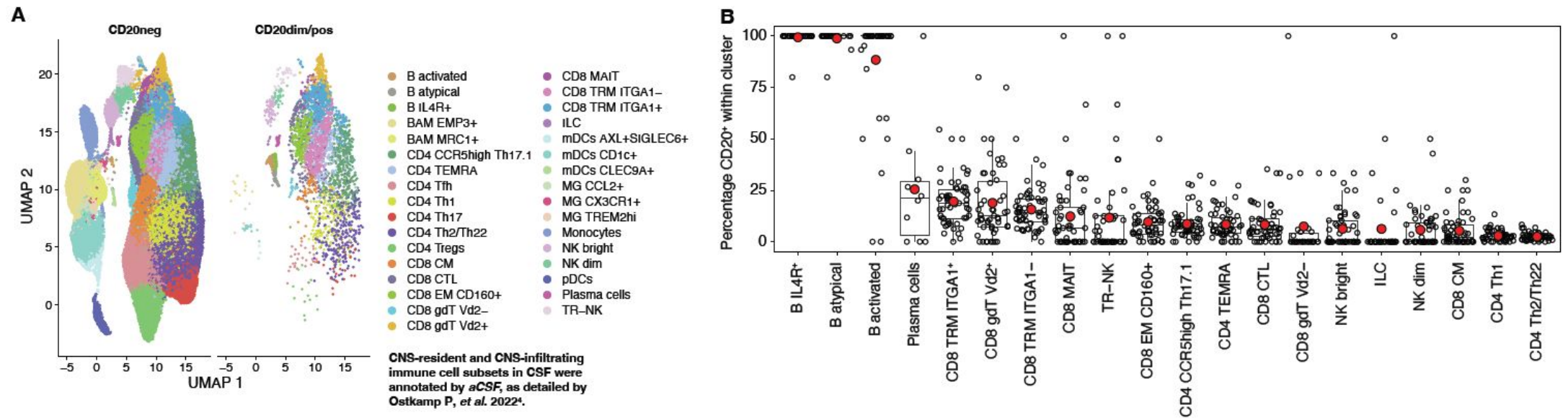
1. Six Months After the Start of Ocrelizumab Treatment, B Cells (A) and Plasma Cells (B) Are Strongly Depleted, While CD8 T Cells Are Reduced to a Lesser Extent (D)



10-colour flow cytometry was performed at baseline (0) and at time points 6 months (1) and 12 months (2) after the start of ocrelizumab treatment.
(A) B cells (gating: live/CD45⁺/CD19⁺ CD20⁺). (B) Plasma cells (gating: live/CD45⁺/CD19⁺ CD138⁺). (C) CD4 T cells (gating: live/CD45⁺/CD3⁺ CD4⁺ CD8⁻).
(D) CD8 T cells (gating: live/CD45⁺/CD3⁺ CD4⁻ CD8⁺).

Results

2. CNS-Resident Immune Cells Have Increased CD20-Expression Compared with CSF-Infiltrating Immune Cell Subsets (A, B)



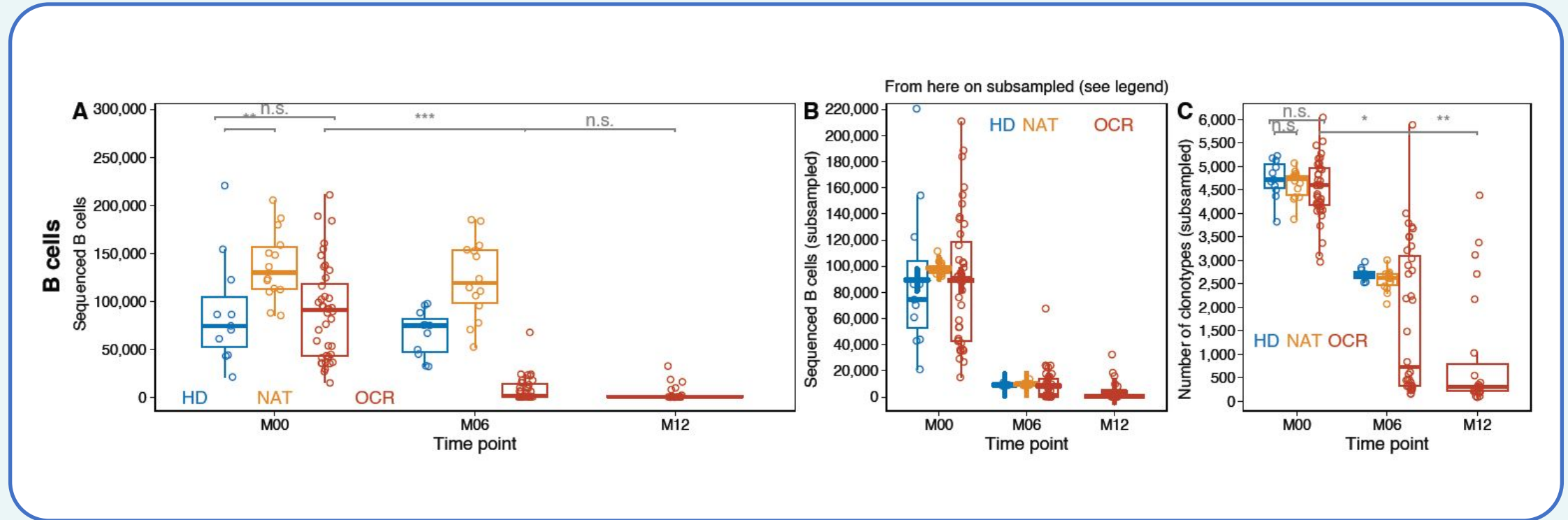
CNS, central nervous system; CSF, cerebrospinal fluid; MS4A1, Membrane Spanning 4-Domains A1; TRM, Tissue-resident memory; UMAP, Uniform Manifold Approximation and Projection. CSF single-cell RNA-sequencing data from 10 MS patients and 11 controls were comprehensively analysed with aCSF¹ to annotate CSF immune cell subsets.

Panel (A) depicts a uniform manifold approximation and projection plot of the CSF immune cell composition annotated by aCSF, divided by MS4A1 (CD20 gene) expression. (B) The panel quantifies immune cell subpopulations from (A), where >1% of cells express MS4A1 transcripts. Apart from cells of the B-cell lineage with expectedly high MS4A1 expression, predominantly immune cells with CNS tissue association show MS4A1 expression according to the aCSF clustering, e.g. TRM CD8 T cells.

4. Ostkamp P, et al. *Sci Transl Med* 2022;14(637):eadc9778.

Results

3. Six Months After the Start of Ocrelizumab Treatment, the Amount of Sequenced B Cells is Strongly Decreased (A); After Accounting for B-Cell Depletion by Subsampling (B), BCR Clonotypes Are Decreased Over-Proportionally at M06 and Decrease Further at M12 (C)

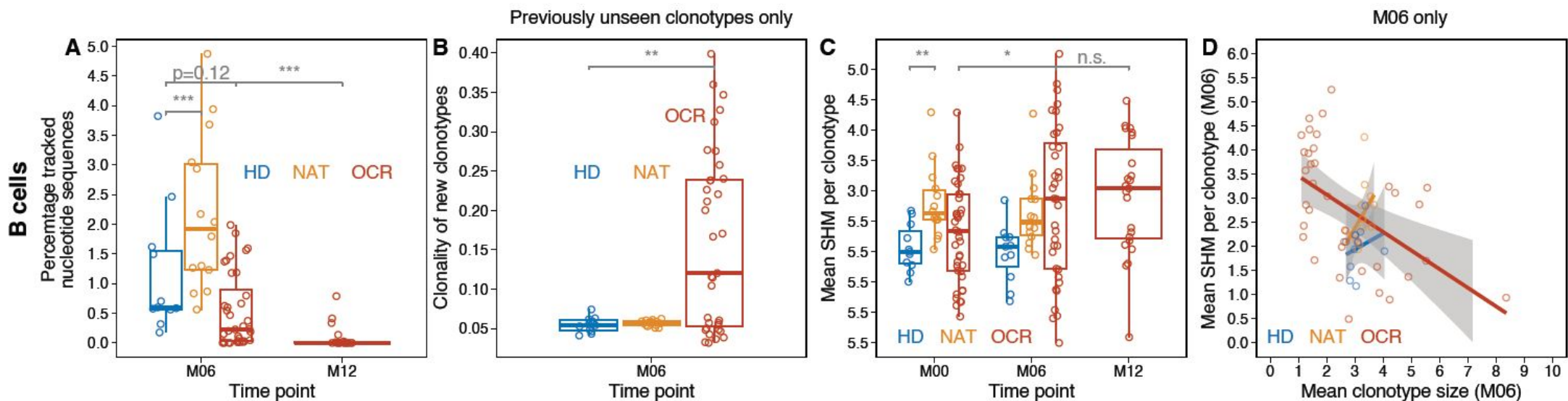


BCR, B-cell receptor; HD, healthy donors; IMGT, international ImMunoGeneTics; mRNA, messenger RNA; MS, multiple sclerosis; NAT, natalizumab; OCR, ocrelizumab; PBMC, peripheral blood mononuclear cells; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

(A) Sequenced B cells per 1x10⁷ PBMC per sample are quantified using UMIs. (B) Sequenced B cells are quantified after subsampling; subsampling was performed to account for differing proportions of B cells in samples within individual groups or time points: for time point M00 NAT was downsampled to the means of HD and OCR to account for increased PBMC B-cell proportions alongside NAT therapy; for time point M06, HD and NAT were downsampled to the mean of OCR to account for the lower proportions of B cells by depletion in OCR samples 6 months after the start of OCR therapy. (C) Numbers of BCR clonotypes are quantified in the subsampled samples; for clonotypes, BCR sequences were grouped that share the same germline sequence according to IMGT annotation. HD (blue) represents healthy controls before (M00) 1st and after 2nd mRNA vaccination (M06) against SARS-CoV-2; NAT (orange) represents MS patients alongside long-term (>18 months) NAT therapy with M00 and M06 being 6 months apart; OCR (red) represents MS patients before (M00), 6 (M06) and 12 months (M12) after the start of OCR treatment. * indicate p-values of *p=0.05, **p=0.01 and ***p=0.001, generated by linear mixed models accounting for the covariates age, sex and history of fingolimod pretreatment.

Results

4. BCR-sequence Tracking Detects Repopulating Memory B cells (A) and Clonal Expansions in Newly Emerging Clonotypes (B); Increased SHM After Depletion Indicate Homeostatic Proliferation (C,D)

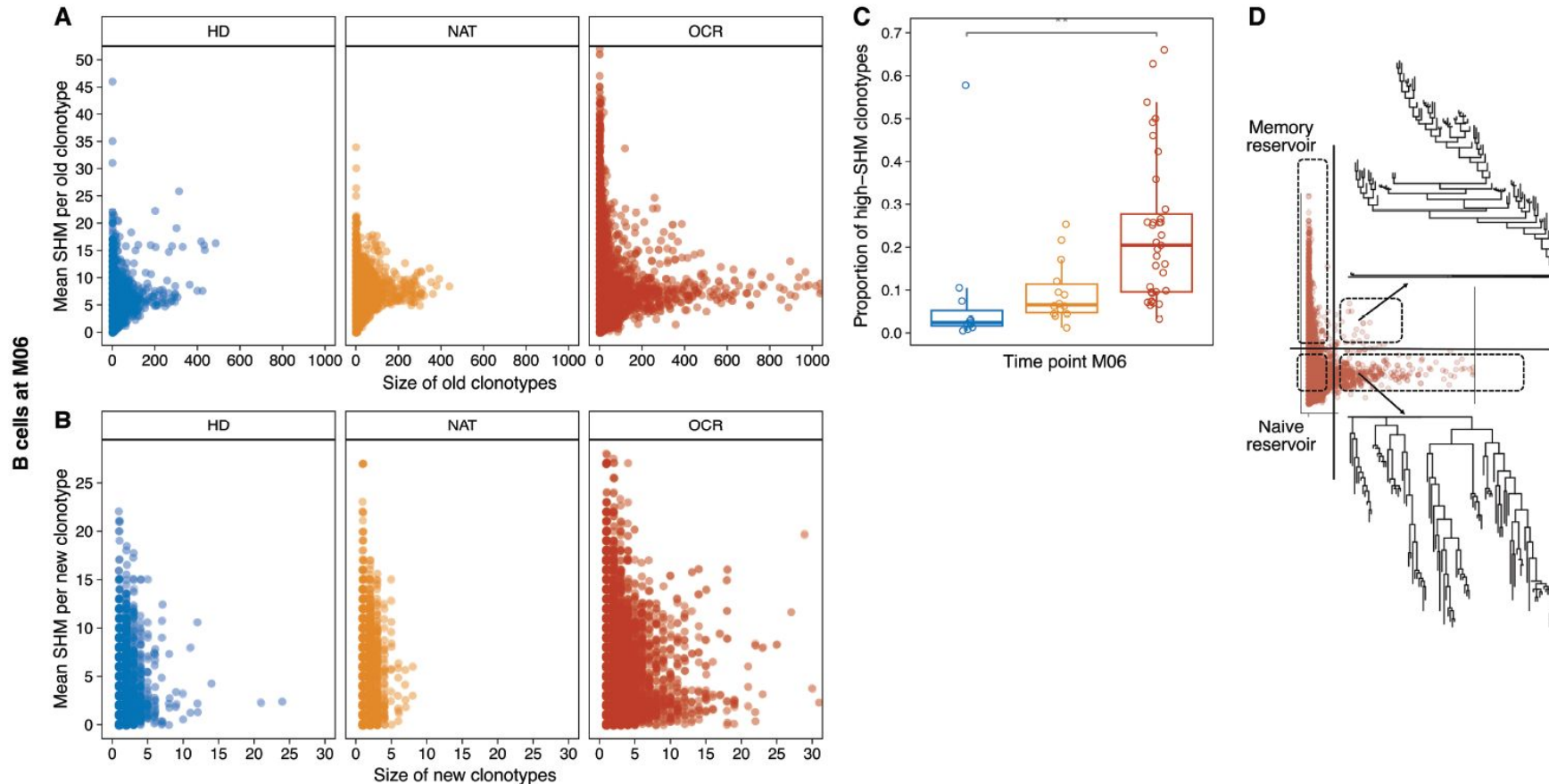


BCR, B-cell receptor; HD, healthy donors; mRNA, messenger RNA; MS, multiple sclerosis; NAT, natalizumab; OCR, ocrelizumab; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SHM, somatic hypermutation.

(A) BCR nucleotide sequences were compared within donors between time points M00 and M06, and between M06 and M12. Proportions of sample M06 found also in M00 (M06) and proportions of M12 found also in M06 (M12) are quantified in percentages of all nucleotide sequences of the respective sample. (B) Simpson clonality of new clonotypes at M06 in subsampled samples was calculated; new clonotypes at M06 are determined by building clonotypes within patients by combining M00 and M06 samples, with new clonotypes only being present at M06. (C) Mean SHM per clonotype per sample were determined. (D) Mean SHM per clonotype per sample are correlated to mean clonotype size at M06, where clonotype size is the amount of cells per clonotype. HD (blue) represents healthy controls before (M00) 1st and after 2nd mRNA vaccination (M06) against SARS-CoV-2; NAT (orange) represents MS patients alongside long-term (>18 months) NAT therapy with M00 and M06 being 6 months apart; OCR represents MS patients before (M00), 6 (M06) and 12 months (M12) after the start of OCR treatment. * indicate p-values of $*p=0.05$, $**p=0.01$ and $***p=0.001$, generated by linear mixed models accounting for the covariates age, sex and history of fingolimod pretreatment.

Results

5. Homeostatic Proliferation is Detectable in B Cells Repopulating From the Memory Reservoir (A, B) as Well as in B Cells Reconstituting From the Naive Reservoir (C), Resulting in Different Phylogenetic Tree Architecture (D)



HD, healthy donors; NAT, natalizumab; OCR, ocrelizumab; SHM, somatic hypermutation.

(A) Mean SHM per old clonotype in relation to clonotype size (amount of cells per clonotype) at time point M06 are depicted. (B) Mean SHM per new clonotype in relation to clonotype size (amount of cells per clonotype) at time point M06 are depicted. (C) Proportion of high-SHM (>10) clonotypes at time point M06. (D) Schematic from (A, OCR): The solid horizontal line indicates a threshold for low-versus high-SHM, where low-SHM indicates naive B cells and high-SHM indicates memory B cells; the vertical line indicates a threshold of small versus large clonotypes, where small clonotypes indicate the naive and memory reservoir while large clonotypes indicate homeostatic proliferation; phylogenetic tree examples for clonotypes of the same size with considered regular architecture showing affinity maturation of one dominant branch of related sequences (upper tree) and clonotypes, where multiple branches from the germline show parallel expansions indicating homeostatic proliferation (lower tree).

Conclusions



- Higher expression of CD20 in CNS tissue-resident immune cells compared with CSF-infiltrating immune cell subsets indicates that part of ocrelizumab efficacy could be associated with depletion of circulating T cells with high potential to CNS tissue retention
- Six months after depletion of circulating B cells, increased clonality in newly emerging clonotypes indicates homeostatic proliferation from memory B cells and/or plasma cells, that were not part of the circulating repertoire at baseline but could originate from lymphoid or non-lymphoid tissue



<https://ter.li/vcu0vz>

Utility and Implementation of a Federated Research Infrastructure to Assess Lack of Disease Stability as a Real-World Surrogate of PIRA, by Combining MS Clinical Trial and Real-World Cohort Data (The INTONATE-MS Consortium)

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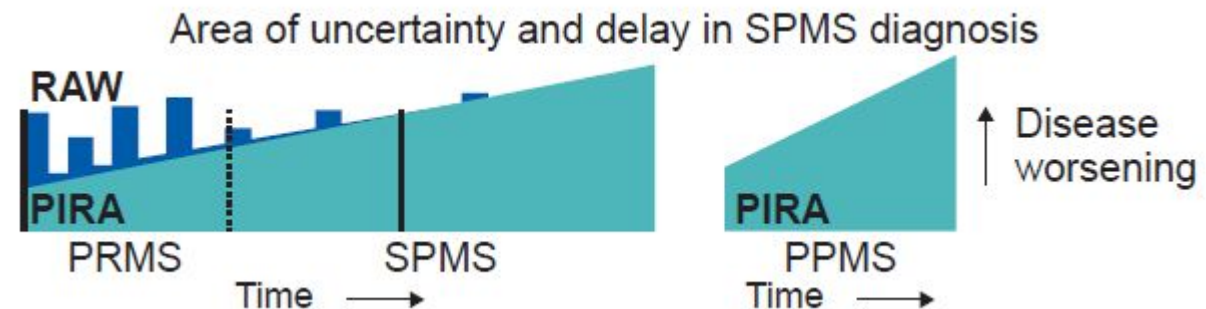
Disclosures

J Oh has received personal compensation for consulting or speaking from EMD-Serono, Sanofi-Genzyme, Biogen-Idec, F. Hoffmann-La Roche Ltd, Bristol Myers Squibb, Horizon Therapeutics, and Novartis, and has received research funding from the MS Society of Canada, National MS Society, Brain Canada, Biogen-Idec, and F. Hoffmann-La Roche Ltd. **J Smolders** received lecture and/or consultancy fees from Biogen, F. Hoffmann-La Roche Ltd, Merck, Novartis and Sanofi-Genzyme. **F Buijs** is an employee of F. Hoffmann-La Roche Ltd. **R Pedotti** is an employee of F. Hoffmann-La Roche Ltd. **F Dahlke** is an employee of impuls GmbH and provides consulting services for F. Hoffmann-La Roche Ltd. **L Kaczmarek** is an employee of F. Hoffmann-La Roche Ltd. **A Kemmisetti** is an employee of Genentech, Inc. **V Sharma** is an employee of F. Hoffmann-La Roche Ltd. **D Heinzmann** is an employee of F. Hoffmann-La Roche Ltd. **B Tackenberg** is an employee of F. Hoffmann-La Roche Ltd. **A Bar-Or** has received consulting fees from Actelion, Atara Biotherapeutics, Biogen-Idec, Celgene/Receptos, Genentech/Roche, Mapi Pharma, MedImmune, Merck/EMD Serono, Novartis, Sanofi-Genzyme, GlaxoSmithKline and BrainStorm, and has received contracted research support through the University of Pennsylvania from Biogen Idec, Roche/Genentech, Merck/EMD Serono and Novartis. **H Wiendl** has received grant/research support from Bayer HealthCare, Biogen-Idec, Deutsche Forschungsgemeinschaft, Else Kröner Fresenius Foundation, German Ministry for Education and Research, Hertie Foundation, Interdisciplinary Centre for Clinical Research, Münster, Germany, Merck Serono, Novartis, NRW Ministry of Education and Research, Sanofi-Aventis/Genzyme and Teva Pharmaceutical Industries, and has received consulting fees from Bayer HealthCare, Biogen Idec, Fresenius Medical Care, GlaxoSmithKline, GW Pharmaceuticals, Merck Serono, Novartis, Sanofi-Genzyme BioVentures and Teva Pharmaceutical Industries.

Background

- Among PwMS, it is increasingly being recognised that progression occurs even during the earliest stages of the disease^{1–3}
- Data from clinical trials^{1,4} and observational studies^{2,5} have indicated PIRA to be a dominant driver of progression in PwMS in early stages of the disease^{2,3}
- While PIRA can be extracted from clinical trial and registry data, it is unclear whether this measure can be readily utilised in routine clinical care
- Research network bottlenecks, such as country-specific legalities of privacy and data protection, data ownership challenges, technical data sharing issues and administrative hurdles, limit scientific collaboration on data across borders and institutions, limiting scientific progress and innovation in the field of neuroscience
- The INTONATE-MS collaborative federated research approach provides an opportunity to overcome these hurdles

Threshold to identify PIRA events in clinical practice is high due to lack of or infrequent assessments of disease worsening, including Expanded Disability Status Scale (EDSS), as compared with randomised-controlled trials (RCTs)



EDSS, Expanded Disability Status Scale; PIRA, progression independent of relapse activity; PPMS, primary progressive multiple sclerosis; RAW, relapse-associated worsening; RCT, randomised-controlled trial; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

1. Kappos L, et al. JAMA Neurol 2020;77:1132–1140; 2. Portaccio E, et al. Brain 2022;145:2796–2805; 3. University of California, San Francisco MS-EPIC Team, et al. Ann Neurol 2019;85:653–666; 4. Lublin FD, et al. Brain 2022;145:3147–3161; 5. Graf J, et al. Brain Commun 2021;3:fcab229.

Objective



Evaluate the novel concept of 'lack of disease stability', as assessed in routine clinical practice, and explore its utility as a surrogate of progression independent of relapse activity (PIRA) in people with multiple sclerosis (PwMS) on high-efficacy treatment (HET) by leveraging and assessing the utility of a federated data infrastructure across participating centres

Methods



Consortium

- INTONATE-MS is a public–private research consortium between Universitätsklinikum Münster, Penn Medicine, Unity Health Toronto, Erasmus MC and Roche



Cohort Selection

- An MS patient cohort was selected retrospectively at each site, with inclusion criteria being multiple sclerosis (MS) diagnosis and HET (ofatumumab, ocrelizumab, natalizumab and alemtuzumab) in any line between 2004 and 2022
- Institutional review board approval was received at each site for use of data in this network, with informed consent procedures followed according to local guidelines



Data Harmonisation^a

- Clinical and biosample data are harmonised locally at each site according to a common data standard and data model⁶ to enable federated analysis across all sites



Data Storage

- The harmonised dataset is stored locally, with the anonymised study data transferred to a local on-premise or private cloud isolated compute environment (owned and controlled locally) called a ‘node’

HET, high-efficacy treatment; MS, multiple sclerosis.

^aData harmonisation is supported by The Hyve, Utrecht, Netherlands.⁶

6. The Hyve. <https://thehyve.nl/>. Accessed 18 September 2023.

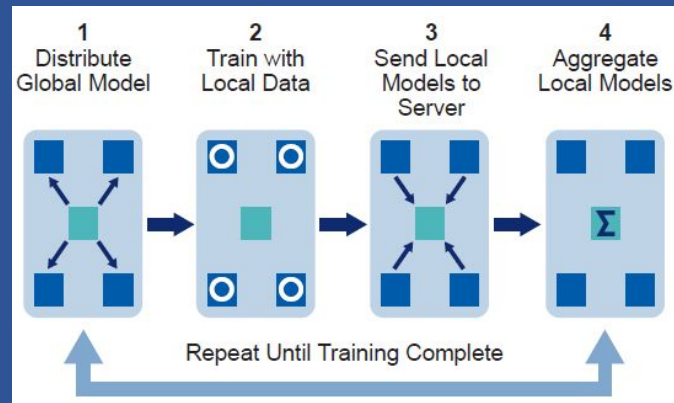
Methods

Lack of Disease Stability

- Characterise the novel endpoint 'lack of disease stability', defined as deterioration of neurological function measured by clinical and paraclinical variables collected in PwMS on HET
- Extract and describe named parameters' proportional contribution to 'lack of disease stability' assessing disease activity and disability worsening
- Deduce a meaningful, novel real-world definition of PIRA (rwPIRA) as a putative key component of the disease state 'lack of disease stability', which can be adapted to clinical practice

'Real-world' PIRA

- Assess the proportional contribution of clinical or paraclinical parameters to 'lack of disease stability' and map them to different existing PIRA definitions from the literature^{1-5, 7-10}
- Define how PIRA can be inferred from sparse clinical data available in a real-world setting and derive a robust definition of rwPIRA from these clinical cohorts
- Focus on PwMS receiving HET ensuring that focal inflammation and relapse biology is mostly abrogated facilitating the identification of a potentially more meaningful "true" PIRA concept



Model of federated architecture used, based on local nodes and a central aggregation server approach¹¹

Federated Architecture

- Data are harmonised locally and transferred to local nodes
- A secure local federated analysis is performed without the local data having to be shared between sites, i.e. no transfer of patient data taking place, in any form, between participating sites
- Analyses are exchanged between sites coordinated by a central aggregation server (Apheris GmbH,¹² Berlin, Germany)
- Local analysis output is combined into a single aggregate result and received by the data scientist executing the query in the form of (anonymous) aggregate statistics
- The federated approach provides scale-enabling assessment of the relevant number of patients required for the purpose of this study

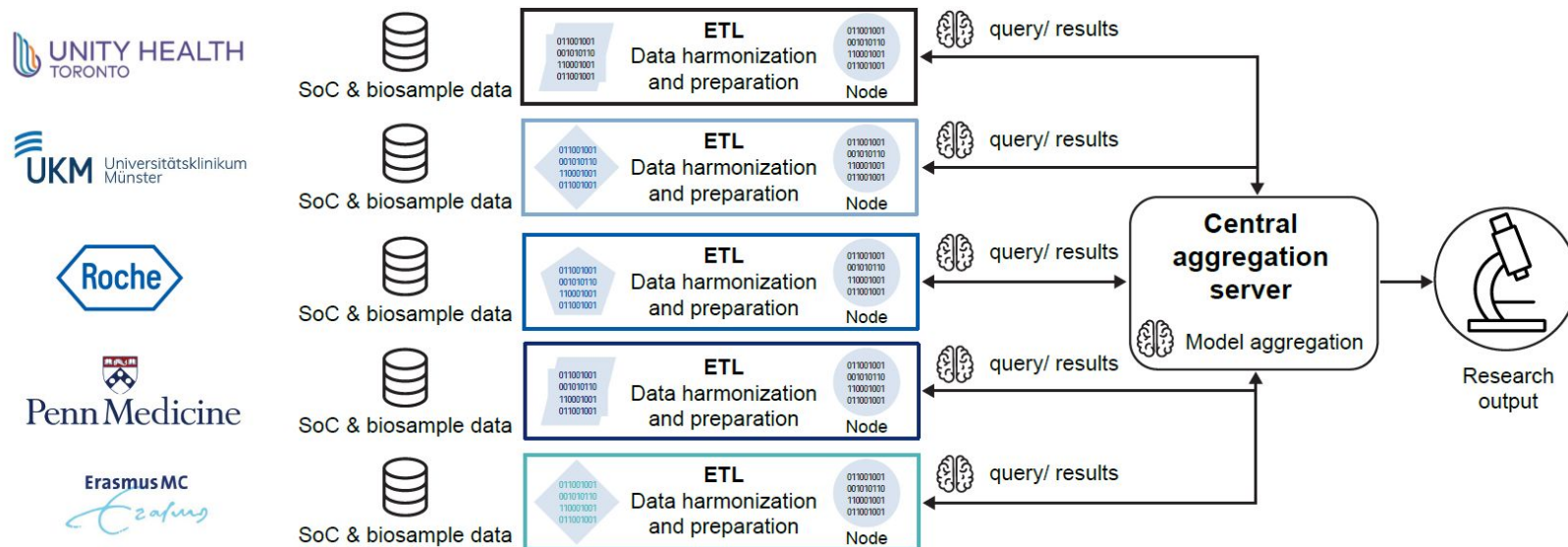
HET, high-efficacy treatment; PIRA, progression independent of relapse activity; PwMS, people with multiple sclerosis; rwPIRA, real-world definition of PIRA.

1. Kappos L, *et al. JAMA Neurol* 2020;77:1132–1140; 2. Portaccio E, *et al. Brain* 2022;145:2796–2805; 3. University of California, San Francisco MS-EPIC Team, *et al. Ann Neurol* 2019;85:653–666; 4. Lublin FD, *et al. Brain* 2022;145:3147–3161; 5. Graf J, *et al. Brain Commun* 2021;3:fcab229; 7. Bsteh G, *et al. Mult Scler J Exp Transl Clin* 2020;6:2055217320966344; 8. Ness N, *et al. J Neurol* 2020;267:1035–1042; 9. Prosperini L, *et al. Neurol Neuroimmunol Neuroinflamm* 2021;8:e1059; 10. von Wyl V, *et al. Mult Scler* 2021;27:439–448; 11. Rieke N, *et al. NPJ Digit Med* 2020;14:3:119; 12. Apheris. <https://www.apheris.com/>. Accessed 18 September 2023.

Results

Federated Architecture of the INTONATE-MS Consortium

- All participating sites and their connection to the federated network
- Each site provides standard of care (SoC) or randomised clinical trial (RCT) and biosample data to the network
- Data are harmonised locally (ETL) into a common data model (CDM). The harmonised, anonymised dataset is transferred to the local node (cloud or on premise) and made available for the federated analysis
- The central aggregation server orchestrates the federated query and aggregation of the results



Conclusions



- To date, this study has shown that a federated network can be implemented between public and private research centres as an innovative approach to overcome research bottlenecks that impede data-driven science
- A federated research approach through the INTONATE-MS consortium will generate a better knowledge of PIRA and will help to better understand rwPIRA and its applicability and relevance in a clinical setting
- This consortium provides a unique opportunity to identify solutions around development and validation of novel real-world endpoints and explore its utility in clinical practice in a single research setting
- The current study sets the stage for future research involving clinical, biological and imaging data that have the potential to innovate and accelerate research in the field of neuroscience



<https://ter.li/amyziq>



MONASH
University

Disease activity during pregnancy and postpartum in women with relapsing-onset MS receiving ocrelizumab and other modern disease-modifying therapies in a real-world cohort

Wei Yeh, Anneke Van der Walt, Olga Skibina, Allan Kermode, Marzena Pedrini, Tomas Kalincik, Jeannette Lechner-Scott, Raed Alroughani, Cavit Boz, Nevin John, Katherine Buzzard, Suzanne Hodgkinson, Richard Macdonell, Vincent Van Pesch, Guy Laureys, Liesbeth Van Hijfte, Barbara Willekens, Julie Prévost, Alexandre Prat, Marc Girard, Pierre Duquette, Mario Habek, Seyedmohammad Baghbanian, Serkan Ozakbas, Dana Horakova, Eva Havrdova, Rana Karabudak, Francesco Patti, Bassem I. Yamout, Samia Khoury, Michael Barnett, Pamela McCombe, Matteo Foschi, Murat Terzi, Davide Maimone, Radek Ampapa, O. Gerlach, Ayse Altintas, Yolanda Blanco, Stella Hughes, Maria José Sá, Pierre Grammond, Daniele L.A. Spitaleri, Koen De Gans, Riadh Gouider, Saloua Mrabet, Guillermo Izquierdo, Sara Eichau Madueño, Elisabetta Cartechini, Mark Slee, Recai Turkoglu, Jiwon Oh, Aysun Soysal, Sabrina Guye, Noemi Pasquarelli, Helmut Butzkueven, Vilija Jokubaitis, on behalf of the MSBase Study Group

Presented at ECTRIMS-ECTRIMS MSMilan2023 | Milan, Italy | 11–13 October 2023

Session 20: Female Health; Oral

Friday, 13 October 2023

A partnership between:



AlfredHealth



Disclosures

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TK served on scientific advisory boards for MS International Federation & World Health Organisation, BMS, Roche, Janssen, Sanofi Genzyme, Novartis, Merck & Biogen, steering committee for Brain Atrophy Initiative by Sanofi Genzyme, received conference travel support &/or speaker honoraria from WebMD Global, Eisai, Novartis, Biogen, Roche, Sanofi-Genzyme, Teva, BioCSL & Merck & received research or educational event support from Biogen, Novartis, Genzyme, Roche, Celgene & Merck. JL-S: travel compensation from Novartis, Biogen, Roche & Merck. Institution receives honoraria for talks & advisory board commitment as well as research grants from Biogen, Merck, Roche, TEVA & Novartis. RA: honoraria as speaker & for serving on scientific advisory boards from Bayer, Biogen, GSK, Merck, Novartis, Roche & Sanofi-Genzyme. CB: conference travel support from Biogen, Novartis, Bayer-Schering, Merck & Teva; participated in clinical trials by Sanofi Aventis, Roche & Novartis. NJ: local principal investigator on commercial studies funded by Novartis, Biogen, Amicus & Sanofi. KB: speaker honoraria &/or education support from Biogen, Teva, Novartis, Genzyme-Sanofi, Roche, Merck & Alexion; has been a member of advisory boards for Merck & Biogen. SH: honoraria & consulting fees from Novartis, Bayer Schering & Sanofi, & travel grants from Novartis, Biogen Idec & Bayer Schering. RM: nil. VVP: travel grants from Merck Healthcare KGaA (Darmstadt, Germany), Biogen, Sanofi, Bristol Meyer Squibb, Almirall & Roche. Institution received research grants & consultancy fees from Roche, Biogen, Sanofi, Merck Healthcare KGaA (Darmstadt, Germany), Bristol Meyer Squibb, Janssen, Almirall & Novartis Pharma. GL: travel &/or consultancy compensation from Sanofi-Genzyme, Roche, Teva, Merck, Novartis, Celgene, Biogen. LVH: travel compensation from Merck. BW: honoraria for acting as a member of Scientific Advisory Boards/Consultancy for Almirall, Biogen, Celgene/BMS, Merck, Janssen, Novartis, Roche, Sandoz, Sanofi-Genzyme & speaker honoraria & travel support from Biogen, Celgene/BMS, Merck, Novartis, Roche, Sanofi-Genzyme; research &/or patient support grants from Biogen, Janssen, Merck, Sanofi-Genzyme, Roche. Honoraria & grants were paid to UZA/UZA Foundation. Further, received research funding from FWO-TBM, Belgian Charcot Foundation, Start2Cure Foundation, Queen Elisabeth Medical Foundation for Neurosciences & the National MS Society USA. JP: travel compensation from Novartis, Biogen, Genzyme, Teva, & speaking honoraria from Biogen, Novartis, Genzyme & Teva. AP: nil. MG: consulting fees from Teva Canada Innovation, Biogen, Novartis & Genzyme Sanofi; lecture payments from Teva Canada Innovation, Novartis & EMD. Received a research grant from Canadian Institutes of Health Research. PD served on editorial boards & has been supported to attend meetings by EMD, Biogen, Novartis, Genzyme, & TEVA Neuroscience. Holds grants from the CIHR & the MS Society of Canada & has received funding for investigator-initiated trials from Biogen, Novartis, & Genzyme. MH: participated as clinical investigator and/or received consultation and/or speaker fees from: Biogen, Sanofi Genzyme, Merck, Bayer, Novartis, Pliva/Teva, Roche, Alvogen, Actelion, Alexion Pharmaceuticals, TG Pharmaceuticals. SMB: nil. SO: nil. DH: supported by the Charles University: Cooperatio Program in Neuroscience, by the project National Institute for Neurological Research (Programme EXCELES, ID Project No. LX22NPO5107) - Funded by the European Union – Next Generation EU, & by General University Hospital in Prague project MH CZ-DRO-VFN64165. Received compensation for travel, speaker honoraria & consultant fees from Biogen Idec, Novartis, Merck, Bayer, Sanofi Genzyme, Roche, & Teva, as well as support for research activities from Biogen Idec. EKH: honoraria/research support from Biogen, Merck Serono, Novartis, Roche, & Teva; has been member of advisory boards for Actelion, Biogen, Celgene, Merck Serono, Novartis, & Sanofi Genzyme; received honoraria/research support from Biogen, Merck Serono, Novartis, Roche, & Teva; has been member of advisory boards for Actelion, Biogen, Celgene, Merck Serono, Novartis, & Sanofi Genzyme; & has been supported by the Czech Ministry of Education – project Cooperatio LF1, research area Neuroscience, & the project National Institute for Neurological Research (Programme EXCELES, ID project No LX22NPO5107) – funded by the European Union-Next Generation EU. RK: nil. FP: personal compensation for serving on advisory board by Almirall, Alexion, Biogen, Bristol, Berck, Novartis & Roche. I further received research grant by Biogen, Merck & Roche & by FISM, Reload Association (Onlus), Italian Health Minister, University of Catania. BY: honoraria as a speaker & member of scientific advisory boards from Sanofi, Bayer, Biogen, Merck, Janssen, Novartis, Roche & Aspen. SK: received compensation for scientific advisory board activity from Merck and Roche, and compensation for serving on the IDMC for Biogen. MB served on scientific advisory boards for Biogen, Novartis & Genzyme & has received conference travel support from Biogen & Novartis. Serves on steering committees for trials conducted by Novartis. Institution has received research support from Biogen, Merck & Novartis. PM: speakers fees & travel grants from Novartis, Biogen, T'evalua, Sanofi. MF: travel and meeting attendance support from Novartis, Biogen, Roche, Sanofi-Genzyme and Merck. MT: travel grants from Novartis, Bayer-Schering, Merck & Teva; participated in clinical trials by Sanofi Aventis, Roche & Novartis. DM: speaker honoraria for Advisory Board & travel grants from Almirall, Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, & Teva. RA: conference travel support from Novartis, Teva, Biogen, Bayer & Merck & has participated in a clinical trials by Biogen, Novartis, Teva & Actelion. OG: nil. AA: speaker honoraria from Novartis & Alexion. YB: speaker honoraria/consulting fees from Merck, Biogen, Roche, Bristol, Novartis, Sanofi & Sandoz. SH: received unrestricted educational grants or speaking honoraria from Biogen, Merck Serono, Novartis, Roche & Sanofi Genzyme. MJS: consulting fees, speaker honoraria, &/or travel expenses for scientific meetings from Alexion, Bayer Healthcare, Biogen, Bristol Myers Squibb, Celgene, Janssen, Merck-Serono, Novartis, Roche, Sanofi & Teva. PG: served in advisory boards for Novartis, EMD Serono, Roche, Biogen idec, Sanofi Genzyme, Pendopharm & has received grant support from Genzyme & Roche, has received research grants for his institution from Biogen idec, Sanofi Genzyme, EMD Serono. DS: honoraria as a consultant on scientific advisory boards by Bayer-Schering, Novartis & Sanofi-Aventis & compensation for travel from Novartis, Biogen, Sanofi Aventis, Teva & Merck. KdG served on scientific advisory boards for Roche, Janssen, Sanofi-Genzyme, Novartis & Merck, received conference fee & travel support from Novartis, Biogen, Sanofi-Genzyme, Teva, Abbvie & Merck & received educational event support from Novartis. RG: nil. SM: MENACTRIMS clinical fellowship grant (2020). GI: speaking honoraria from Biogen, Novartis, Sanofi, Merck, Roche, Almirall & Teva. SE: speaker honoraria & consultant fees from Biogen Idec, Novartis, Merck, Bayer, Sanofi Genzyme, Roche & Teva. EC: nil. MS: nil. RT: nil. JO: research funding from the MS Society of Canada, National MS Society, Brain Canada, Biogen, Roche, EMD Serono (an affiliate of Merck KGaA); & personal compensation for consulting or speaking from Alexion, Biogen, Celgene (BMS), EMD Serono (an affiliate of Merck KGaA), Novartis, Roche, & Sanofi-Genzyme. AS: nil. SG & NP are employees & shareholders of F Hoffmann-La Roche Ltd. HB: institutional (Monash University) funding from Biogen, F. Hoffmann-La Roche Ltd, Merck, Alexion, CSL & Novartis; carried out contracted research for Novartis, Merck, F. Hoffmann-La Roche Ltd & Biogen; taken part in speakers' bureaus for Biogen, Genzyme, UCB, Novartis, F. Hoffmann-La Roche Ltd & Merck; received personal compensation from Oxford Health Policy Forum for the Brain Health Steering Committee. VJ: conference travel support from Merck & Roche & speaker's honoraria from Biogen & Roche outside of the submitted work.



Introduction



Family planning is an integral aspect in the care of women with MS



Disease modifying therapy discontinuation or highly active disease may increase the risk of postpartum relapses



Ocrelizumab may be a suitable option to control postpartum MS disease activity, but data are limited

Objective

A faint, light blue target icon with concentric circles and an arrow hitting the bullseye is positioned on the left side of the objective text box.

To investigate disease activity during pregnancy and postpartum in women with relapse-onset MS exposed to ocrelizumab and other MS disease modifying therapies preconception

Data from the international MSBase pregnancy, neonatal outcomes and women's health registry (data extracted 1st July 2023)

Inclusion criteria



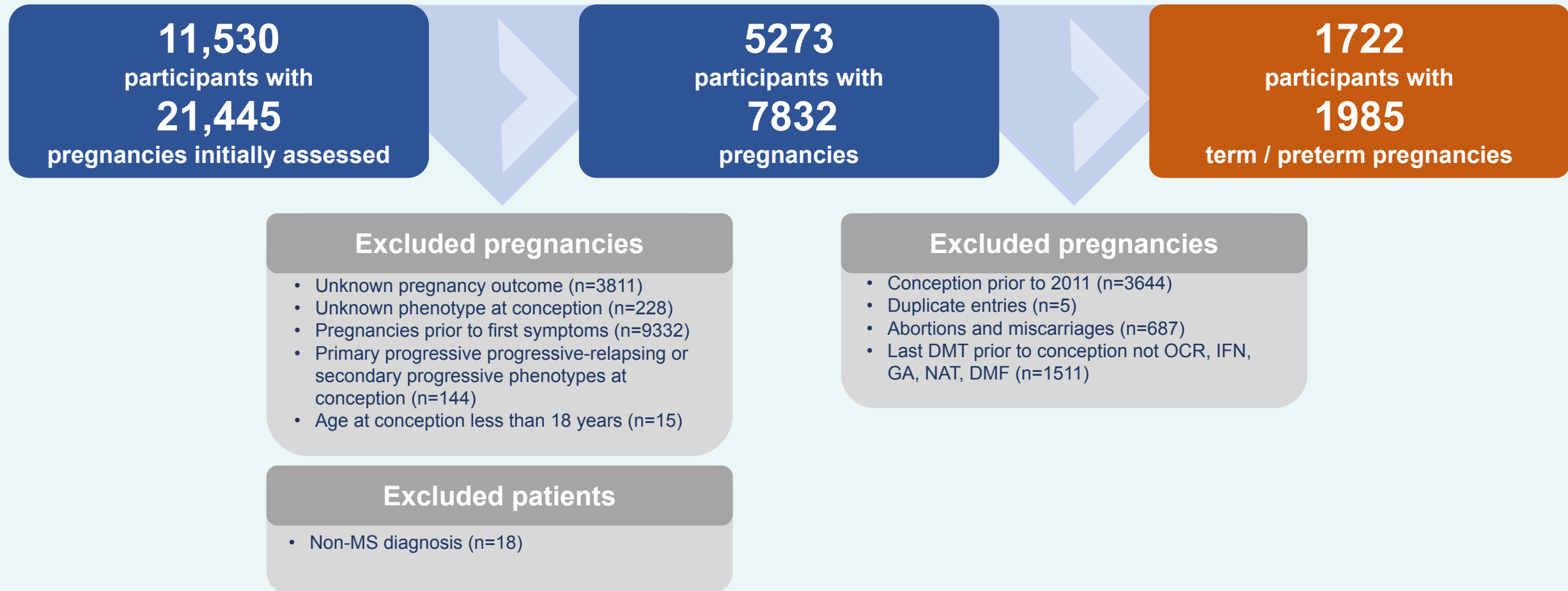
- Women aged ≥ 18 years
- CIS or relapsing-remitting MS at conception
- Term and preterm pregnancies conceived from 2011 onwards
- OCR or NAT, DMF, Low Efficacy (IFN-B or GA) as most recent DMT used prior to pregnancy

Outcomes



- Annualised relapse rates (ARR)
 - Preconception – while on preconception DMT or after stopping
 - Pregnancy
 - Postpartum – while on no DMT or after initiating preconception DMT

Analysis included 1985 term / preterm pregnancies



Preconception baseline characteristics were generally balanced except women receiving OCR were slightly older

	Preconception DMT			
	OCR (n=73)	NAT (n=419)	DMF (n=164)	Low (n=1329)
Pregnancy duration, median (IQR), mo	9.0 (8.7, 9.2)	8.9 (8.4, 9.2)	9.0 (8.6, 9.2)	9.0 (8.6, 9.2)
Age at conception, median (IQR), y	33.8 (30.7, 37.3)	31.5 (28.6, 34.4)	31.4 (28.4, 34.2)	31.5 (28.2, 34.6)
Time from first symptoms to conception, median (IQR), y	7.1 (3.9, 10.5)	7.4 (4.2, 11.7)	5.7 (3.0, 9.2)	5.8 (3.3, 9.5)
DMT used prior, median (IQR), n	1 (0,2)	1 (1,2)	1 (0,2)	0 (0,1)
EDSS score at conception, ^a n (%)				
<2	25 (34.2)	198 (47.3)	95 (57.9)	674 (50.8)
≥2	28 (38.4)	122 (29.1)	28 (17.1)	213 (16.0)
Missing	20 (27.4)	99 (23.6)	41 (25.0)	441 (33.2)
EDSS score at conception, ^a median (IQR)	2 (1, 2.5)	1.5 (1,2)	1 (1,1.5)	1 (0,1.5)
Range	0,5	0,6	0,6	0,6.5
ARR in 1 y before conception, mean (SD)	0.1 (0.5)	0.1 (0.5)	0.2 (1.1)	0.2 (0.7)
DMT preconception duration, median (IQR), mo	10.0 (5.8, 18.1)	18.1 (9.1, 32.0)	14.1 (8.1, 24.8)	23.5 (10.7, 44.8)
DMT washout preconception, median (IQR), mo	1.9 (0, 4.8)	0.9 (0, 6.4)	0 (0, 1.3)	0 (0, 0.8)
DMT duration into pregnancy, median (IQR), mo	0 (0, 0.5)	0 (0, 0)	0.2 (0, 1.1)	0.5 (0, 1.4)
DMT initiated post-delivery, n (%)				
Preconception DMT class reinitiated	50 (68.5)	326 (77.8)	84 (51.2)	822 (61.9)
Other DMT	7 (9.6)	59 (14.1)	34 (20.7)	169 (12.7)
None	16 (21.9)	34 (8.1)	46 (28.0)	338 (25.4)
Time to DMT initiation post-delivery, ^b median (IQR), months	1.4 (0.5, 3.0)	0.9 (0.1, 2.3)	2.3 (0.5, 4.4)	2.4 (0.4, 5.0)

**EDSS
(where known)
was generally
slightly higher
among women
with MS
receiving OCR**

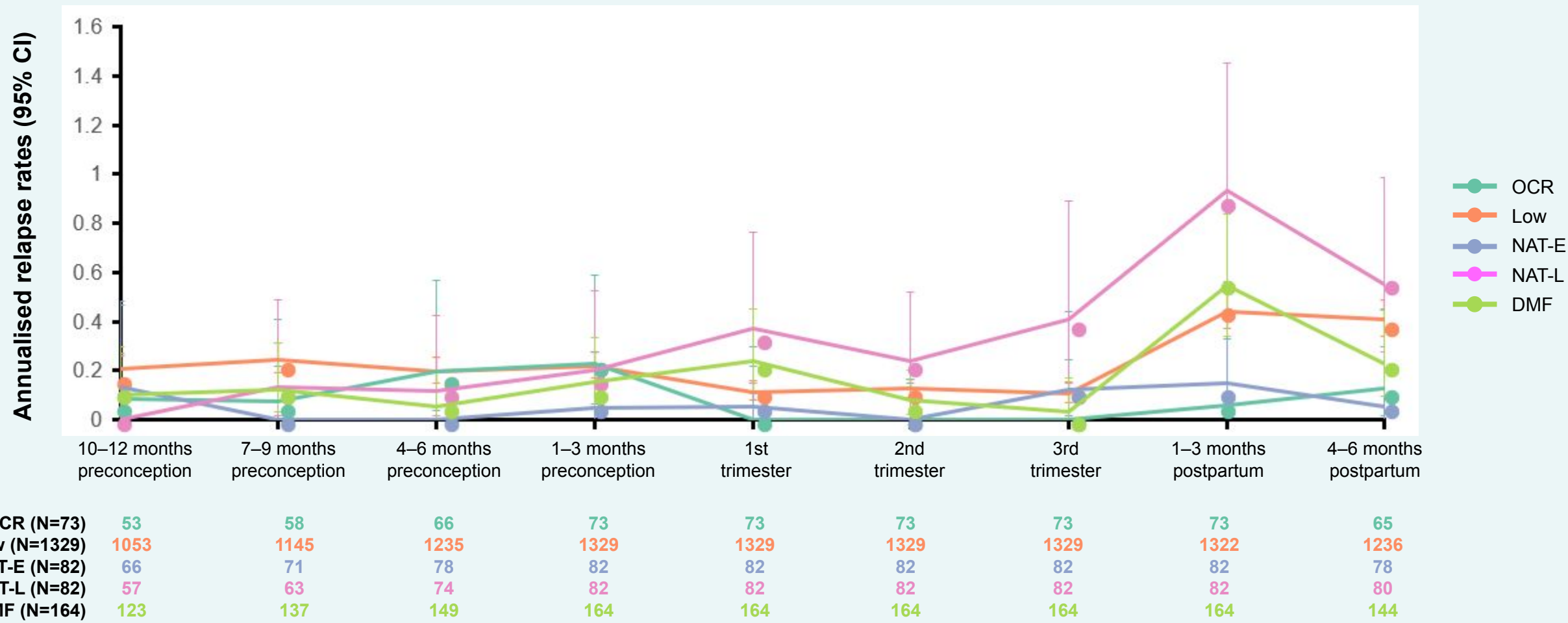


^aEDSS score closest to conception (within one year preconception)

^bParticipants who initiated either preconception DMT or other DMT

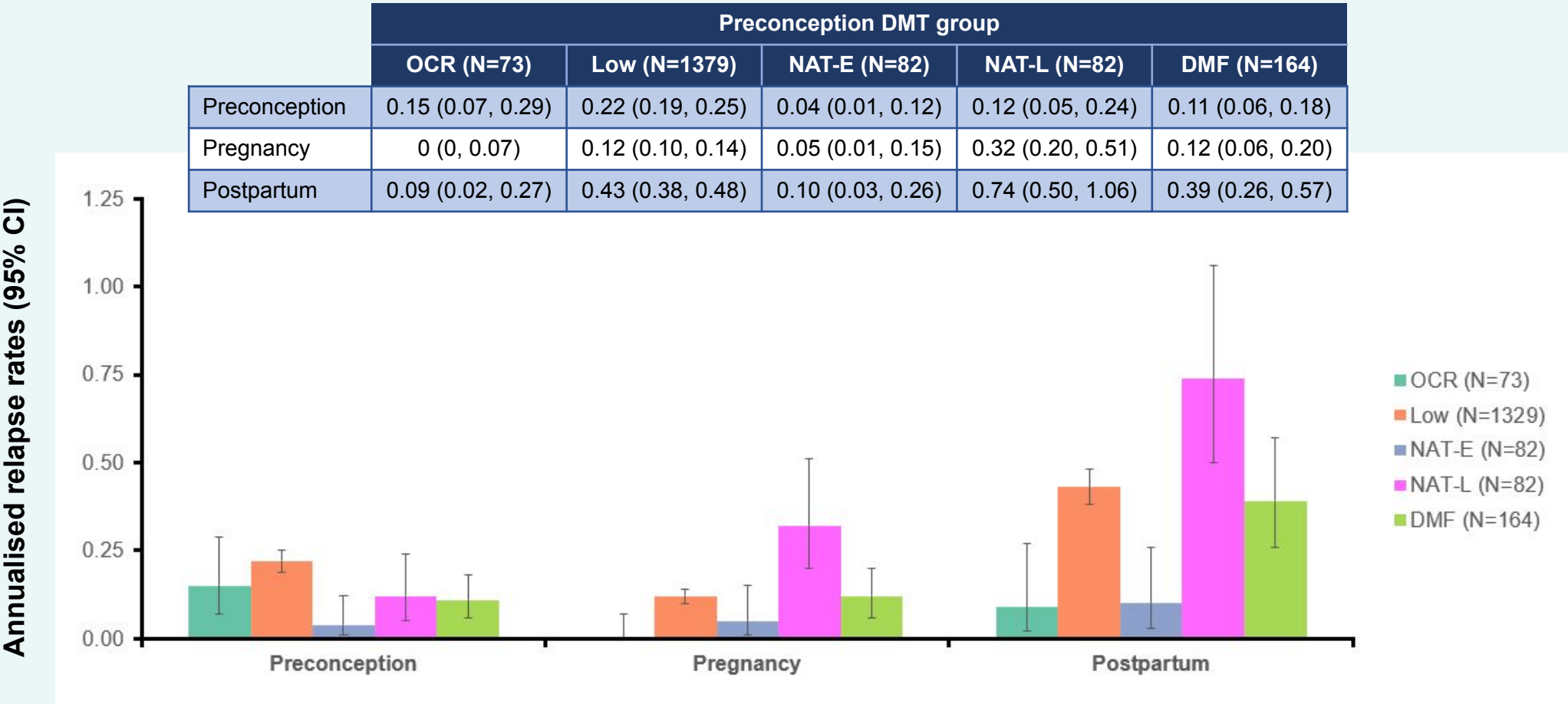
DMF, dimethyl fumarate; DMT, disease modifying therapies; EDSS, Expanded Disability Status Scale; IQR, interquartile range; Low, interferon-beta or glatiramer acetate; NAT, natalizumab; OCR, ocrelizumab; SD, standard deviation.

Minimal MS disease activity was observed in the first trimester postpartum among women treated with OCR



DMF, dimethyl fumarate; Low, interferon-beta or glatiramer acetate; NAT-E: (E=early re-initiation) natalizumab, continued ≥ 28 weeks pregnancy & restarted ≤ 1 month after delivery; NAT-L: (L=late re-initiation) natalizumab, continued ≤ 4 weeks pregnancy & restarted > 1 month after delivery; OCR, ocrelizumab.

ARR was lowest during pregnancy and postpartum among women treated with OCR prior to conception



DMF, dimethyl fumarate; Low, interferon-beta or glatiramer acetate; NAT-E: (E=early re-initiation) natalizumab, continued ≥28 weeks pregnancy & restarted ≤1 month after delivery; NAT-L: (L=late re-initiation) natalizumab, continued ≤4 weeks pregnancy & restarted >1 month after delivery; OCR, ocrelizumab.

Discussion



Women treated with ocrelizumab prior to conception were observed to have the lowest relapse rates during pregnancy and postpartum compared to other DMTs used in the context of family planning



Use of ocrelizumab pre-conception represents an option to effectively control disease activity in the peri-pregnancy period, including reducing the risk of postpartum relapses



Further evidence to understand relapse predictors and safety during pregnancy will be generated through future analyses as well as ongoing Phase IV studies (pregnancy registry, MINORE and SOPRANINO studies)¹⁻³



Counselling remains an important approach to ensure optimal outcomes for mothers and infants

1. OCREVUS® (ocrelizumab) Pregnancy Registry; <https://www.ocrevuspregnancyregistry.com/> (accessed 19 Sept 2023); 2. Bove R, et al. Mult Scler Relat Disord 2022;64:103963; 3. Additional data presented at ECTRIMS 2023: Hellwig K, et al. P061. Pregnancy and Infant Outcomes in Women Receiving Ocrelizumab for the Treatment of Multiple Sclerosis: Analysis of the Largest Available Outcome Database.

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AlfredHealth

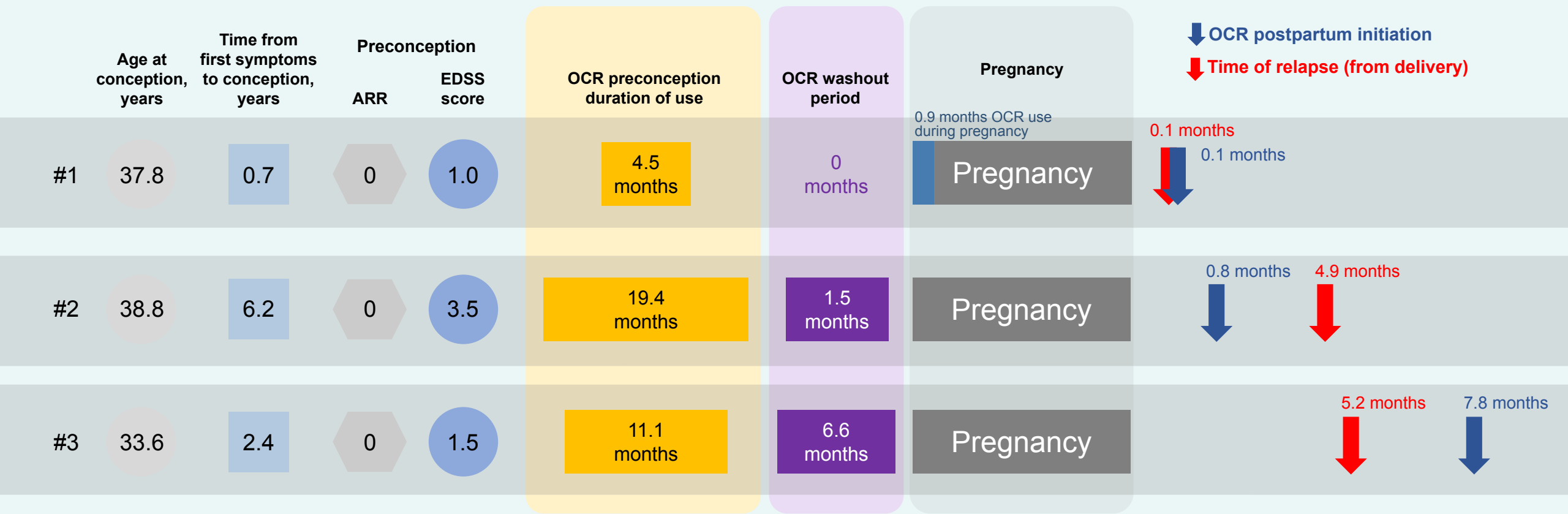


Supplementary Information

Characteristics of OCR-treated women with postpartum relapses

		Women with MS		
		#1	#2	#3
Demographics and disease characteristics	Age at conception, years	37.8	38.8	33.6
	Time from first symptoms to conception, years	0.7	6.2	2.4
	ARR preconception	0	0	0
	EDSS score preconception	1	3.5	1.5
OCR information	OCR preconception duration of use, months	4.5	19.4	11.1
	OCR washout period, months	0	1.5	6.6
	OCR during pregnancy — time from conception, months	0.9	—	—
Postpartum information	DMT initiated postpartum	OCR	OCR	OCR
	DMT initiated postpartum — time from delivery, months	0.1	0.8	7.8
	Time of relapse from delivery, months	0.1	4.9	5.2

Characteristics of OCR-treated women with postpartum relapses



ARR, annualised relapse rate; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; OCR, ocrelizumab.

Proportion of women with relapse before, during and after pregnancy

	Preconception DMT group				
	OCR (N=73)	Low (N=1379)	NAT-E (N=82)	NAT-L (N=82)	DMF (N=164)
Preconception, n (%)	6 (8.2)	215 (16.2)	3 (3.7)	7 (8.5)	14 (8.5)
Pregnancy, n (%)	0 (0)	101 (7.6)	3 (3.7)	13 (15.9)	13 (7.9)
Postpartum, n (%)	3 (4.1)	234 (17.7)	4 (4.9)	25 (30.5)	25 (15.2)



<http://ter.li/iac7zw>

Cerebrospinal Fluid Neurofilament Heavy Levels Correlate With Spinal Cord Lesions and Disability in Multiple Sclerosis

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Y-A Shen is an employee of Genentech, Inc., and a shareholder in F. Hoffmann-La Roche Ltd. **C Harp** is an employee of Genentech, Inc., and a shareholder in F. Hoffmann-La Roche Ltd. **H-C von Büdingen** is an employee of and shareholder in F. Hoffmann-La Roche Ltd. **AE Herman** is an employee of Genentech, Inc., and a shareholder in F. Hoffmann-La Roche Ltd. **J Jiang** is an employee of Genentech, Inc., and a shareholder in F. Hoffmann-La Roche Ltd. **N Strauli** is an employee of Genentech, Inc., and a shareholder in F. Hoffmann-La Roche Ltd. **SL Hauser** serves on the scientific advisory boards of Accure, Annexon and Alector, serves on the board of directors of Neurona, has consulted for NGM Bio and has received travel reimbursement and writing assistance from F. Hoffman-La Roche Ltd and Novartis for CD20-related meetings and presentations. **BAC Cree** has received consulting fees from Alexion, Atara, Autobahn, Avotres, Biogen, EMD Serono, Gossamer Bio, Horizon, Neuron23, Novartis, Sanofi, TG Therapeutics and Therini and received research support from Genentech, Inc. **X Jia** is an employee of Genentech, Inc., and a shareholder in F. Hoffmann-La Roche Ltd.

Objective



To characterise correlations between levels of neurofilament heavy and light chains (NfH and NfL) in serum and cerebrospinal fluid (CSF) with measures of acute disease activity, disease burden and lesion location in people with relapsing-remitting or progressive multiple sclerosis (pwRRMS or pwPMS)

Results

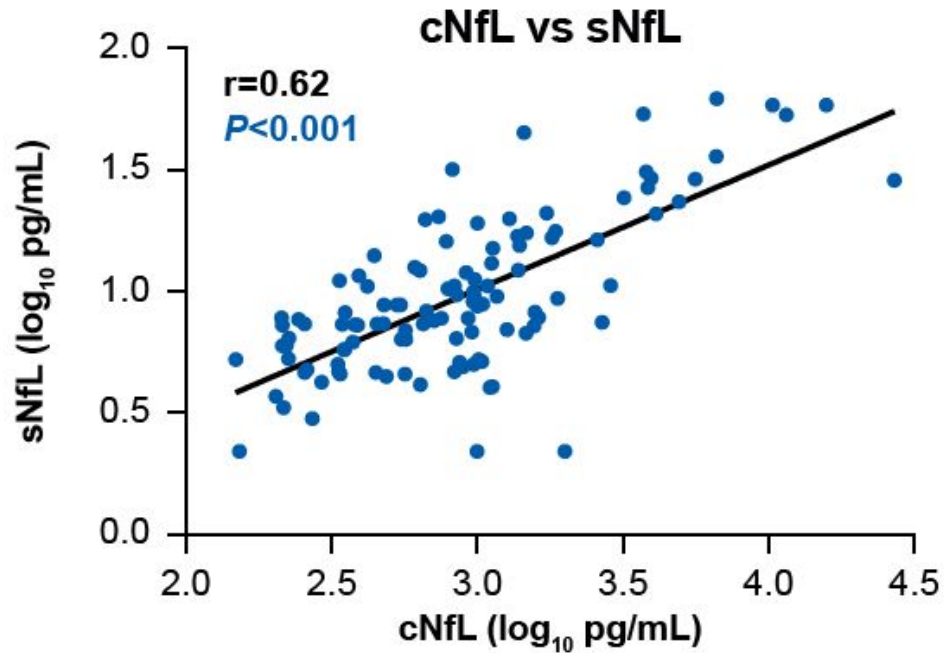
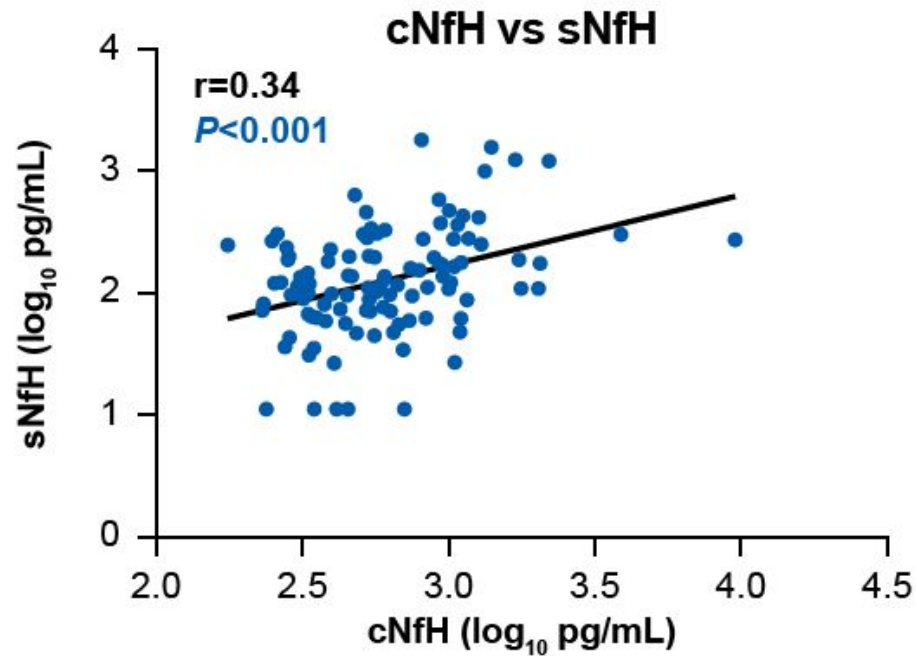
Demographics and Clinical Characteristics

Characteristic	RRMS (n=90)	PMS (n=22) PPMS (n=17) + SPMS (n=5)	All (N=112)
Age, mean (SD), years	37.0 (9.1)	56.1 (11.7)	40.7 (12.3)
Female, n (%)	61 (67.8)	10 (45.5)	71 (63.4)
EDSS score, mean (SD)	2.0 (1.3)	4.5 (1.7)	2.5 (1.7)
Participants receiving steroids, n (%)	7 (7.7)	1 (4.5)	8 (7.1)
Participants receiving DMTs, n (%)	15 (16.7)	4 (18.2)	19 (17.0)
OCB positivity, n (%)	72 (80.0)	17 (77.3)	89 (79.5)
Received brain MRI ≤90 days before LP	n=75	n=13	n=88
Time from MRI to LP, median (IQR), days	0 (0–15)	0 (0–28)	0 (0–15)
Presence of brain Gd+ lesions, n (%)	30 (40.0)	2 (15.4)	32 (36.4)
Presence of brain T2 lesions, n (%)	68 (90.7)	11 (84.6)	79 (89.8)
Received spinal cord MRI ≤90 days before LP	n=53	n=8	n=61
Time from MRI to LP, median (IQR), days	0 (0–9)	0 (0–0)	0 (0–4)
Presence of spinal cord Gd+ lesions, n (%)	14 (26.4)	0	14 (23.0)
Presence of spinal cord T2 lesions, n (%)	32 (60.4)	6 (75.0)	38 (62.3)

- Paired CSF and serum samples were analysed in 112 participants with MS
- The PMS cohort was older, had higher EDSS scores and more male participants than the RRMS cohort
- Overall, 83% of participants were not receiving a DMT

Results

Significant Correlations Were Observed Between Serum and CSF Levels of NfH and NfL^a

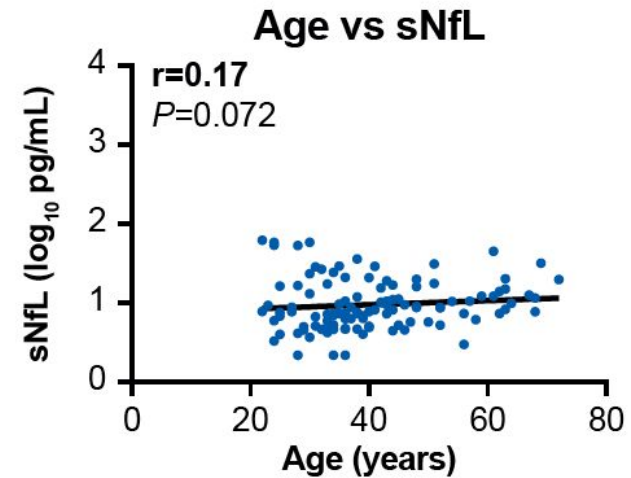
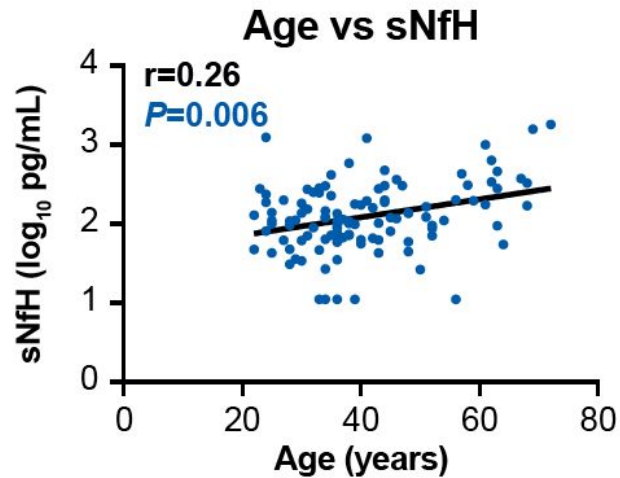
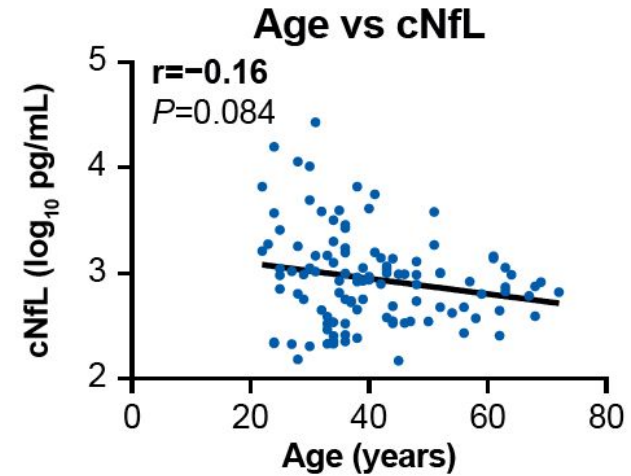
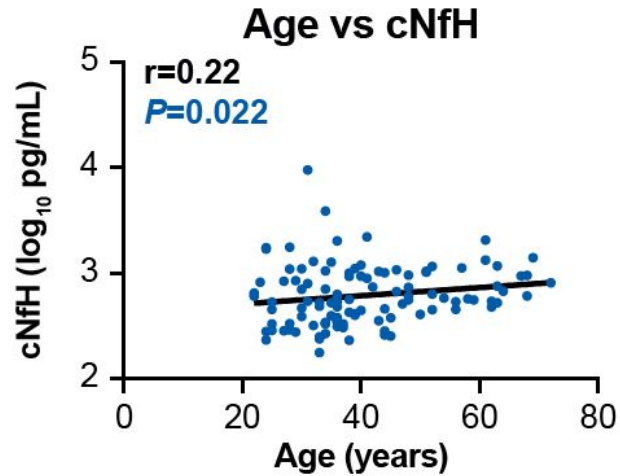


cNfH, cerebrospinal fluid neurofilament heavy chain; cNfL, cerebrospinal fluid neurofilament light chain; CSF, cerebrospinal fluid; sNfH, serum NfH; sNfL, serum NfL.

^aAnalysis of paired serum and CSF samples in the combined MS cohort. All $P<0.001$.

Results

Age Correlated Positively With cNfH and sNfH Levels^a

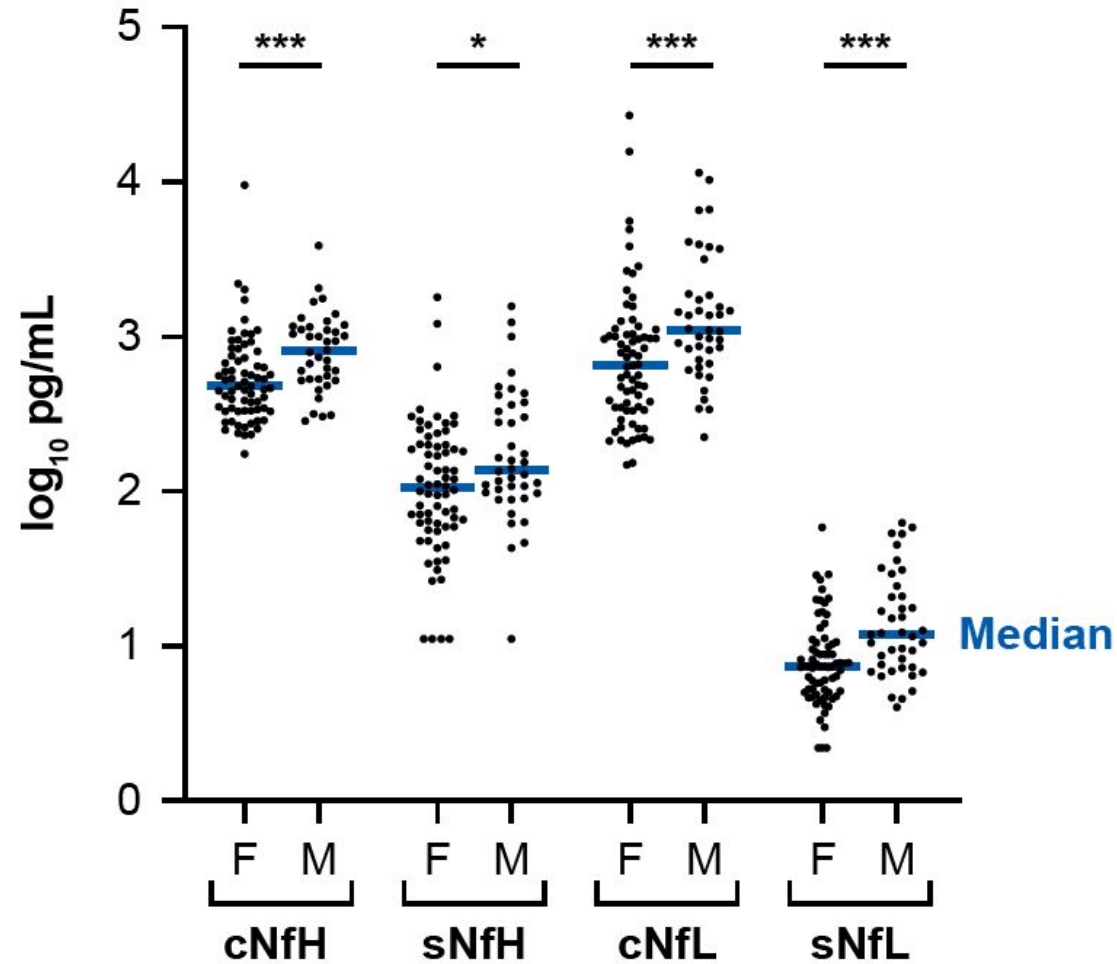


cNfH, CSF neurofilament heavy chain; cNfL, CSF neurofilament light chain; sNfH, serum neurofilament heavy chain; sNfL, serum neurofilament light chain.

^aAssociations between biomarkers and participant demographic factors (age, sex) were determined using Spearman's r analysis and Mann Whitney U, respectively.

Results

Male Participants Had Significantly Higher Levels of NfH and NfL in CSF and Serum^a



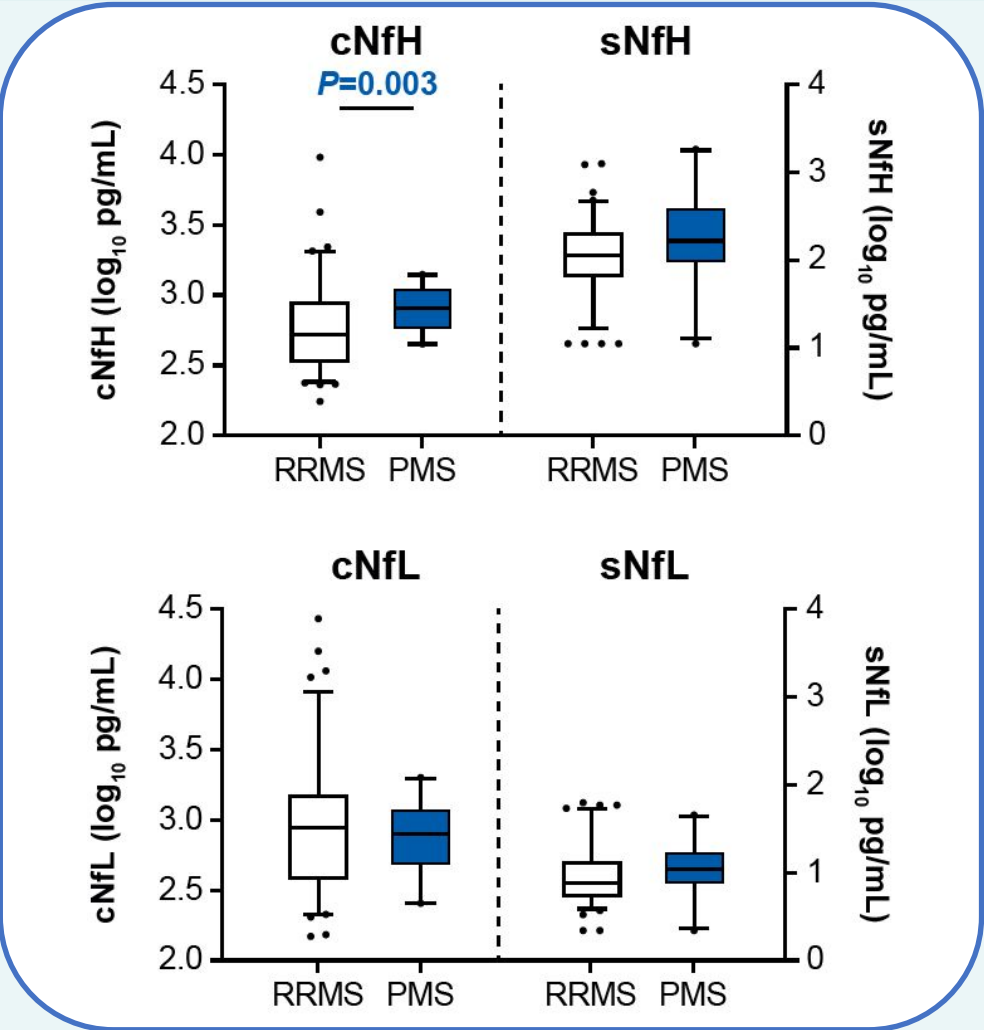
* $P < 0.05$; *** $P < 0.001$.

CSF, cerebral spinal fluid; cNfH, CSF neurofilament heavy chain; cNfL, CSF neurofilament light chain; sNfH, serum neurofilament heavy chain; sNfL, serum neurofilament light chain.

^aAssociations between biomarkers and participant demographic factors (age, sex) were determined using Spearman's r analysis and Mann Whitney U, respectively.

Results

cNfH Levels Were Elevated in People With PMS vs RRMS ($P=0.0025$)^a



Median (IQR)	RRMS n=90	PMS n=22	P value
cNfH	526 (338–870)	809 (607–1094)	0.003
sNfH	111.5 (65.7–200.3)	165.0 (95.3–365.3)	0.108
cNfL	880 (382–1472)	788 (511–1121)	0.842
sNfL	7.64 (5.42–12.91)	11.11 (8.02–16.37)	0.079

However, this may be driven by differences in demographic factors.^a

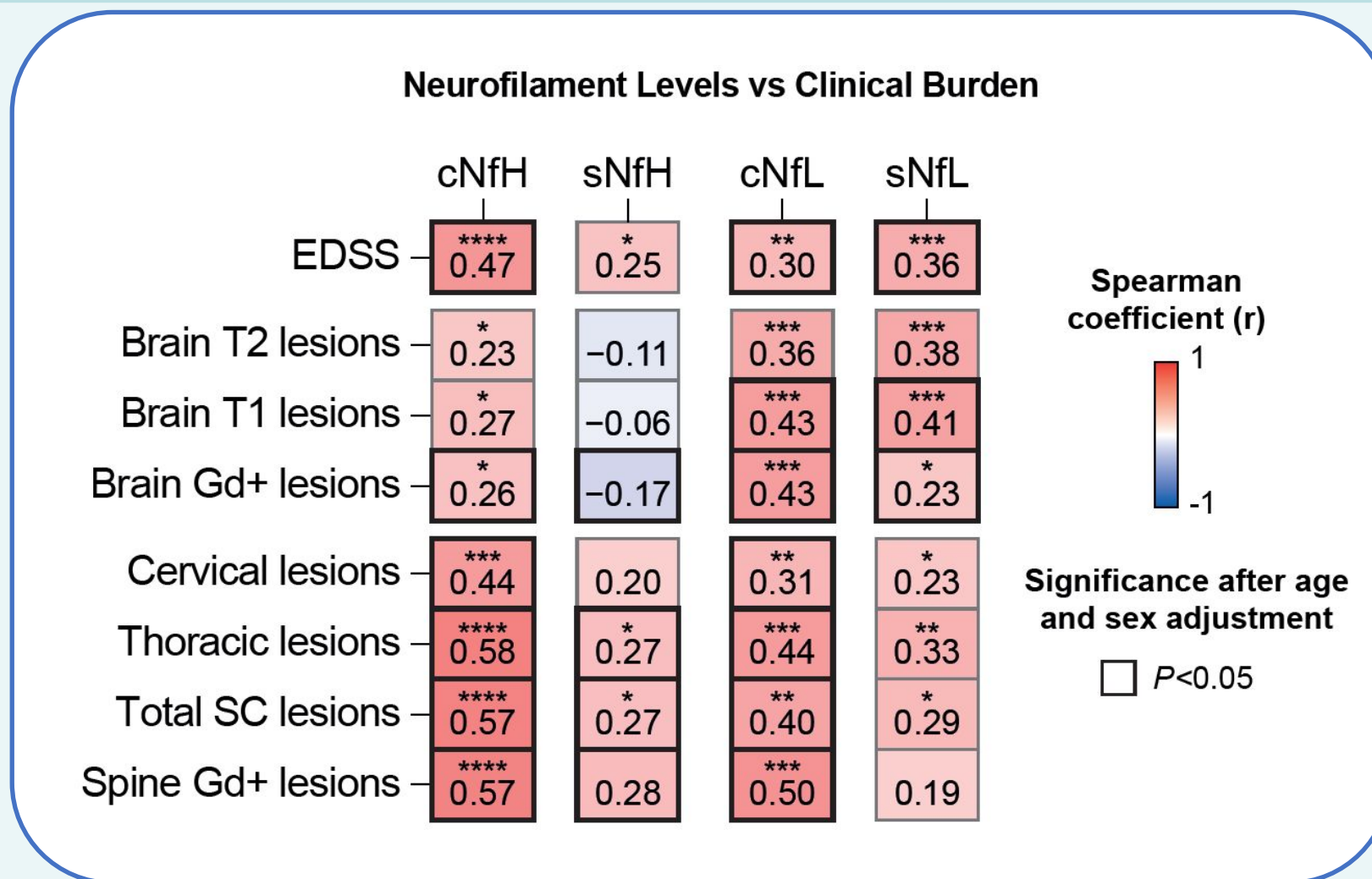
Covariates to log ₁₀ (cNfH)	Coefficient	P value
RRMS vs PMS	0.075	0.381
Age	0.002	0.484
Sex	0.169	0.003

cNfH, cerebrospinal fluid neurofilament heavy chain; cNfL, cerebrospinal fluid neurofilament light chain; NfH, neurofilament heavy chain; NfL, neurofilament light chain; PMS, progressive MS; RRMS, relapsing-remitting MS; sNfH, serum NfH; sNfL, serum NfL.

^aData are presented as the median, with boxes defining 25–75% percentiles and whiskers defining 5–95% percentiles. Statistical significance was determined via the Mann-Whitney U test.

Results

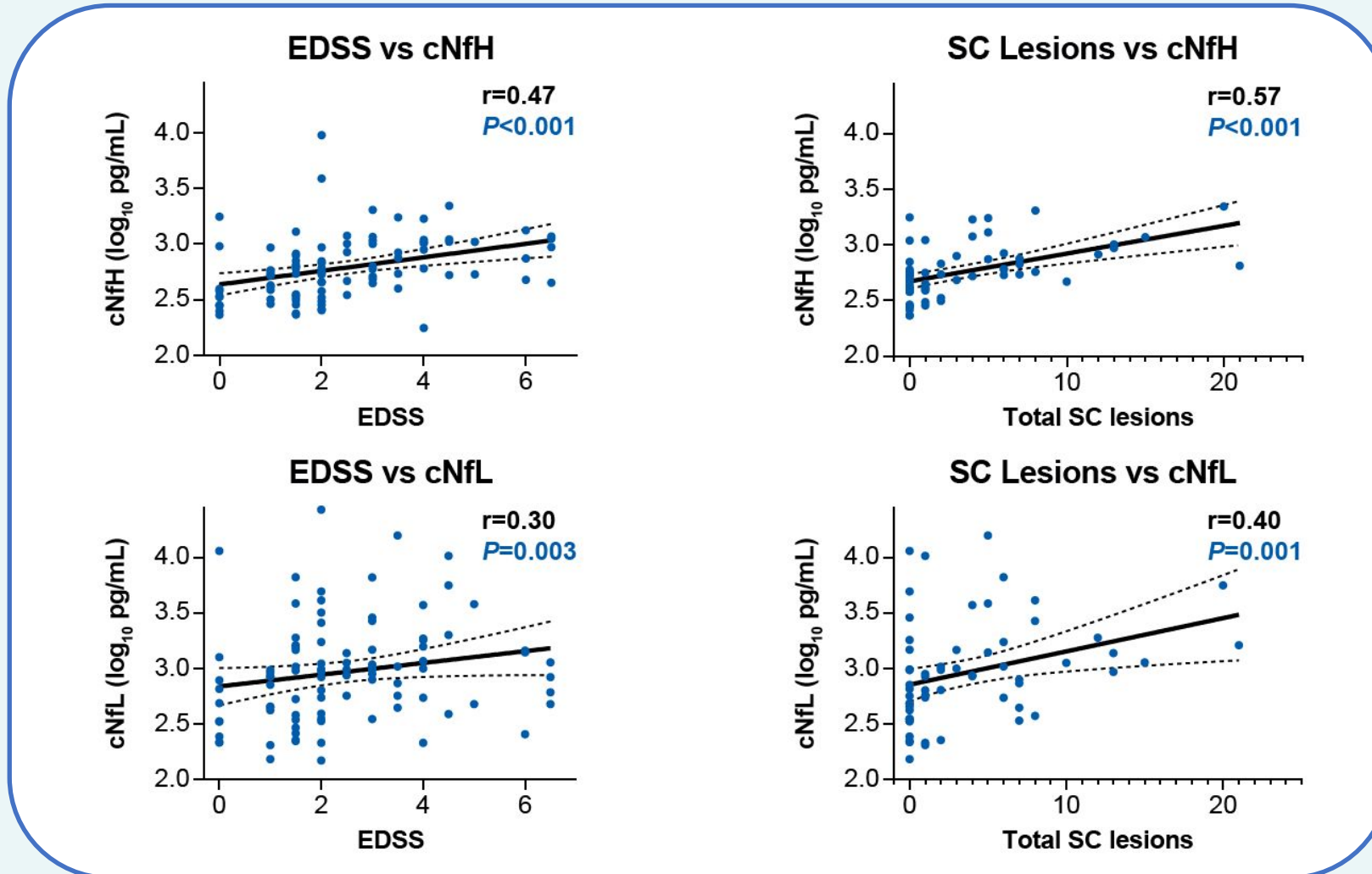
Compared With cNfL, cNfH Levels Showed Greater Correlations With EDSS and Spinal Cord Lesion Burden in the Combined RRMS and PMS Cohort



* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$; cNfH, cerebrospinal fluid neurofilament heavy chain; cNfL, cerebrospinal fluid neurofilament light chain; EDSS, Extended Disability Status Scale; Gd+, gadolinium enhancing; PMS, primary multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SC, spinal cord; sNfH, serum neurofilament heavy chain; sNfL, serum neurofilament light chain.

Results

Compared With cNfL, cNfH Levels Showed Greater Correlations With EDSS and Spinal Cord Lesion Burden in the Combined RRMS and PMS Cohort



* $P<0.05$; ** $P<0.01$; *** $P<0.001$; **** $P<0.0001$; cNfH, cerebrospinal fluid neurofilament heavy chain; cNfL, cerebrospinal fluid neurofilament light chain; EDSS, Extended Disability Status Scale; Gd+, gadolinium enhancing; PMS, primary multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SC, spinal cord; sNfH, serum neurofilament heavy chain; sNfL, serum neurofilament light chain.

Conclusion



NfH levels in CSF correlated with spinal cord lesions and disability in MS, suggesting that NfH may complement NfL for the purpose of assessing MS disease outcomes

Supplementary Material

Background

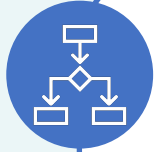


- NfH is released with neuroaxonal injury¹ and is a promising biomarker in MS.²
- Spinal cord tissue shows greater NfH expression than in the brain;^{1,3,4} whether this difference in expression impacts the use of NfH as a biomarker for MS remains to be elucidated.

MS, multiple sclerosis; NfH, neurofilament heavy chain; NfL, neurofilament light chain.

1. Shaw G, et al. *Biochem Biophys Res Comm.* 2005;336:1268–1277; 2. Kuhle J, et al. *Neurol.* 2011;76:1206–1213. 3. Petzold A, et al. *Exp Neurol.* 2008;213:326–328; 4. Anderson K, et al. *J Neurotrauma.* 2008;25(9):1079–1085.

Methods



- Paired CSF and serum samples were collected from pwRRMS or pwPMS at the University of California, San Francisco from 2012 to 2017.
- NfH (phosphorylated) and NfL levels were measured using Simple Plex and Simoa platforms, respectively, in serum and CSF.
- Correlations with clinical measures—EDSS score and MRI results—were assessed in the combined cohort using Spearman correlation.
 - Inclusion criteria for MRI analysis included receiving MRI within 90 days prior to LP.
 - Exclusion criteria for MRI analysis included LP within 90 days prior to MRI.
- Associations were confirmed using a linear model adjusted for age and sex.

Supplemental Table 1

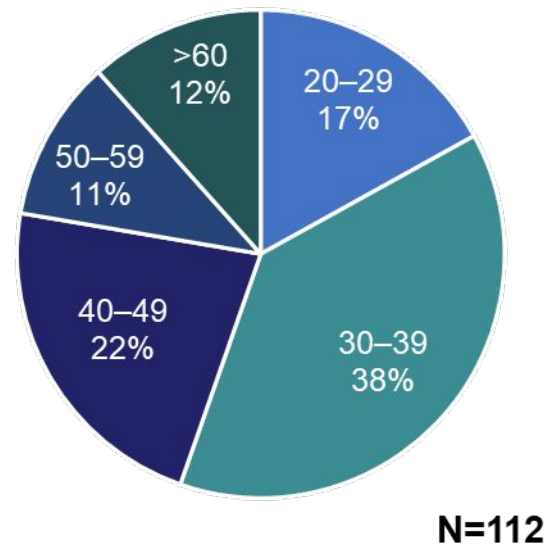
Most Participants Were Not Receiving DMTs at the Time of Sampling

Therapy category	Therapy	Participants, n (%)
Untreated/DMT naive		84 (75.0)
DMTs	Any DMT	19 (17.0)
	Fingolimod	4 (3.6)
	Glatiramer acetate	4 (3.6)
	Dimethyl fumarate	3 (2.7)
	Interferon beta-1b	3 (2.7)
	Natalizumab	3 (2.7)
	Rituximab	1 (0.9)
	Teriflunomide	1 (0.9)
Steroids (non-DMTs)	Methylprednisolone	8 (7.1)
Not applicable		1 (0.9)

Supplemental Figure 1

Additional Demographics and Clinical Characteristics

Participant Age (Years)

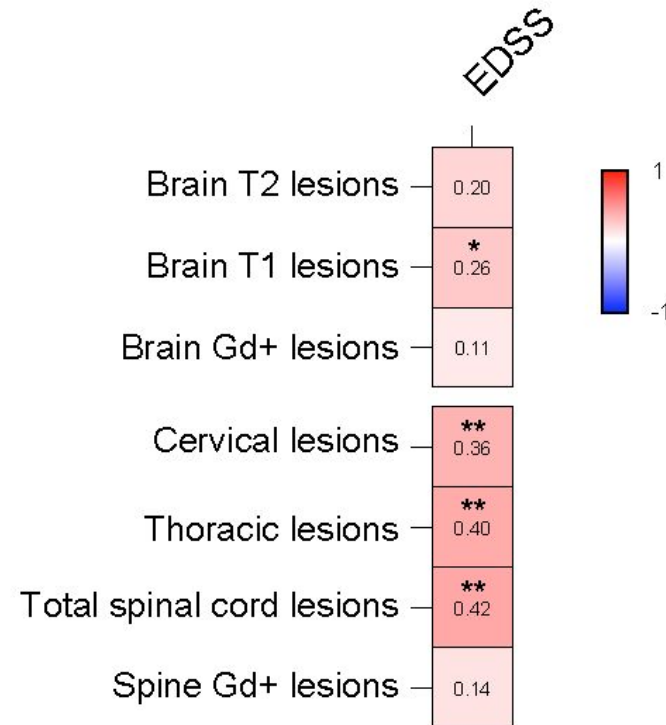


Characteristic, n (%)	RRMS (n=90)	PMS (n=22)	All (N=112)
Brain MRI			
≤90 days before LP	75 (83.3)	13 (59.1)	88 (78.6)
≤30 days before LP	67 (74.4)	10 (45.5)	77 (68.8)
Same day as LP	50 (55.6)	8 (36.4)	58 (51.8)
Spinal cord MRI			
≤90 days before LP	53 (58.9)	8 (36.4)	61 (54.5)
≤30 days before LP	46 (51.1)	7 (31.8)	53 (47.3)
Same day as LP	38 (42.2)	7 (31.8)	45 (40.2)

- A majority of participants were 30 to 39 years old
- More participants received brain vs spinal cord MRI (78.6% vs 54.5%) within 90 days of LP
- Most eligible participants received an MRI on the same day as LP

Supplemental Figure 2

Spinal Cord Lesion Burden Showed a Greater Correlation to Disability Status (by EDSS), Reflecting Others' Findings¹⁻⁴



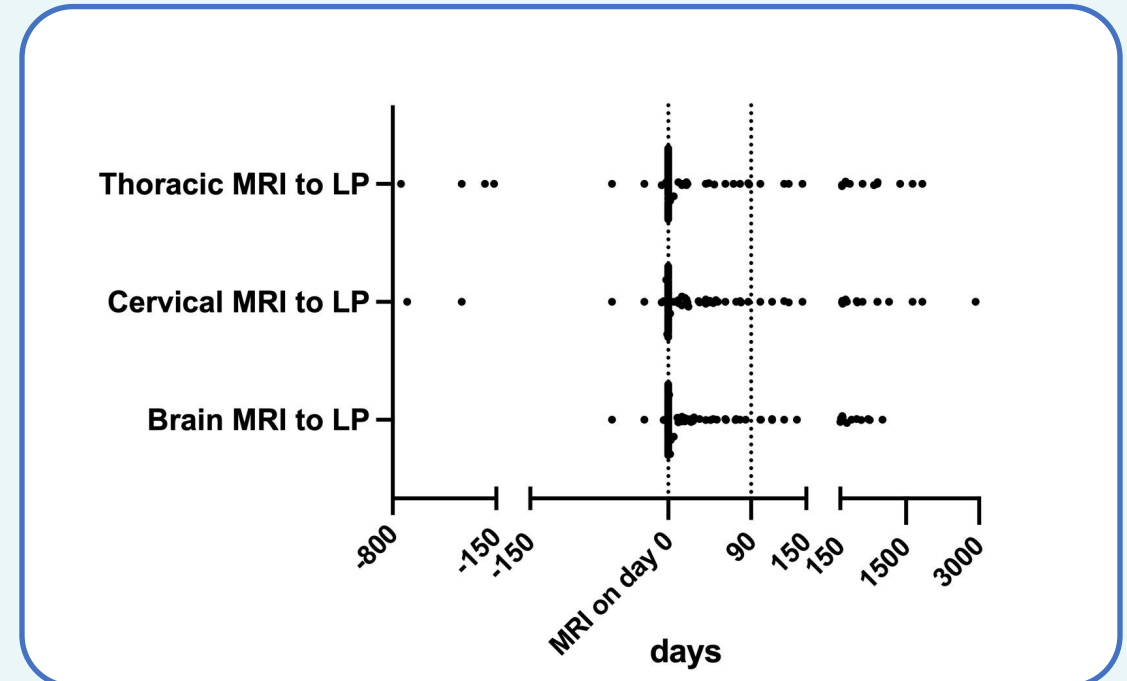
EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; SC, spinal cord.

1. Ruggieri S, et al. *J Neurol*. Published online 29 June 2023; 2. Kerbrat A, et al. *Brain*. 2020;143:2089–2105; 3. Rocca M, et al. *J Neurol Neurosurg Psychiatry*. 2023;94:10–18; 4. Bonacchi R, et al. *Radiol*. 2020;296:605–615.

Supplemental Figure 3

Intervals Between MRI and Sample Collection for Combined MS Cohort

Clinical measurement		Participants, n
Age		112
EDSS		95
MRI ≤90 days before LP	Brain	88
	Cervical	72
	Thoracic	61
	Total SC and Gd+	61



- Samples from participants who received MRIs 0 to 90 days prior to LP were included in the analysis of correlation and regression models between biomarkers and MRI outcomes



<https://ter.li/1602m8>

Persistence to Ocrelizumab Compared with Other Disease-Modifying Therapies for Multiple Sclerosis in the German NeuroTransData Registry

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Disclosures

S Braune received honoraria from Kassenärztliche Vereinigung Bayerns and health maintenance organisations for patient care; and from Biogen, Bristol Myers Squibb, Merck, NeuroTransData, Novartis and Roche for consulting, project management, clinical studies and lectures; he also received honoraria and expense compensation as a board member of NeuroTransData. **P Dirks** is an employee of and shareholder in F. Hoffmann-La Roche Ltd. **S Colloud** is an employee of and shareholder in F. Hoffmann-La Roche Ltd. **E Davies** is an employee of and shareholder in F. Hoffmann-La Roche Ltd. **Q Wang** is an employee of and shareholder in F. Hoffmann-La Roche Ltd. **Y Heer** was contracted to perform statistical projects for NeuroTransData and was an employee of PricewaterhouseCoopers AG during completion of this work. **M Zürcher** was contracted to perform statistical projects for NeuroTransData and was an employee of PricewaterhouseCoopers AG during completion of this work. **D Sun** is an employee of Genentech, Inc., and a shareholder in F. Hoffmann-La Roche Ltd.

Background and Objective



- Ocrelizumab (OCR) is given twice a year as intravenous (IV) infusions for the treatment of multiple sclerosis (MS) and has shown higher persistence than other disease-modifying therapies (DMTs) in US claims data^{1,2}
- High persistence is important for controlling disease worsening and can be an indicator of a favourable outcome³



To examine the persistence to OCR compared with other DMTs and its association with outcomes in patients with RRMS from the NTD MS registry



- NTD is a Germany-wide network of neurologists and psychiatrists, founded in 2008. Currently, the NTD network includes 164 specialists in 56 practices serving ~600,000 outpatients per year
- The NTD MS registry is a disease-specific database run by the NTD network. Currently, the NTD MS registry includes ~25,000 patients with MS

Methods

Study Design and Population



- This was a retrospective cohort analysis of German outpatients diagnosed with RRMS enrolled in the NTD MS registry who initiated an approved DMT between January 2014 and April 2022
- Patients had to be ≥ 18 years of age at index; had a minimum of 2 years (or 3 years) of follow-up after their index date; and had minimal data availability at index (Expanded Disability Status Scale [EDSS] score, date of diagnosis, date of manifestation). Index date was defined as the date of DMT initiation during the study period
- DMTs were grouped into: 1) OCR, 2) injectable (interferon β -1a/1b, glatiramer acetate), 3) oral (teriflunomide, dimethyl fumarate), 4) oral for highly active disease (HA) (oral HA; cladribine, fingolimod) and 5) other IV (natalizumab). Ozanimod, ponesimod, ofatumumab, diroximel fumarate and subcutaneous natalizumab were excluded due to insufficient follow-up
- Persistence was defined as no discontinuation of the index DMT group or switch to a new group of DMT during follow-up. Persistence was evaluated within each index DMT group, and in-group switches of DMT were allowed

Methods

Study Outcomes and Analyses



- Descriptive statistics were used to summarise patient characteristics at baseline
- Kaplan–Meier analysis was used to estimate the time to discontinuation of the index DMT group (i.e. persistence). An unadjusted Cox regression model was performed to compare the risk of discontinuation across index DMT groups
- Marginal structural models were performed to estimate the effect of persistence on study outcomes while accounting for time-dependent confounders
 - Risk of relapse was defined as the annualised relapse rate (total number of relapses divided by the total person-years at risk). A marginal structural Poisson model, adjusted for time-dependent confounders, was used to estimate the effect of persistence on annualised relapse rate
 - Risk of 3-months confirmed disability progression (3mCDP) was defined as the presence of a 3mCDP (an increase in EDSS score of at least 1.0 if baseline EDSS score was 3.0–5.0, or of at least 0.5 if baseline EDSS score was 5.5–6.5, confirmed after at least 3 months). A marginal structural logistic model, adjusted for time-dependent confounders, was used to estimate the effect of persistence on the proportion of patients with 3mCDP
 - Risk of sick leave was defined as the presence of a sick leave day. A marginal structural logistic model, adjusted for time-dependent confounders, was used to estimate the effect of persistence on the proportion of patients with sick leave

Results

Baseline Characteristics of Patients With RRMS With 2 Years of Follow-Up

Characteristic	Overall (N=3,907)	OCR (n=103)	Injectable (n=984)	Oral (n=2,095)	Oral HA (n=581)	Other IV (n=144)
Age at index date,^a mean (SD), years	40.7 (10.9)	42.8 (11.6)	37.6 (11.1)	42.3 (10.7)	40.6 (10.3)	37.4 (9.0)
Females, n (%)	2,816 (72.1)	64 (62.1)	740 (75.2)	1,489 (71.1)	411 (70.7)	112 (77.8)
EDSS score at index date,^a mean (SD)	1.95 (1.6)	2.62 (1.8)	1.49 (1.3)	1.94 (1.5)	2.48 (1.6)	2.64 (1.8)
Number of relapses in 1 year before index date,^a mean (SD)	0.56 (0.7)	0.57 (0.7)	0.59 (0.7)	0.45 (0.6)	0.79 (0.8)	0.88 (0.8)
Time from date of diagnosis to index date,^a mean (SD), years	6.9 (7.1)	10.6 (8.5)	3.9 (5.8)	7.5 (7.2)	8.8 (6.9)	8.2 (6.2)

- A total of 3,907 patients with RRMS with 2 years of follow-up (OCR: 103; injectable: 984; oral HA: 581; oral: 2,095; other IV: 144) were included

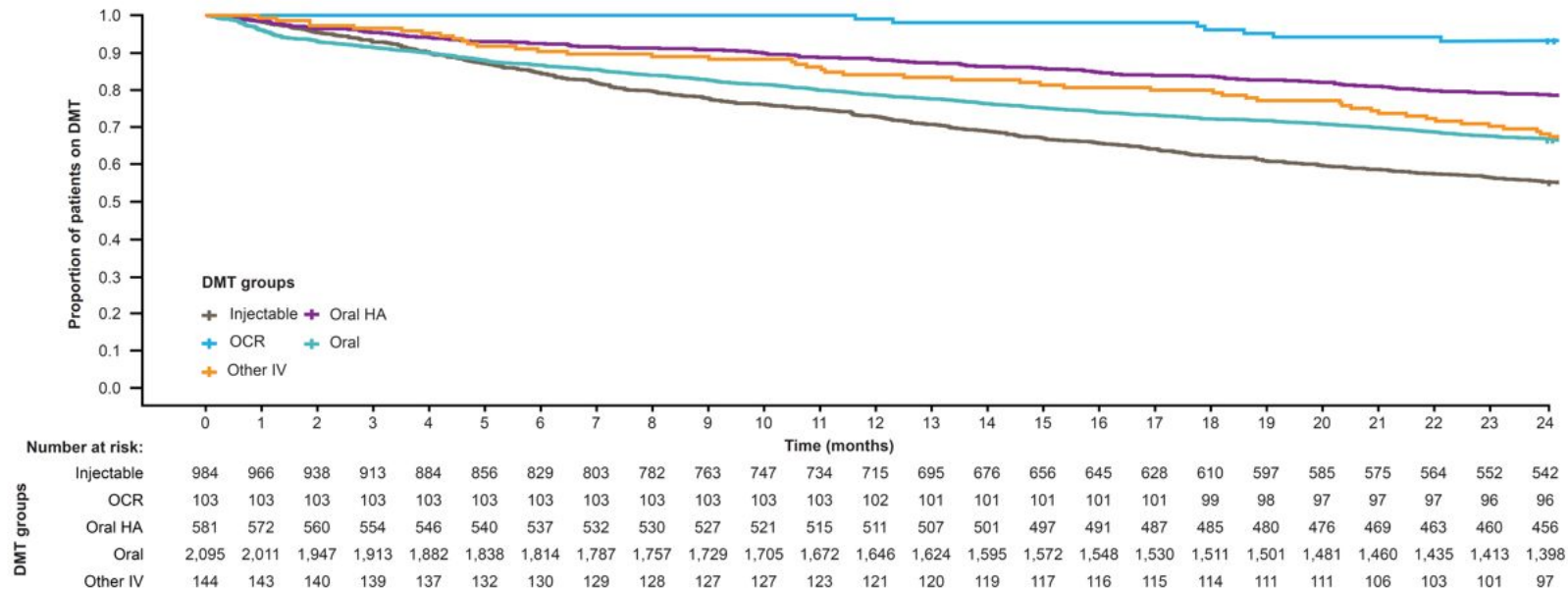
DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; HA, highly active disease; IV, intravenous; OCR, ocrelizumab; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation.

^aIndex date: Date of DMT initiation during the study period.

DMTs were grouped into the following categories: 1) OCR, 2) injectable (interferon β -1a/1b, glatiramer acetate), 3) oral (teriflunomide, dimethyl fumarate), 4) oral for highly active disease (oral HA; cladribine, fingolimod) and 5) other intravenous (other IV; natalizumab). Ozanimod, ponesimod, ofatumumab, diroximel fumarate and subcutaneous natalizumab were excluded due to insufficient follow-up.

Results

Persistence With Index DMT Group in Patients With RRMS Over 2 Years of Follow-Up



- OCR users had the highest persistence at 2 years (93%), followed by oral HA (78%), oral (67%), other IV (67%) and injectable (55%) therapies
 - Compared with OCR users, patients initiating injectable (hazard ratio [HR]: 8.51, 95% confidence interval [CI]: 4.03–17.90), oral (HR: 5.92, 95% CI: 2.81–12.50), oral HA (HR: 3.49, 95% CI: 1.63–7.48) and other IV (HR: 5.47, 95% CI: 2.47–12.10) therapies were more likely to discontinue within 2 years

DMT, disease-modifying therapy; HA, highly active disease; IV, intravenous; OCR, ocrelizumab; RRMS, relapsing-remitting multiple sclerosis.

DMTs were grouped into the following categories: 1) OCR, 2) injectable (interferon β -1a/1b, glatiramer acetate), 3) oral (teriflunomide, dimethyl fumarate), 4) oral for highly active disease (oral HA; cladribine, fingolimod) and 5) other intravenous (other IV; natalizumab). Ozanimod, ponesimod, ofatumumab, diroximel fumarate and subcutaneous natalizumab were excluded due to insufficient follow-up.

Results

Reasons for Discontinuation of Index DMT Group in Patients With RRMS During the 2-Year Follow-Up

Reason for discontinuation	Overall (N=3,907)	OCR (n=103)	Injectable (n=984)	Oral (n=2,095)	Oral HA (n=581)	Other IV (n=144)
Number of patients who discontinued, n (%)^a	1,318 (33.7)	7 (6.8)	442 (44.9)	697 (33.3)	125 (21.5)	47 (32.6)
Adverse events, n (%) ^b	428 (32.5)	0 (0.0)	126 (28.5)	262 (37.6)	37 (29.6)	3 (6.4)
Patient driven, n (%) ^b	260 (19.7)	0 (0.0)	86 (19.5)	143 (20.5)	17 (13.6)	14 (29.8)
Lack of efficacy, n (%) ^b	279 (21.2)	3 (42.9)	101 (22.9)	131 (18.8)	39 (31.2)	5 (10.6)
Pregnancy or child wish, n (%) ^b	132 (10.0)	2 (28.6)	64 (14.5)	48 (6.9)	13 (10.4)	5 (10.6)
Other, n (%) ^b	220 (16.7)	1 (14.3)	82 (18.6)	102 (14.6)	17 (13.6)	18 (38.3)
Unknown, n (%) ^b	23 (1.8)	1 (14.3)	7 (1.6)	11 (1.6)	2 (1.6)	2 (4.3)

- Overall, adverse events (32.5%), lack of efficacy (21.2%) and patient driven (19.7%) were the main reasons for discontinuation

DMT, disease-modifying therapy; HA, highly active disease; IV, intravenous; OCR, ocrelizumab; RRMS, relapsing-remitting multiple sclerosis.

^aPercentage was calculated among all patients; ^bPercentage was calculated among patients who discontinued.

DMTs were grouped into the following categories: 1) OCR, 2) injectable (interferon β -1a/1b, glatiramer acetate), 3) oral (teriflunomide, dimethyl fumarate), 4) oral for highly active disease (oral HA; cladribine, fingolimod) and 5) other intravenous (other IV; natalizumab). Ozanimod, ponesimod, ofatumumab, diroximel fumarate and subcutaneous natalizumab were excluded due to insufficient follow-up.

Results



- Compared with persisters, non-persisters at 2 years were associated with higher risk for relapse (rate ratio: 2.18, 95% CI: 1.98–2.39), 3mCDP (risk ratio: 1.52, 95% CI: 1.28–1.77) and sick leave (risk ratio: 1.71, 95% CI: 1.49–1.98) across index DMT groups
- Similar results were observed over 3 years of follow-up (**Supplementary Materials**)

Conclusions



- In a real-world setting, ocrelizumab users showed higher persistence compared with those taking other DMTs within 2 and 3 years of follow-up, and persistence was found to be associated with lower risk of clinical disease activity, disease progression and sick leave
- Our findings indicate that high persistence reflects better disease control

Supplementary Materials

Results

- A total of 3,216 patients with RRMS with 3 years of follow-up (OCR: 47; injectable: 806; oral: 1,771; oral HA: 477; other IV: 115) were included (**Table 1b**)
- OCR users had the highest persistence at 3 years (79%), followed by oral HA (73%), oral (59%), other IV (57%) and injectable (45%) (**Figure 1b**)
 - Compared with OCR users, patients initiating injectable (HR: 3.5, 95% CI: 1.9–6.5), oral (HR: 2.3, 95% CI: 1.3–4.4), oral HA (HR: 1.4, 95% CI: 0.7–2.6) and other IV (HR: 2.3, 95% CI: 1.2–4.5) were more likely to discontinue at 3 years
- Overall, adverse events (29.4%), lack of efficacy (23.4%) and patient driven (20.4%) were the main reasons for discontinuation (**Table 2b**)
- Compared with persisters, non-persisters at 3 years were associated with higher risk of relapse (risk ratio: 2.0, 95% CI: 1.8–2.2), 3mCDP (risk ratio: 1.5, 95% CI: 1.3–1.6) and sick leave (risk ratio: 1.8, 95% CI: 1.5–2.0) across index DMT groups

Results

Table 1b. Baseline characteristics of patients with RRMS with 3 years of follow-up

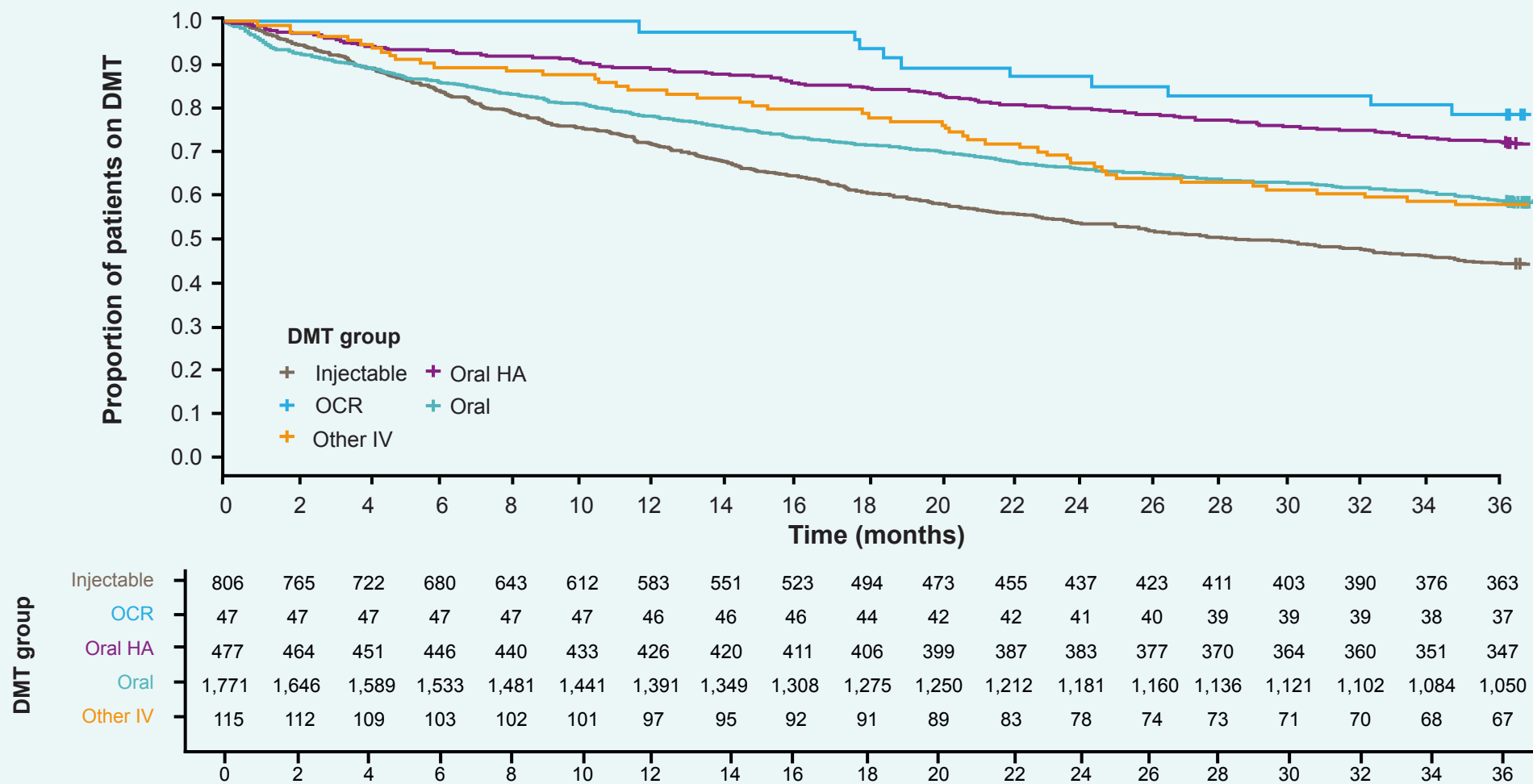
Characteristic	Overall (N=3,216)	OCR (n=47)	Injectable (n=806)	Oral (n=1,771)	Oral HA (n=477)	Other IV (n=115)
Age at index date, ^a mean (SD), years	40.9 (10.9)	43.4 (11.6)	37.9 (11.4)	42.4 (10.5)	40.8 (10.4)	37.6 (8.7)
Females, n (%)	2,311 (71.9)	33 (70.2)	611 (75.8)	1,252 (70.7)	330 (69.2)	85 (73.9)
EDSS score at index date, ^a mean (SD)	1.98 (1.6)	2.43 (1.9)	1.53 (1.3)	1.99 (1.5)	2.52 (1.6)	2.69 (1.9)
Number of relapses in 1 year before index date, ^a mean (SD)	0.57 (0.71)	0.60 (0.68)	0.60 (0.68)	0.46 (0.65)	0.83 (0.82)	0.92 (0.86)
Time from date of diagnosis to index date, ^a mean (SD), years	7.0 (7.1)	9.9 (9.1)	4.0 (5.9)	7.8 (7.3)	8.6 (6.9)	8.4 (6.4)

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; HA, highly active disease; IV, intravenous; OCR, ocrelizumab; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation. DMTs were grouped into the following categories: 1) OCR; 2) injectable (interferon β -1a/1b, glatiramer acetate); 3) oral (teriflunomide, dimethyl fumarate); 4) oral HA (cladribine, fingolimod) and 5) other IV (natalizumab). Ozanimod, ponesimod, ofatumumab, diroximel fumarate and subcutaneous natalizumab were excluded due to insufficient follow-up.

^aIndex date: Date of DMT initiation during the study period.

Results

Figure 1b. Persistence to index DMT group in patients with RRMS over 3 years of follow-up



DMT, disease-modifying therapy; HA, highly active disease; IV, intravenous; OCR, ocrelizumab; RRMS, relapsing-remitting multiple sclerosis. DMTs were grouped into the following categories: 1) OCR; 2) injectable (interferon β -1a/1b, glatiramer acetate); 3) oral (teriflunomide, dimethyl fumarate); 4) oral HA (cladribine, fingolimod) and 5) other IV (natalizumab). Ozanimod, ponesimod, ofatumumab, diroximel fumarate and subcutaneous natalizumab were excluded due to insufficient follow-up.

Results

Table 2b. Patients with RRMS who discontinued their index DMT group during the 3-year follow-up

Reason for discontinuation	Overall (N=3,216)	OCR (n=47)	Injectable (n=806)	Oral (n=1,771)	Oral HA (n=477)	Other IV (n=115)
Number of patients who discontinued, n (%) ^a	1,352 (42.0)	10 (21.3)	443 (55.0)	721 (40.7)	130 (27.3)	48 (41.7)
Adverse events, n (%) ^b	398 (29.4)	0 (0)	120 (27.1)	249 (34.5)	25 (19.2)	4 (8.3)
Patient driven, n (%) ^b	276 (20.4)	1 (10.0)	88 (19.9)	153 (21.2)	19 (14.6)	15 (31.2)
Lack of efficacy, n (%) ^b	317 (23.4)	3 (30.0)	106 (23.9)	149 (20.7)	53 (40.8)	6 (12.5)
Pregnancy or child wish, n (%) ^b	141 (10.4)	1 (10.0)	65 (14.7)	52 (7.2)	16 (12.3)	7 (14.6)
Other, n (%) ^b	220 (16.3)	3 (30.0)	81 (18.3)	107 (14.8)	16 (12.3)	13 (27.1)
Unknown, n (%) ^b	23 (1.7)	2 (20.0)	6 (1.4)	11 (1.5)	1 (0.8)	3 (6.3)

DMT, disease-modifying therapy; HA, highly active disease; IV, intravenous; OCR, ocrelizumab; RRMS, relapsing-remitting multiple sclerosis.
DMTs were grouped into the following categories: 1) OCR; 2) injectable (interferon β -1a/1b, glatiramer acetate); 3) oral (teriflunomide, dimethyl fumarate); 4) oral HA (cladribine, fingolimod) and 5) other IV (natalizumab). Ozanimod, ponesimod, ofatumumab, diroximel fumarate and subcutaneous natalizumab were excluded due to insufficient follow-up.
^aPercentage was calculated among all patients; ^bPercentage was calculated among patients who discontinued.



<https://ter.li/lal929>

Reduction of Intrathecal Immunoglobulin Levels With Ocrelizumab Treatment in Relapsing and Primary Progressive Multiple Sclerosis

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Disclosures

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Objective



To evaluate the longitudinal dynamics of cerebrospinal fluid (CSF) immunoglobulin (Ig)M, IgG, IgA and κ and λ free light chain (KFLC and LFLC) levels following ocrelizumab treatment in people with relapsing MS (pwRMS) or primary progressive MS (pwPPMS) from the OBOE (Ocrelizumab Biomarker Outcome Evaluation) study (NCT02688985)

Results

At Baseline, IgG and KFLC Indices Were Elevated in PwRMS and PwPPMS Relative to Reference Ranges^a

Immunoglobulin index, median (IQR)	Reference interval or cutoff value	RMS (n=93)	PPMS (n=29)	P value
CSF IgG	0.0–0.7^b	0.79 (0.63–1.28)	0.94 (0.74–1.32)	0.34
CSF IgM ^c		0.16 (0.10–0.29)	0.06 (0.04–0.16)	<0.001
CSF IgA ^c		0.32 (0.28–0.39)	0.27 (0.24–0.36)	0.02
KFLC	<6.6^{d,e}	12.5 (4.49–41.7)	27.0 (11.7–48.7)	0.04
LFLC	<6.9 ^{d,e}	3.51 (0.81–7.95)	2.59 (0.58–14.9)	0.98

CSF, cerebrospinal fluid; Ig, immunoglobulin; KFLC, κ free light chain; LFLC, λ free light chain; PPMS, primary progressive multiple sclerosis; pwPPMS, people with primary progressive multiple sclerosis; pwRMS, people with relapsing multiple sclerosis; RMS, relapsing multiple sclerosis.

^aP values compare pwRMS vs pwPPMS and were reported from Kruskal-Wallis analysis of variance test and unadjusted.

^bLabCorp, Accessed 21 August 2023. https://files.labcorp.com/testmenu-d8/sample_reports/002238.pdf

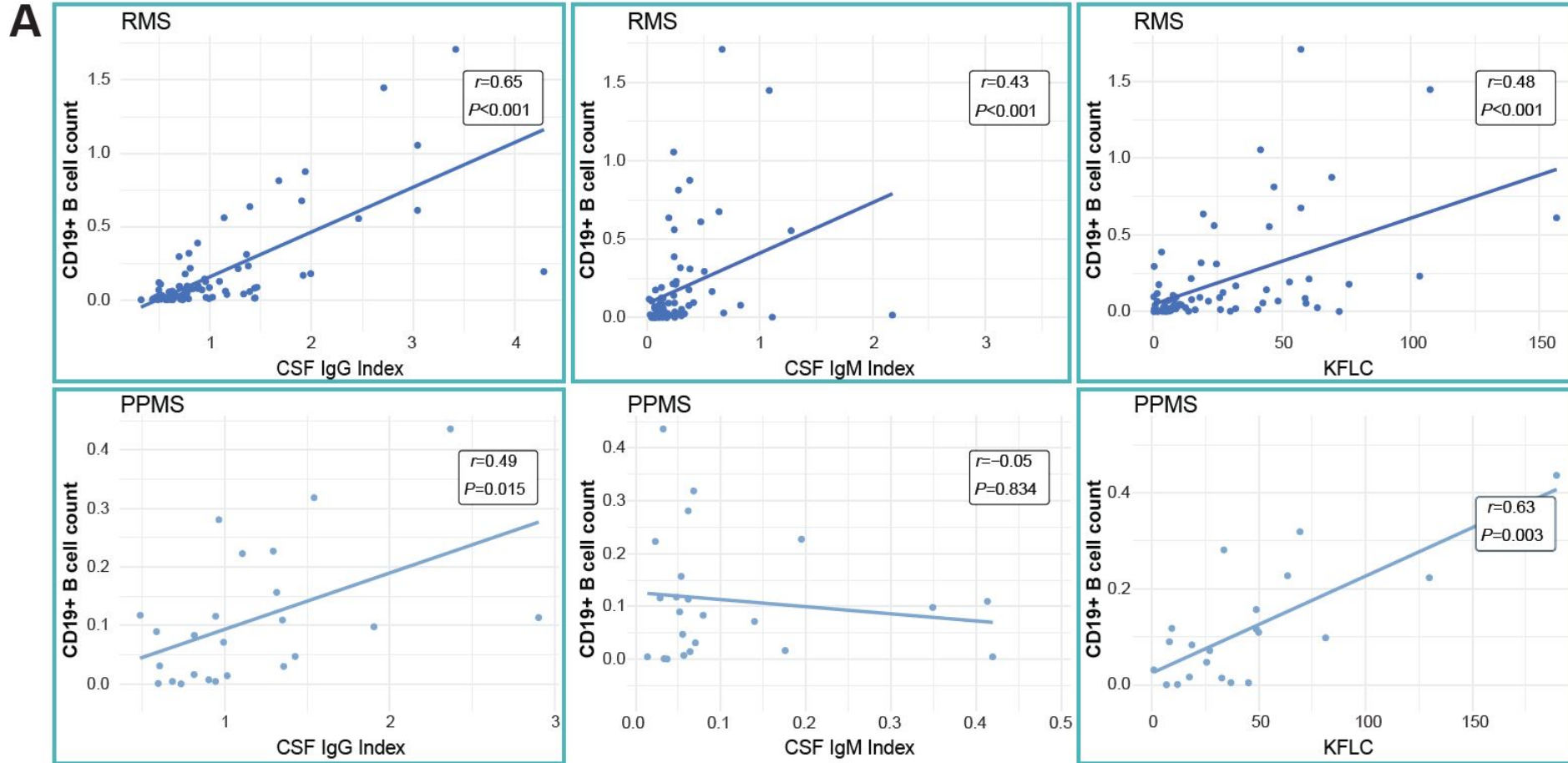
^cNormative reference values are not well characterized.

^dBerek K, et al. *Neuroimmunol Neuroinflamm* 2021;8(4):e1005.

^eIndex values below these cutoffs denote the absence of intrathecal synthesis.

Results

CSF IgG, CSF IgM and KFLC Indices Correlate With CSF B-Cell Levels at Baseline^a

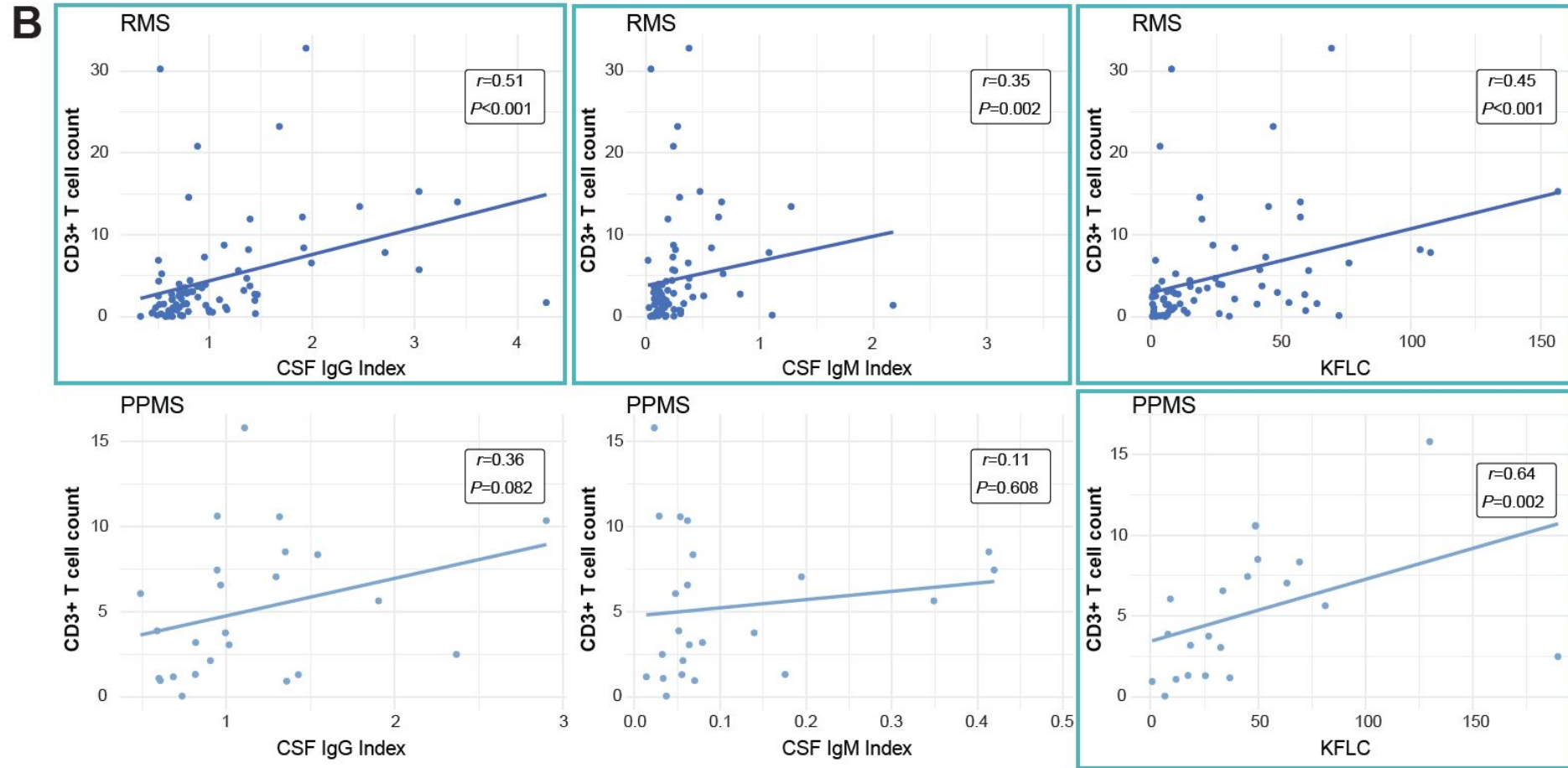


CSF, cerebrospinal fluid; Ig, immunoglobulin; KFLC, κ free light chain; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis.

^aCorrelations with CSF B cells and T cells are significant in the combined RMS and PPMS cohort (plots for separate cohorts are shown). Teal boxes indicate correlations with $P < 0.05$.

Results

CSF IgG, CSF IgM and KFLC Indices Correlate With CSF T-Cell Levels at Baseline^a

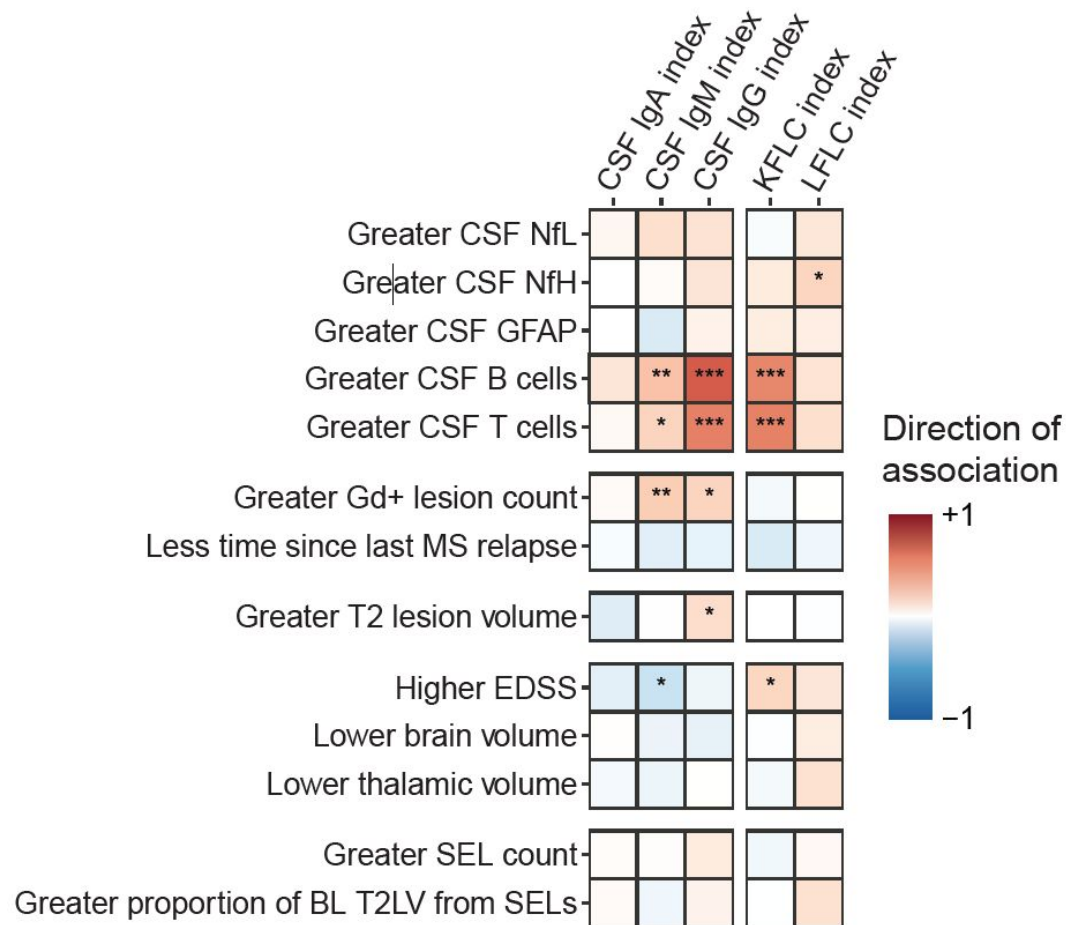


CSF, cerebrospinal fluid; Ig, immunoglobulin; KFLC, κ free light chain; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis.

^aCorrelations with CSF B cells and T cells are significant in the combined RMS and PPMS cohort (plots for separate cohorts are shown). Teal boxes indicate correlations with $P < 0.05$.

Results

IgG and IgM Indices Correlated With Gd+ Lesion Count, IgG Index Correlated With T2LV and KFLC Index Correlated With EDSS in the OBOE Cohort at Baseline^a



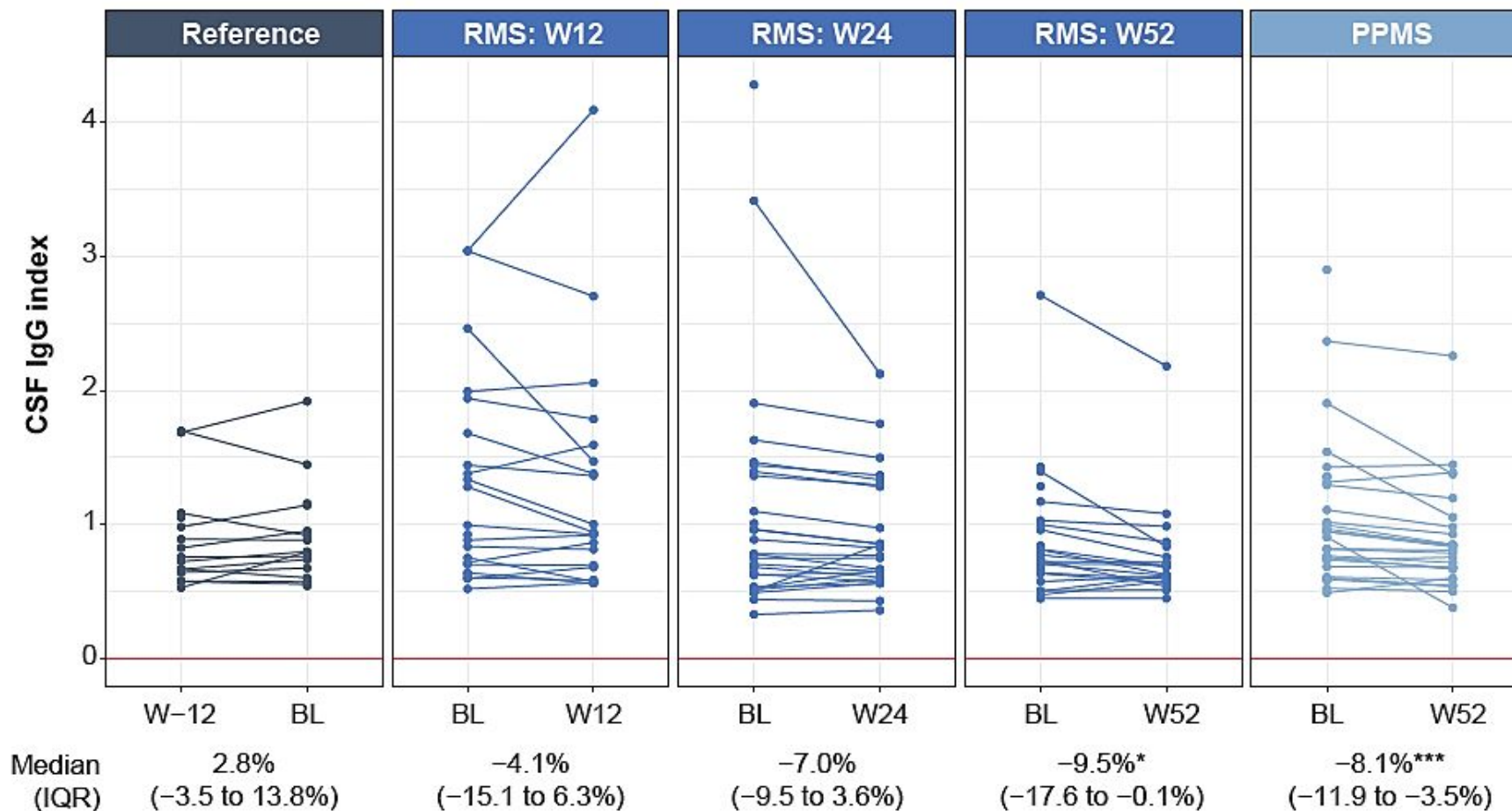
BL, baseline; CSF, cerebrospinal fluid; EDSS, Expanded Disability Status Scale; FDR, false discovery rate; Gd+, gadolinium enhancing; GFAP, glial fibrillary acidic protein; Ig, immunoglobulin; KFLC, κ free light chain; LFLC, λ free light chain; MS, multiple sclerosis; NfH, neurofilament heavy chain; NfL, neurofilament light chain; RMS, relapsing multiple sclerosis; SEL, slowly expanding lesion; T2LV, T2 lesion volume.

^aFDR was calculated for the included CSF biomarkers and clinical readouts, and direction of association was reported when FDR was ≤0.05.

* $P < 0.05$. ** $P < 0.01$. *** $P < 0.001$.

Results

Significant Reductions Were Observed in CSF IgG Index at Week 52 in PwRMS and PwPPMS Following Ocrelizumab Treatment^a



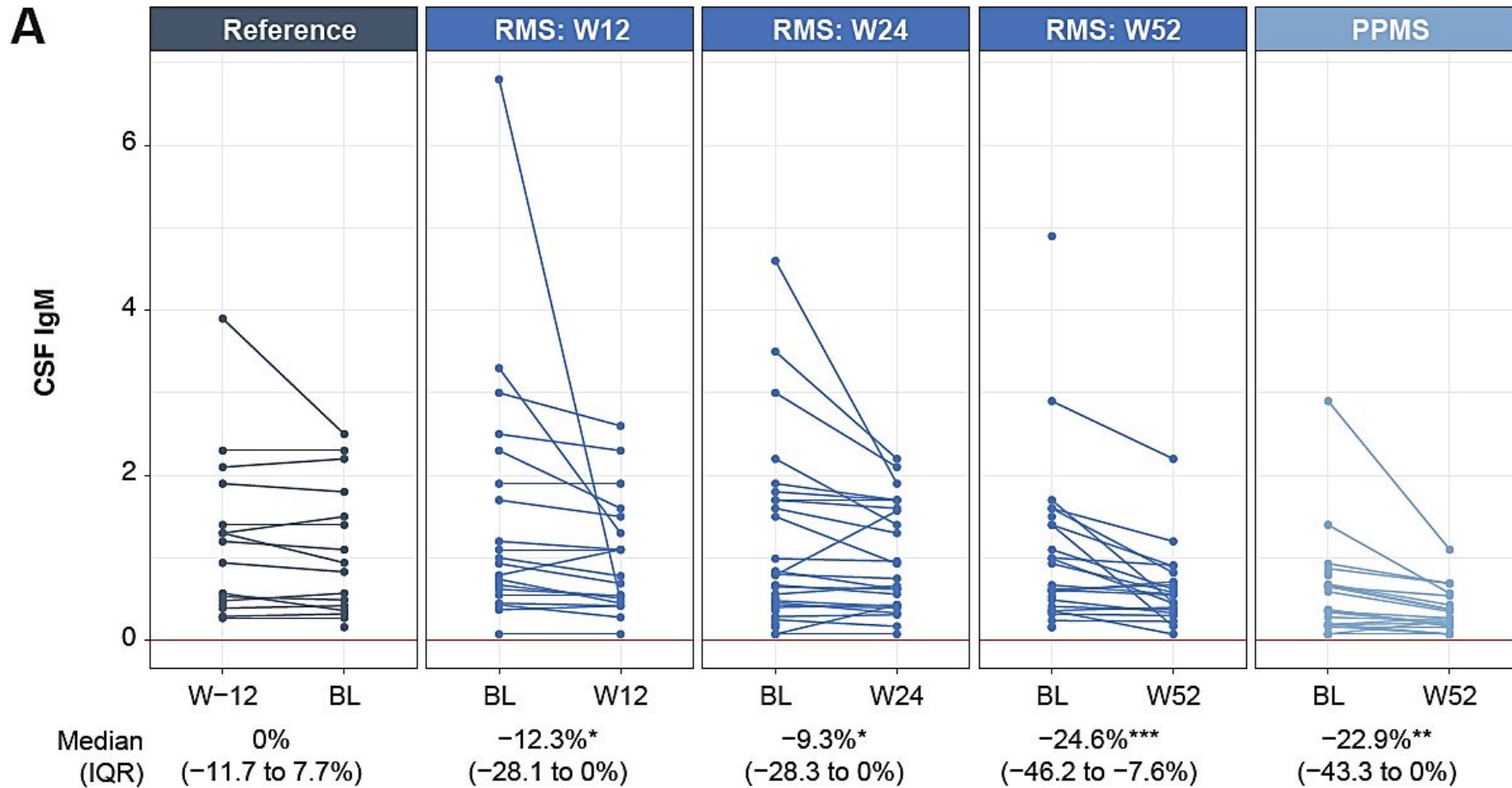
BL, baseline; CSF, cerebrospinal fluid; Ig, immunoglobulin; PPMS, primary progressive multiple sclerosis; pwPPMS, people with primary progressive multiple sclerosis; pwRMS, people with relapsing multiple sclerosis; RMS, relapsing multiple sclerosis; W, week.

^a Median percent change from baseline (IQR).

*Wilcoxon *P* value percent change from baseline, *P* ≤ 0.05. ***Wilcoxon *P* value percent change from baseline, *P* ≤ 0.001.

Results

Significant Reductions Were Observed in CSF IgM Levels in PwRMS and PwPPMS Following Ocrelizumab Treatment^a



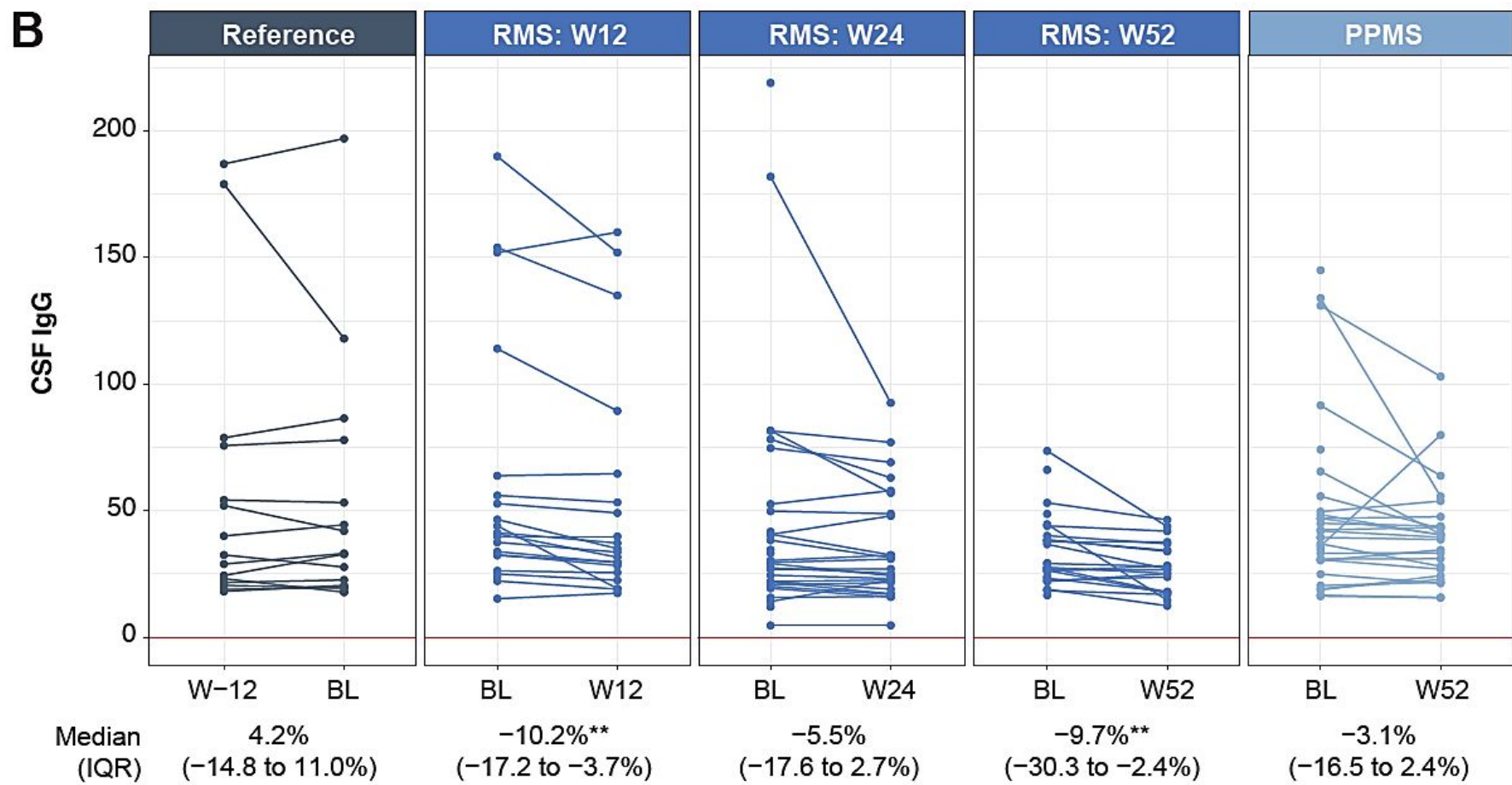
BL, baseline; CSF, cerebrospinal fluid; Ig, immunoglobulin; PPMS, primary progressive multiple sclerosis; pwPPMS, people with primary progressive multiple sclerosis; pwRMS, people with relapsing multiple sclerosis; RMS, relapsing multiple sclerosis; W, week.

^a Median percent change from baseline (IQR).

*Wilcoxon *P* value % change from baseline, $P \leq 0.05$. **Wilcoxon *P* value % change from baseline, $P \leq 0.01$. ***Wilcoxon *P* value % change from baseline, $P \leq 0.001$.

Results

Significant Reductions Were Observed in CSF IgG Levels in PwRMS and PwPPMS Following Ocrelizumab Treatment^a



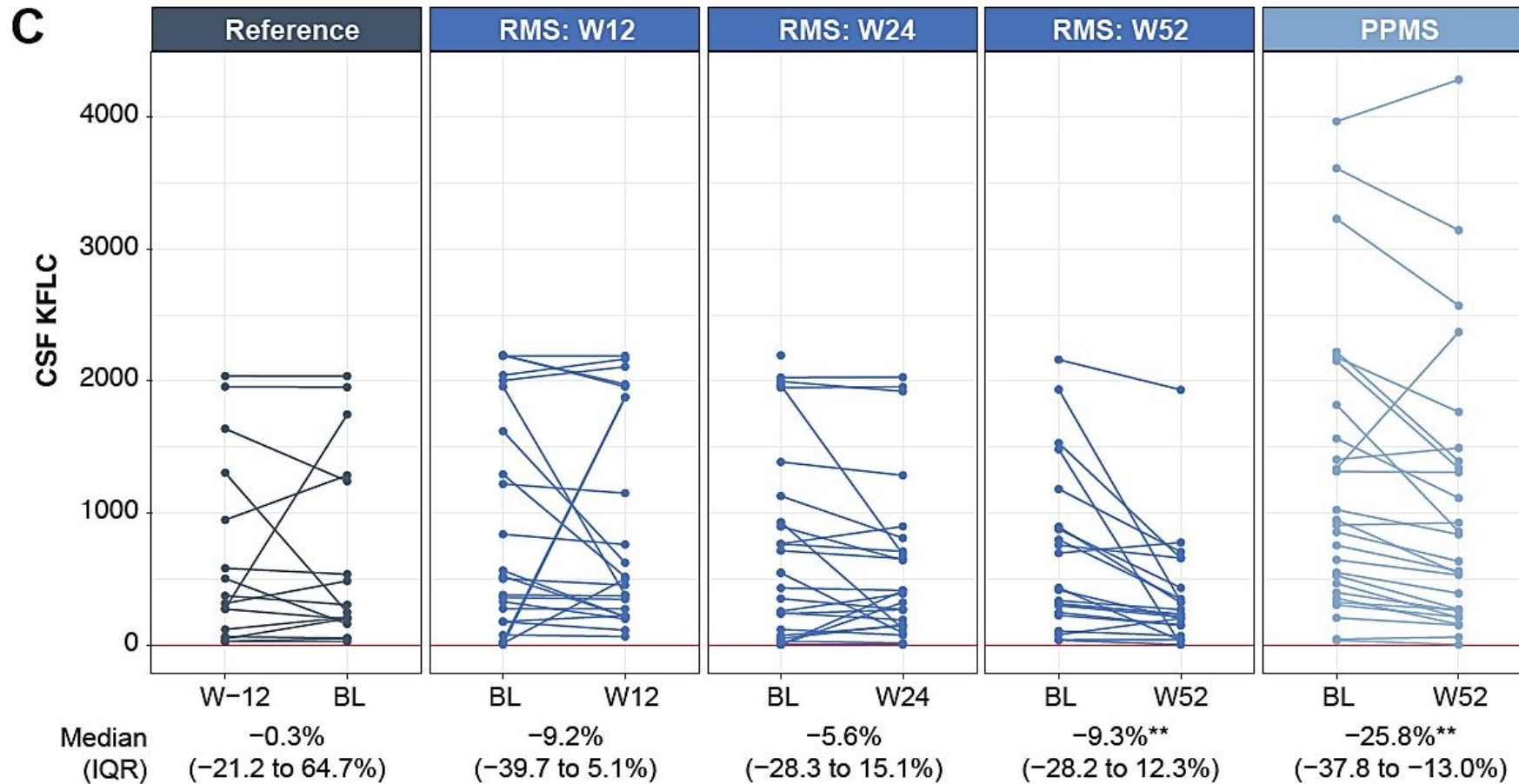
BL, baseline; CSF, cerebrospinal fluid; Ig, immunoglobulin; PPMS, primary progressive multiple sclerosis; pwPPMS, people with primary progressive multiple sclerosis; pwRMS, people with relapsing multiple sclerosis; RMS, relapsing multiple sclerosis; W, week.

^a Median percent change from baseline (IQR).

*Wilcoxon *P* value % change from baseline, *P*≤0.05. **Wilcoxon *P* value % change from baseline, *P*≤0.01. ***Wilcoxon *P* value % change from baseline, *P*≤0.001.

Results

Significant Reductions Were Observed in CSF KFLC Levels in PwRMS and PwPPMS Following Ocrelizumab Treatment^a



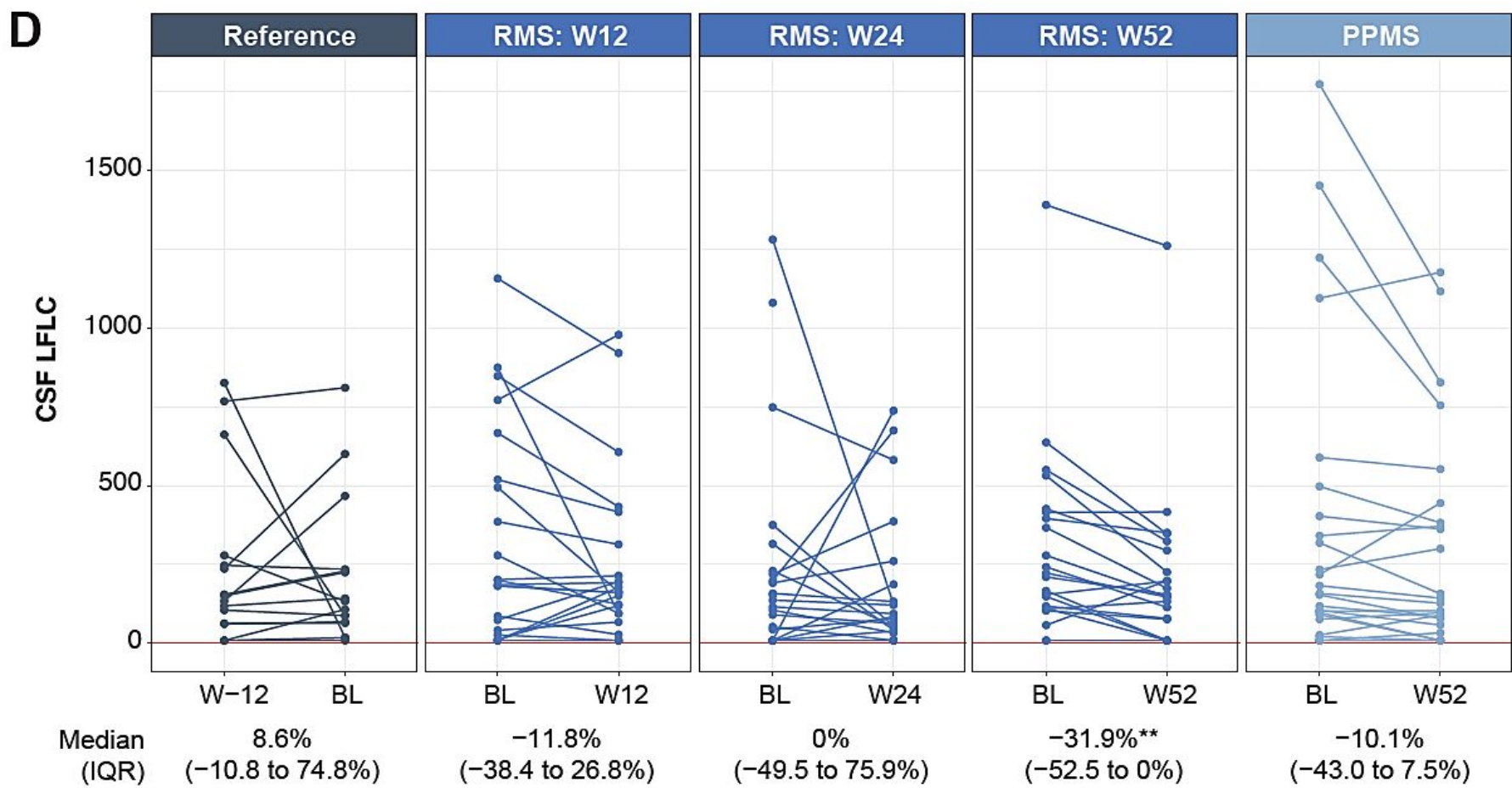
BL, baseline; CSF, cerebrospinal fluid; KFLC, κ free light chain; PPMS, primary progressive multiple sclerosis; pwPPMS, people with primary progressive multiple sclerosis; pwRMS, people with relapsing multiple sclerosis; RMS, relapsing multiple sclerosis; W, week.

^a Median percent change from baseline (IQR).

*Wilcoxon P value % change from baseline, $P \leq 0.05$. **Wilcoxon P value % change from baseline, $P \leq 0.01$. ***Wilcoxon P value % change from baseline, $P \leq 0.001$.

Results

Significant Reductions Were Observed in CSF LFLC Levels in PwRMS and PwPPMS Following Ocrelizumab Treatment^a



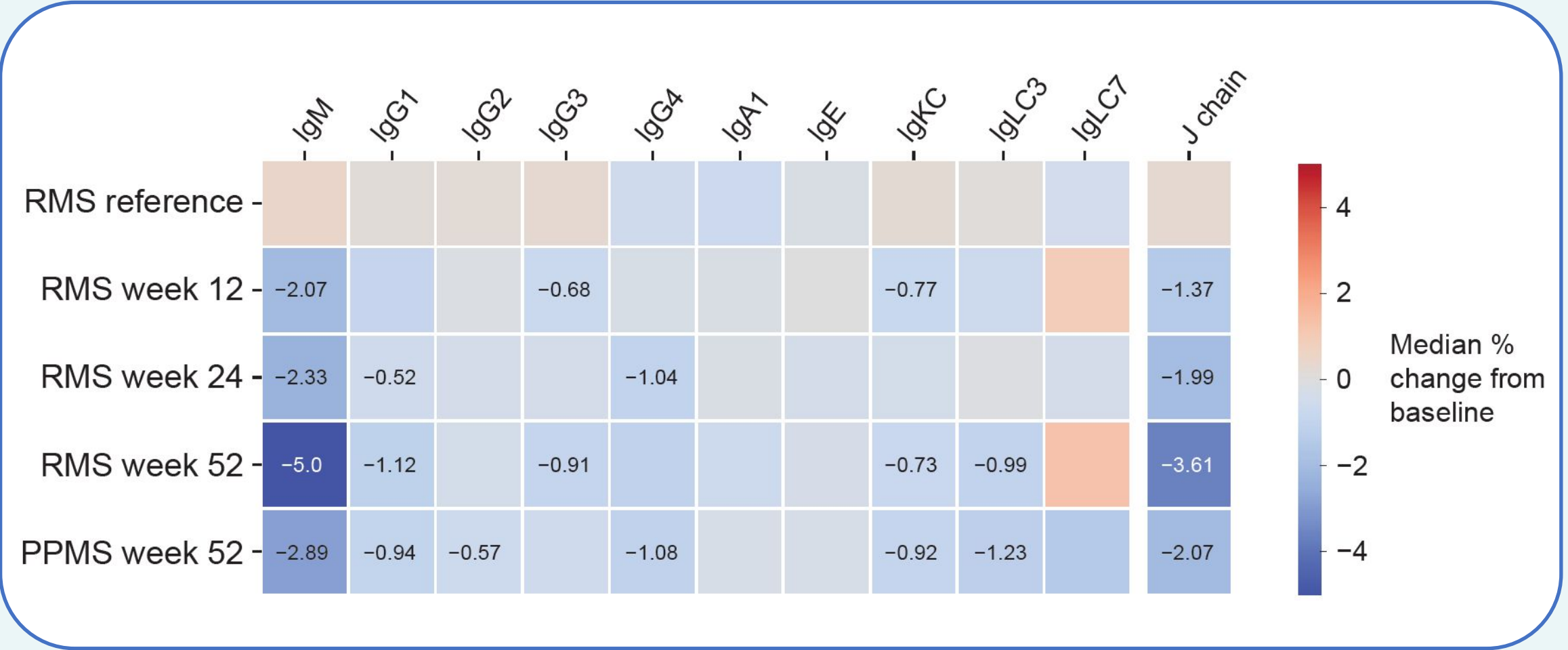
BL, baseline; CSF, cerebrospinal fluid; LFLC, λ free light chain; PPMS, primary progressive multiple sclerosis; pwPPMS, people with primary progressive multiple sclerosis; pwRMS, people with relapsing multiple sclerosis; RMS, relapsing multiple sclerosis; W, week.

^a Median percent change from baseline (IQR).

*Wilcoxon P value % change from baseline, $P \leq 0.05$. **Wilcoxon P value % change from baseline, $P \leq 0.01$. ***Wilcoxon P value % change from baseline, $P \leq 0.001$.

Results

CSF Proteomics Confirmed Reductions in IgG, IgM, KFLC and LFLC Levels in PwRMS and PwPPMS at Week 52 Following Ocrelizumab Treatment^a



CSF, cerebrospinal fluid; FDR, false discovery rate; Ig, immunoglobulin; KFLC, κ free light chain; LFLC, λ free light chain; PPMS, primary progressive multiple sclerosis; pwPPMS, people with primary progressive multiple sclerosis; pwRMS, people with relapsing multiple sclerosis; RMS, relapsing multiple sclerosis.

^aImmunoglobulin constant region proteins are shown. FDR was calculated for the included Ig genes, and median percent changes from baseline were included when FDR was ≤0.05.

Conclusions



Baseline CSF IgG and IgM indices correlated with CSF levels of B and T cells and Gd+ lesions; T2 lesion volume correlated with baseline IgG index; and KFLC index correlated with CSF B and T cells and EDSS



Moderate but significant reductions were observed in CSF IgG index and CSF levels of IgG, IgM, KFLC and LFLC in pwRMS and/or pwPPMS at Week 52 following ocrelizumab treatment



These data suggest that ocrelizumab impacts central nervous system-compartmentalized inflammation and CSF Ig production in both RMS and PPMS, a hallmark of MS¹ not previously thought to be affected by B-cell-depletion therapy



These 1-year observations require confirmation with longer-term data, oligoclonal band analysis and correlation with clinical response

Supplementary Material

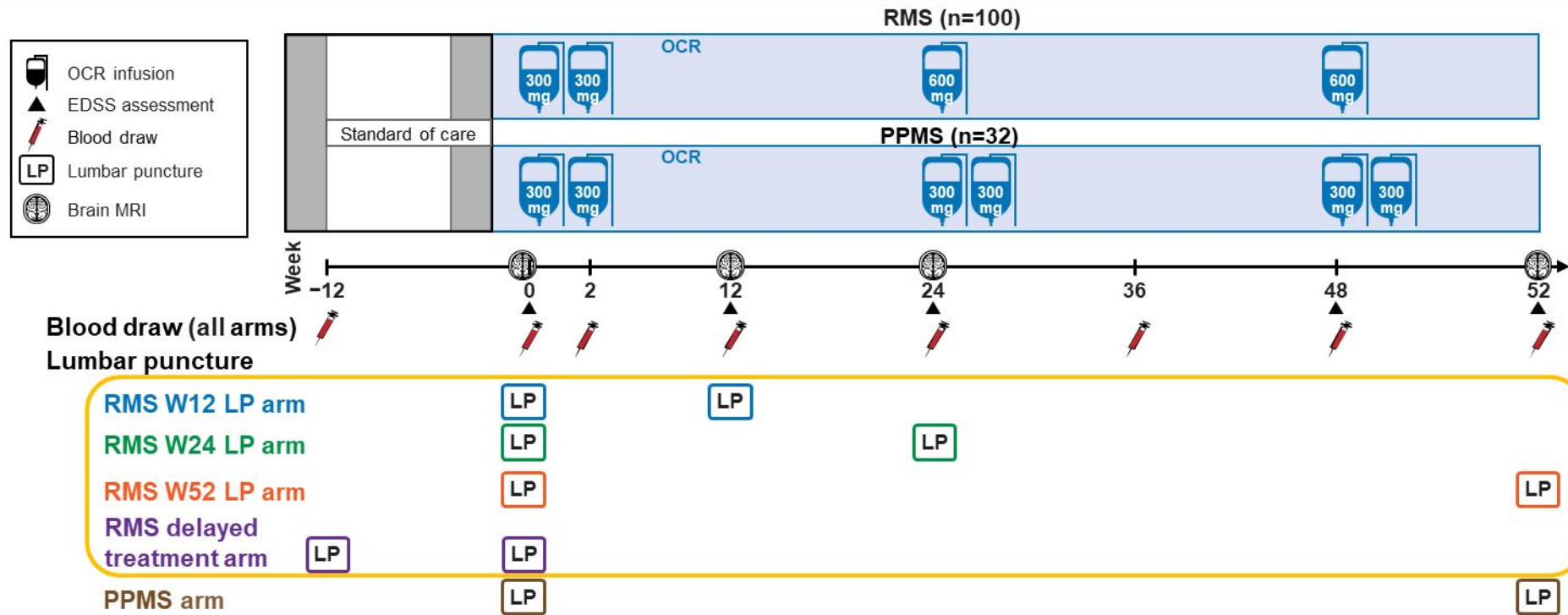
Background



- Reduction or loss of CSF oligoclonal bands in pwMS following ocrelizumab treatment has been reported¹
- CSF levels of Igs, including KFLC, are elevated in MS² and may have utility in assessing the impact of systemically administered anti-CD20 therapy

Supplemental Figure 1

OBOE Study Design



- Paired CSF and serum samples from 93 pwRMS and 29 pwPPMS were assessed by ELISA for IgM, IgG, IgA, KFLC and LFLC levels at baseline and indicated study weeks when LP occurred

Supplemental Table 1

OBOE Baseline Demographic and Clinical Characteristics

Characteristic	RMS cohort					PPMS cohort
	Control arm (n=18)	Week 12 LP arm (n=23)	Week 24 LP arm (n=31)	Week 52 LP arm (n=28)	Pooled RMS arms (n=100)	Week 52 LP arm (n=31)
Age, mean (SD), years	36.4 (9.8)	36.0 (10.4)	38.7 (10.4)	34.6 (10.8)	36.6 (10.4)	44.9 (7.4)
Sex, %						
Female	61	65	71	71	68	48
Male	39	35	29	29	32	52
Race, %						
Asian	5.6	0	0	3.6	2	3.2
Black or African American	16.7	8.7	9.7	3.6	9	0
White	72.2	91.3	90.3	89.3	87	93.5
Multiple	5.6	0	0	0	1	0
Unknown	0	0	0	3.6	1	3.2
DMT status, %						
Previous treatment	56	35	39	39	41	26
Previously untreated	44	65	61	61	59	74
Last DMT before study entry, %^a						
Interferons	30	37.5	50	54.5	43.9	37.5
Dimethyl fumarate	20	12.5	8.3	9.1	12.2	0
Fingolimod	20	12.5	0	0	7.3	0
Glatiramer acetate	30	37.5	33.3	36.4	34.1	62.5
Teriflunomide	0	0	8.3	0	2.4	0
EDSS at screening, mean (SD)	2.14 (0.61)	2.61 (1.18)	2.39 (1.45)	2.25 (1.21)	2.36 (1.20)	4.15 (1.05)
Patients with relapse as only qualifying event, %	67	39	36	36	42	..
Patients with >1 relapse in the past 12 months out of patients enrolled due to relapse, n/N (%)	6/14 (42.9)	1/21 (4.8)	4/24 (16.7)	2/24 (8.3)	13/83 (15.7)	..
Patients with Gd+ lesions, %	61.1	43.5	32.3	39.3	42	22.6
No. of Gd+ lesions, mean (SD)	2.0 (3.3)	8.8 (17.6)	2.4 (6.4)	1.6 (3.7)	3.6 (9.8)	0.7 (2.4)
T2w lesion volume, mean (SD), mL	9.6 (10.7)	12.0 (12.0)	15.2 (18.5)	5.6 (5.0)	10.8 (13.3)	13.5 (16.8)
Normalized brain volume, mean (SD) cm³	1421.2 (59.5)	1445.3 (78.9)	1420.5 (61.9)	1452.1 (71.6)	1435.0 (68.9)	1409.3 (41.62)
Years since diagnosis, mean (SD)	6.3 (9.8)	3.3 (6.8)	3.5 (5.6)	3.0 (5.7)	3.8 (6.8)	1.6 (2.3)
Baseline serum NfL, mean (SD), pg/mL	18.2 (24.8)	20.3 (20.2)	14.8 (12.1)	12.8 (9.6)	16.1 (16.5)	12.0 (9.0)
No. of baseline T2w lesions that develop into SEL, mean (SD)	4.5 (5.5)	4.9 (5.3)	7.6 (11.7)	2.7 (4.7)	5.1 (7.9)	7.8 (9.9)
SEL proportion of baseline T2 lesion volume, mean (SD)	0.10 (0.05)	0.06 (0.05)	0.09 (0.07)	0.07 (0.06)	0.08 (0.06)	0.11 (0.09)

DMT, disease modifying therapy; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; LP, lumbar puncture; NfL, neurofilament light chain; OCR, ocrelizumab; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; T2w, T2 weighted.

^aOnly includes patients that were previously treated.

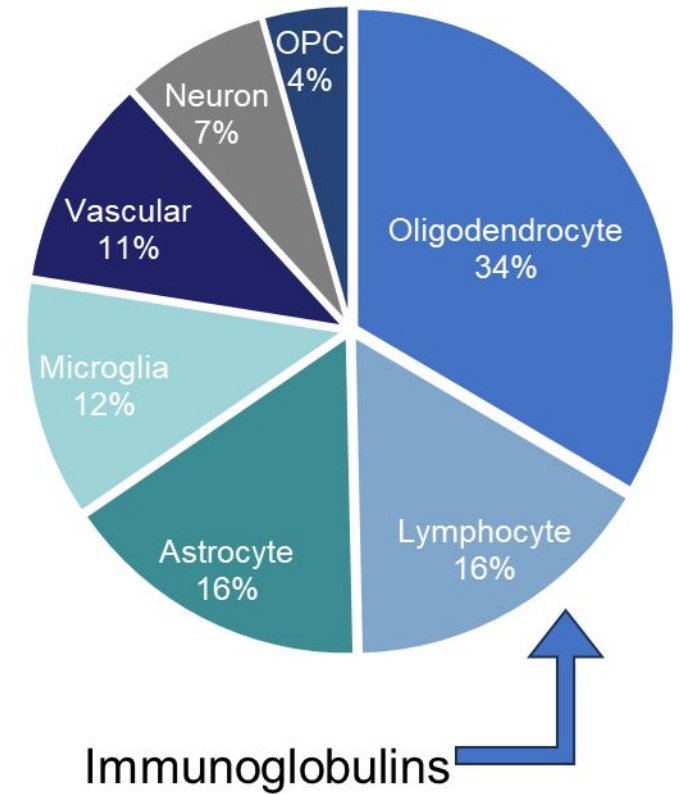


- CSF proteins were analyzed using label-free DIA nano-liquid chromatography tandem mass spectrometry
- Final protein abundances were generated using Spectronaut, MSstats and a CSF-specific spectral library
- All immunoglobulin constant region proteins identified were included in the analysis
- Baseline associations in the combined OBOE cohort were analyzed by Spearman correlation analysis
- Comparisons of pre vs post treatment CSF protein levels were performed by paired Mann-Whitney U test
- All statistical tests were adjusted for multiple testing using Benjamini-Hochberg procedure (FDR<0.05)

Supplemental Figure 2

DIA Mass Spectrometry of CSF Identified 1583 Proteins, 709 of Which Were Mapped to CNS Cell Types

- CSF proteins were analyzed using label-free DIA nano-liquid chromatography tandem mass spectrometry
- Final protein abundances were generated using Spectronaut, MSstats and a CSF-specific spectral library



Supplemental Figure 3

CSF Proteomics Confirmed Baseline Correlations Between IgG and IgM Levels With Gd+ Lesion Count and Between IgG Levels and T2LV^a





<https://ter.li/bmz1mw>

Subcutaneous Ocrelizumab in Patients with Multiple Sclerosis: Results of the Phase Ib Dose-Finding OCARINA I study

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Wednesday, 11 October 2023

Disclosures

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Background and Objective

- 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 >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 offers a choice of administration route and site of patient care, and could deliver clinical benefit, significantly reduced time and treatment burden, and improved resource use^{7,8}



The objective of OCARINA I (NCT03972306) was to select the appropriate OCR SC dose for use in the Phase III OCARINA II trial, based on safety, tolerability and PK data in PwRMS or PwPPMS

IV, intravenous; OCR, ocrelizumab; PK, pharmacokinetic; PwPPMS, people with primary progressive multiple sclerosis; PwRMS, people with relapsing multiple sclerosis;; SC, subcutaneous.

^aIn combination 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 large volume and rapid delivery of SC-administered drugs.

1. OCREVUS [ocrelizumab] Full Prescribing Information. Genentech, Inc., 2020; 2. OCREVUS [ocrelizumab] Summary of Product Characteristics. Roche Pharma AG, 2020;

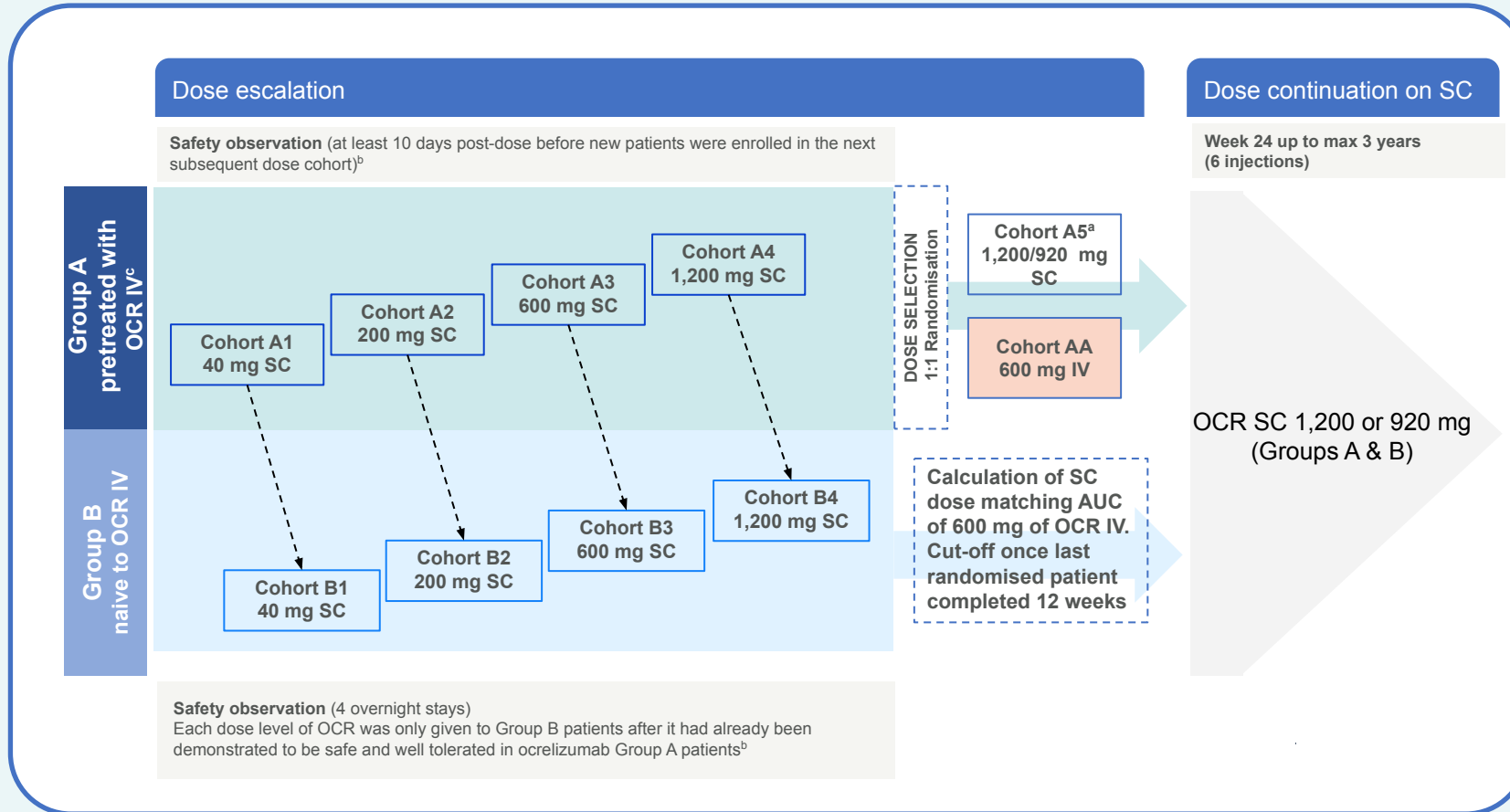
3. Hauser SL, *et al. Neurology* 2020;95(13):e1854–e1867; 4. Wolinsky JS, *et al. Lancet Neurol* 2020;19:998–1009; 5. Kappos L, *et al.ECTRIMS-ACRIMS* 2023;Poster P302;

6. Roche data on file; 7. ClinicalTrials.gov. <https://classic.clinicaltrials.gov/ct2/show/NCT03972306>. Updated 25 July 2023. Accessed 25 August 2023;

8. ClinicalTrials.gov. <https://classic.clinicaltrials.gov/ct2/show/NCT05232825>. Updated 25 July 2023. Accessed 25 July 2023.

Methods

OCARINA I Study Design



- A dose escalation approach was chosen to ensure the safety of all patients participating in the study. Assuming a bioavailability of 50%, 1,200 mg OCR SC would provide similar exposure to the approved OCR IV 600 mg dose.

AUC, area under the serum concentration–time curve; CCOD, clinical cut-off date; IV, intravenous; OCR, ocrelizumab; PK, pharmacokinetic; SC, subcutaneous; SMC, Safety Monitoring Committee.

^aPatients were initially randomised to Cohort A5 to receive 1,200 mg SC. An analysis of preliminary PK data from patients with at least 12 weeks of observation time indicated that a lower 920 mg OCR SC dose was more likely to meet the criteria for equivalent exposure to OCR 600 mg IV, based on the estimated bioavailability. To confirm this assumption, SMC recommended dose de-escalation from 1,200 mg SC to 920 mg SC; consequently, all newly randomised patients in Cohort A5 were treated with 920 mg OCR SC. Thus, some patients received 1,200 mg and 920 mg, while others received 920 mg only; ^bIn addition to the close safety observation at site, patients continued to be observed for safety throughout the study and could report AEs at any time, as well as have periodic laboratory analyses performed;

^cPatients in Group A were treated with OCR IV for at least 1 year (two 600 mg OCR doses separated by 24 weeks).

Methods

Patient Population and Study Objectives

PATIENT POPULATION

RMS or PPMS
(McDonald 2017)⁹

Age 18–65 years, inclusive

Disease duration from onset
of MS symptoms <15 years

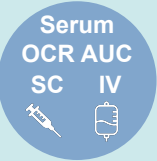
EDSS 0.0–6.5 inclusive^a

Group A: Patients pretreated
with OCR IV for ≥1 year prior to
screening

Group B: Patients who are
treatment naive to OCR or
other B-cell depleting drugs

STUDY OBJECTIVES

PK



Compare PK of OCR SC with OCR IV (area under the concentration–time curve)

Safety



Evaluate and compare the safety and tolerability profile following administration of OCR SC and 600 mg OCR IV in patients with MS

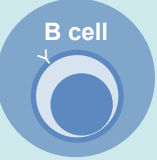
ADAs



Evaluate the formation of ADAs to OCR SC and OCR IV, and antibodies to rHuPH20

EXPLORATORY OBJECTIVES

B cells



Evaluate the change from baseline for B-cell count in blood at selected timepoints following administration of OCR SC

PROs



Evaluate patient experience with SC or IV administration of OCR using the patient satisfaction questionnaire, TASQ

ADA, antidrug antibody; AUC, area under the serum concentration–time curve; EDSS, Expanded Disability Status Scale; IV, intravenous; MS, multiple sclerosis; OCR, ocrelizumab; PK, pharmacokinetic; PPMS, primary progressive multiple sclerosis; PRO, patient-reported outcome; RMS, relapsing multiple sclerosis; SC, subcutaneous; TASQ, Treatment Administration Satisfaction Questionnaire.

^aPatients must have had an EDSS score <2.0 at screening.

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

Results

Baseline Demographics and Exposure to Study Drug

Demographics^a

	Group A – OCR all patients (N=88)	Group B – OCR all patients (N=46)
Age years, mean (SD)	45.7 (10.2)	39.7 (9.2)
Female/ male n (%)	64/24 (72.7/27.3)	29/17 (63.0/37.0)
Weight (kg) mean (SD)	92.5 (25.0)	87.9 (23.5)

Drug exposure^b

- Initially 1,200 mg was selected as the candidate SC dose. 920 mg OCR was subsequently chosen as the final SC dose based on all data available
- N=131 patients received at least 1 dose of OCR 1,200 mg or 920 mg SC
- Median overall OCR SC treatment duration was 2 years, and 95% of patients were treated for at least 1 year (i.e. 3 doses)
- 92.4% of patients were treated with OCR SC for 48 weeks

- Baseline demographics and disease characteristics were representative of the spectrum of MS disease. 95% of patients were treated for at least 1 year i.e. 3 doses

Results

Pharmacokinetics for Dose Selection

Predicted OCR exposures:^a Group A (patients pretreated with OCR)

Study		Cohorts	Dose	N	Weight (kg) Mean	AUC (µg/mL* day)			
						Mean (SD)	Median (range)	Q25	Q75
	OCARINA I	AA	600 mg IV	35	94.2	2,960 (997)	2,850 (1,230–6,080)	2,350	3,400
	OPERA I/II	-	600 mg IV	782	74.9	3,510 (962)	3,450 (1,420–11,300)	2,820	4,070
	OCARINA I	A4–A5	800 mg SC	41	92.9	3,320 (1,040)	3,300 (1,620–5,720)	2,570	3,860
	OCARINA I	A4–A5	900 mg SC	41	92.9	3,730 (1,170)	3,720 (1,830–6,430)	2,890	4,340
	OCARINA I	A4–A5	1,200 mg SC	41	92.9	4,970 (1,570)	4,960 (2,440–8,580)	3,860	5,790

Predicted OCR exposures:^a Group B (OCR-naïve patients)

Study		Cohorts	Dose	N	Weight (kg) Mean	AUC (µg/ml* day)			
						Mean (SD)	Median (range)	Q25	Q75
	OPERA I/II	-	600 mg IV	782	74.9	2,900 (754)	2,840 (1,260–8,850)	2,370	3,350
	OCARINA I	B4	800 mg SC	37	88.5	2,810 (1,130)	2,540 (909–5,530)	1,940	3,620
	OCARINA I	B4	900 mg SC	37	88.5	3,160 (1,280)	2,860 (1,020–6,220)	2,190	4,070
	OCARINA I	B4	1,000 mg SC	37	88.5	3,510 (1,420)	3,170 (1,140–6,910)	2,430	4,250
	OCARINA I	B4	1,200 mg SC	37	88.5	4,210 (1,700)	3,810 (1,360–8,290)	2,910	5,420

Dose selection

Selected SC dose 920 mg

- **PopPK model** for SC was developed based on PK data collected in this study and individual PK parameter estimates were obtained
- **Various SC dose** levels were simulated and compared vs 600 mg OCR IV arm (Cohort AA), and the pivotal Phase III OCR studies

- Based on matching the Q25 in the exposure (AUC) distribution after OCR SC and 600 mg OCR IV, a dose of OCR SC 900 mg was selected, and adjusted to 920 mg resulting in a volume of 23 ml which is more practical for filling the syringe as it is a whole number

AUC, area under the serum concentration–time curve; CCOD, clinical cut-off date; IV, intravenous; OCR, ocrelizumab; PK, pharmacokinetic; PopPK, population pharmacokinetics; Q, quartile; SC, subcutaneous; SD, standard deviation.

^aThe CCOD for these analyses was 9 November 2021.

Results

Overall Safety Data and Immunogenicity Data

- During the dose escalation phase,^a OCR SC was well-tolerated across all dose levels tested in both treatment-naïve and previously OCR-treated patients. These data supported exploration of the initial candidate 1,200 mg SC dose and the later selected final dose of 920 mg SC.

Patients with n (%)	Patients receiving 1,200 mg or 920 mg OCR (N=131)
Total safety observation time ^b	258.63 PY
AE	127 (96.9)
SAE	16 (12.2)
Infection	89 (67.9)
IR ^c	107 (81.7)
Local IR	102 (77.9)
Systemic IR	31 (23.7)

AE, adverse event; IR, injection reaction; OCR, ocrelizumab; PY, patient year; SAE, serious adverse event; SC, subcutaneous.

^aAEs defined by preferred terms. No dose-limiting toxicities, significant laboratory abnormalities or other significant safety issues were reported. Most AEs were Grade 1 or 2; ^bPY at risk amongst patients who received at least 1 dose of OCR 1,200 mg SC, was 94.9 PY in Group A and 68.2 PY in Group B, and in patients who received at least 1 dose of OCR 920 mg SC was 63.5 PY in Group A and 30.6 PY in Group B. These are not parallel comparison groups; ^cSystemic IR and local IR belong to the overall concept of IR.

Results

Overall Safety Data and Immunogenicity Data

Adverse Events

- **One AE** leading to **withdrawal** from treatment at **both the 1,200 mg and 920 mg dose** of OCR^a
- In the **1,200 mg** and **920 mg** OCR SC Group, **3 (2.4%)** and **4 (3.4%)** patients experienced an AE leading to dose modification or interruption^b respectively

Serious Adverse Events

- In patients who received at least 1 dose of 1,200 mg OCR SC, 12 patients (9.6%) experienced SAEs
- These were **COVID-19** (n=4, **3.2%**), **COVID-19 pneumonia** (n=4, **3.2%**), **pneumonia** (n=3, **2.4%**), **multiple sclerosis relapse** (n=2, **1.6%**), and **encephalitis, asthenia, muscular weakness, and pulmonary embolism** (n=1, **0.8% each**)
- In patients who received at least 1 dose of 920 mg OCR SC, 4 patients (3.4%) experienced SAEs
- These were **COVID-19, COVID-19 pneumonia, pneumonia, papillary thyroid cancer, and nephrolithiasis** (n=1, **0.8% each**)

Antidrug Antibodies

- No **treatment-emergent ADAs to OCR** were reported post-baseline in evaluable patients, **n=88 (Group A)** and **n=46 (Group B)**
- Low incidence of **treatment-emergent antibodies to rHuPH20^c** was reported; **1/87 (1.1%, Group A)** and **2/45 (4.4%, Group B)**

- Safety results were consistent with the known OCR profile; there were no new safety signals, but the known risk of IRRs observed with IV was further characterised to accommodate the IR observed with SC administration^d

ADA, antidrug antibody; AE, adverse event; CCOD, clinical cut-off date; IR, injection reaction; MS, multiple sclerosis; OCR, ocrelizumab; PY, patient year; SAE, serious adverse event; SC, subcutaneous.

^aGrade 3: MS relapse was observed in a patient who received 1,200 mg OCR SC and worsening MS was observed in a patient who received 920 mg OCR SC; ^bPatients switched from 1,200 mg OCR SC to 920 mg SC after selection of the 920 mg SC dose for OCARINA II except for 6 patients randomized to Cohort A5 who started and continued on 920 mg SC. These are not parallel comparison groups; ^cNo safety concerns have been observed in patients with anti-rHuPH20 antibodies; ^dThe CCOD for these analyses is 27 January 2023.

Results

Safety – Injection Reactions^a

	OCR SC 1,200 mg or 920 mg (N=131)
Most common local IR symptoms	
Pain	69 (52.7)
Erythema	67 (51.1)
Swelling	46 (35.1)
Most common systemic IR symptoms^c	
Headache	11 (8.4)
Flushing	4 (3.1)
Dyspnoea	3 (2.3)

Local Injection Reactions

- Most common AE, expected for the SC route of administration
- Reported in 72.0% and 52.5% of patients who received 1,200 mg or 920 mg OCR SC, respectively
- Highest incidence at first injection, and decreased thereafter
- All non-serious, Grade 1–2, non-treatment limiting and resolved

Systemic Injection Reactions

- Reported in 20% and 11% of patients who received 1,200 mg or 920 mg OCR SC, respectively
- Highest incidence at first injection, and decreased thereafter
- All non-serious, and all Grade 1–2, except for single Grade 3^b event after 1,200 mg OCR SC administration

- Injection site reactions were the most common adverse events, all of which were mild/moderate

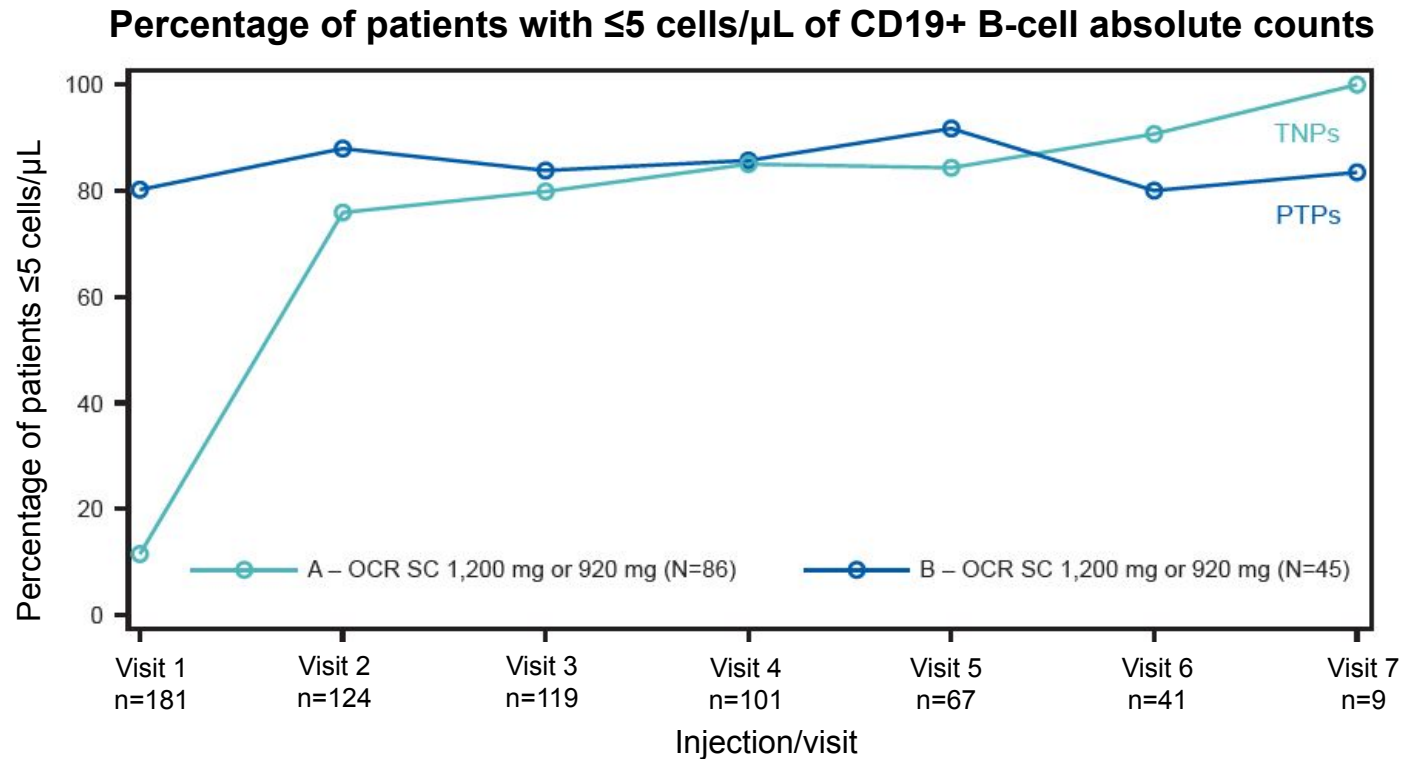
AE, adverse event; IV, intravenous; OCR, ocrelizumab; SC, subcutaneous.

^aPatients switched from 1,200 mg OCR SC to 920 mg OCR SC after selection of the 920 mg SC dose for OCARINA II except for 6 patients randomised to Cohort A5 who started and continued on 920 mg SC. These are not parallel comparison groups. ^bThis patient was previously treated with OCR IV prior to study. The onset of the AE was 4 hours following completion of study drug administration and resolved with anti-allergy treatment after another hour. Symptoms were wheezing and shortness of breath, both Grade 3. This patient had experienced repeated mild hypersensitivity reactions upon prior IV administration;

^cIn patients who received 1 dose 920 mg OCR SC, the most common systemic IR symptom was headache; all other systemic IR symptoms occurred in only one patient each including flushing and tachycardia.

Results

Exploratory Biomarker Assessment^a



- Treatment with OCR SC led to rapid and sustained B-cell depletion in between doses, in patients who were both treatment naïve, and previously treated

- Treatment with OCR SC led to rapid and sustained B-cell depletion, similar to that seen with OCR IV

IV, intravenous; OCR, ocrelizumab; PTP, pretreated patient; SC, subcutaneous; TNP, treatment-naïve patient.

^aThis analysis shows data for all patients who received at least one dose of 1,200 or 920 mg. The X-axis shows OCR SC injection visits which occur every 24 weeks. Thus visit 1 refers to the first planned injection of 1,200 mg or 920 mg. Visits 2–7 are all subsequent injections of 1,200 mg or 920 mg. The N number refers to the number of patients at that visit. B cells are measured before injection, hence the low proportion of patients with B cells ≤ 5 cells/ μ L in Group B at that visit.

Results

Exploratory Patient-Reported Outcomes (TASQ SC)^{a,b}

- The majority of patients were either satisfied or very satisfied with the SC procedure (n=92, 93.9%)
 - The majority of patients felt that the SC procedure was convenient or very convenient (n=86, 87.8%)
 - The majority of patients felt that the time taken to get the injection was just right (n=92, 93.9%)
-
- TASQ data demonstrated a high level of satisfaction for OCR SC; most patients who received OCR SC 1,200 mg or 920 mg reported being satisfied with the SC treatment administration

OCR, ocrelizumab; SC, subcutaneous; TASQ, Treatment Administration Satisfaction Questionnaire.

^aTASQ responses are based on TASQ completion after the first injection of 1,200 mg or 920 mg. The general pattern of responses to each item at Day 1 is consistent with that from later visits (Day 14 and injection 2); ^bPercentages are based on evaluable patients, n=98.

Conclusions



- **The PK, safety, immunogenicity and PD data from the OCARINA I study supports the selected dose of 920 mg ocrelizumab SC to be evaluated in the Phase 3 OCARINA II study.**
- The candidate dose of 1,200 mg ocrelizumab and the selected ocrelizumab SC 920 mg dose were generally well-tolerated. The overall safety profile observed for ocrelizumab SC in this study is consistent with the well-established safety profile for ocrelizumab IV.
- Similar B-cell depletion was achieved with ocrelizumab SC and IV. No treatment-emergent ADAs to ocrelizumab SC and IV were observed, and antibodies to rHuPH20 were low.
- Patients reported high level of satisfaction with ocrelizumab SC.

Supplementary Materials

Results

Baseline Demographics and Disease Characteristics; Group A – Patients Pretreated with OCR

	A1 OCR SC 40 mg (N=4)	A2 OCR SC 200 mg (N=4)	A3 OCR SC 600 mg (N=4)	A4 OCR SC 1,200 mg (N=6)	A5 OCR SC 920 mg (N=6)	A5 OCR SC 1,200 mg (N=29)	AA OCR IV 600 mg (N=35)	All patients (N=88)
Age years, mean (SD)	41.3 (9.9)	46.5 (12.6)	44.5 (9.5)	48.8 (11.7)	36.8 (13.1)	49.1 (9.1)	44.5 (9.6)	45.7 (10.2)
Female/Male n (%)	2/2 (50.0/50.0)	2/2 (50.0/50.0)	3/1 (75.0/25.0)	6/0 (100/0.0)	4/2 (66.7/33.3)	19/10 (65.5/34.5)	28/7 (80.0/20.0)	64/24 (72.7/27.3)
Weight (kg) mean (SD)	91.5 (29.4)	77.2 (7.9)	89.2 (29.6)	85.5 (29.4)	82.8 (20.3)	96.6 (26.3)	94.2 (24.6)	92.5 (25.0)
RMS/PPMS n (%)	3/1 (75.0/25.0)	3/1 (75.0/25.0)	4/0 (100.0/0.0)	6/0 (100.0/0.0)	5/1 (83.3/16.7)	26/3 (89.7/10.3)	34/1 (97.1/2.9)	81/7 (92.0/8.0)
Time since symptom onset years, mean (SD)	13.9 (9.4)	8.9 (4.4)	13.6 (11.1)	17.8 (4.7)	9.2 (6.8)	11.8 (8.8)	10.6 (5.9)	11.6 (7.4)
Duration since diagnosis years, mean (SD)	11.1 (6.1)	6.4 (3.7)	9.4 (7.0)	18.1 (5.1)	7.7 (7.0)	9.9 (7.3)	9.2 (6.0)	9.9 (6.7)



Baseline demographics and disease characteristics were representative of the spectrum of MS disease

Results

Baseline Demographics and Disease Characteristics; Group B – OCR-Naïve Patients

	B1 OCR SC 40 mg (N=3)	B2 OCR SC 200 mg (N=3)	B3 OCR SC 600 mg (N=3)	B4 OCR SC 1,200 mg (N=37)	All patients (N=46)
Age years, mean (SD) 	43.3 (7.8)	37.0 (11.5)	44.3 (5.9)	39.2 (9.4)	39.7 (9.2)
Female/Male n (%) 	2/1 (66.7/33.3)	2/1 (66.7/33.3)	2/1 (66.7/33.3)	23/14 (62.2/37.8)	29/17 (63.0/37.0)
Weight (kg) mean (SD) 	67.3 (13.7)	85.1 (15.5)	104.1 (37.3)	88.5 (23.0)	87.9 (23.5)
RMS/PPMS n (%) 	1/2 (33.3/66.7)	3/0 (100.0/0.0)	2/1 (66.7/33.3)	35/2 (94.6/5.4)	41/5 (89.1/10.9)
Time since symptom onset years, mean ± SD 	19.1 (13.0)	7.9 (0.8)	7.3 (4.6)	6.3 (5.5)	7.3 (6.6)
Duration since diagnosis years, mean (SD) 	8.7 (10.9)	6.1 (3.7)	5.1 (4.3)	5.1 (5.5)	5.4 (5.6)



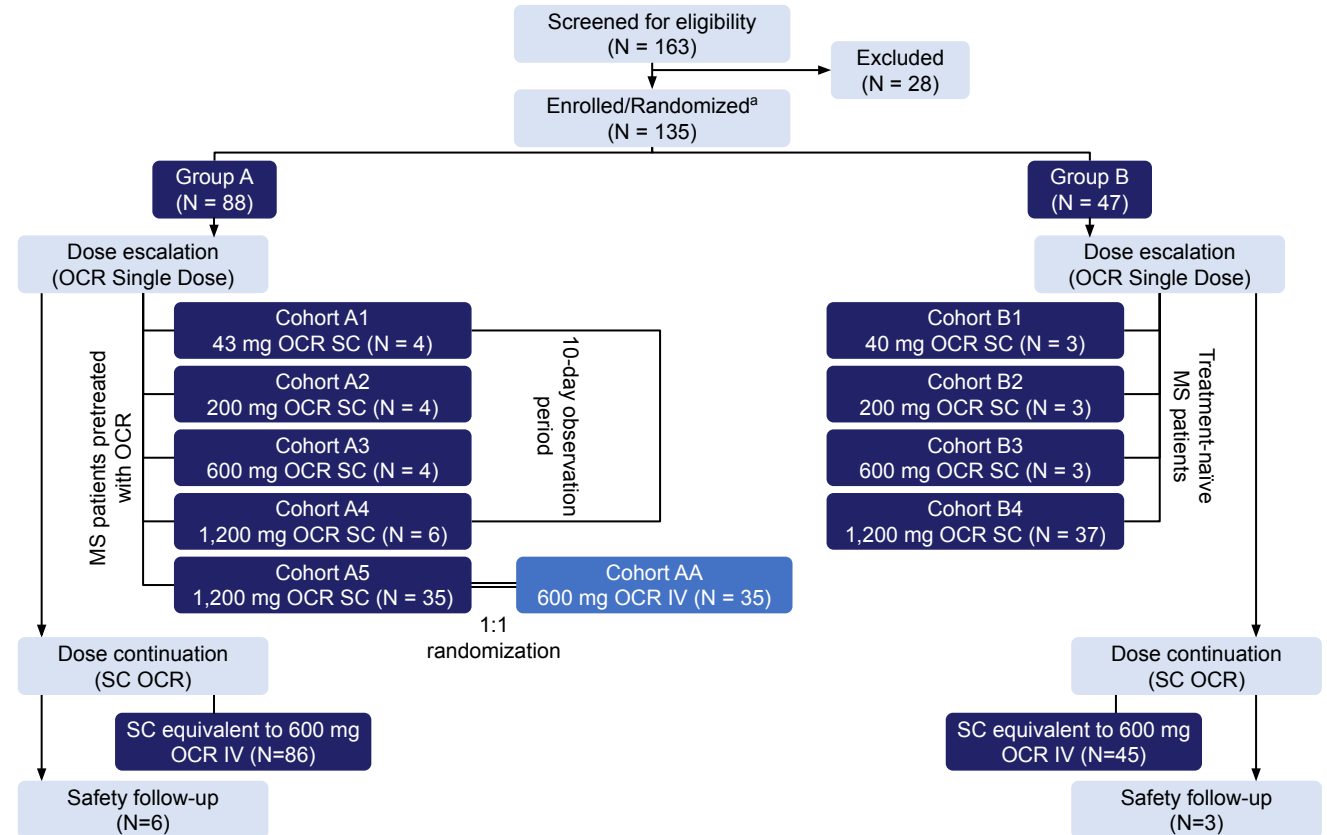
Baseline demographics and disease characteristics were representative of the spectrum of MS disease

Results

Patient Disposition

Patient disposition

- N=135 patients enrolled: 88 in Group A and 47 in Group B
- Eighty-six patients (97.7%, Group A) and 45 patients (95.7%, Group B) entered the dose continuation phase^a
- Nineteen patients discontinued from treatment, most commonly due to withdrawal by subject (n=12), which included:
 - Travel distance and/or time commitment (n=3)
 - Reason not specified (n=4)
 - Personal or family reasons (n=2)
 - Preference for OCR IV (n=2)
 - Disease progression (n=1)



Overall, 10 patients (11.4%) in Group A and nine (19.1%) in Group B discontinued from study treatment

IV, intravenous; MS, multiple sclerosis; OCR, ocrelizumab; SC, subcutaneous.

^aOf patients reaching the dose continuation phase, six patients started on a dose of 920 mg OCR, with the remaining starting on 1,200 mg OCR. All patients received 920 mg OCR for all subsequent doses.

Results

Summary of Exposure to ≥ 1 Dose of 920 mg or 1,200 mg OCR SC

	All patients (N=131)
Overall SC treatment duration (weeks)	
Mean (SD)	94.3 (39.3)
Median	96.0
Min–Max	0.1–159.1
Overall SC treatment duration, (weeks, %)	
0–<24	3 (2.3)
24–<48	7 (5.3)
48–<72	22 (16.8)
72–<96	32 (24.4)
96–<120	26 (19.8)
120–<144	20 (15.3)
144–<168	21 (16.0)
Number of overall SC doses, n (%)	
1	3 (2.3)
2	4 (3.1)
3	19 (14.5)
4	33 (25.2)
5	28 (21.4)
6	20 (15.3)
7	23 (17.6)
8	1 (0.8)



Most patients received OCR SC for a year and were exposed to at least 3 doses

Results

Summary of AEs in Patients Who Received ≥ 1 Dose of 1,200 mg or 920 mg OCR SC

	Patients receiving 1,200 mg or 920 mg OCR (N=131)
Total number of infusions/injections	608
Total safety observation time	258.63
Total number of patients with ≥ 1	
AE, n (%)	127 (96.9)
AE $\geq$ Grade 3, n (%)	31 (23.7)
SAE, n (%)	16 (12.2)
AE with fatal outcome	1 (0.8)
AE leading to withdrawal from treatment, n (%)	2 (1.5)
IRR, n (%)	0
IR, n (%)	107 (81.7)
Local IR, n (%)	102 (77.9)
Systemic IR, n (%)	31 (23.7)
Infections, ^a n (%)	89 (67.9)
Serious infection, n (%)	13 (9.9)
Medical concepts	
Anaphylactic reaction ^b	18 (13.7)
Hypersensitivity ^c	44 (33.6)

- **No dose-limiting toxicities, significant laboratory abnormalities** or other significant safety issues were reported
- The only newly observed safety finding with the SC formulation was **injection reactions**, which were related to the route of administration



OCR SC was well-tolerated at the selected dose (920 mg) and the higher dose (1,200 mg) in both OCR treatment-naïve patients and patients previously treated with OCR IV

AE, adverse event; IR, injection reaction; IRR, infusion-related reaction; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; OCR, ocrelizumab; PY, patient years; SAE, serious adverse event; SC, subcutaneous; SMQ, Standardised MedDRA Queries.

^aInfections were identified by MedDRA System Organ Class 'Infections and Infestations'; ^bIdentified using the 'Anaphylactic reactions (SMQ)'; ^cIdentified using the 'Hypersensitivity (SMQ)'.

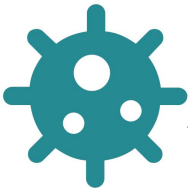
Results

Safety and Most Common AEs in >10% of Patients in Either Group^a

Patients receiving ≥1 dose of 1,200 mg OCR SC
All patients^a (N=125)



Local injection reaction
All: 90 (72.0%)



COVID-19
All: 42 (33.6%)



Systemic injection reaction
All: 26 (20.8%)



Headache
All: 17 (13.6%)



Fatigue
All: 20 (16.0%)

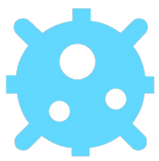


UTI
All: 14 (11.2%)

Patients receiving ≥1 dose of 920 mg OCR SC
All patients^a (N=118)



Local injection reaction
All: 62 (52.5%)



COVID-19
All: 25 (21.2%)



Systemic injection reaction
All: 13 (11.0%)

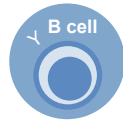


Safety results were consistent with the known OCR profile, the only newly observed safety finding with the SC formulation was injection reaction, which is related to the route of administration

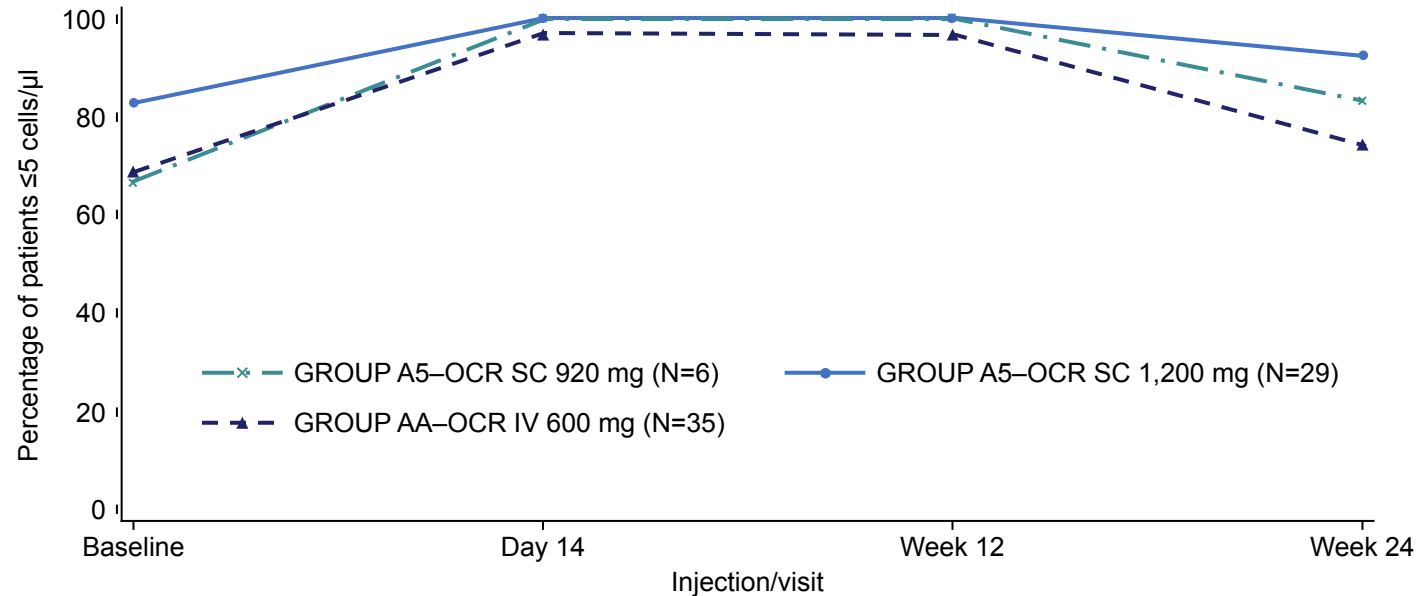
AE, adverse event; COVID-19, coronavirus disease 2019; IRR, infusion-related reaction; OCR, ocrelizumab; SC, subcutaneous; UTI, urinary tract infection.
^aAll patients included individuals from the whole study cohort receiving different doses of OCR.

Results

Exploratory Biomarker Assessment



Percentage of patients with ≤ 5 cells/ μ l of CD19+ B-cell absolute counts (Groups AA and A5)



During the dose escalation phase, after receiving 1 dose of OCR SC (920 mg or 1,200 mg), the proportion of patients who experienced CD19+ B-cell absolute counts ≤ 5 cells/ μ l in the OCR SC arm was comparable to the OCR IV arm



Treatment with OCR SC led to rapid and sustained B-cell depletion, similar to that seen with OCR IV



<https://ter.li/5aclwu>

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

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Disclosures

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Background and Objective

- 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 >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, could deliver clinical benefit, significantly reduced time and treatment burden, improved resource use, and offered greater flexibility in administration and site of patient care^{7,8}



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

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.

^aIn combination 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.

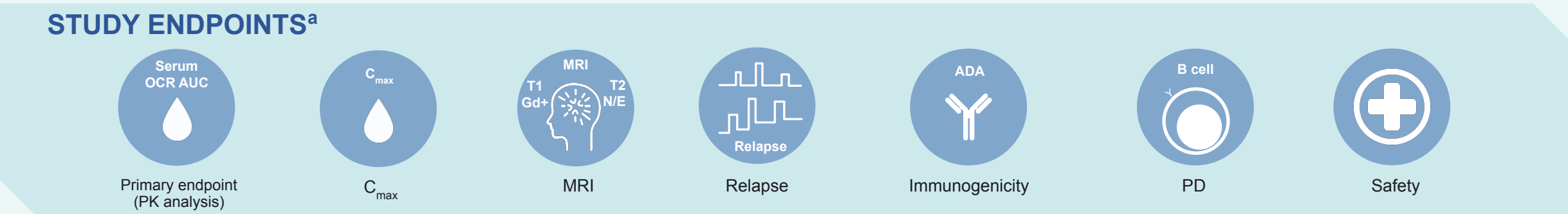
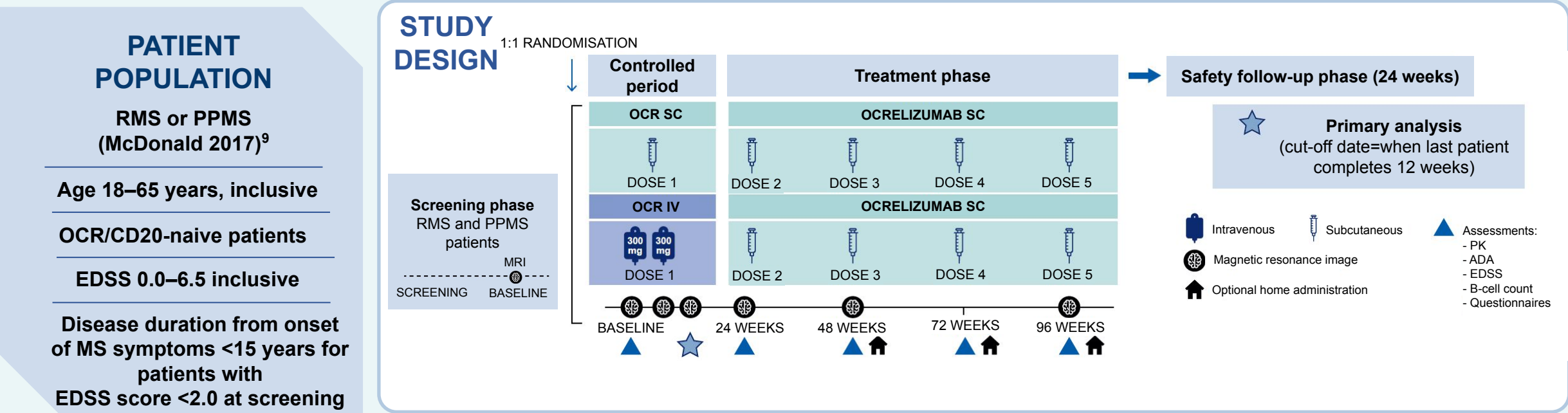
1. OCREVUS [ocrelizumab] Full Prescribing Information. Genentech, Inc., 2020. 2. OCREVUS [ocrelizumab] Summary of Product Characteristics. Roche Pharma AG, 2020.

3. Hauser SL, et al. *Neurology* 2020;95(13):e1854–e1867. 4. Wolinsky JS, et al. *Lancet Neurol* 2020;19:998–1009. 5. Weber, et al. ECTRIMS-ECTRIMS 2023;Poster P302. 6. Roche data on file.

7. ClinicalTrials.gov. <https://classic.clinicaltrials.gov/ct2/show/NCT03972306>. Updated 25 July 2023. Accessed 25 August 2023. 8. ClinicalTrials.gov. <https://classic.clinicaltrials.gov/ct2/show/NCT05232825>. Updated 25 July 2023. Accessed 25 July 2023.

Methods

Patient population, study design and end points



ADA, antidrug antibody; AUC, area under the serum concentration–time curve; C_{max}, maximum serum concentration; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IV, intravenous; MRI, magnetic resonance imaging; MS, multiple sclerosis; N/E, new/enlarging; OCR, ocrelizumab; PD, pharmacodynamic; PK, pharmacokinetic; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; SC, subcutaneous.

^aPK analysis was the study primary end point determined at Week 12. All other endpoints and assessments were determined up to Week 24.

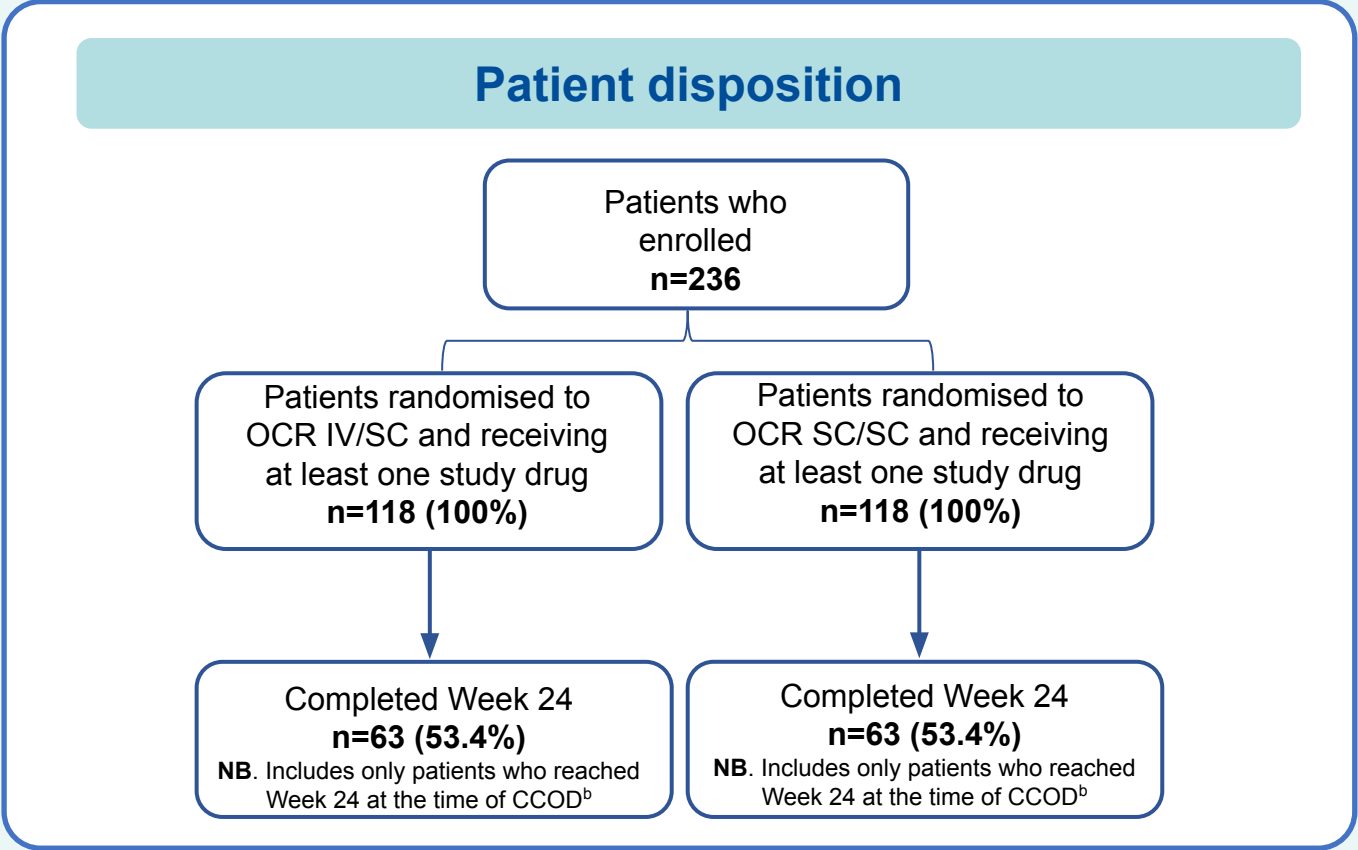
9. Thompson AJ, et al. *Lancet Neurol* 2018;17:162–173.

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Results

Baseline demographics, disease characteristics and patient disposition^a

	OCR IV (N=118)	OCR SC (N=118)
Age years, mean ± SD	40.0 ± 11.9	39.9 ± 11.4
Female n (%)	70 (59.3)	77 (65.3)
Male n (%)	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
RMS n (%)	105 (89.8)	105 (89.0)
PPMS n (%)	12 (10.2)	11 (9.3)
Number of patients with no T1 Gd+ lesions n (%)	78 (66.1)	82 (69.5)
T2 lesions mean ± SD	49.84 (34.56)	44.48 (32.25)
EDSS at baseline median, range	3.0, 0–6.5	2.5, 0–6.5



Baseline demographics and disease characteristics in the OCARINA II study were reflective of the broad MS population for which OCR IV is currently indicated, and overall, were comparable between the two arms

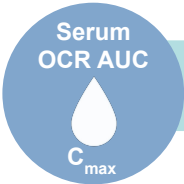
EDSS, Expanded Disability Status Scale; IV, intravenous; MS, multiple sclerosis; OCR, ocrelizumab; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; SC, subcutaneous; SD, standard deviation

^aFurther patient disposition and patient demographics are available in the Supplementary Materials. ^bThe CCOD was on 10th March 2023.

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Results

Week 12 PK (AUC_{W1-12} , C_{max}) OCR SC vs IV and B-cell depletion



OCR PK SC vs IV

Comparison OCR SC 920 mg vs OCR IV 600 mg

	SC 920 mg (n=116)	IV 600 mg (n=116)	GMR ^a SC vs IV (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) PRIMARY ENDPOINT
Max Concentration (C_{max})	132 µg/ml	137 µg/ml	0.96 (0.92–1.01)



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

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.

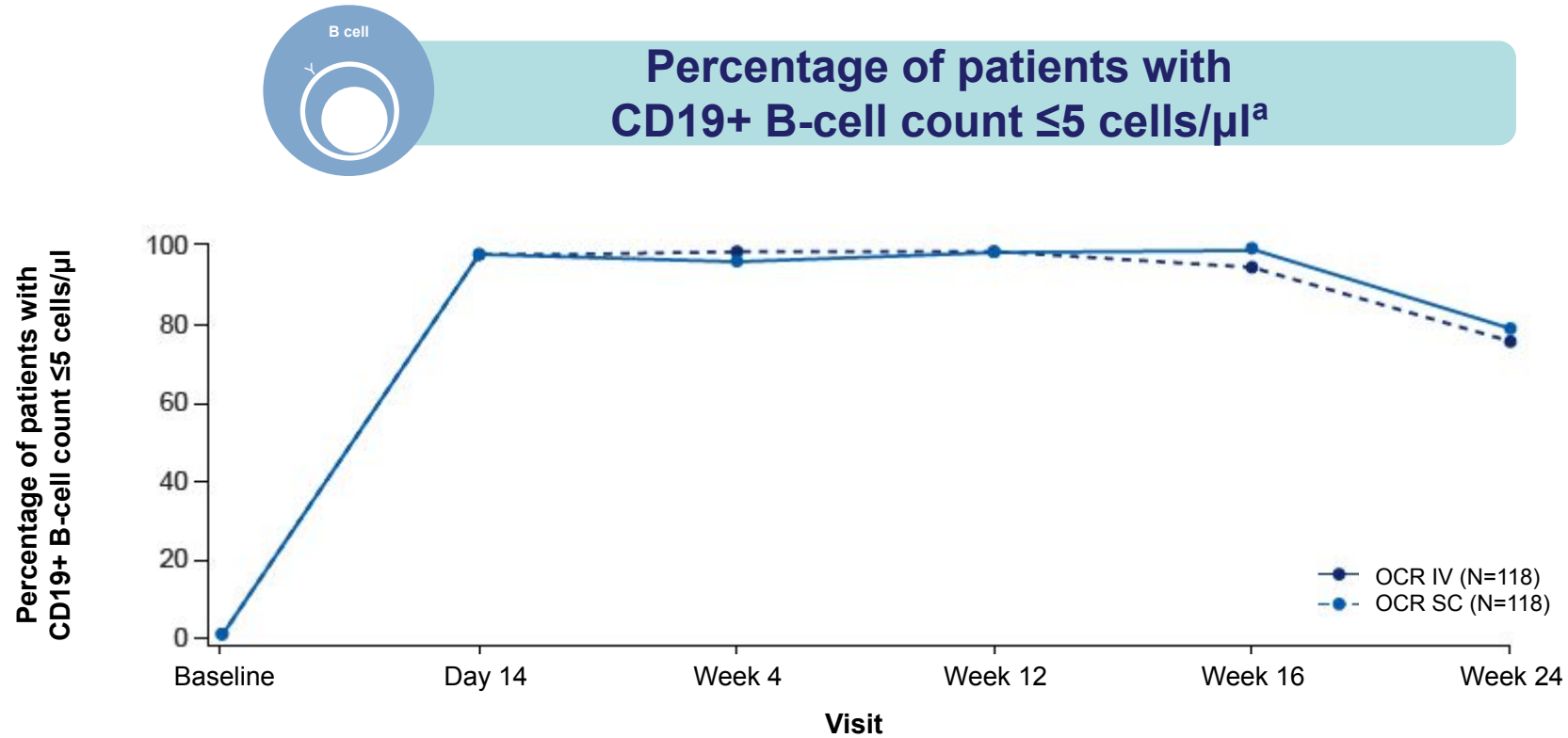
^aGMR and two-sided 90% CI of SC vs IV AUC between Week 1 and Week 12. Non-inferiority would be established if the lower end of the two-sided 90% CI is >0.8; the non-inferiority limit of 0.8 corresponds to a maximal 20% loss in AUC for the SC administration compared with IV, as recommended in the regulatory guidance documents for demonstration of bioequivalence for PK bridging.^{10,11}

10. 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 02 October 2023.

11. 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-ind-general-considerations>. Accessed 02 October 2023.

Results

Week 12 PK (AUC_{W1-12} , C_{max}) OCR SC vs IV and B-cell depletion



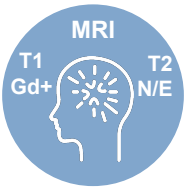
Treatment with OCR led to rapid and sustained B-cell depletion in blood, which was similar in both treatment arms (OCR SC 920 mg and OCR IV 600 mg)

IV, intravenous; OCR, ocrelizumab; PK, pharmacokinetic; SC, subcutaneous.

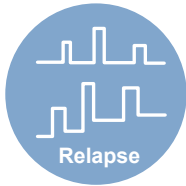
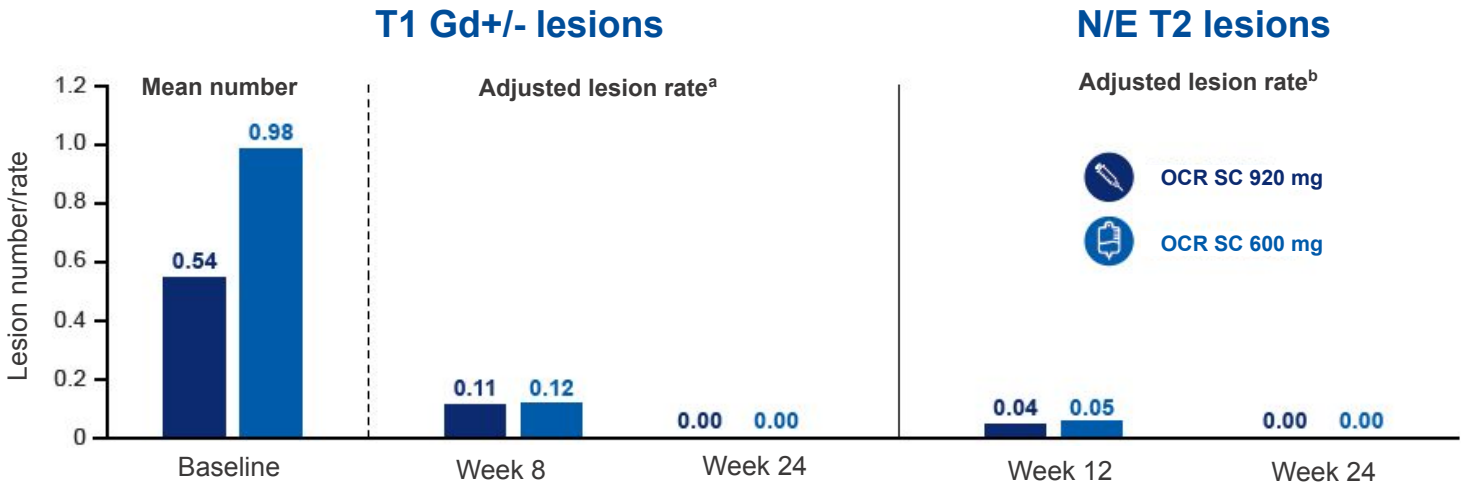
^aOne patient in the SC arm had sample collected both at baseline and at 'Day 1' visit; the 'Day 1' visit assessment has been removed from the plot for this patient.

Results

Radiological and clinical effects



	Patient numbers	
	OCR SC 920 mg	OCR IV 600 mg
T1 Gd+/- lesions		
Baseline	118	118
Week 8	98	98
Week 24 ^c	49	52
T2 Lesions		
Baseline	118	118
Week 12	116	116
Week 24 ^c	61	65



99% of patients had no relapse during the controlled period up to Week 24

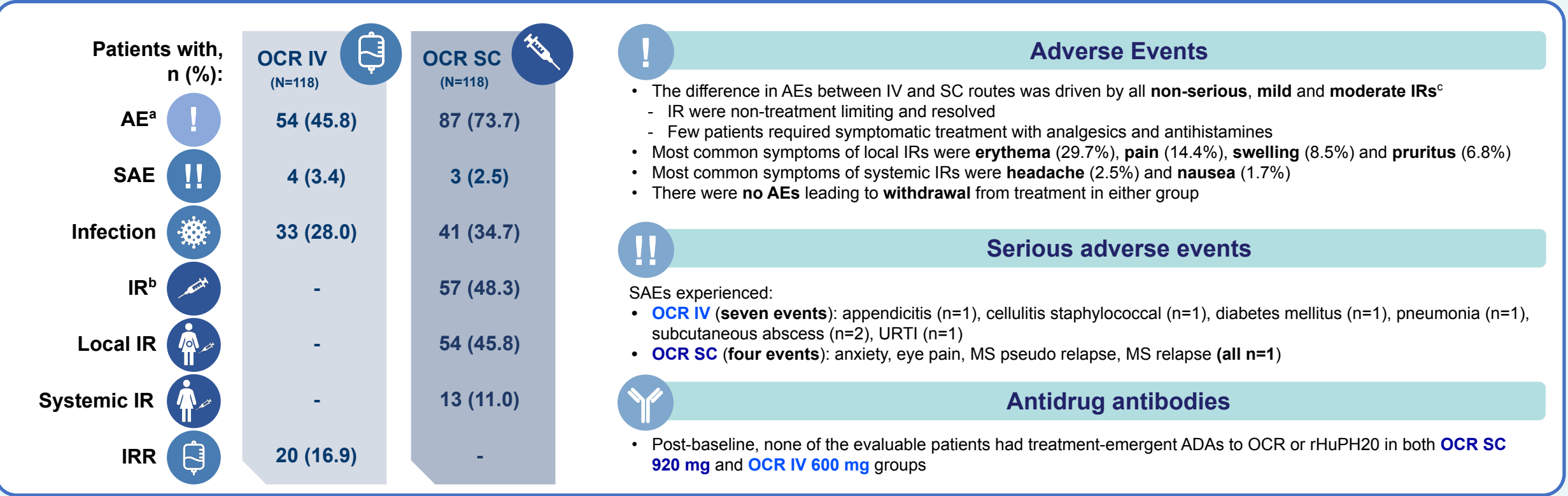
	OCR SC (n=107)	OCR IV (n=106)
Number of patients with:		
0 relapses n (%)	106 (99.1)	105 (99.1)
1 relapse n (%)	1 (0.9)	1 (0.9)
Relapse rate (per year), unadjusted ^d	0.02	0.02

OCR SC 920 mg administration resulted in near-complete suppression of radiological (MRI) and clinical (relapses) disease activity up to Week 24, similar to OCR IV

CCOD, clinical cut-off date; CI, confidence interval; Gd+, gadolinium-enhancing; IV, intravenous; N/E, new/enlarging; OCR, ocrelizumab; SC, subcutaneous.
^aThe adjusted rate and two-sided 95% CI are from a Poisson regression model, with log (lesion count) as the response variable, adjusted for baseline T1 Gd+ lesion (present or not) and geographical region (United States of America vs rest of the world); ^bT2 is evaluated against a previous scan rather than a fixed time point; ^cBased on the number of readable scans at time of Week 24, which was before CCOD of primary analysis; ^dThe unadjusted annualised relapse rate is the total number of relapses for all patients in the considered group divided by the total follow-up time.

Results

Safety Data – Controlled Period (Week 24)



 The safety profile of OCR SC was consistent with that of OCR IV, and both OCR IV and OCR SC were well-tolerated. No new safety concerns were identified, in addition to the known risks associated with OCR or the new route of administration. No ADA to OCR or antibodies to rHuPH20 were detected

ADA, antidrug antibody; AE, adverse event; IR, injection reaction; IRR, infusion-related reaction; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; MS, multiple sclerosis; OCR, ocrelizumab; PT, preferred term; rHuPH20, recombinant human hyaluronidase PH20; SAE, serious adverse event; SC, subcutaneous; URTI, upper respiratory tract infections.

^aAEs defined by preferred terms; ^bIRs 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; ^cThe majority of IRs did not require treatment, and if needed it was per standard of care treatment including mostly analgesics (e.g. paracetamol, oral or topical antihistamines). All patients who had experienced an IR (local and systemic) recovered.

253

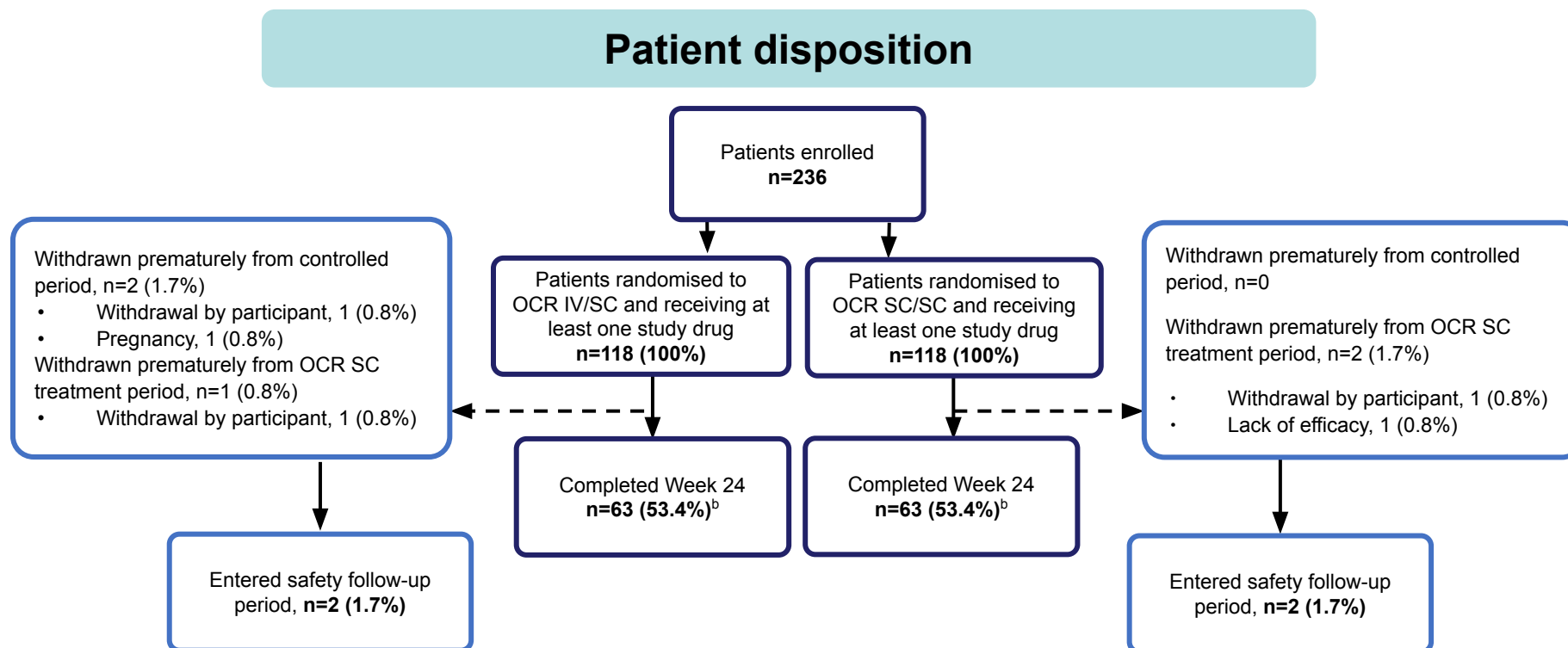
Conclusions



- **These data suggest that ocrelizumab SC delivers similar clinical benefits as ocrelizumab IV, while providing treatment flexibility along with an additional treatment choice for patients and HCPs**
- 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}
- The selected ocrelizumab SC 920 mg dose was well-tolerated, and achieved similar levels of B-cell depletion as seen with ocrelizumab IV 600 mg, with no treatment emergent ADAs to ocrelizumab
- Administration of ocrelizumab SC 920 mg resulted in near-complete suppression of radiological (MRI) and clinical (relapses) disease activity as measured up to Week 24, similarly to ocrelizumab IV 600 mg
- The safety profile of IRs was consistent with the characteristics identified in OCARINA I⁸ (Poster P371) and did not limit treatment

Supplementary Materials

Results: Patient Demographics and Patient Disposition^a



Overall, the treatment withdrawal rate was low and similar between the OCR SC and OCR IV arms. As of the CCOD, 126 patients completed the 24-week controlled period and entered the OCR SC treatment period (63 in OCR SC and 63 in OCR IV)

CCOD, clinical cut-off date; IV, intravenous; OCR, ocrelizumab; SC, subcutaneous.

^aThe first patient was enrolled on 3 May 2022 and the CCOD was on the 10 March 2023; ^bBased on the number of readable scans at time of Week 24, which was before CCOD of primary analysis.



<https://ter.li/360jlf>

The Patient Impact of 10 Years of Ocrelizumab Treatment in Multiple Sclerosis: Long-Term Data from the Phase III OPERA and ORATORIO Studies

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OPERA I and II (NCT01247324/NCT01412333); ORATORIO (NCT01194570)

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P302

Wednesday, 11 October 2023

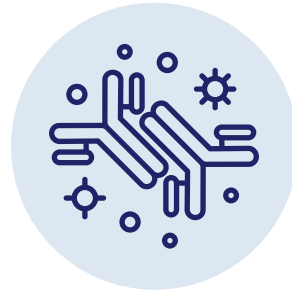
Disclosures

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Background



Preserving patient function, by optimally **slowing disease progression**, is the **key treatment goal** across the MS continuum^{1–3}



OCR, the **only anti-CD20 monoclonal antibody approved for the treatment of both RMS and PPMS**,^{4,5} has a decade of safety and efficacy experience in clinical trials, and over **300,000 patients treated** in trial and post-marketing settings^{6–9}

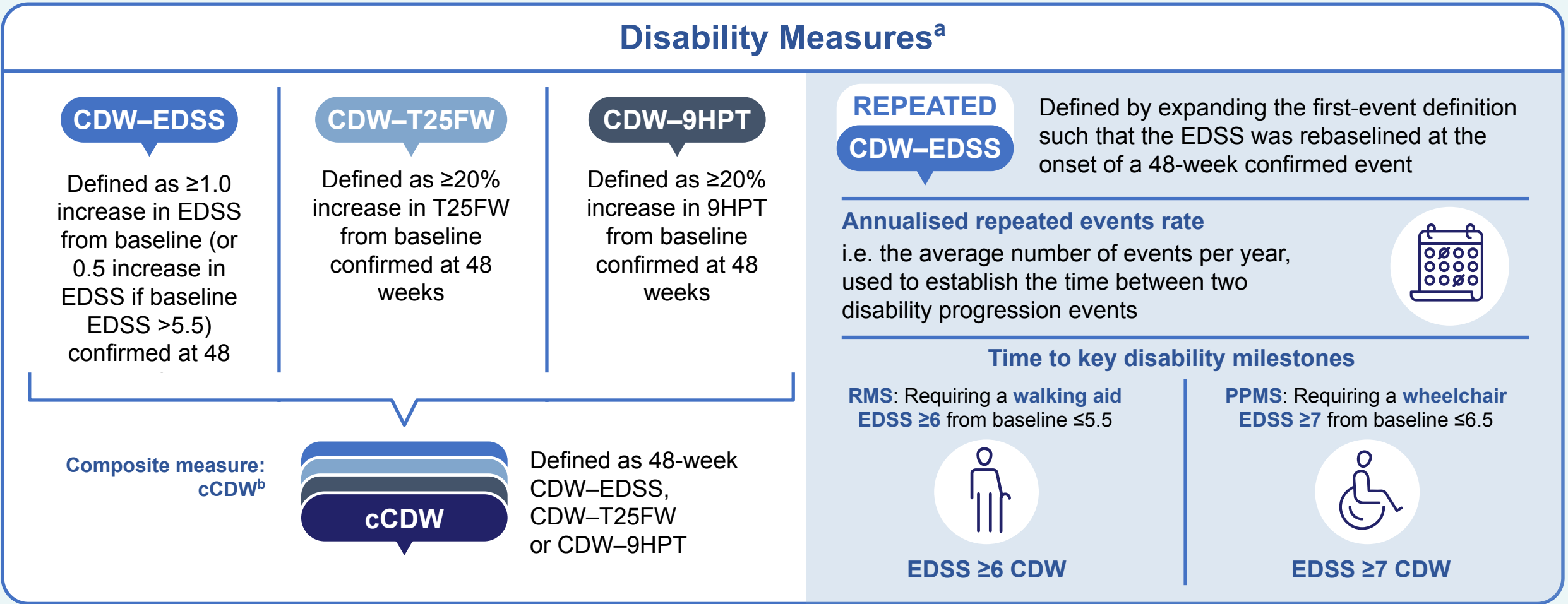


Objectives

To assess the long-term (10-year) impact of OCR on disability accumulation in patients with relapsing and primary progressive MS

MS, multiple sclerosis; OCR, ocrelizumab; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis.

1. Wilson LS, *et al. Int J MS Care* 2015;17:74–82. 2. Ontaneda D, *et al. Lancet Neurol* 2019;18:973–980. 3. Cree BAC, *et al. Curr Opin Neurol* 2022;35:262–270. 4. OCREVUS [ocrelizumab] Full Prescribing Information. Genentech, Inc., 2020. 5. OCREVUS [ocrelizumab] Summary of Product Characteristics. Roche Pharma AG, 2020. 6. Roche data on file. 7. Hauser SL, *et al. Neurology* 2020;95:e1854–e1867. 8. Wolinsky JS, *et al. Lancet Neurol* 2020;19:998–1009. 9. Cerqueira J, *et al. ECTRIMS* 2022;Poster 723.



Methods

Patient Populations, Baseline Demographics and Disease Characteristics^a

OPERA I/II PATIENT POPULATION	ORATORIO PATIENT POPULATION			OPERA I/II RMS (OCR; N=827)	OPERA I/II RMS (IFN; N=829)	ORATORIO PPMS (OCR; N=488)	ORATORIO PPMS (PBO; N=244)
RMS diagnosis (McDonald 2010) ¹⁰	PPMS diagnosis (McDonald 2005) ¹¹						
Age 18–55 years, inclusive	Age 18–55 years, inclusive						
MRI activity consistent with MS	MS disease duration <10 years if EDSS ≤5.0 <15 years if EDSS >5.0						
EDSS 0.0–5.5, inclusive	EDSS 3.0–6.5, inclusive	EDSS	EDSS score	2.8 ± 1.3	2.8 ± 1.3	4.7 ± 1.2	4.7 ± 1.2
≥2 relapses in the previous 2 years or one relapse in prior 12 months	Documented history or presence of elevated IgG or ≥1 IgG OCB	T25FW	T25FW seconds, mean ± SD	7.9 ± 9.9	7.2 ± 9.2	14.8 ± 21.2	12.9 ± 15.5
Treatment naïve or previously treated	Treatment naïve or previously treated	9HPT	9HPT seconds, mean ± SD	24.5 ± 13.1	24.0 ± 8.3	31.9 ± 23.3	30.6 ± 13.4
			Age years, mean ± SD	37.1 ± 9.2	37.2 ± 9.2	44.7 ± 7.9	44.4 ± 8.3
			Female n (%)	541 (65.4)	552 (66.6)	237 (48.6)	124 (50.8)
			Time since symptom onset years, mean ± SD	6.7 ± 6.2	6.5 ± 6.1	6.7 ± 4.0	6.1 ± 3.6
</							



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

9HPT, Nine-Hole Peg Test; DBP, double-blind period; EDSS, Expanded Disability Status Scale; IFN, interferon β-1a; IgG, immunoglobulin G; MS, multiple sclerosis; OCB, oligoclonal band; OCR, ocrelizumab; PBO, placebo; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; SD, standard deviation; T25FW, Timed 25-Foot Walk.

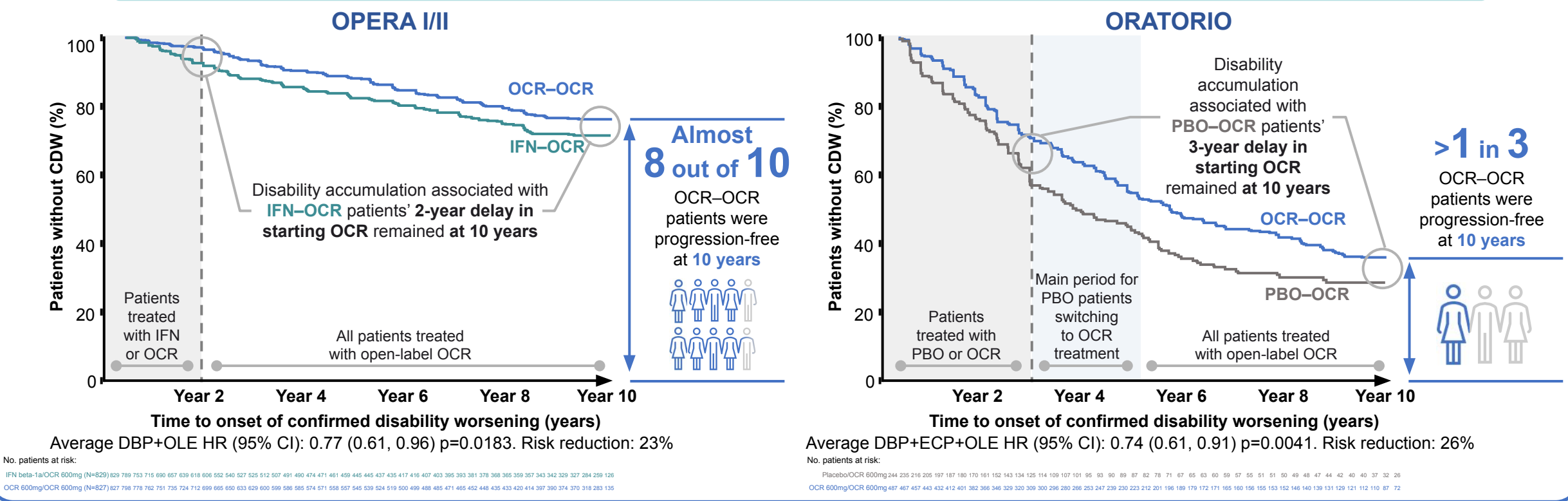
^aData shown for DBP; clinical cut-off date for the analyses was 25 November 2022; for OPERA I/II and ORATORIO, data from patients up to Week 528 were used for the 10-year analyses. Patient disposition is available in the Supplementary Materials.

10. Polman CH, *et al. Ann Neurol* 2011;69:292–302. 11. Polman CH, *et al. Ann Neurol* 2005;58:840–846.

Results

Effect of a Delay in OCR Initiation on 48W-CDW on EDSS^a

After 10 years, almost 8 out of 10 of PwRMS and >1/3 of PwPPMS treated with continuous OCR were progression-free



After 10 years, most PwRMS did not experience disability accumulation with continuous OCR treatment. In RMS and PPMS, patients who initiated OCR early maintained the benefit compared with patients who switched after just 2 years (RMS) or 3 years (PPMS)

48W-cCDW, 48-week composite confirmed disability worsening; 48W-CDW, 48-week confirmed disability worsening; CDW, confirmed disability worsening; CI, confidence interval; DBP, double-blind period; ECP, extended controlled period; EDSS, Expanded Disability Status Scale; HR, hazard ratio; IFN, interferon β -1a; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; PPMS, primary progressive multiple sclerosis; PwPPMS, patients with primary progressive multiple sclerosis; PwRMS, patients with relapsing multiple sclerosis; RMS, relapsing multiple sclerosis.

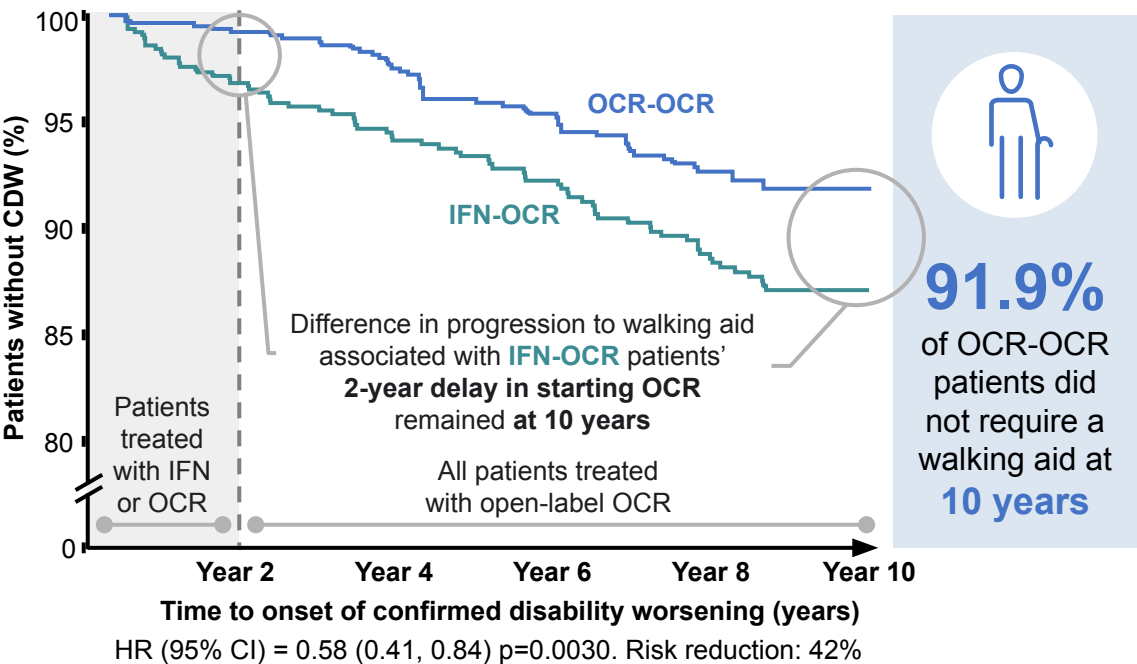
^aFor results on the effect of a delay in OCR initiation on 48W-cCDW on EDSS, please see the Supplementary Materials.

Results

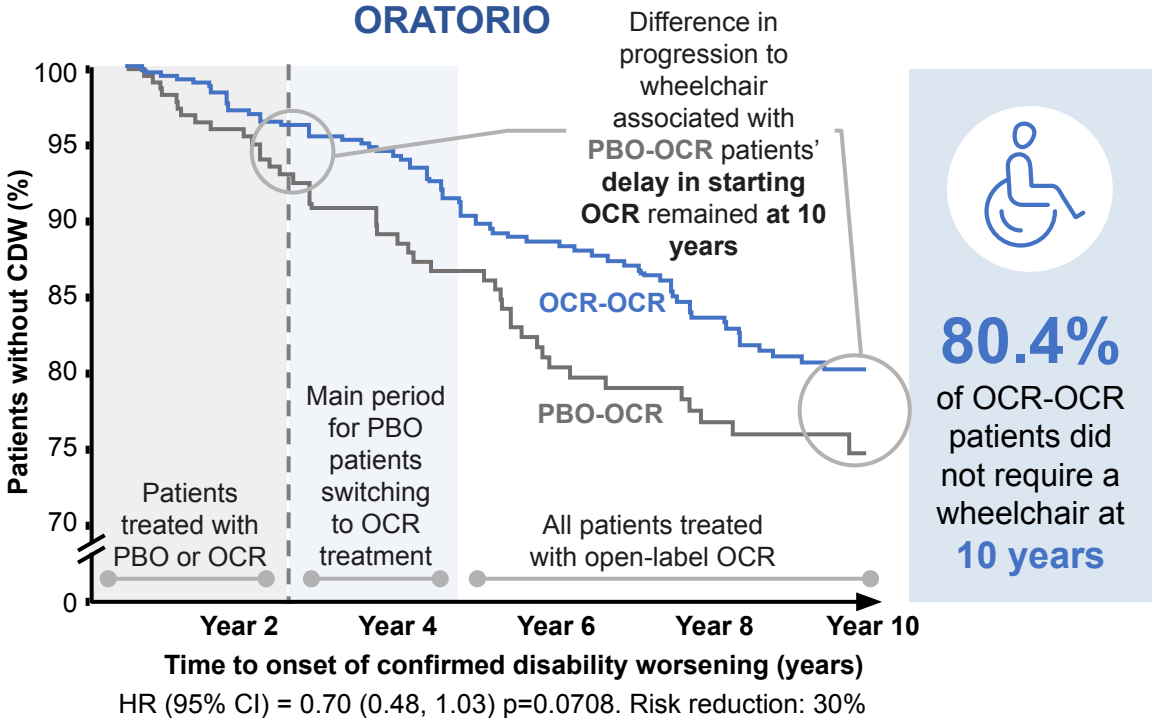
Time to Walking Aid (RMS) and Time to Wheelchair (PPMS)

After 10 years, >90% PwRMS and >80% PwPPMS treated with continuous OCR did not require a walking aid or wheelchair, respectively

OPERA I/II



ORATORIO

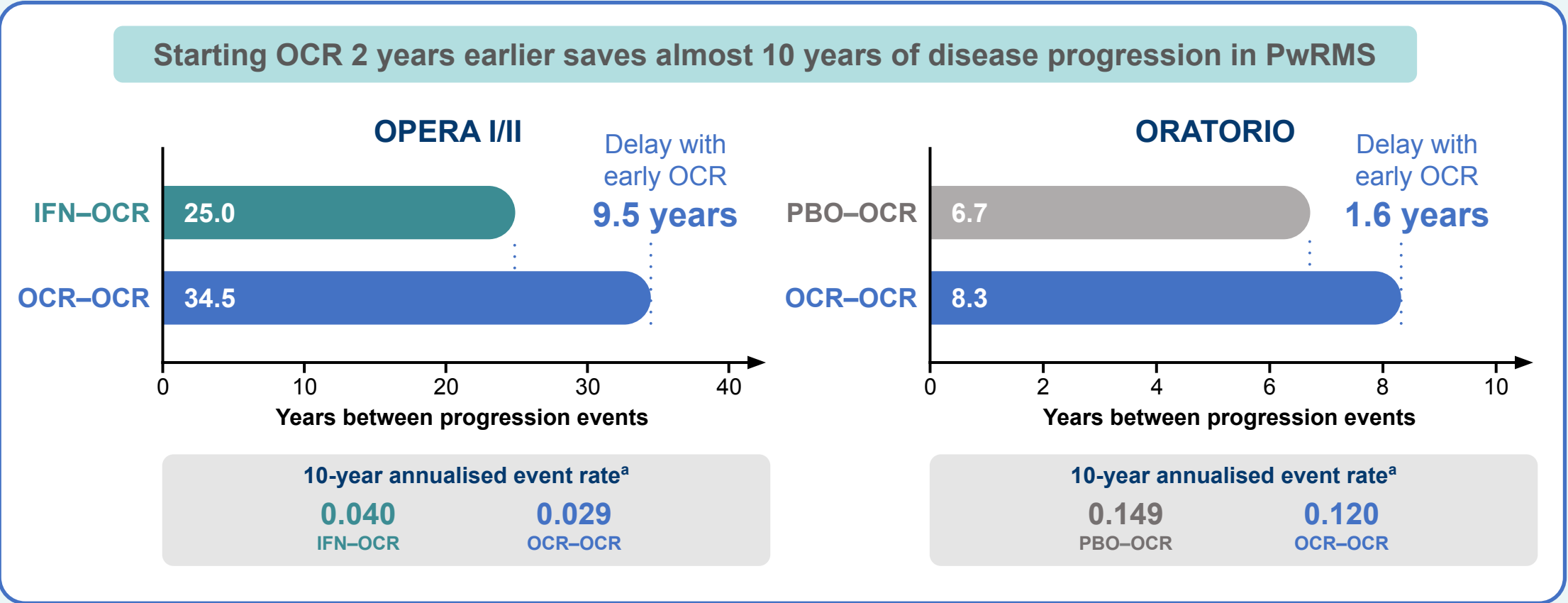


Over 10 years, in PwRMS and PwPPMS there was a 42% and 30% reduction in the risk of requiring a walking aid or a wheelchair in those who initiated OCR earlier vs delayed treatment

CDW, confirmed disability worsening; CI, confidence interval; HR, hazard ratio; IFN, interferon β -1a; OCR, ocrelizumab; PPMS, primary progressive multiple sclerosis; PwPPMS, patients with primary progressive multiple sclerosis; PwRMS, patients with relapsing multiple sclerosis; RMS, relapsing multiple sclerosis.

Results

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



Over 10 years, the annualised, repeated 48W-CDW-EDSS event rate infers patients would be expected to be progression-free for the next 34.5 and 8.3 years after the last event, in PwRMS and PwPPMS

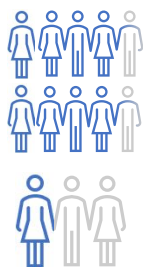
48W-CDW, 48-week confirmed disability worsening; EDSS, Expanded Disability Status Scale; IFN, interferon β -1a; OCR, ocrelizumab; PBO, placebo; PwPPMS, patients with primary progressive multiple sclerosis; PwRMS, patients with relapsing multiple sclerosis.

^aSee Supplementary Materials for annualised repeated event rate plots.

Conclusions

After long-term (10 years) continuous ocrelizumab treatment:

Almost 8 out of 10 PwRMS and a **third** of PwPPMS were **progression-free** on EDSS



>90% of PwRMS did not need a walking aid and **>80% of PwPPMS did not need a wheelchair**



Early treatment with ocrelizumab **extends the progression-free event window by almost 10 years** in PwRMS, compared with a lower efficacy DMT

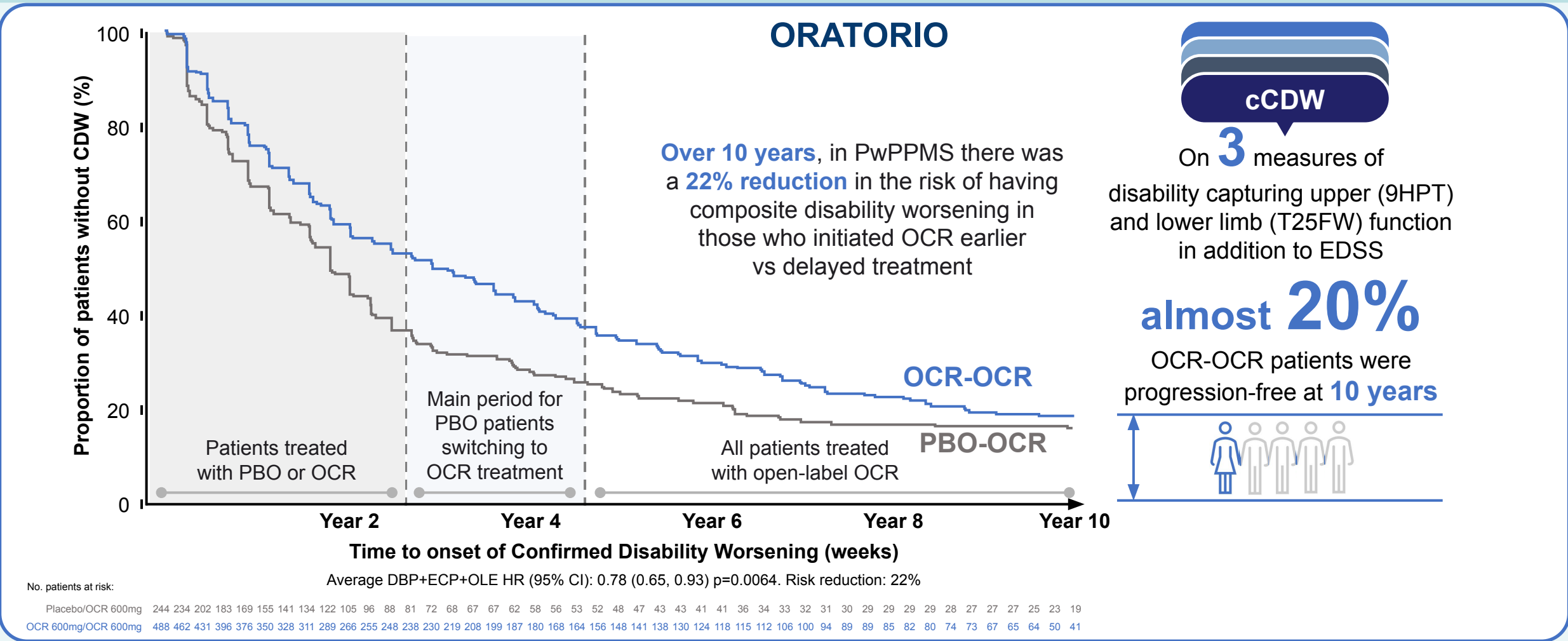


The notable impact of a decade of ocrelizumab treatment in reducing disability accumulation reinforces the role of **early treatment in preserving patient function** across the MS spectrum

Supplementary Materials

Results

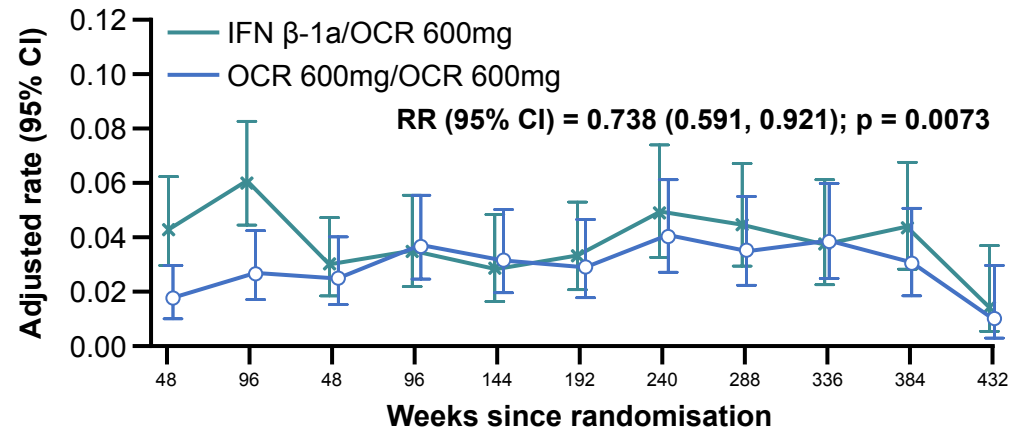
Disability accumulation on three measures of function (48W-cCDW) in PPMS



Results

Disability event rate expressed as Annualised Repeated 48W-CDW EDSS

OPERA I/II



Number of patients at risk

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

10-year annualised event rate

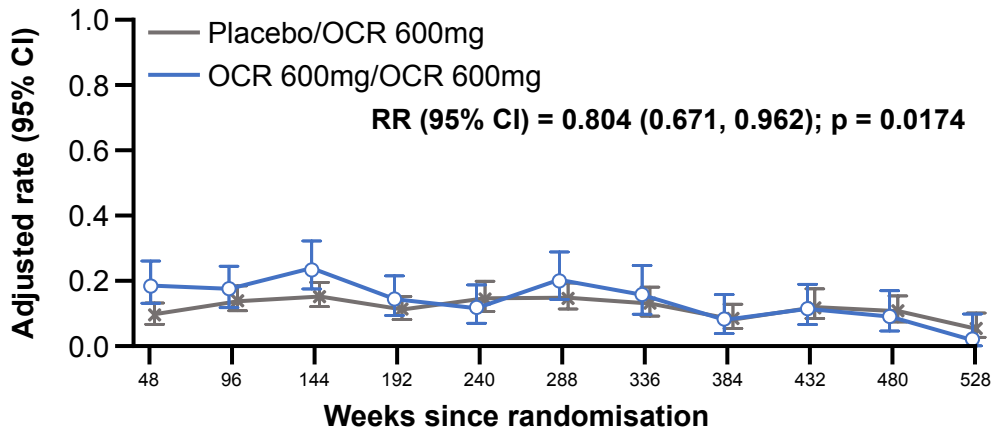
0.040

IFN-OCR

0.029

OCR-OCR

ORATORIO



Number of patients at risk

Placebo/OCR 600mg	243	222	196	171	163	156	146	135	128	119	104
OCR 600mg/OCR 600mg	481	452	428	399	366	349	325	308	289	267	244

10-year annualised event rate

0.149

PBO-OCR

0.120

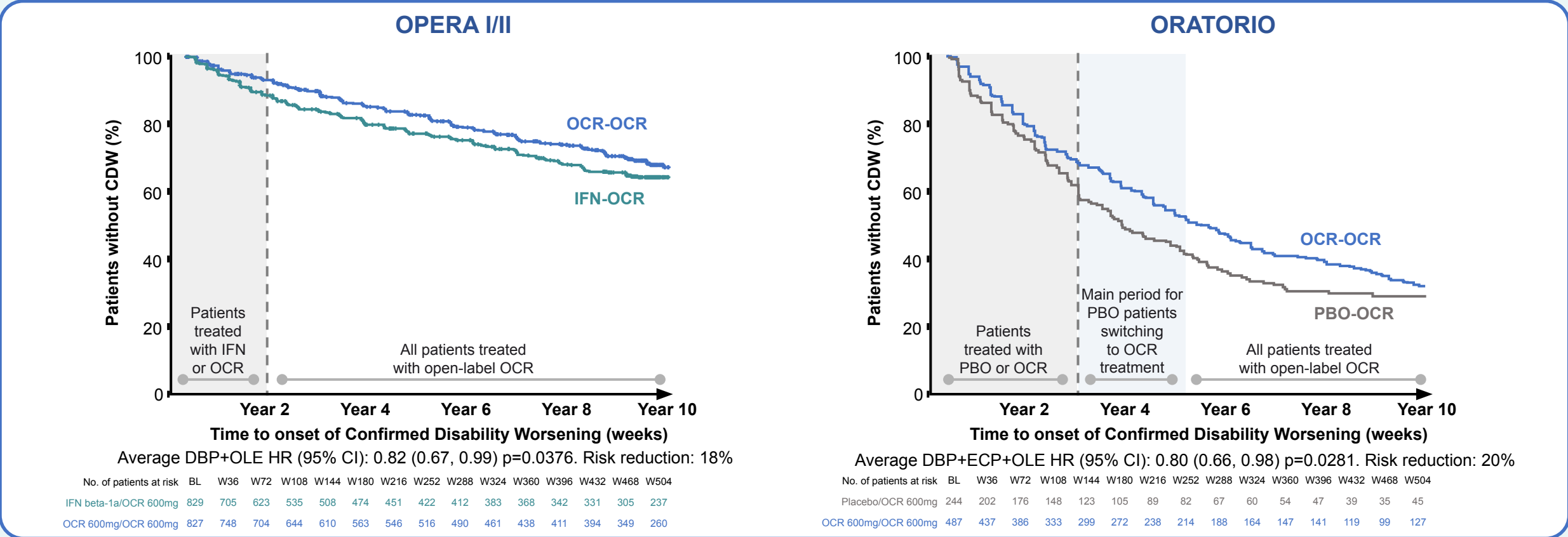
OCR-OCR



Over 10 years, the annualised, repeated 48W-CDW-EDSS event rate infers patients would be expected to be progression free for the next 34.5 and 8.3 years after the last event, in PwRMS and PwPPMS

Results

Effect of a Delay in OCR Initiation on 24W-CDW on EDSS^a



After 10 years, most PwRMS did not experience disability accumulation with continuous OCR treatment. In RMS and PPMS, patients who initiated OCR early maintained the benefit compared with patients who switched after just 2 years (RMS) or 3 years (PPMS)

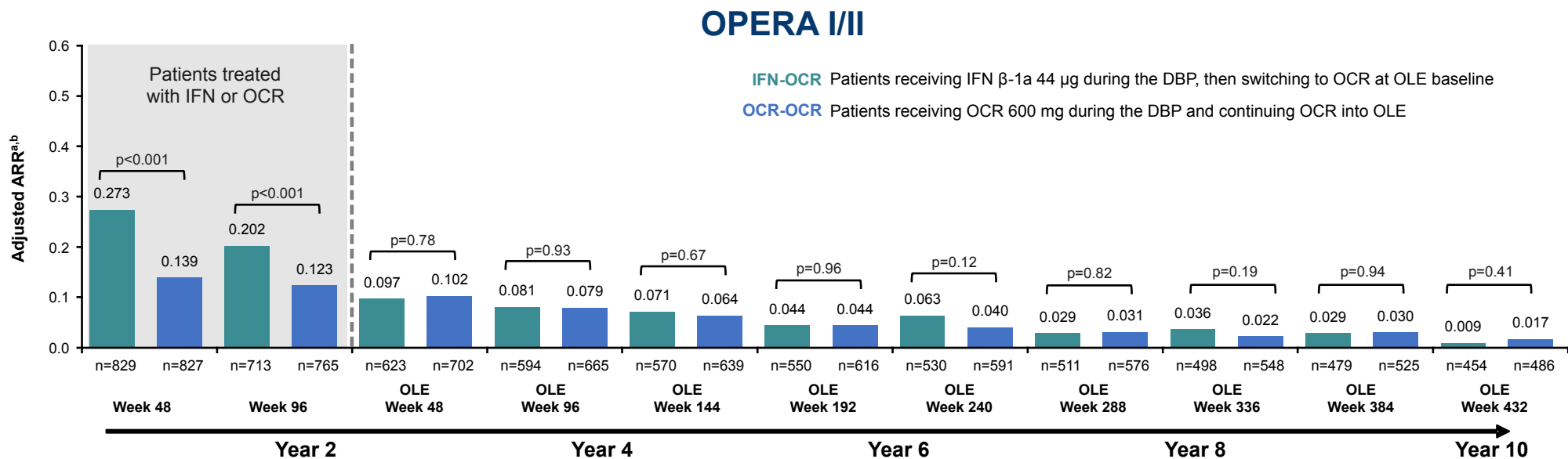
24W-cCDW, 24-week composite confirmed disability worsening; 24W-CDW, 24-week confirmed disability worsening; BL, baseline; CDW, confirmed disability worsening; CI, confidence interval; DBP, double-blind period; ECP, extended controlled period; EDSS, Expanded Disability Status Scale; HR, hazard ratio; IFN, interferon β -1a; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; PPMS, primary progressive multiple sclerosis; PwRMS, patients with relapsing multiple sclerosis; RMS, relapsing multiple sclerosis; W, week.

^aFor results on the effect of a delay in OCR initiation on 48W-cCDW on EDSS, please see the Supplementary Materials.

Results

OPERA I/II Annualised Protocol Defined Relapse Rate by Year

After 10 years in PwRMS continuously treated with OCR, the ARR (0.017) was equivalent to a relapse almost every 60 years



ARR decreased year-on-year from the pre-switch year to Year 10 in IFN–OCR switchers, and was maintained at low levels in all patients treated with OCR

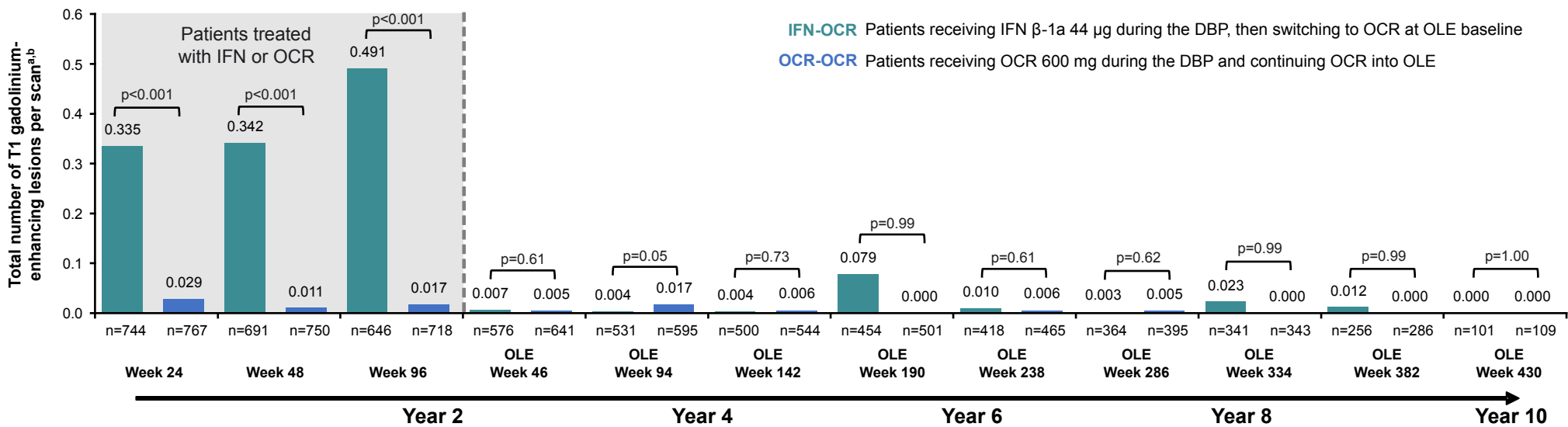
ARR, annualised relapse rate; DBP, double-blind period; EDSS, Expanded Disability Status Scale; GEE, generalised estimating equation; IFN, interferon; ITT, intention-to-treat; OCR, ocrelizumab; OLE, open-label extension; PwRMS, patients with RMS; ROW, rest of world; RMS, relapsing multiple sclerosis.
^aThe total number of relapses for all patients in the treatment group divided by the total patient-years of exposure to that treatment. ^bDBP year 1 and DBP year 2 data include the intention-to-treat population (number of patients available); for years 4-10 (OLE years 1-8), data include the OLE ITT population (number of patients available). Clinical cutoff date: November 25, 2022. GEE Poisson Model ITT population. Adjusted ARR from Week 48 to OLE Week 432 (Year 10). Adjusted by randomised treatment, study, baseline EDSS (<4.0 vs ≥ 4.0), geographical region (US vs ROW), year and treatment-by-year interaction.

Results

OPERA I/II MRI – Mean T1 Gd+ lesions

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

OPERA I/II



Over 10 years, early and continuous OCR treatment led to an almost complete suppression of MRI activity in PwRMS; these benefits were also seen in patients once they switched from IFN- β -1a to OCR

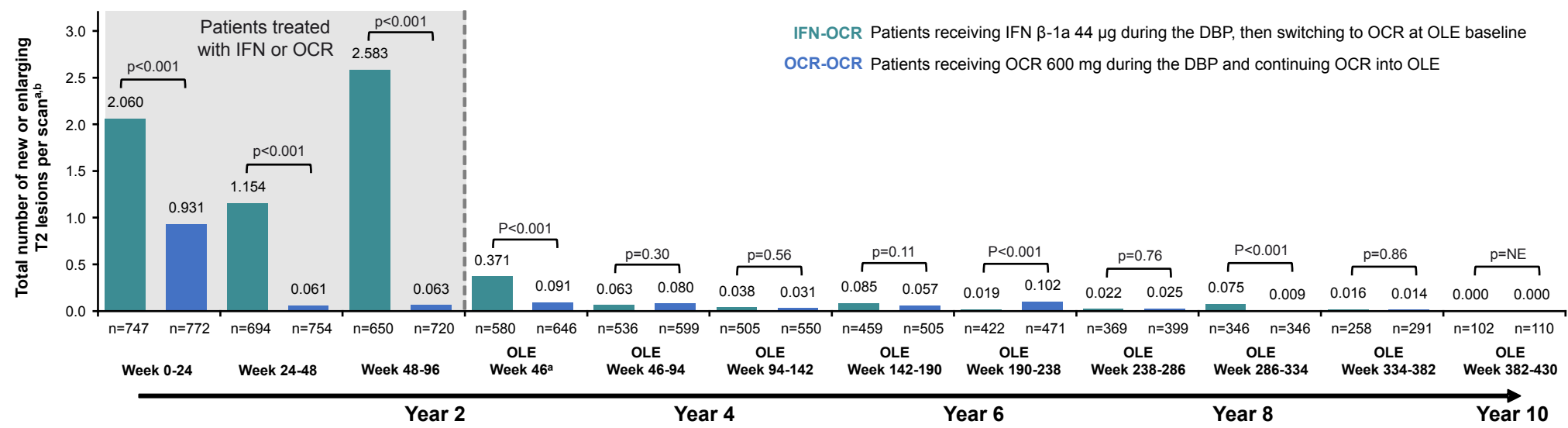
DBP, double blind period; Gd+, gadolinium-enhancing; OCR, ocrelizumab; OLE, open-label extension; PwRMS, patients with RMS; RMS, relapsing multiple sclerosis. The number of new T1 Gd-enhancing lesions and the number of new or enlarging T2 lesions were analyzed using a negative binomial model; in previously reported analysis³ of lesion outcomes during the DBP, results were adjusted for study, T1 Gd-enhancing lesion status (present or not) or baseline T2 lesion volume, baseline EDSS score (≤ 4.0 vs > 4.0), and geographic region (United States vs rest of the world). However, as patients had no new T1 Gd-enhancing lesions/new or enlarging T2 lesions at several time points, it was impossible to fit a statistical model, and unadjusted rates were adopted for the OLE instead. Baseline number of T1 Gd-enhancing lesions, mean (unadjusted) T1 Gd+ lesion rate: IFN-OCR, 1.908; OCR-OCR, 1.753.

Results

OPERA I/II MRI – Mean N/E T2 lesions

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

OPERA I/II

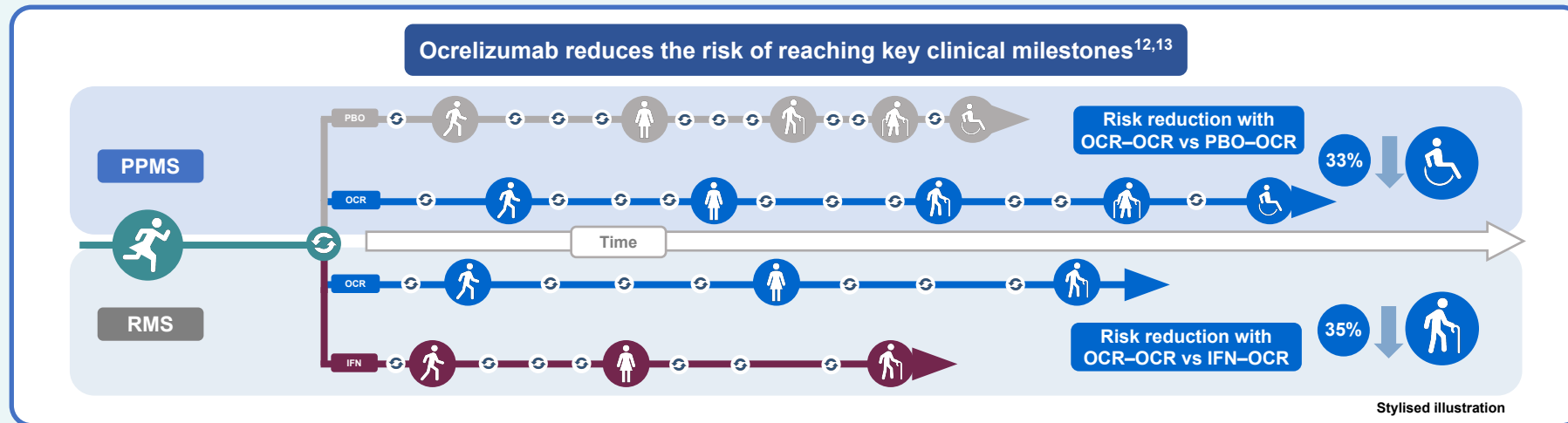


Over 10 years, early and continuous OCR treatment led to an almost complete suppression of MRI activity in PwRMS; these benefits were also seen in patients once they switched from IFN- β -1a to OCR

NE, not evaluable; OCR, ocrelizumab; PwRMS, patients with RMS; RMS, relapsing multiple sclerosis.
The number of new T1 Gd-enhancing lesions and the number of new or enlarging T2 lesions were analyzed using a negative binomial model; in previously reported analysis³ of lesion outcomes during the DBP, results were adjusted for study, T1 Gd-enhancing lesion status (present or not) or baseline T2 lesion volume, baseline EDSS score (≤ 4.0 vs >4.0), and geographic region (United States vs rest of the world). However, as patients had no new T1 Gd-enhancing lesions/new or enlarging T2 lesions at several time points, it was impossible to fit a statistical model, and unadjusted rates were adopted for the OLE instead. Baseline number of T1 Gd-enhancing lesions, mean (unadjusted) T1 Gd+ lesion rate: IFN-OCR, 1.908; OCR-OCR, 1.753.

Background

- In MS, reaching irreversible key clinical milestones is usually the result of repeated progression events^{1–3}
- Progression to requiring a walking aid (EDSS score ≥ 6.0) or wheelchair (EDSS score ≥ 7.0) is associated with a major reduction in patients' QoL and increased societal burdens, e.g. decreased employment rates; physical, emotional and financial challenges^{4–8}
 - Long-term disability is an important outcome for patients with MS;⁹ delaying the time to reach disability milestones is a significant treatment goal in RMS and PPMS
- In patients with MS, OCR reduced the risk of reaching key disability milestones vs comparator^{10–13}
 - Using extrapolation analysis, OCR delayed the time to requiring a wheelchair by 7 years in patients with MS, vs comparator¹¹



Ocrelizumab reduces the risk of reaching key clinical milestones

EDSS, Expanded Disability Status Scale; IFN, interferon β -1a; MS, multiple sclerosis; OCR, ocrelizumab; PBO, placebo; PPMS, primary progressive multiple sclerosis; QoL, quality of life; RMS, relapsing multiple sclerosis.

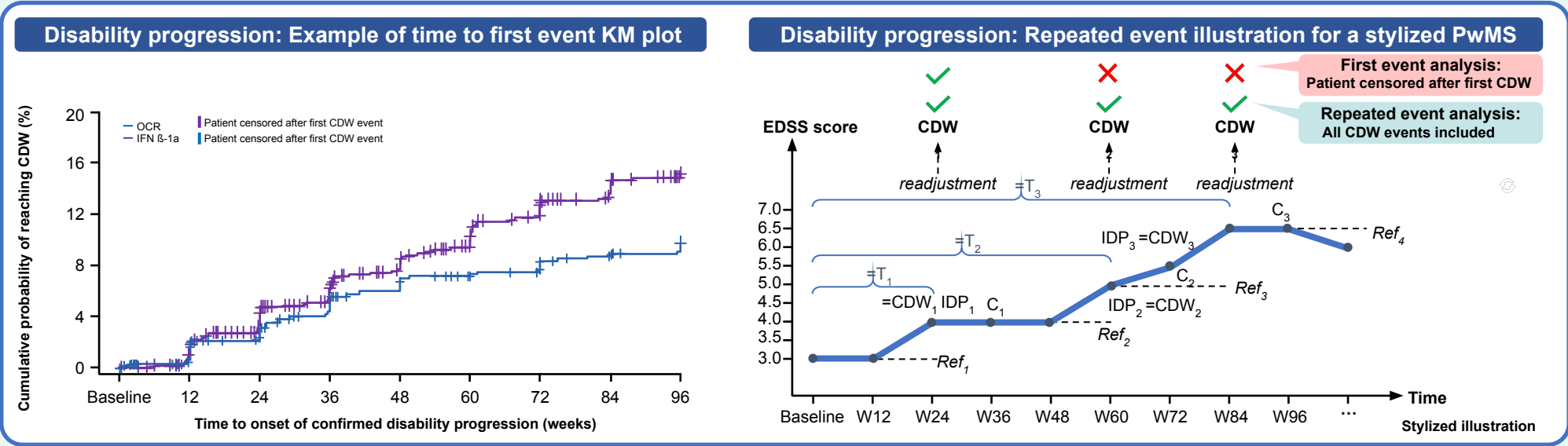
1. Roche/Genentech. Data on file; 2. Kappos L, et al. *JAMA Neurol* 2020;77:1132–1140; 3. Lublin FD, et al. *Brain* 2022 Feb 1; online ahead of print; 4. Jones E, et al. *BMC Health Serv Res* 2016;16:294;

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Background

- The current gold standard **endpoint** to assess **disability accumulation** in Phase III MS clinical trials is the **time to the first** disability progression^a
- This time-to-first event approach **does not** take into **account subsequent** on-trial **repeated progression events** that may occur but are excluded from analysis, thereby potentially missing the overall effect of a DMT
- Including **repeated progression events** in trial analysis may permit a more **comprehensive assessment of DMT** effects on disability progression
 - Repeated disability progression events can be defined by expanding the first-event definition such that the EDSS is rebaselined at the onset of a confirmed event
 - Compared with conventional time-to-first-event analyses, repeated event analyses captured more progression events, reflecting an increase of 9.5% to 29.0% in the control arms of studies in RMS and PPMS respectively¹



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

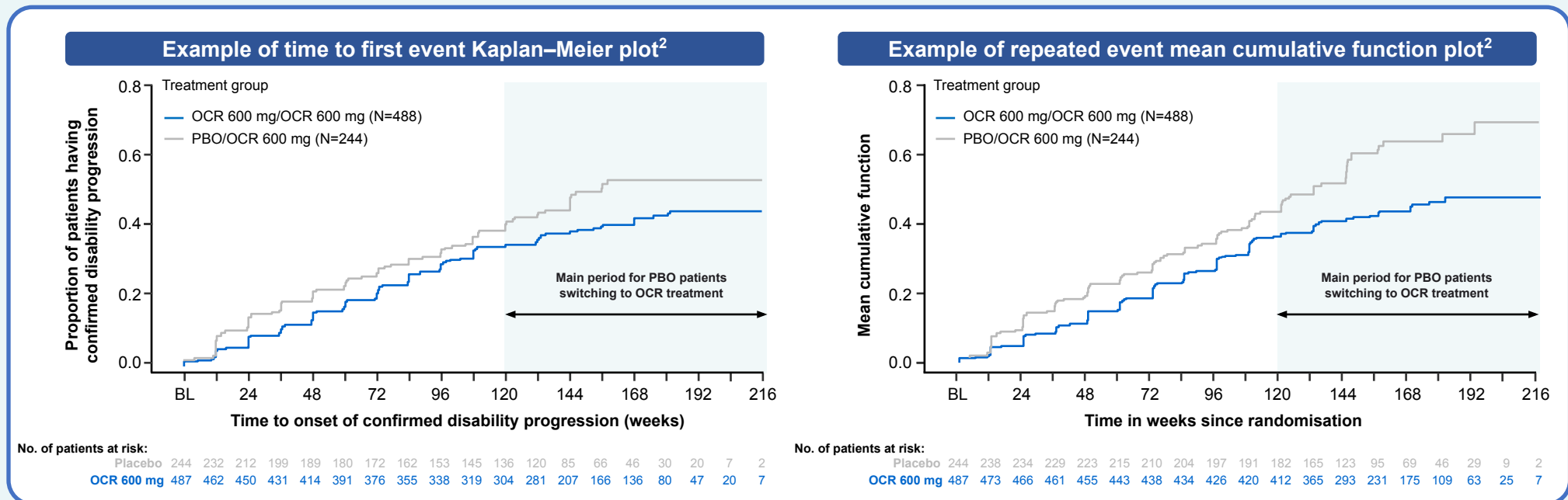
C, confirmation of initial disability progression; CDW, confirmed disability worsening (event); DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; IDP, initial disability progression; IFN, interferon β-1a; KM, Kaplan-Meier; MS, multiple sclerosis; OCR, ocrelizumab; PPMS, primary progressive multiple sclerosis; PwMS, patient with multiple sclerosis; Ref, reference EDSS score for confirmed disability progression; RMS, relapsing multiple sclerosis; T, time to onset of the confirmed disability progression; W, week.

^aTypically confirmed at 12-weeks; 12-week CDW.
¹. Manuscript submitted MSJ 2022.

Methods

Statistical Analysis

- A rate-based method, the Negative Binomial model, was used for the analysis of repeated CDW events¹
 - The treatment effect estimate can be interpreted as a rate ratio (RR)
- Repeated events over time were visualised by estimates of the mean cumulative function (MCF)
 - The MCF represents the estimated average number of progression events per patient, over time
- Adjusted annualised repeated event rates and CIs were plotted over time



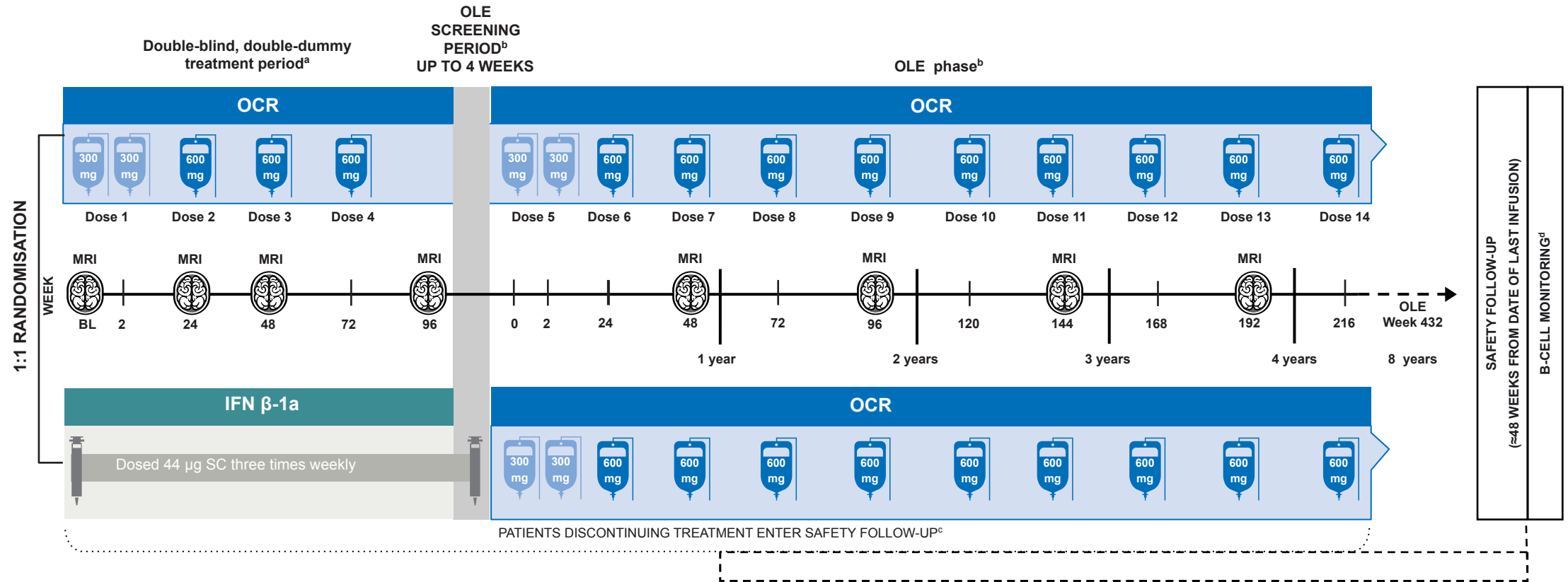
BL, baseline; CDW, confirmed disability worsening; CI, confidence interval; MCF, mean cumulative function; OCR, ocrelizumab; PBO, placebo; RR, rate ratio.

At Week 120, the start of the main switching period in the ORATORIO study, 494 patients were available for analysis using repeated CDW events vs 404 patients using the Kaplan–Meier approach.

1. Lin D, *et al. J R Stat Soc Ser B Stat Methodol* 2000;62:711–730. 2. Bühler A, *et al.* manuscript submitted MSJ 2022.

Methods

OPERA I/OPERA II study design



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

BL, baseline; DBP, double-blind period; IFN, interferon β -1a; OCR, ocrelizumab; OLE, open-label extension; SC, subcutaneous.

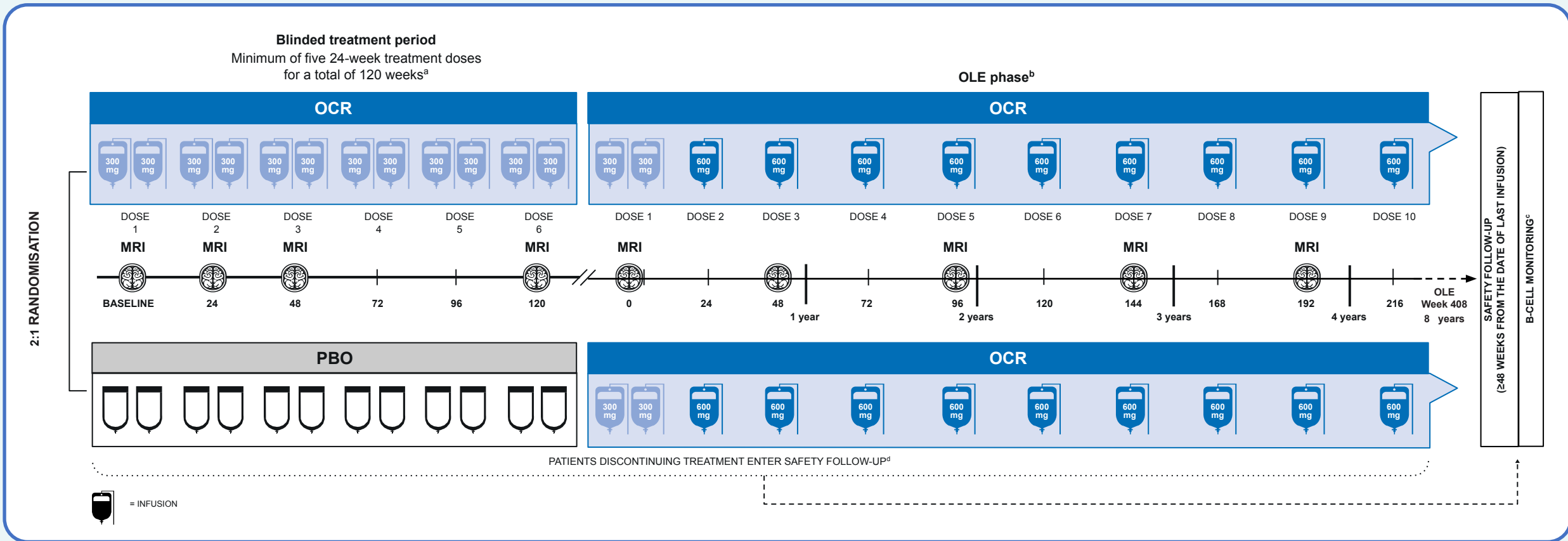
^aPatients in the OCR group received placebo injections three times weekly, while patients in the IFN β -1a group received placebo infusions on Days 1 and 15 and at Weeks 24, 48 and 72;

^bDuring OLE screening, patients received IFN β -1a or placebo until first infusion of Dose 5; ^cOLE was not mandatory – patients who declined to participate in the OLE entered safety follow-up;

^dContinued monitoring occurs if B cells are not replenished. Data cut-off: 25 November 2022.

Methods

ORATORIO study design



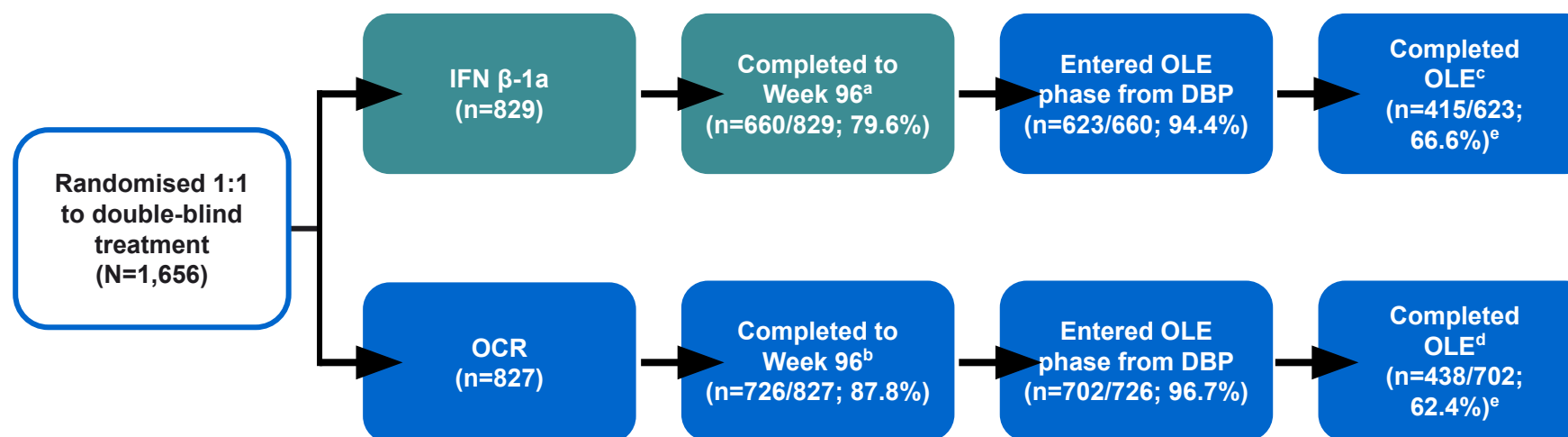
**In the DBP, patients were randomised to OCR or PBO.
At OLE initiation, patients continued OCR or switched from PBO to OCR**

CDW, confirmed disability progression; DBP, double-blind period; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo.

^aThe blinded treatment period continued until the last patient completed 120 weeks and a target of 253 CDW events was reached; ^bOLE was not mandatory – patients who declined to participate in the OLE entered safety follow-up; ^cContinued monitoring occurs if B cells are not repleted. Data cut-off: 25 November 2022.

Results

OPERA I/II OLE – Patient disposition after 10 years of follow-up



After 10 years, 52% of patients initially randomised completed the OLE period of the OPERA I/II study

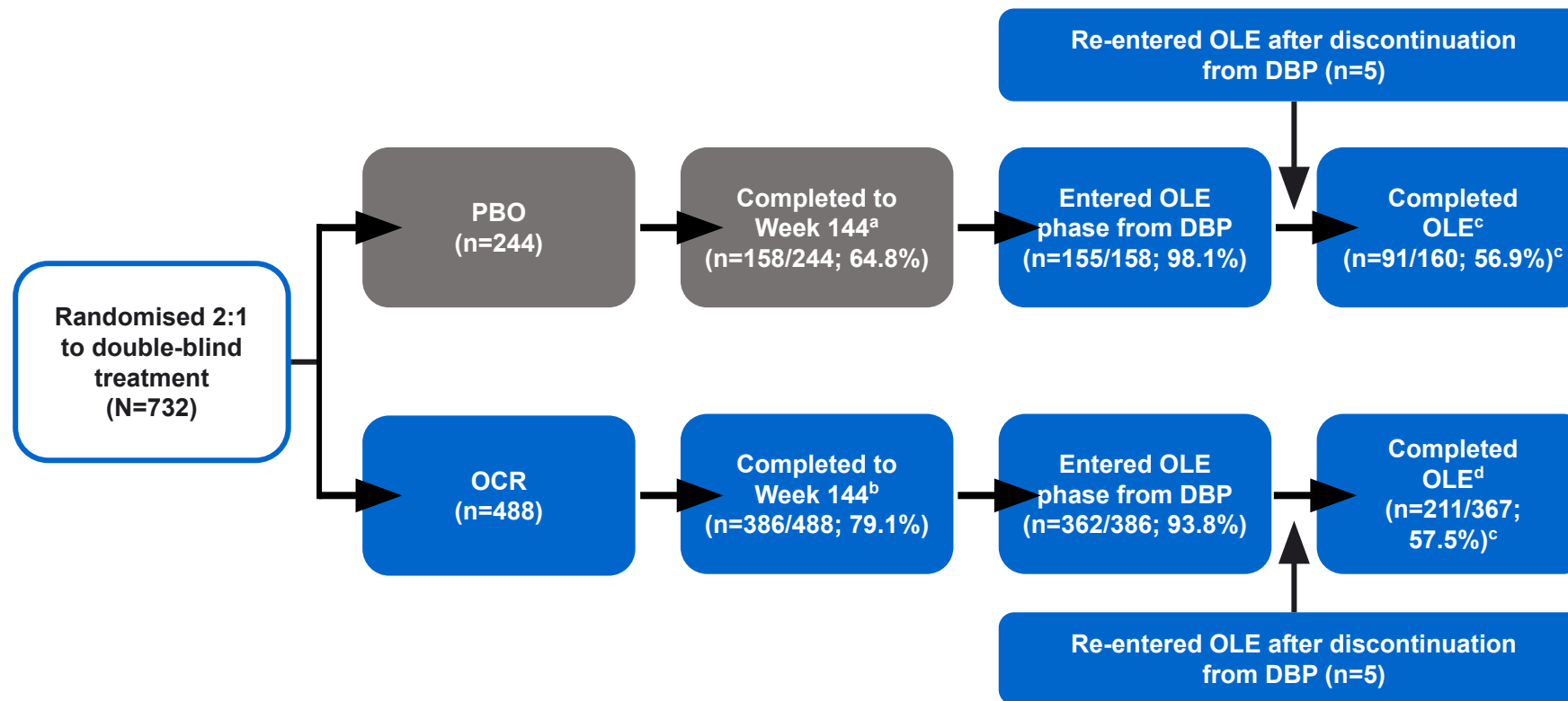
DBP, double-blind period; IFN, interferon; OCR, ocrelizumab; OLE, open-label extension.

Percentages in parentheses are of the ITT population. Clinical cut-off date: November 2022. ^a142 (17.2%) patients entered safety follow-up from DBP; ^b80 (9.7%) patients entered safety follow-up from DBP;

^c156 (25%) patients entered safety follow-up from OLE; ^d143 (20.4%) patients entered safety follow-up from OLE; ^ePercentages in parentheses are of the OLE population.

Results

ORATORIO OLE – Patient disposition after 10 years of follow-up



After 10 years, 41% of patients initially randomised completed the OLE period of the ORATORIO study

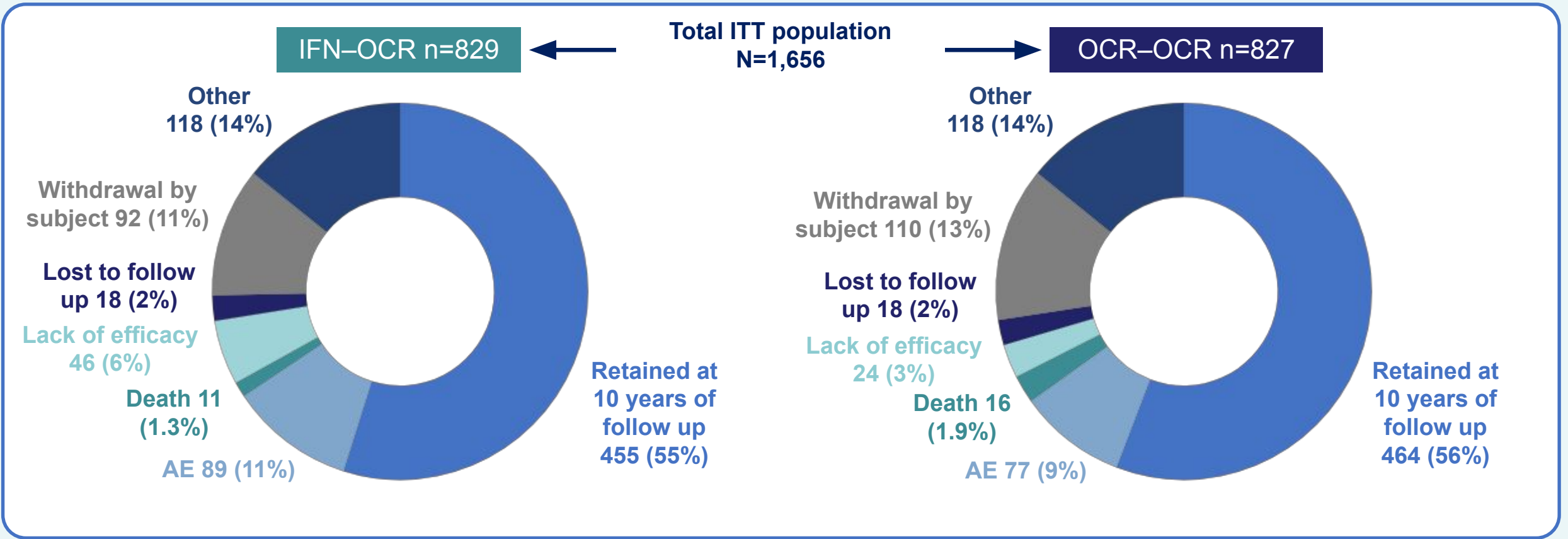
DBP, double-blind period; ITT, intention-to-treat; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo.

Percentages in parentheses are of the ITT population. Clinical cut-off date: November 2022. ^a47 (19.3%) patients entered safety follow-up from DBP; ^b75 (15.6%) patients entered safety follow-up from DBP;

^cPercentages in parentheses are of the OLE population.

Results

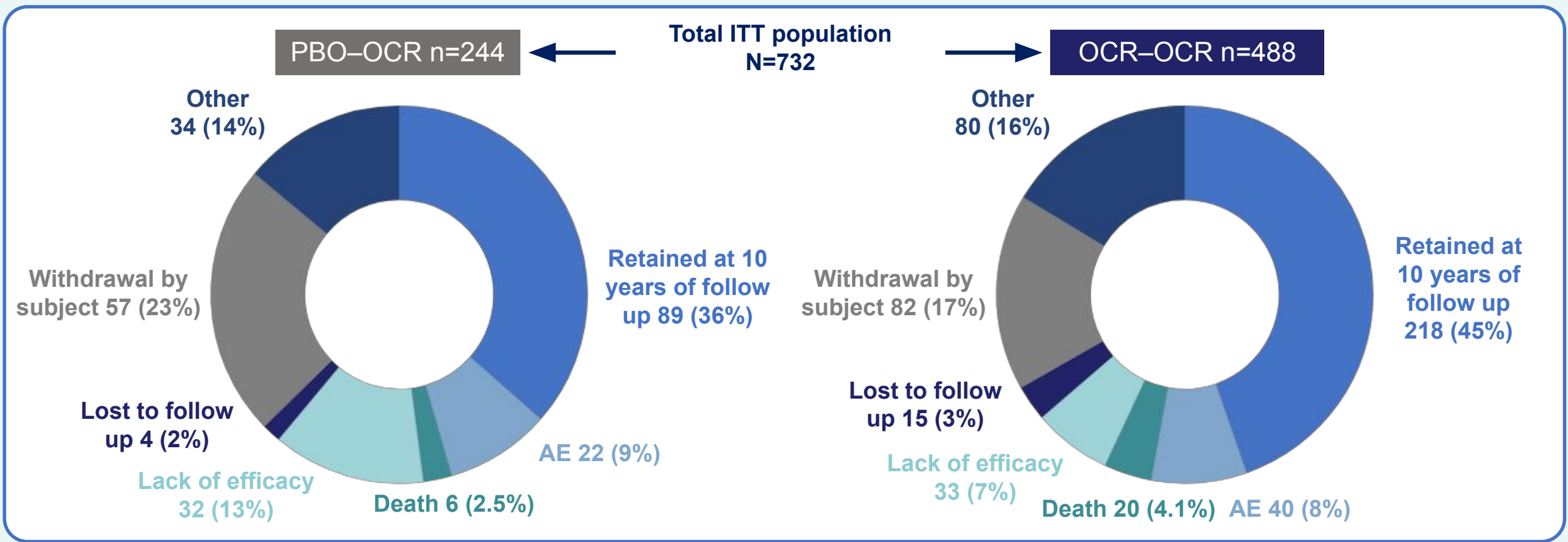
OPERA I/II treatment disposition at 10 years^a of follow-up



 **The majority of patients with RMS remained on OCR treatment throughout the 10 years of follow-up**

Results

ORATORIO treatment disposition at 10 years^a of follow-up



Almost a half of patients with PPMS receiving continuous OCR remained on treatment throughout the 10 years of follow-up

AE, adverse event; ITT, intention-to-treat; OCR, ocrelizumab; PBO, placebo; PPMS, primary progressive multiple sclerosis.
^aAt completion of the open-label extension.



<https://ter.li/xmj06m>

Ocrelizumab Dose Selection for Treatment of Paediatric Relapsing-Remitting Multiple Sclerosis: Updated Preliminary Pharmacokinetic, Safety and Efficacy Results from the OPERETTA 1 Study

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P034

Wednesday, 11 October 2023

Disclosures

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Background



Paediatric multiple sclerosis (MS) is a highly active disease, with frequent relapses and rapid accrual of MRI lesions occurring early in the disease course



Optimisation of drug treatment early in the disease has previously been shown to reduce the accrual of disability and accumulation of cognitive deficits^{1,2}



Current paediatric treatment strategies are largely based on those used in adults and treatment optimisation using highly effective therapies is required



Approximately 30–70% of patients prematurely discontinue current DMTs and 25–59% are consistently non-adherent with their medications, supporting a need for developing new therapies in this population³



Ocrelizumab (OCR) may improve outcomes, treatment adherence and offer a new treatment option for patients based on its proven efficacy in adult-onset MS



The ultimate therapeutic goal of a more potent DMT would be to achieve remission of clinical and MRI activity with minimal safety issues and high tolerability



Several studies have now demonstrated comparable tolerability and efficacy of DMTs in paediatric patients with MS compared with that reported in adults^{3–5}

DMT, disease-modifying therapy; MRI, magnetic resonance imaging.

1. Pena JA, Lotze TE. *Autoimmune Dis* 2013;2013:673947; 2. Thomas T, Banwell B. *Semin Neurol* 2008;28:69–83; 3. Narula S, et al. *Curr Treat Options Neurol* 2015;17:336; 4. Alroughani R, et al. *Pediatr Neurol* 2018;83:19–24; 5. Chitnis T, et al. *N Engl J Med* 2018;379:1017–1027.

Study Objectives and Aim



To determine the OCR dosing regimen in paediatric patients with RRMS with comparable PK and PD profiles to those of adult patients (at the approved dose of 600 mg IV)



To further investigate this regimen in the OPERETTA 2 Phase III study



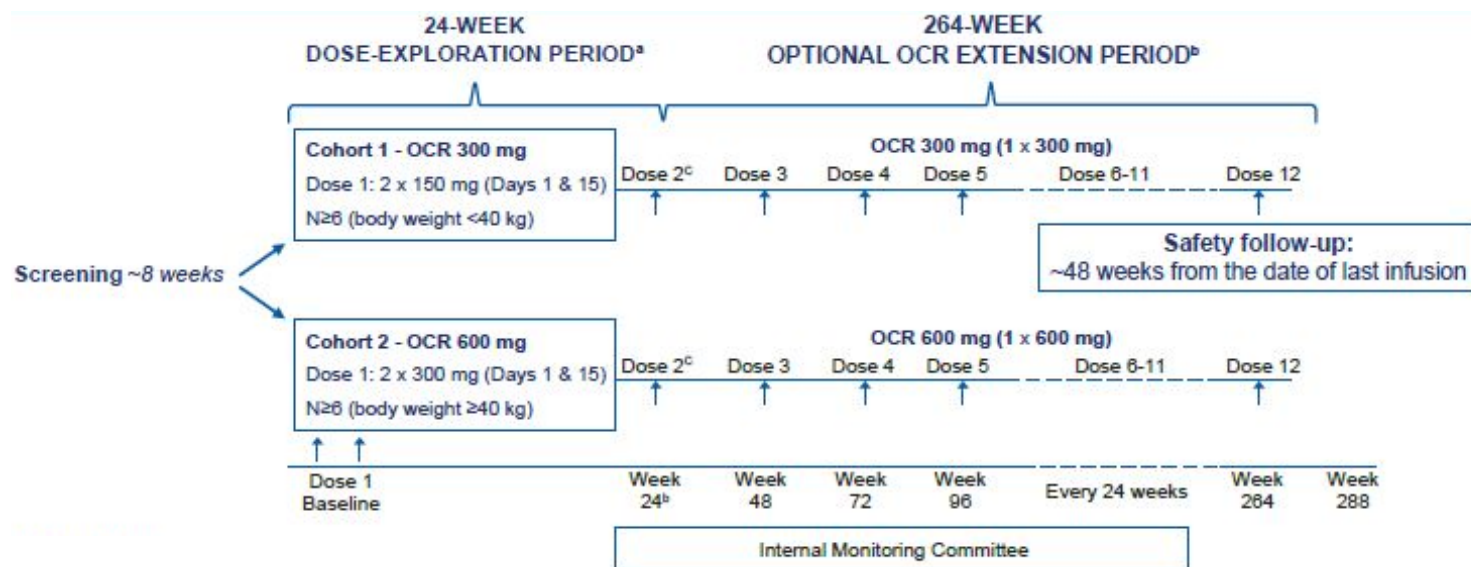
Exploratory endpoints include:

- Protocol-defined relapses
- MRI activity
 - New T1 gadolinium-enhancing (T1 Gd+) lesions at W12
 - New/enlarging T2-weighted lesion (N/E T2w-L) at W12, W24 and every 24 weeks until W96 and 48 weeks thereafter



To present updated PK, PD, safety and efficacy results from the OPERETTA 1 Phase II paediatric dose-finding study (NCT04075266)

OPERETTA I Study Design



PK and PD blood samplings
(predose, W2, W4, W8, W12, W16 and W24).

Key inclusion criteria^d

- Patients aged ≥10 to <18 years with RRMS
- Body weight ≥25 kg
- Patients naive to prior DMT or <6 months of DMT treatment within the last year and one of the following:
 - At least two relapses in the last 2 years with at least one relapse experienced in the previous year, or
 - At least two relapses in the last 2 years and ≥1 Gd+ lesion on T1-weighted brain MRI at any time within the previous year, or
 - At least one relapse in the previous year and ≥1 Gd+ on T1-weighted brain MRI at any time within the last year

Key exclusion criteria^d

- Known presence or suspicion of other neurological disorders that may mimic MS
- Infection requiring hospitalisation or treatment with IV anti-infective agents
- History or known presence of recurrent or chronic infection
- Previous treatment with B-cell-targeted therapies

DMT, disease-modifying therapy; Gd, gadolinium; IV, intravenous; MS, multiple sclerosis; OCR, ocrelizumab; PD, pharmacodynamic; PK, pharmacokinetic; RRMS, relapsing-remitting multiple sclerosis; W, week.
^aEligible patients will be allocated into one of two treatment groups depending on their body weight at screening. The first dose of OCR for the 24W period must be administered as two infusions of half the dose 14 days apart; ^bThe Optional OCR Extension period was extended by 96 weeks to allow further access to study drug. Additional data will also contribute to understanding the long-term benefit-risk profile of OCR in paediatric population; ^cAt W24, patients will have the opportunity to continue with OCR treatment by entering a 264W optional OCR extension period. For patients continuing the extension, subsequent doses of OCR will be administered if all retreatment criteria are met; ^dFor full inclusion and exclusion criteria please see Supplementary Materials.

Results

Patient Demographics and Disease Characteristics at Baseline

	Cohort 1 (N=5)	Cohort 2 (N=17)
Mean age at screening, year (range)	11.2 (10–12)	15.3 (11–17)
Female, n (%)	4 (80.0)	10 (58.8)
Race, n (%)		
White	4 (80.0)	16 (94.1)
Black	–	1 (5.9)
Asian	1 (20.0)	–
Unknown	–	–
Mean weight at screening, kg (range)	34.2 (26.4–39.0)	62.5 (42.1–105.2)
Previous DMT use, n (%)	0 (0.0)	4 (23.5)
EDSS, median (range)	1.5 (0.0–2.5)	1.0 (0.0–3.5)
T1 Gd+ lesions, mean (SD)	3.2 (4.5)	4.4 (11.9)
Hyperintense T2 lesions, mean (SD)	39.2 (18.8)	49.4 (48.9)



As for October 2022, 22 patients were enrolled in OPERETTA 1: Cohort 1 (N=5) and Cohort 2 (N=17)

Results

IRRs Within Cohort 1 and 2

	Cohort 1 (N=5)	Cohort 2 (N=17)
Total IRRs	2	34
Dose 1, Day 1	2 (n=5)	10 (n=17)
Dose 1, Day 15	0 (n=5)	4 (n=16)
Dose 2, Week 24	0 (n=4)	6 (n=17)
Dose 3, Week 48	0 (n=4)	6 (n=17)
Dose 4, Week 72	0 (n=3)	5 (n=13)
Dose 5, Week 96	0 (n=1)	2 (n=6)
Dose 6, Week 122	N/A	1 (n=4)
Dose 7, Week 146	N/A	0 (n=2)

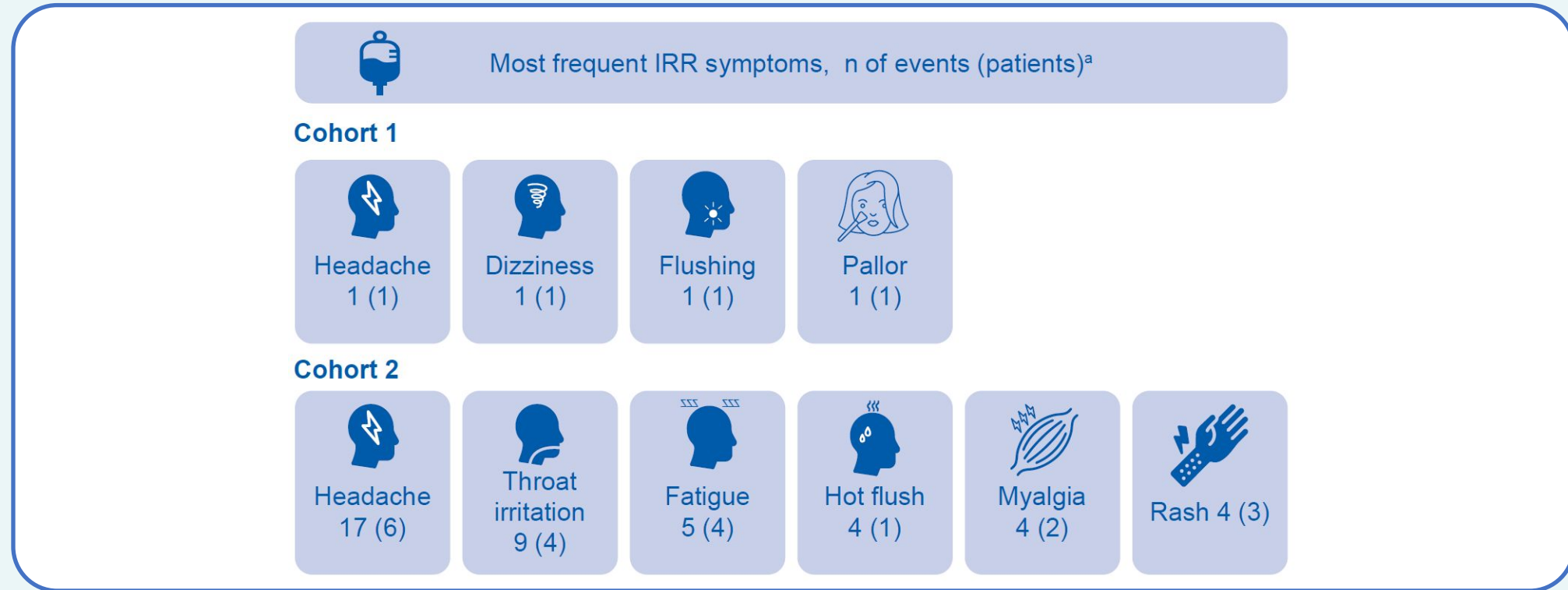
- Median treatment duration was 72.1 weeks (2–100) and 73.0 weeks (47–145) in Cohorts 1 and 2, respectively
- IRRs were reported in 14 patients (Grade 1: n=8, Grade 2: n=5 and Grade 3: n=1), who experienced 36 total events mostly observed at the first dose



Within Cohort 2, all patients completed the 24W-DEP by April 2022 and showed a similar safety profile to adult patients

Results

Most Frequent Symptoms of IRRs



Most IRR symptoms were of Grade 1 or Grade 2 intensity with only rhinorrhoea (n=2), urticaria (n=1) and dyspnoea (n=1) being of Grade 3

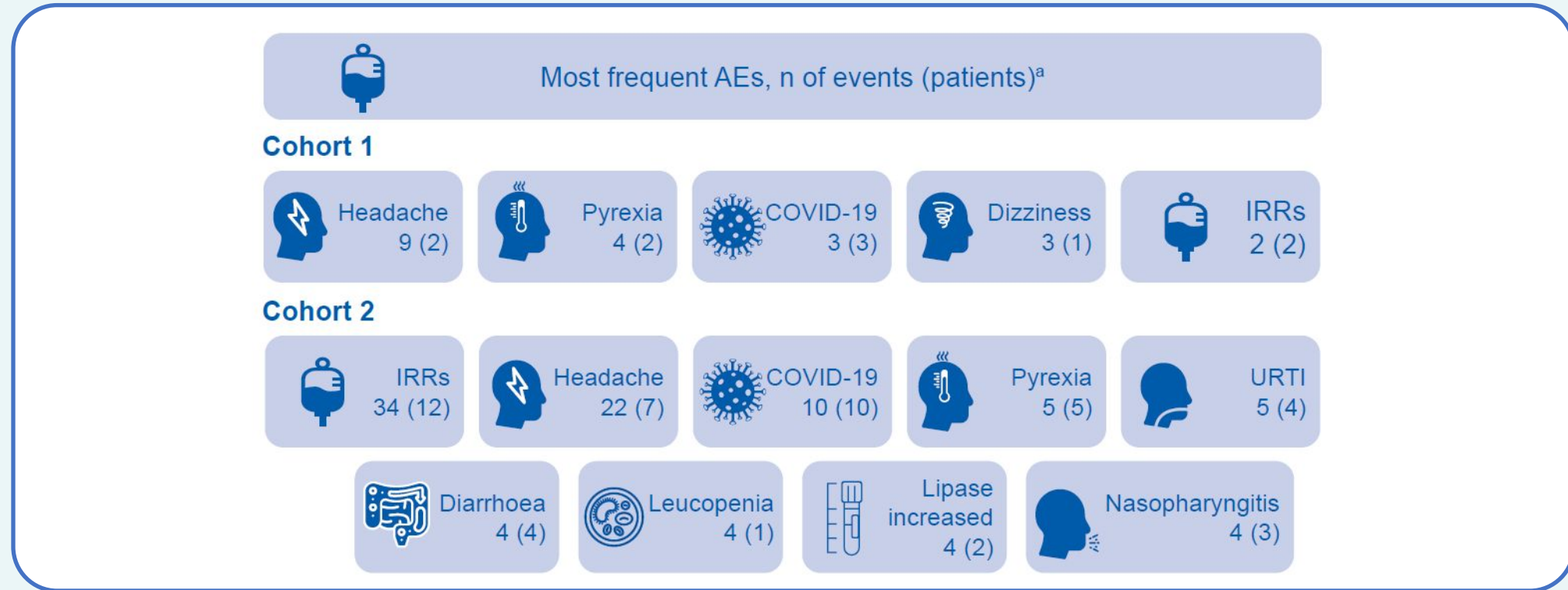
IRR, infusion-related reaction.

Data cut off: October 2022.

^aEvent frequency is given as a number of events (number of patients).

Results

Frequency and Type of AEs



Most AEs were of Grade 1 or Grade 2 intensity with IRRs (n=36, observed in 14 patients) and headache (n=31, observed in 9 patients) being the most frequent

AE, adverse event; COVID-19, coronavirus disease 2019; IRR, infusion-related reaction; URTI, upper respiratory tract infection.

Data cut off: October 2022.

^aEvent frequency is given as a number of events (number of patients).

Results

Frequency and Type of AEs (cont.)



SAEs in Cohort 1: One patient with appendicitis



SAEs in Cohort 2 (three patients):

- One patient with candida/gonococcal infection and pneumonia (all Grade 3); pain in extremity, peripheral swelling and a limb abscess (all Grade 3)
- One patient with dehydration, hypotension, conversion disorder, muscular weakness (all Grade 3) and abdominal pain (Grade 1)
- One patient with an increased blood creatine phosphokinase and alanine transaminase increase (Grade 4) started before study treatment initiation, with no underlying cause despite intensive workup

Results

Frequency and Severity of AEs

AEs ^a	Cohort 1 (OCR 300 mg) (N=5)	Cohort 2 (OCR 600 mg) (N=17)
Patients with at least one AE, n (%)	4 (80.0)	17 (100.0)
Total AEs, n	57	226
AEs by severity, n (%)		
Grade 1	1 (20.0)	4 (23.5)
Grade 2	2 (40.0)	8 (47.1)
Grade 3	1 (20.0)	4 (23.5)
Grade 4 ^b	0 (0.0)	1 (5.9)
Number of patients receiving treatment for an AE, n (%)	4 (80.0)	16 (94.1)
Number of patients with at least one SAE, n (%)	1 (20.0)	3 (17.6)
Number of patients with at least one AE deemed related to study drug by PI, n (%)	3 (60.0)	14 (82.4)

AE, adverse event; OCR, ocrelizumab; PI, principal investigator; SAE, serious adverse event.

Data cut off: October 2022.

^aNo AE led to treatment discontinuation; ^bOne Grade 4 SAE reported for the patient with an increased blood creatine phosphokinase and alanine transaminase increase (Grade 4) started before study treatment initiation, with no underlying cause.

Results

PK and B-Cell Levels in Paediatric Patients ≥ 40 kg (as of October 2022)



PK data collected from all Cohort 2 patients (N=17, body weight ≥ 40 kg) receiving 600 mg IV, showed consistent results with data observed in adult MS patients from the Phase II, OPERA I/II and ORATORIO clinical trials (WA21493, WA21092, WA21093, WA25046). Therefore, from a PK standpoint, 600 mg IV is confirmed as the appropriate dose for paediatric MS patients with a body weight of ≥ 40 kg

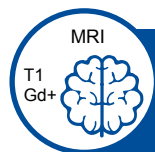


In Cohort 2 patients (N=17, body weight ≥ 40 kg), a rapid **B-cell** depletion was observed at Week 2 (median 0, range 0–3 cells/ μ l) and was prolonged until Week 24. Eight patients experienced partial B-cell reconstitution at Week 24, which remained below the lower limit of normal of the age-specific reference range^{6,7}

- This appears to be similar to what has been observed in young adult patients treated in the OPERA I/II trials

Results

Efficacy of OCR Treatment for Reducing T1 Lesions

 MRI T1 Gd+	Number of T1 Gd+ lesions	
	Cohort 1 (N=5)	Cohort 2 (N=17)
T1 lesions at baseline, mean (SD)	3.2 (4.5)	4.4 (11.9)
New T1 Gd+ lesions	57	226
Week 12	0 (n=5)	0 (n=17)

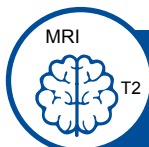
Since OCR treatment start, no patient experienced clinical relapse



No new T1 Gd+ lesions were reported at W12 in patients in either cohort

Results

Efficacy of OCR Treatment for Reducing T2 Lesions



	Number of T2 lesions	
	Cohort 1 (N=5)	Cohort 2 (N=17)
T2 lesions at baseline, mean (SD)	39.2 (18.8)	49.4 (48.9)
New/enlarging T2 lesions		
Week 12	22 (n=5)	65 (n=17)
Week 24	0 (n=4)	3 (n=17)
Week 48	0 (n=4)	1 (n=17)
Week 72	0 (n=2)	0 (n=13)
Week 96	0 (n=1)	0 (n=7)



In Cohort 2, N/E T2w-L were observed in 11 patients at W12, three at W24, one at W48, with none reported in patients who completed W72 and W96

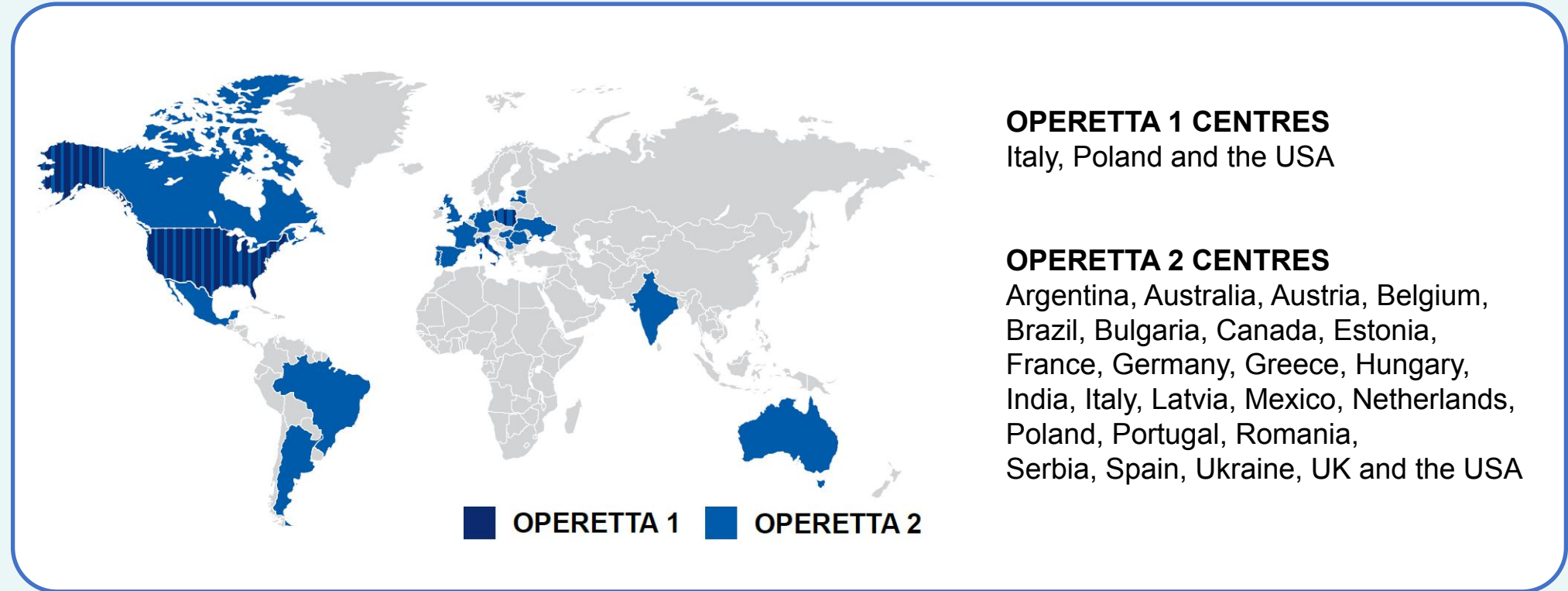
Conclusions



- Paediatric patients ≥ 40 kg treated with 600 mg ocrelizumab showed a similar PK/PD and short/mid-term safety profile to adult patients with MS, with no relapses reported to date
- The 600 mg ocrelizumab dose was chosen for further study in these patients in the OPERETTA 2 Phase III trial, which has started and is currently recruiting
- Enrolment of patients < 40 kg in OPERETTA 1 has ended

Next Steps

OPERETTA 1 and OPERETTA 2 Centres



OPERETTA 2 study (NCT05123703), a double-blind, double-dummy study, which is now recruiting, is evaluating the safety and efficacy of ocrelizumab compared with fingolimod in children and adolescents with RRMS aged between 10 and <18 years

Supplementary Materials

Methods

Study inclusion and exclusion criteria

Inclusion Criteria:

- Body weight ≥ 25 kg
- Diagnosis of RRMS
- EDSS 0–5.5 (inclusive)
- Neurologic stability for ≥ 30 days prior to screening, and between screening and baseline
- Patients naïve to prior DMT (or patients <6 months of DMT within the past year) must have: ≥ 2 relapses in the last 2 years, with at least one relapse experienced in the previous year or ≥ 2 relapses in the last 2 years and 1 Gd-enhancing T1 lesion on brain MRI at any time within the previous year or ≥ 1 relapse in the previous year and 1 Gd-enhancing T1 lesion on brain MRI within the last year
- Patients who have had at least 6 contiguous months of DMT (e.g., any IFN or GA) within the past 1 year must have evidence of disease activity occurring after the full 6-month course of treatment, that is, ≥ 1 relapse or 1 Gd-enhancing T1 lesion on brain MRI

Exclusion Criteria

- Known presence or suspicion of other neurologic disorders that may mimic MS
- AQP4 and/or MOG antibody positive
- Infection requiring hospitalization or treatment with IV anti-infective agents
- History or known presence of recurrent or chronic infection
- Previous treatment with B-cell-targeted therapies
- Percentage of CD4 $< 30\%$
- Absolute Neutrophil Count $< 1.5 \times 1000/\text{microliter}$
- Lymphocyte count below LLN for age- and sex-specific reference range



<https://ter.li/wbr1yr>

Pregnancy and Infant Outcomes in Women Receiving Ocrelizumab for the Treatment of Multiple Sclerosis: Analysis of the Largest Available Outcomes Database

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¹Katholisches Klinikum Bochum, St. Josef Hospital, Universitätsklinikum, Bochum, Germany; ²Neurology, Hospital Clínico San Carlos, Idissc, Madrid, Spain; ³Service de Neurologie et Sclérose en Plaques, Fondation Eugène Devic EDMUS contre la Sclérose en Plaques, Hôpital Neurologique Pierre Wertheimer, Lyon, France; ⁴NICU, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; ⁵Division of Maternal-Fetal Medicine, Brigham and Women's Hospital, Boston, MA, USA; ⁶Preventive Neurology Unit, Wolfson Institute of Population Health, Queen Mary University of London, London, UK ⁷F. Hoffmann-La Roche Ltd, Basel, Switzerland; ⁸Roche Products Ltd, Welwyn Garden City, UK; ⁹Department of Neurology, UCSF Weill Institute for Neurosciences, University of California San Francisco, San Francisco, CA, USA.

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P061

Wednesday, 11 October 2023

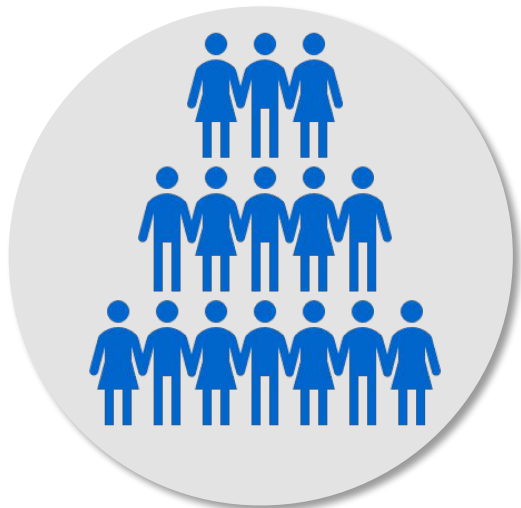
Disclosures

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C Oreja-Guevara received honoraria for consulting and serving on advisory boards from Biogen Idec., F. Hoffmann-La Roche Ltd, Genzyme, Merck, Novartis and Teva. **S Vukusic** received grants and research support from Biogen, Novartis, Merck-Serono, F. Hoffmann-La Roche Ltd and Sanofi-Genzyme; consulting fees from F. Hoffmann-La Roche Ltd, Biogen, BMS-Celgene, Janssen, Novartis, Merck-Serono, Sanofi-Genzyme and Teva; and payment/honoraria for lectures, speaking etc. from F. Hoffmann-La Roche Ltd, Biogen, BMS-Celgene, Novartis, Merck-Serono, Sanofi-Genzyme and Teva. **C Pietrasanta** received consulting fees from F. Hoffmann-La Roche Ltd. **T McElrath** received research support from the National Institutes of Health and NX Prenatal Inc. compensation for service on the scientific advisory boards of Mirvie Inc., F. Hoffmann-La Roche Ltd and Momenta Pharmaceuticals, Inc. and consulting fees from F. Hoffmann-La Roche Ltd and Comanche Biopharma.

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Background and Objective



As of March 2023, more than 300,000 people with MS had initiated ocrelizumab globally¹



Women with MS of childbearing potential represent a significant number of people with MS²



The number of women with MS exposed to ocrelizumab before, during and after pregnancy is increasing³



To report on pregnancy and infant outcomes among women with MS exposed to ocrelizumab before or during pregnancy up to July 2023

Methods:

Sources, Reporting Period and Type, and Definition of In Utero Exposure

Sources

- Reports from the Roche Global Safety Database:
(1) interventional or non-interventional clinical studies, (2) spontaneous reports, (3) non-interventional programme, (4) published literature

Reporting type

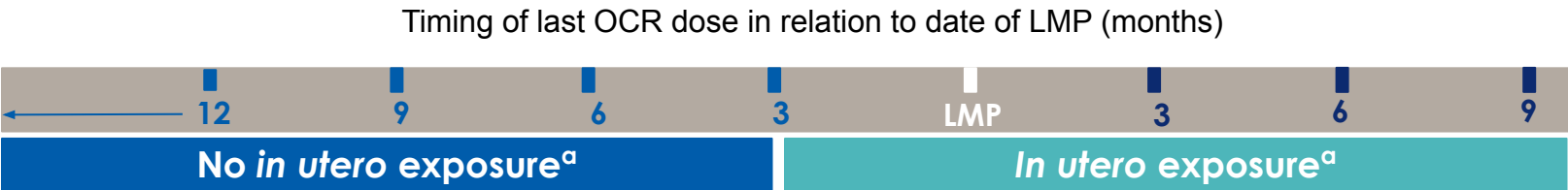
- **Prospective:** Final outcomes were unknown at initial notification
- **Retrospective:** Final outcomes were known at initial notification

Reporting period

- Cumulative pregnancies reported from

November 2008 to 12 July 2023

Exposure



IgG1, immunoglobulin G1; LMP, last menstrual period; OCR, ocrelizumab; t_{1/2}, half-life.
^aExposure classification is based on OCR t_{1/2}=26 days (full elimination from the body is expected by approximately 4.5 months) and assuming no relevant placental transfer of IgG1 antibodies occurs prior to 12 weeks of gestation.^{10,11} **In utero exposure:** The last OCR infusion was received ≤3 months prior to the LMP or throughout pregnancy. **No in utero exposure:** The last OCR infusion was received >3 months prior to the LMP. **Unknown exposure:** Where the exposure timing could not be determined or was missing.
10. Palmeira P, et al. *Clin Dev Immunol* 2012;2012:985646; 11. Simister NE. *Vaccine* 2003;21:3365–3369.

Methods:

Definitions of Pregnancy and Infant Outcomes

Pregnancy outcomes

Infant outcomes

Pregnancy

Ectopic pregnancy

Elective termination

Intrauterine foetal death 22 gestational weeks^a

Spontaneous abortion

Stillbirth¹²

Live births

37 gestational weeks

Preterm

Full-term

Major congenital anomalies

Classified based on EUROCAT Guide 1.5¹³

First year of life^b

- Infections and hospitalisations
- Breastfeeding status
- Adverse laboratory outcomes (e.g. decreased B cell counts)
- Vaccinations

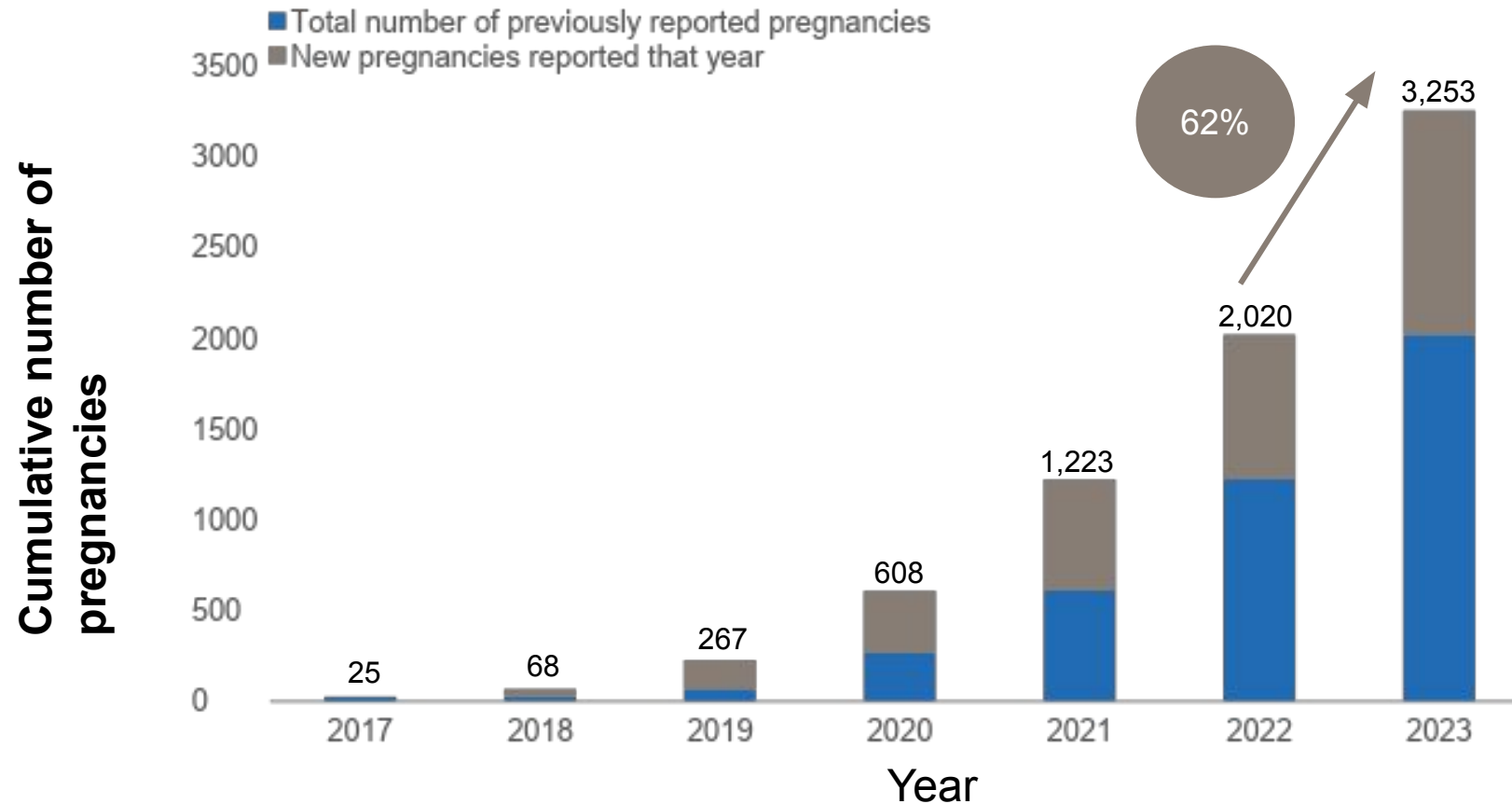
EMA, European Medicines Agency; EUROCAT, European Surveillance of Congenital Anomalies.

^aAccording to EMA definition⁶ (other definitions use different thresholds, e.g. 20 or 24 completed weeks); ^bCollected via guided questionnaires provided at birth and at 3, 6 and 12 months of age for follow-up.

12. Tavares Da Silva F, et al. *Vaccine* 2016;34:6057–6068; 13. European Surveillance of Congenital Anomalies (EUROCAT) Guide 1.5. Available from: https://eu-rdplatform.jrc.ec.europa.eu/eurocat/data-collection/guidelinesfor-data-registration_en Accessed September 2023; 6. European Medicines Agency (EMA). Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation data. November 2005. Available from: https://www.ema.europa.eu/en/documents/regulatoryprocedural-guideline/guideline-exposure-medicinal-productsduring-pregnancy-need-post-authorisation-data_en.pdf.

Results

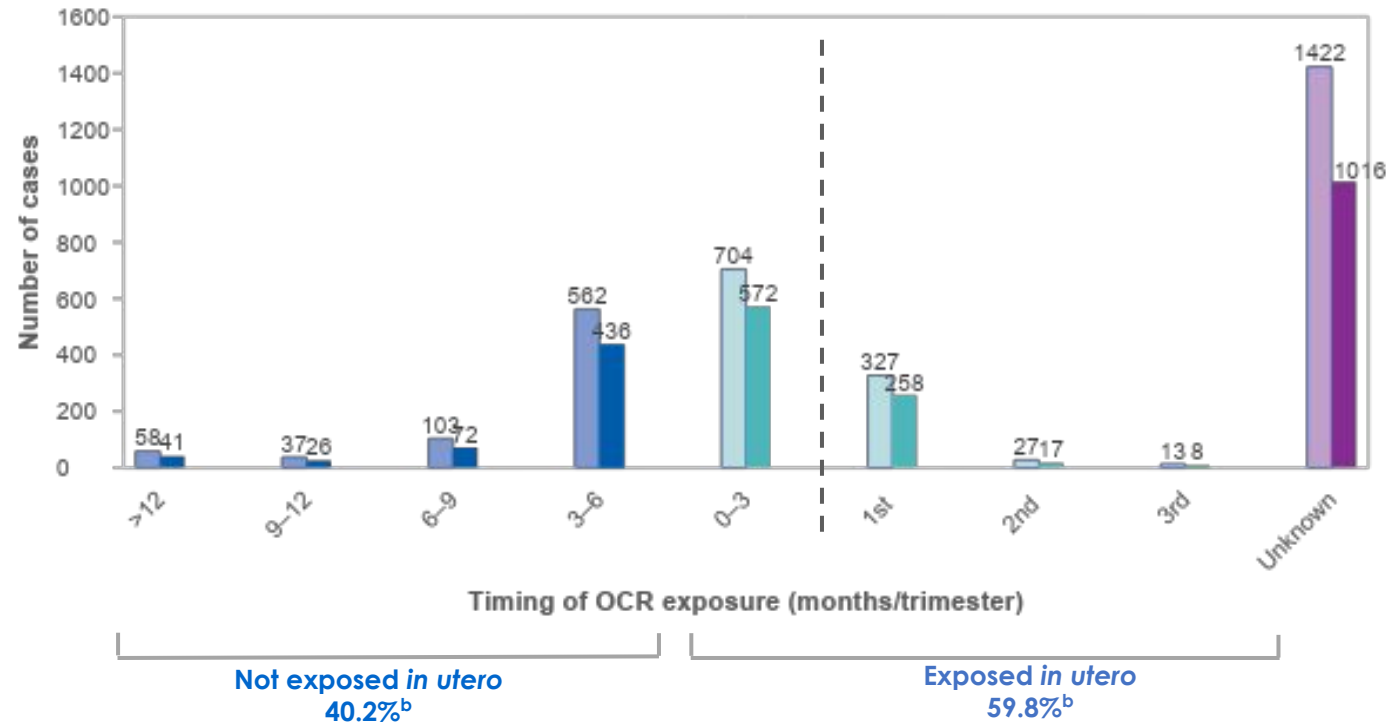
The cumulative number of pregnancies reported among women with MS treated with OCR continues to grow⁷



There was a 62% increase in the number of cases from 2022 to 2023

Results

MS Pregnancies by In Utero Exposure:^a All Cases and Prospective Cases



- Median age at LMP (range) was 32.0 (16–60) years^c
- Timing of last OCR dose in relation to LMP was known for 58% of all or prospective cases
- Where exposure was known, most cases were reported as exposed *in utero* and most exposed to the last OCR dose 0–3 months before LMP followed by 1st trimester of pregnancy
- For cases with no exposure *in utero*, most were reported in mothers exposed to the last OCR dose 3–6 months before LMP

IgG1, immunoglobulin G1; LMP, last menstrual period; OCR, ocrelizumab; $t_{1/2}$, half-life.

^aDetermined according to timing of last OCR dose in relation to date of LMP (months); exposure classification is based on OCR $t_{1/2}$ =26 days (full elimination from the body is expected by approximately 4.5 months) and assuming no relevant placental transfer of IgG1 antibodies occurs prior to 12 weeks of gestation; ^bPercentages represent fractions of prospective cases with known outcome and known timing of last OCR dose ^cCases with known age: n=2,676 (82.3%).

Results

Pregnancy Outcomes by Exposure in Prospective Cases^a

- **Most pregnancies resulted in live births** (83.6%), and proportions were similar in the exposed and non-exposed groups
- **Most live births were full term** (61.4%) and a smaller proportion were preterm (8.5%)
 - Proportions were similar in the exposed and non-exposed groups
 - **Gestational age was unknown** in (30.2%) of cases
- **A higher proportion of elective terminations** occurred in the exposed group, but the overall cumulative proportion of elective abortions is decreasing (5.1% in 2023 versus 11.5% in 2022 and 15.7% in 2021)⁷
- **A smaller proportion of spontaneous abortions** occurred in the exposed group (**7.4%**) compared with the non-exposed group (**9.1%**)
- The overall rate of **stillbirths** (<0.1%) remained low

Number of MS pregnancies	Non-exposed (N=575)	Exposed (N=855)	Unknown (N=1,016)	Total (N=2,446)	Epidemiological rates	
Known outcomes	 n=351	 n=512	 n=282	 n=1,145	MS background rate	General population background rate
Live births^b	 88.3%	 84.2%	 76.6%	 83.6%	 70.2–77.2 ¹	 70.2 ¹
Full term (≥37 weeks) ^c	 70.9%	 65.7%	 39.1%	 61.4%	–	–
Preterm (<37 weeks) ^c	 8.4%	 9.5%	 6.5%	 8.5%	 7.2–15.4 ^{1,4}	 6.5–10.1 ⁴
Unknown gestational age ^c	 20.7%	 24.8%	 54.4%	 30.2%	–	–
Ectopic pregnancy^b	 0.9%	 0.8%	 2.5%	 1.2%	 0.6–1.3 ^{1,2}	 1.1–2.0 ^{1,2}
Elective termination^b	 1.7%	 7.4%	 5.0%	 5.1%	 10.7–18.1 ¹	 18.2 ¹
Intrauterine foetal death^b						
Spontaneous abortion, ≤22 weeks ^b	 9.1%	 7.4%	 16.0%	 10.0%	 10.5–11.6 ^{1–3}	 10.0–20.0 ^{1,2}
Stillbirth, >22 weeks ^b	–	 0.2%	–	 <0.1%	 0.3–0.6 ^{1,4}	 0.2–0.7 ^{1,4}

LMP, last menstrual cycle; MS, multiple sclerosis; OCR, ocrelizumab.

1. Anderson JB, et al. *Eur J Neurol* 2022; 30 (1): 162–171; 2. Khan E, et al. *J Neuroimmunol* 2023; 24; 383: 578178; 3. Lopez-Leon S, et al. *J Neurol* 2020; 267(9): 2721–2731;

4. MacDonald SC, et al. *Am J Epidemiol* 2019; 1;188 (1): 57–66. 7. Oreja-Guevara C, et al. *ECTRIMS* 2022;PO038.

The dash indicates that no cases were reported; Please see Supplementary Materials for details on all cases, pregnancy outcomes by more granular timings of OCR exposure and listing of stillbirths.

^aIn utero exposure based on timing of last OCR dose relative to LMP; ^bPercentages represent fractions of the total known outcomes of the respective exposure categories (not exposed *in utero*, exposed *in utero*, unknown exposure, total);

^cPercentages represent fractions of the total live births for the respective exposure categories (not exposed *in utero*, exposed *in utero*, unknown exposure, total).

Results

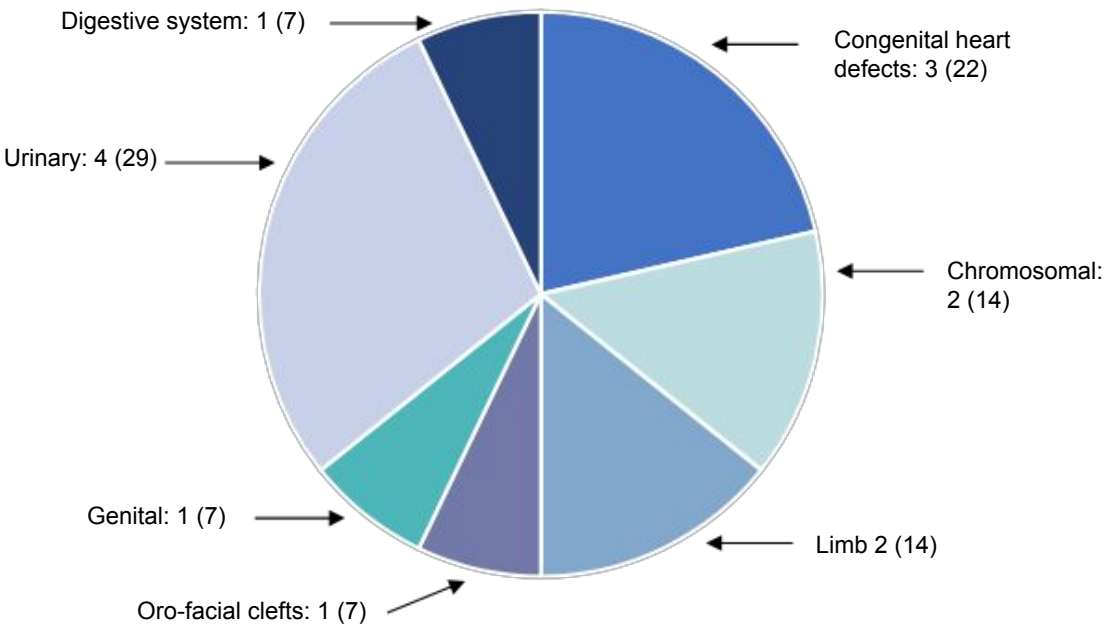
Major Congenital Anomalies in Pregnancies with Known Outcomes

Proportions and types are consistent with epidemiological background^{1–6}

	Non-exposed	Exposed	Unknown exposure	Total
Live births	N=310	N=431	N=216	N=957
Live birth with MCA, n (%) ^a	4 (1.3%)	7 (1.6%)	1 (0.5%)	12 (1.3%)
Full term with MCA, n	3	4	1	8
Preterm with MCA, n	1	3	–	4
Unknown GA with MCA, n	–	–	–	–
Stillbirths >22 weeks	N=0	N=1	N=0	N=1
Stillbirth with MCA, n	–	1	–	1
Live birth/stillbirth with MCA, n(%)^b	4 (1.3%)	8 (1.9%)	1 (0.5%)	13 (1.4%)

Around 2–4% of all children born every year will have a MCA^{1–5}

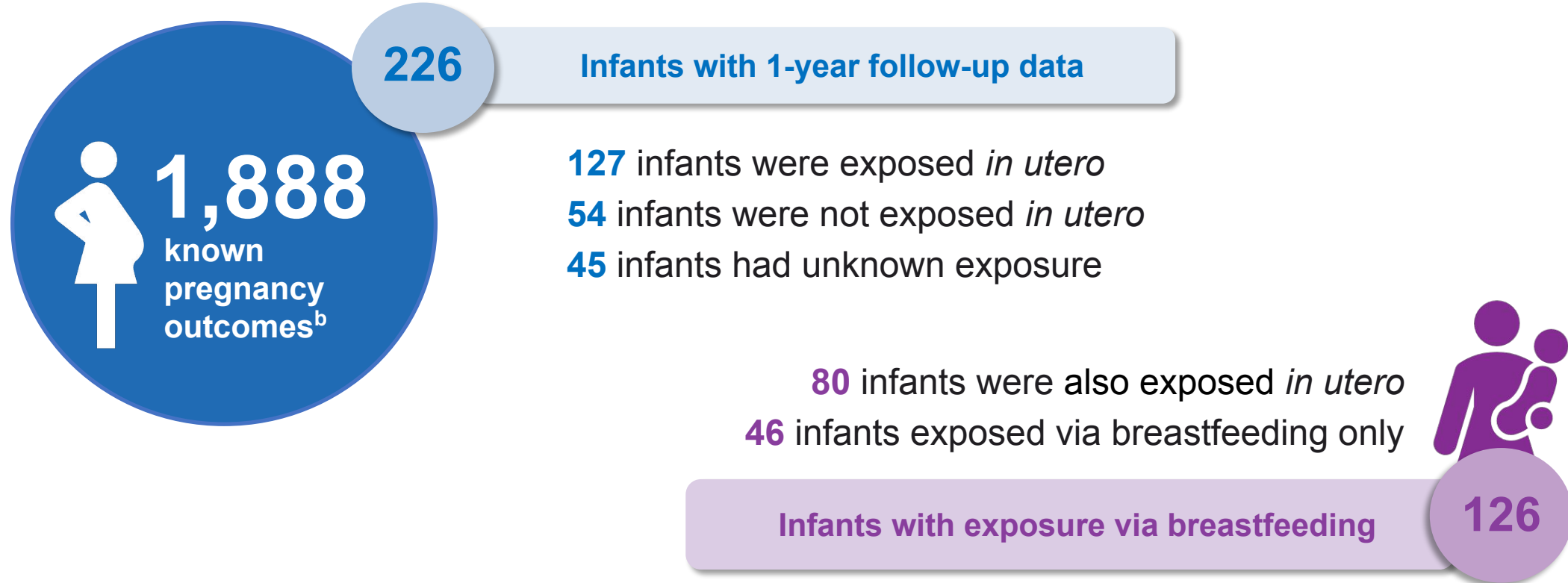
Distribution of Major Congenital Anomalies by EUROCAT¹³ Category, n (%)^c



EUROCAT, European Surveillance of Congenital Anomalies; GA, gestational age; MCA, major congenital anomaly. Please see Supplementary Materials for details on the listing of major congenital anomalies. The dash indicates that no cases were reported. ^aPercentages represent fractions of total live births for the respective exposure category; ^bPercentages represent fractions of the total stillbirths/live births for the respective exposure category; ^cThe number of major congenital anomalies prospectively reported is 14, as one live birth reported two MCAs; see Supplementary Materials for all cases. 1. Anderson JB, et al. *Eur J Neurol* 2022; 30 (1): 162–171; 2. Khan E, et al. *J Neuroimmunol* 2023; 24; 383: 578178; 3. Lopez-Leon S, et al. *J Neurol* 2020; 267(9): 2721–2731; 4. MacDonald SC, et al. *Am J Epidemiol* 2019; 1;188 (1): 57–66; 5. Centers for Disease Control and Prevention (CDC). *MMWR Morb Mortal Wkly Rep* 2008;57:1–5. Available from: <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5701a2.htm>. Accessed: September 2023; 6. European Medicines Agency (EMA). Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation data. November 2005. Available from: https://www.ema.europa.eu/en/documents/regulatoryprocedural-guideline/guideline-exposure-medicinal-productsduring-pregnancy-need-post-authorisation-data_en.pdf. 13. European Surveillance of Congenital Anomalies (EUROCAT) Guide 1.5. Available from: https://eu-rdplatform.jrc.ec.europa.eu/eurocat/data-collection/guidelinesfor-data-registration_en Accessed September 2023.

Results

Reports of Infant Outcomes Throughout the First Year of Life are Very Limited^a



^aFor further details, see the Supplementary Materials. ^bIncludes all known outcomes, either prospectively or retrospectively reported.

Conclusions



In utero exposure to ocrelizumab did not increase the risk of adverse pregnancy or infant outcomes compared with epidemiological background of both MS and general population^{1–6}



This is the largest dataset of pregnancy outcomes for an anti-CD20 therapy in MS⁷



Reports of infant outcomes throughout the first year of life are very limited; continuous improvement of reporting by healthcare professionals remains a critical component to increase available evidence



Pregnancy and infant outcomes are important to women with MS. Patients and data continue to be collected through post-marketing commitments (OCREVUS pregnancy registry)⁸ and two prospective Phase IV studies examining infant B cell levels and ocrelizumab pharmacokinetics across the placenta (MINORE, MN42988) and breastmilk (SOPRANINO, MN42989)⁹

1. Anderson JB, et al. *Eur J Neurol* 2022; 30 (1): 162–171; 2. Khan E, et al. *J Neuroimmunol* 2023; 24; 383: 578178; 3. Lopez-Leon S, et al. *J Neurol* 2020; 267(9): 2721–2731; 4. MacDonald SC, et al. *Am J Epidemiol* 2019; 1;188 (1): 57–66; 5. Centers for Disease Control and Prevention (CDC). *MMWR Morb Mortal Wkly Rep* 2008;57:1–5. Available from: <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5701a2.htm>. Accessed: September 2023; 6. European Medicines Agency (EMA). Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation data. November 2005. Available from: https://www.ema.europa.eu/en/documents/regulatoryprocedural-guideline/guideline-exposure-medicinal-productsduring-pregnancy-need-post-authorisation-data_en.pdf. 7. Oreja-Guevara C, et al. *ECTRIMS* 2022;PO038; 8. OCREVUS® Pregnancy Registry. 2021. Available from: <https://www.ocrevuspregnancyregistry.com/>. Accessed September 2023; 9. Bove R, et al. *Mult Scler Relat Disord* 2022;64:103963.

Supplementary Material

Contents

- **Background**
- **Methods**
 - *Definition of pregnancy and infant outcomes*
- **Results**
 - *MS pregnancies by outcome status, data source, and reporting type*
 - *Pregnancy outcomes by exposure: prospective cases and all cases*
 - *Pregnancy outcomes by exposure: different ocrelizumab washout periods*
 - *Stillbirths/Intrauterine foetal deaths: case characteristics*
 - *Major congenital anomalies: summary of data*
 - *Major Congenital Anomalies in Pregnancies with Known Outcomes in all cases*
 - *Major congenital anomalies: case characteristics*

Methods

Definitions of pregnancy and infant outcomes^{1,2}

Pregnancy outcome ¹	Definition		
Ectopic pregnancies	Extrauterine pregnancy, most often in the fallopian tube.		
Elective or therapeutic terminations	Induced or voluntary foetal loss during pregnancy due to medical or any other reasons.		
Intrauterine foetal death^a	Death prior to complete expulsion or extraction from the mother of a foetus, irrespective of the duration of pregnancy:		
	Spontaneous abortion* Loss of a foetus before 22 completed weeks of gestation.	Stillbirth* Loss of a foetus after 22 completed weeks of gestation and prior to birth.	Intrauterine foetal death If gestational age unknown, not reported or could not be determined.
*For cases of spontaneous abortion or stillbirth where the exact gestational age was not reported or could not be calculated, a definition of gestational age ≤22 or >22 completed weeks was assumed if there was reliable and objective documentation that confirmed the spontaneous abortion or stillbirth, respectively (this includes an autopsy report, results of prenatal tests [e.g. ultrasound] or a well-documented clinical diagnosis recorded in the healthcare records).			
Live birth	Complete expulsion or extraction from the mother of a foetus, irrespective of the duration of the pregnancy, that, after such separation, breathes or shows any evidence of life.		
	Pre-term live birth Birth at less than 37 completed weeks (less than 259 days) of gestation.	Full-term birth Birth at any time from 37 completed weeks (more than 259 days) of gestation.	Unknown Gestational age at birth unknown or not reported.
Infant outcome ²	Definition		
Major congenital anomaly	Congenital anomalies (birth defects) are defined as any morphological, functional and/or biochemical developmental disturbance in the embryo or foetus whether detected at birth or not. The term congenital anomaly is broad and includes congenital abnormalities (structural birth defect, sometimes congenital malformation, foetal defect), foetopathies, genetic diseases with early onset or developmental delay. Congenital anomalies are classified as major according to the EUROCAT Classification System Version 1.5.		

EMA, European Medicines Agency; EUROCAT, European Surveillance of Congenital Anomalies; FDA, Food and Drug Administration; WHO, World Health Organization. ^aThreshold of 22 weeks according to the EMA definition; global variations in the definition of spontaneous abortion versus stillbirths exist (FDA 20 weeks, UK 24 weeks, WHO 28 weeks).³

1. EMA Guideline on the exposure to Medicinal Products during pregnancy.

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-exposure-medicinal-products-during-pregnancy-need-post-authorisation-data_en.pdf. Accessed September 2023; 2. European Surveillance of Congenital Anomalies (EUROCAT) Guide 1.5. Available from: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/data-collection/guidelines-for-data-registration_en.

Accessed September 2023; 3. Tavares Da Silva F, *et al.* *Vaccine* 2016;34:6057–6068.

MS pregnancies by outcome status, data source, and reporting type

- Of 3,253 cumulative MS pregnancies, 1888 (58.0%) had a known outcome
- 2,515 (77.3%) cases were from non-interventional studies, of which 231 from the OCREVUS pregnancy registry (WA40063)
- 2,446 (75.2%) cases were prospectively reported

Distribution of cases, n (%) ^a		N=3,253
By outcome status (%)		
Known outcome		1,888 (58.0)
Unknown, not reported or lost to follow-up		1,098 (33.8)
Pregnancy ongoing		267 (8.2)
By data source (%)		
Non-interventional study/program		2,515 (77.3)
Ocrevus pregnancy registry		231 (7.1)
Spontaneous report		448 (13.8)
Clinical studies		210 (6.5)
Literature review (case reports, case series)		80 (2.5)
By reporting type (%)		
Prospective		2,446 (75.2)
Retrospective		800 (24.6)
Unknown		7 (0.2)

Pregnancy outcomes by exposure^a: prospective cases and all cases

	Prospective cases				All cases			
Number of MS pregnancies	Non-exposed, % (N=575)	Exposed, % (N=855)	Unknown, % (N=1,016)	Total, % (N=2,446)	Non-exposed, % (N=760)	Exposed, % (N=1,071)	Unknown, % (N=1,422)	Total, % (N=3,253)
Known outcomes	 n=351	 n=512	 n=282	 n=1,145	 n=528	 n=715	 n=645	 n=1,888
Live births^b	 88.3	 84.2	 76.6	 83.6	 84.5	 82.4	 70.4	 78.9
Full term (≥37 weeks) ^c	 70.9	 65.7	 39.1	 61.4	 67.2	 61.1	 27.9	 52.9
Pre-term (<37 weeks) ^c	 8.4	 9.5	 6.5	 8.5	 7.2	 9.2	 5.6	 7.5
Unknown gestational age ^c	 20.7	 24.8	 54.4	 30.2	 25.6	 29.7	 66.5	 39.6
Live birth with MCA	 1.3	 1.6	 0.5	 1.3	 0.9	 1.5	 0.4	 1.0
Ectopic pregnancy^b	 0.9	 0.8	 2.5	 1.2	 0.9	 0.6	 2.0	 1.2
Elective/therapeutic termination^b	 1.7	 7.4	 5.0	 5.1	 2.8	 7.0	 5.0	 5.1
Intrauterine foetal death^b								
Spontaneous abortion ≤22 weeks	 9.1	 7.4	 16.0	 10.0	 11.4	 9.4	 22.3	 14.4
Stillbirth, >22 weeks	 -	 0.2	 -	 <0.1	 0.2	 0.7	 -	 0.3
Unknown gestational age	 -	 -	 -	 -	 0.4	 -	 0.3	 0.2
Live/still births/unknown gestational age with MCA ^d	 1.3	 1.9	 0.5	 1.4	 0.9	 1.7	 0.7	 1.1

^aIn utero exposure based on timing of last OCR dose relative to the last menstrual period; ^bPercentages represent fractions of the total known outcomes of the respective exposure categories (not exposed *in utero*, exposed *in utero*, unknown exposure, total); ^cPercentages represent fractions of the total live births for the respective exposure categories (not exposed *in utero*, exposed *in utero*, unknown exposure, total); ^dPercentages represent fractions of total live births and still births. MCA, major congenital anomaly; MS, multiple sclerosis; OCR, ocrelizumab.

Pregnancy outcomes by exposure^a: different ocrelizumab washout periods

Exposure based on last ocrelizumab dose	Not exposed <i>in utero</i> , prospective cases			Exposed <i>in utero</i> , prospective cases			Total prospective cases (n=2,446)
Number of MS pregnancies	<6 months (n=139)	<3-6 months (n=436)	Total not exposed <i>in utero</i> (n=575)	0-3 months (n=572)	During pregnancy (n=283)	Total exposed <i>in utero</i> (n=855)	
Known outcomes	 n=81	 n=270	 n=351	 n=343	 n=169	 512	 1,145
Live births^b	 91.4%	 87.4%	 88.3%	 82.5%	 87.6%	 84.2%	 83.6%
Full term (≥37 weeks) ^c	 68.5%	 71.6%	 70.9%)	 67.1%	 62.8%	 65.7%	 61.4%
Preterm (<37 weeks) ^c	 6.8%	 8.9%	 8.4%	 9.9%	 8.8%	 9.5%	 8.5%
Unknown gestational week ^c	 24.7%	 19.5%	 20.7%	 23.0%	 28.4%	 24.8%	 30.2%
Major congenital anomalies ^c	-	 1.7%	 1.3%	 1.8%	 1.4%	 1.6%	 1.3%
Ectopic pregnancy^b	-	 1.1%	 0.9%	 1.2%	-	 0.8%	 1.2%
Therapeutic/elective abortion	-	 2.2%	 1.7%	 6.7%	 8.9%	 7.4%	 5.1%
<i>Intrauterine/foetal death^b</i>							
Spontaneous abortion (≤22 weeks)	 8.6%	 9.3%	 9.1%	 9.3%	 3.6%	 7.4%	 10.0%
Stillbirth (>22 weeks)	-	-	-	 0.3%	-	 0.2%	 <0.1%
Live births/stillbirths with MCA^d	-	 1.7%	 1.3%	 2.1%	 1.4%	 1.9%	 1.4%

Data as of 12 July 2023. Dash indicates a data value of 0. ^a*In utero* exposure based on timing of last OCR dose relative to the last menstrual period; ^bPercentages represent fractions of the total known outcomes of the respective exposure categories (not exposed *in utero*, exposed *in utero*, unknown exposure, total); ^cPercentages represent fractions of the total live births for the respective exposure categories (not exposed *in utero*, exposed *in utero*, unknown exposure, total). ^dPercentages represent fractions of total live births and still births MCA, major congenital anomaly; MS, multiple sclerosis; OCR, ocrelizumab.

Stillbirths/Intrauterine foetal deaths: case characteristics (n=9)

- As of July 2023, one prospectively reported stillbirth occurred
- No new prospective cases have been reported since the 2022 datacut
- The majority of cases presented with comorbidities and/or concomitant medications as potential confounders

Type ¹	Case description	Maternal age, years	Gestational age, weeks	Time of last OCR infusion	Medical history including medication	Reporting
Stillbirth	First trimester screening, non-invasive prenatal testing 9/10 estimated risk of trisomy 21 (amniocentesis declined)	35	30	0-3 months before LMP	History of miscarriage and premature birth, family history of diabetes C: docosahexaenoic acid, eicosapentanoic acid, bupropion, gabapentin, calcium, macrogol, baclofen, vitamin D, cannabis oil	Prospective
Stillbirth	NR	25	Unknown	0-3 months before LMP	Blood clots in legs, stroke and unable to walk P: warfarin; C: enoxaparin and apixaban for thrombosis	Retrospective
Stillbirth	Mother hospitalized for mild COVID-19 pneumonia during pregnancy (recovered)	24	27	0-3 months before LMP	D: enoxaparin and corticosteroids for COVID-19 pneumonia	Retrospective
Stillbirth	Short-term inhalation of fluid, retroplacental hematoma and multiple infarctions with the placenta (autopsy confirmed). No infections.	28	Unknown	1 st trimester	No previous history of spontaneous or therapeutic abortions P: interferon-beta-1a/1b; C: fexofenadine, paracetamol, sertraline, bromazepam, etilefrine, ascorbic acid, quetiapine fumarate	Retrospective
Stillbirth	True knot in umbilical cord confirmed upon autopsy	32	39	1 st trimester	Obesity, wheelchair-bound and venous stasis in lower extremities	Retrospective
Intrauterine foetal death	Foetal encephalocele and retrognathia. Unknown if autopsy performed	Unknown	Unknown	Unknown	NR	Retrospective
Intrauterine foetal death (maternal death)	Maternal death due to acute bacterial pneumonia (autopsy confirmed, 11 weeks post-mortem)	36	21-24 weeks (reported as 6 months)	3-6 months before LMP	Mother was healthy with no clinical symptoms (e.g. cough, trouble breathing, problem exercising)	Retrospective
Stillbirth	NR	Unknown	24	>12 months before LMP	Obesity	Retrospective
Intrauterine foetal death	Mother experienced oligohydramnios	29	Unknown	Unknown	NR	Retrospective

¹Stillbirth refers to the death of a foetus after 22 completed weeks of gestation and prior to birth. For cases of stillbirth where the exact gestational age is not reported or cannot be calculated, a definition of gestational age >22 completed weeks was assumed if there was reliable and objective documentation that confirms the stillbirth (this includes an autopsy report, results of prenatal tests [e.g., ultrasound], or a well-documented clinical diagnosis recorded in the healthcare records. If gestational age unknown, not reported or could not be determined case was simply defined as intrauterine foetal death.
C, concurrent medication; D, disease treatment; P, previous medication; LMP, last menstrual period; NR, not reported; OCR, ocrelizumab.

Major congenital anomalies: summary of data



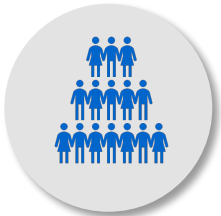
18 total MCA in 17 live births and stillbirths were reported, of which 13 are prospective (compared to a total of 10 MCA in 10 newborns in 2022)



Three cases originally reported as minor anomaly were reclassified as major due to the EUROCAT 1.5 update^{1,2}



Some cases were potentially confounded by risk factors (concomitant medications, medical/family history)



Similar background rates have been reported in both MS (2.2-4.2)^{3,4,5} and general population (2.0-4.4)^{3,5,6}

EUROCAT, European Surveillance of Congenital Anomalies; MCA, major congenital anomalies; MS, multiple sclerosis.

1. Oreja-Guevara C, et al. *ECTRIMS* 2022; P O038; 2. European Surveillance of Congenital Anomalies (EUROCAT) Guide 1.5.

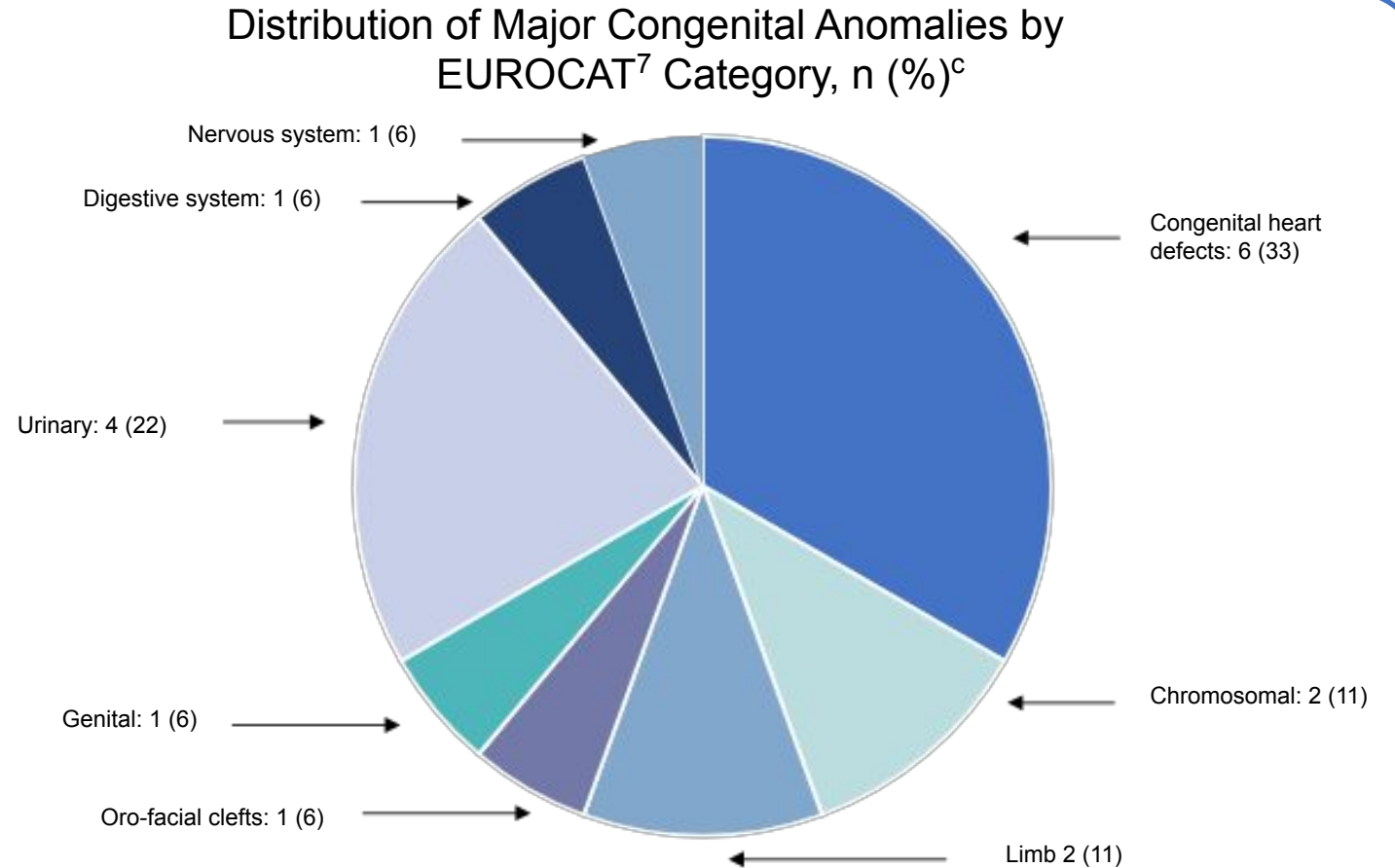
https://eu-rd-platform.jrc.ec.europa.eu/eurocat/data-collection/guidelines-for-data-registration_en. Accessed September 2023; 3. Anderson JB, et al. *Eur J Neurol* 2023;30:162–171. 4. Lopez-Leon S, et al. *J Neurol* 2020;267:2721–2731;

5. MacDonald SC, et al. *Am J Epidemiol* 2019;188:57–66; 6. Centers for Disease Control and Prevention (CDC). *MMWR Morb Mortal Wkly Rep* 2008;57:1–5.

Results

Major Congenital Anomalies in Pregnancies with Known Outcomes in all cases

Proportions and type are consistent with epidemiological background¹⁻⁶



^aThe number of major congenital anomalies reported in all cases is 18, as one live birth reported two MCAs. EUROCAT, European Surveillance of Congenital Anomalies; MCA, major congenital anomaly.

1. Anderson JB, et al. *Eur J Neurol* 2022; 30 (1): 162–171; 2. Khan E, et al. *J Neuroimmunol* 2023; 24: 383: 578178; 3. Lopez-Leon S, et al. *J Neurol* 2020; 267(9): 2721–2731; 4. MacDonald SC, et al. *Am J Epidemiol* 2019; 1;188 (1): 57–66; 5. Centers for Disease Control and Prevention (CDC). *MMWR Morb Mortal Wkly Rep* 2008;57:1–5. Available from: <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5701a2.htm>.

Accessed: September 2023; 6. European Medicines Agency (EMA). Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation data. November 2005. Available from:

https://www.ema.europa.eu/en/documents/regulatoryprocedural-guideline/guideline-exposure-medicinal-productsduring-pregnancy-need-post-authorisation-data_en.pdf. 7. European Surveillance of Congenital Anomalies (EUROCAT) Guide 1.5. Available from: https://eu-rdplatform.jrc.ec.europa.eu/eurocat/data-collection/guidelinesfor-data-registration_en Accessed September 2023.

Major congenital anomalies: case characteristics (n=17)

EUROCAT v1.5 Anomaly class	Anomaly type	Maternal age, years	Pregnancy outcome	GA, weeks	Time of last OCR infusion	Pregnancy history	Medical history including current and past medication	Reporting
Congenital heart defects	Unclear if ASD, VSD or PFO	35	Live birth Full-term	38	2 nd trimester	3 full-term LB	Current Grave's disease C: Carbimazole; P: Alemtuzumab, Dimethyl Fumarate, Fingolimod	Retrospective
Congenital heart defects	<i>Aortic valve dysfunction, "two holes in the heart"</i>	32	Live birth	Unknown	Unknown	NR	NR	Retrospective
Congenital heart defects	Ventricular septal defect	31	Live birth Full-term	Term	2 nd trimester	NR	Diabetes type I P: alemtuzumab; C: insulin	Retrospective
Congenital heart defects	Atrial and ventricular septal defect	35	Live birth Full-term	40	3-6 months before LMP	No SA or TA	Obesity, hypertension, anxiety, thyroid disorder, fatigue, peripheral venous disease, malnutrition, pre-eclampsia, oedema, nasopharyngitis, anemia, vitamin D deficiency; partial placenta previa C: Folic Acid, Venlafaxine, Levothyroxine, Methylodopa, Acetylsalicylic Acid, Ferrous Sulfate, Candesartan, Dimetindene, Cortisone, tobacco and alcohol, COVID-19 and pertussis vaccine	Prospective
Congenital heart defects	Atrial septal defect	33	Live birth Full-term	40	0-3 months before LMP	Primigravida	No maternal complications, maternal medical history and risk factors	Prospective
Congenital heart defects Urinary	Ventricular septal defect Hydronephrosis, bilateral, stage III, with ureteric dilatation	36	Live birth Full-term	40	3-6 months before LMP	1 SA	Anxiety disorder, Thyroid disorder, Fructose/Sorbitol intolerance, Vitamin B12 deficiency/malnutrition, Urinary tract infection, Influenza, Caffeine consumption (<TID) C: Naproxen, Cyanocobalamin, Levothyroxine, Cortisone Acetate, Paracetamol, Cefuroxime, Caffeine	Prospective
Urinary	Renal agenesis, unilateral	30	Live birth Full-term	37	Unknown	NR	Affective disorder P: Rituximab, Oseltamivir, Interferon beta-1b, Natalizumab, Glatiramer Acetate, Fingolimod, Dimethyl Fumarate; C: vitamins, Bupropion	Prospective
Urinary	Renal agenesis, unilateral	33	Live birth Pre-term	36	0-3 months before LMP	NR	NR P: Natalizumab; C: alcohol (occasionally during pregnancy), marijuana (daily)	Prospective
Urinary	Ectopic kidney, unilateral	30	Live birth Pre-term	30	3-6 months before LMP	NR	fetofetal transfusion syndrome (FFTS), twin pregnancy P: dimetindene, cortisone, propionate, cannabis; C: DHA, EHA	Prospective
Genital	Hypospadias (non-confirmed)	32	Live birth Full-term	40	3-6 months before LMP	Primigravida	Migraine, Hyperthyroidism, COVID-19, no personal/family history of birth defects C: vitamins, colecalciferol, iron, ibuprofen, paracetamol, dalteparin, amoxicillin, phenylephrine, carbetocin, bupivacaine	Prospective

ASD, atrial septal defect; C, concurrent; DHA, docosahexaenoic acid; GA, gestational age; LMP, last menstrual period; MCA, major congenital anomaly; NR, not reported; OCR, ocrelizumab; P, previous; PFO, patent foramen ovale; RMS, relapsing multiple sclerosis; SA, spontaneous abortion; VSD, ventricular septal defect.

Major congenital anomalies: case characteristics (n=17)

EUROCAT v1.5 Anomaly class	Anomaly type	Maternal age, years	Pregnancy outcome	GA, weeks	Time of last OCR infusion	Pregnancy history	Medical history including current and past medication	Reporting
Chromosomal	Down Syndrome	36	Live birth Pre-term	34	0-3 months before LMP	1 full-term LB	NR	Prospective
Chromosomal	Down Syndrome	35	Stillbirth	30	0-3 months before LMP	1 SA, 1 pre-term LB	Family history of diabetes C: DHA, EPA, bupropion, gabapentin, calcium. macrogol, baclofen for neuralgia, vitamin D, cannabis oil	Prospective
Limb	Polydactyly	35	Live birth Full-term	37	1 st trimester	1 LB	Father had polydactyly C: Paclitaxel, cannabidiol	Prospective
Limb	Polydactyly	18	Live birth Pre-term	35	2 nd trimester	NR	Smoking, diplopia, dysarthria, ataxia C/P: Natalizumab; unknown if C: marijuana (THC) [started at 16.5 years]	Prospective
Oro-facial clefts	Cleft lip and palate	22	Live birth Full-term	38	0-3 months before LMP	NR	Concurrent depression, anxiety C: clonazepam, escitalopram, bupropion	Prospective
Nervous system	Encephalocele	Unknown	Intrauterine foetal death	Unknown	Unknown	NR	NR	Retrospective
Digestive system	Atresia of small intestine	29	Live birth Full-term	41	0-3 months before LMP	1 full-term LB	Ichthyosis; no previous pregnancy complications P: Glatiramer Acetate	Prospective

Infants with follow-up in the first year of life (n=226)

Vaccinations, infections and B-cell level data remain limited

		Not exposed <i>in utero</i> (N=54)	Exposed <i>in utero</i> (N=127)	Unknown exposure (N=45)	Total (N=226)	Additional information reported
Live or live-attenuated vaccines administered, n(%)	Yes	14 (25.9%)	29 (22.8%)	7 (15.6%)	50 (22.1%)	As of July 2023, there have been no reports of breakthrough infections following administration of common childhood vaccines in infants born to mothers receiving ocrelizumab within 6 months prior to the LMP and/or during pregnancy, enrolled in WA40063 (OCREVUS pregnancy registry).
	No	—	—	—	—	
	NR/Unk/NA	40 (74.1%)	98 (77.2%)	38 (84.4%)	176 (77.9%)	
Infections and other adverse events reported, n(%)	Yes	9 (16.7%) ^c	33 (26.0%) ^b	17 (37.8%) ^d	59 (26.1%)	^b Asphyxia (n=1), common cold (n=1), COVID-19 (n=3), COVID-19, influenza and hand-foot-mouth disease (n=1), hyperbilirubinemia and anemia (n=1), acidosis (n=1), Kawasaki disease (n=1), nasopharyngitis (n=1), non-specified infection (n=5), prematurity (n=1), respiratory distress (n=6), respiratory syncytial virus (n=5), sepsis (n=2), URTI (n=1), UTI and ear infection (n=1), volvulus (n=1), vomiting/swelling (n=1) ^c cold (n=1), COVID-19 (n=1), ear infection (n=1), hyperbilirubinemia (n=2), UTI (n=1), respiratory syncytial virus (n=1), vomiting and fever after 6-month vaccine (n=1), non-specified infection (n=1) ^d bradycardia (n=1), COVID-19 (n=1), COVID-19, enterococcus faecalis, staphylococcus and respiratory syncytial virus (n=1), netye infection (n=1), gastrointestinal infection and otitis (n=1), group B streptococcus (n=2), non-specified infection (n=3), oral candidiasis and UTI (n=1), oral candidiasis (n=1), nephritis (n=1), respiratory distress (n=1), sepsis and pneumonia (n=1), pneumonia (n=1), UTI (n=1)
	No	21 (38.9%)	34 (26.8%)	17 (37.8%)	72 (31.9%)	
	NR/Unk	24 (44.4%)	60 (47.2%)	11 (24.4%)	95 (42.0%)	
B-cell levels reported, n(%) ^a	Normal	4 (7.4%)	39 (30.7%)	12 (26.7%)	55 (24.3%)	^e lower B cell levels at birth, not further specified (n=3); at 2 weeks, CD19 of 0 (n=1); at 17 days of age, B cell levels were 85/ul (n=1); lower B cell levels with timing and levels not specified (n=1)
	Abnormal	—	6 (4.7%) ^e	—	6 (2.65%)	
	NR/Unk/ indeterminable	50 (92.6%)	82 (64.6%)	33 (73.3%)	165 (73.0%)	

CD19, cluster of differentiation 19; NA, not applicable; NICU, neonatal intensive care unit; NR, not reported; Unk, unknown; UTI, urinary tract infection.

^aWhere actual B-cell levels were reported, adjudication on whether results were below the lower limit of normal was made according to Borriello *et al.*, 2022¹.

1. Borriello F, *et al.* *J Allergy Clin Immunol* 2022;18:S0091-6749(22)00835-1.

Infants with potential exposure to OCR through breastfeeding (n=126)

Vaccinations, infections and B-cell level data remain limited

	Live or live-attenuated vaccines administered, n(%)	Infections and other adverse events reported, n(%)	B-cell levels reported, n(%) ^{a,b}	Also exposure <i>in utero</i> , n(%)	Additional information reported
Yes	5 (4.0%)	11 (8.7%) ^b	Normal 7 (5.6%) Abnormal -	80 (63.5%)	^b Conjunctivitis and otitis media (n=1); eye infection (n=1); pelvic inflammation/nephritis (n=1); excessive vomiting/swelling due to potential dairy allergies (n=1) live-threatening breathing disorder and mild neurodermatitis (n=1); vomiting and fever after 6-month vaccine (n=1); unspecified neonatal infection (n=2); respiratory syncytial virus infection (n=2); upper respiratory tract infection (n=1)
No	—	4 (3.2%)	—	46 (36.5%)	
NR/Unk/NA	121 (96.0%)	111 (88.1%)	119 (94.4%)	—	

NA, not applicable; NR, not reported; Unk, unknown; OCR, ocrelizumab
^aPercentages represent fractions of the total reports of potential infant OCR exposure through breastfeeding for the respective outcomes (vaccines administered, infections/adverse events reported, B cell levels reported, also exposed in utero). ^bWhere actual B-cell levels were reported, adjudication on whether results were below the lower limit of normal was made according to Borriello *et al.*, 2022¹.
 1. Borriello F, *et al. J Allergy Clin Immunol* 2022;18:S0091-6749(22)00835-1.



<https://ter.li/2cxrmv>

Composite Confirmed Disability Worsening is a Useful Clinical Trial Endpoint for Multiple Sclerosis Focusing on Disability Progression

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**ENSEMBLE (NCT03085810); OPERA I and II (NCT01247324/NCT01412333);
ORATORIO (NCT01194570); CONSONANCE (NCT03523858); OLYMPUS (NCT00087529)**

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Background

There is a need for more sensitive methods of measuring disability worsening in future MS controlled clinical trials, specifically, when comparing higher-efficacy therapies

Combining CDW^a as measured by the Expanded Disability Status Scale (CDW–EDSS), the current gold standard, with established performance tests of ambulation and dexterity (T25FW, 9HPT) may address this need^{1–4}.

The T25FW may change before EDSS,⁴ but is linked and thus not measuring the same dimension, while arm function is not readily assessed by EDSS

Understanding the clinical meaningfulness of cCDW^b and its components (CDW–EDSS, and performance tests [CDW–T25FW and CDW–9HPT]) is therefore important

Clinical trials with OCR, an anti-CD20 monoclonal antibody approved for the treatment of RMS and PPMS,^{5,6} with a well-established efficacy and safety profile, allow characterisation of cCDW in a higher-efficacy trial setting

Objectives: To determine the sensitivity of cCDW vs CDW–EDSS and the clinical relevance of T25FW and 9HPT in prognosticating CDW–EDSS in patients with relapsing and progressive MS

9HPT, Nine-Hole Peg Test; cCDW, composite confirmed disability worsening; CDW, confirmed disability worsening; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; OCR, ocrelizumab; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; T25FW, Timed 25-Foot Walk.

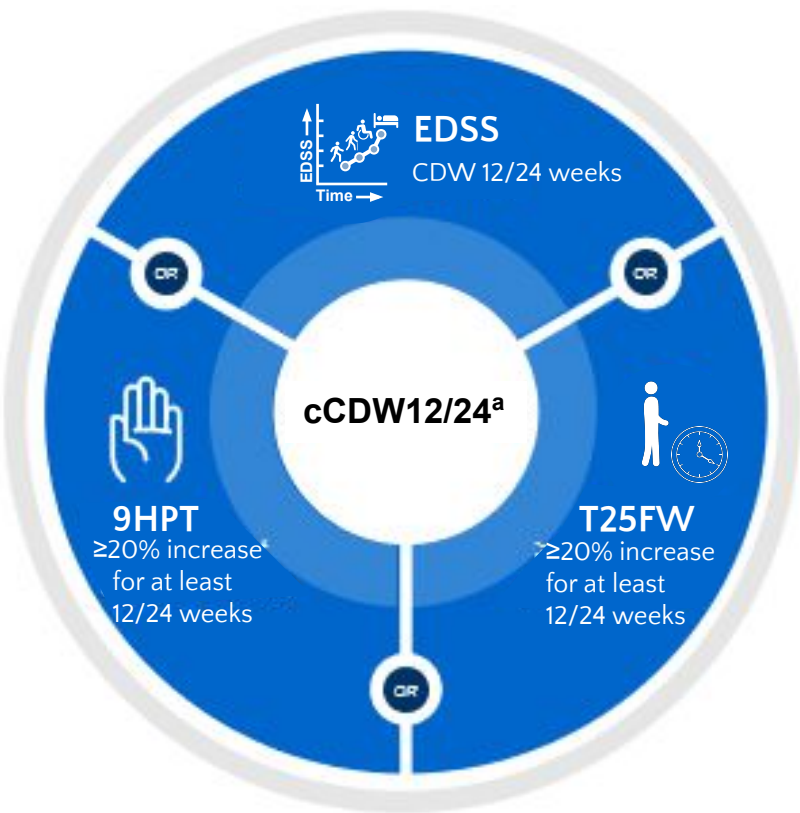
^aCDW was previously termed confirmed disability progression; ^bThe term cCDW is inclusive of all progression independent of its relation to relapses.

1. Cadavid D, *et al. Mult Scler* 2017;23:94–105. 2. Wolinsky JS, *et al. Ann Neurol* 2018;84:527–536. 3. Kappos L, *et al. JAMA Neurol* 2020;77:1132–1140. 4. Kalinowski A, *et al. Mult Scler* 2022;28:289–299. 5. OCREVUS [ocrelizumab] Full Prescribing Information. Genentech, Inc., August 2022. 6. OCREVUS [ocrelizumab] Summary of Product Characteristics. Roche Pharma AG, April 2023.

Methods

cCDW, Assessments and Clinical Studies

COMPOSITE ENDPOINT: cCDW



ASSESSMENTS

The **temporal relation** of **CDW** performance tests (**T25FW** and **9HPT**) with **CDW–EDSS**

The **clinical association** of **CDW** performance tests (**T25FW** and **9HPT**) with **CDW–EDSS**

The association of **treatment effects** on **cCDW** with treatment effects on **CDW–EDSS** from an MS study literature review

FIVE LARGE CLINICAL STUDIES

Study	Patient numbers	Median time on treatment
OPERA I/II RMS DBP+OLE	OCR N=827 IFN N=829	DBP 96W+ OLE 409W
ENSEMBLE RRMS Open-Label Study	OCR N=1,225	193W
CONSONANCE PMS Open-Label Study	OCR N=629 ^c	186W
ORATORIO PPMS DBP+OLE	OCR N=488 PBO N=244	DBP 171W+ OLE 341W
OLYMPUS PPMS DBP	RTX N=292 PBO N=147	96W

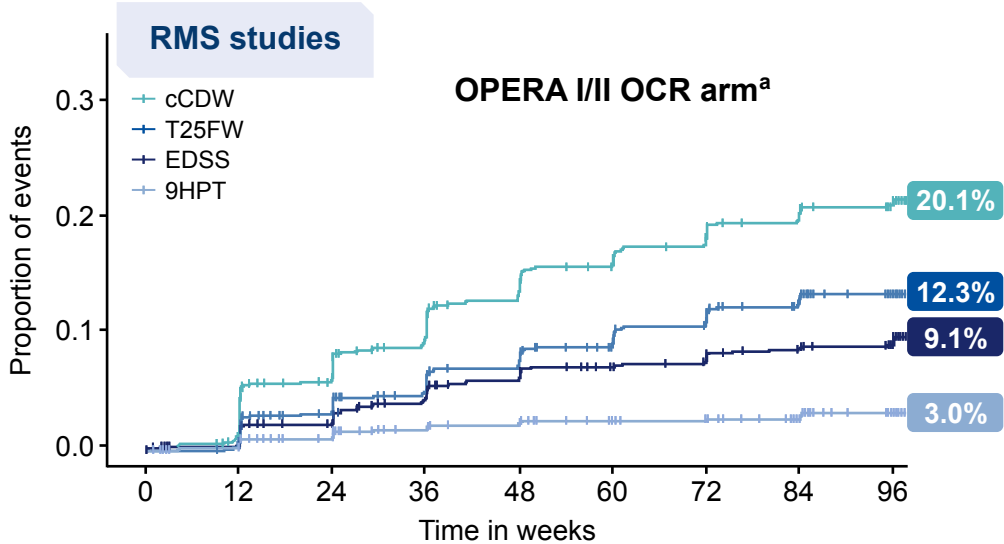
9HPT, Nine-Hole Peg Test; BL, baseline; cCDW12/24, composite confirmed disability worsening at 12 and 24 weeks; cCDW, composite confirmed disability worsening; CDW, confirmed disability worsening; DBP, double-blind period; EDSS, Expanded Disability Status Scale; IFN, interferon; MS, multiple sclerosis; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; PMS, progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; RTX, rituximab; T25FW, Timed 25-Foot Walk; W, weeks.

^acCDW12/24 requires at least one of the following: (1) an increase in EDSS score of ≥ 1.0 point from a BL score of ≤ 5.5 points, or a ≥ 0.5 -point increase from a BL score of > 5.5 points; (2) a 20% increase from BL in time to complete the 9HPT; (3) a 20% increase from BL in the T25FW. ^bENSEMBLE NCT03085810; OPERA I and II NCT01247324/NCT01412333; ORATORIO NCT01194570; CONSONANCE NCT03523858; OLYMPUS NCT00087529. The OLYMPUS study evaluated rituximab, an anti-CD20 antibody, in patients with PPMS. ^cSubcohort of the total population, N=922.

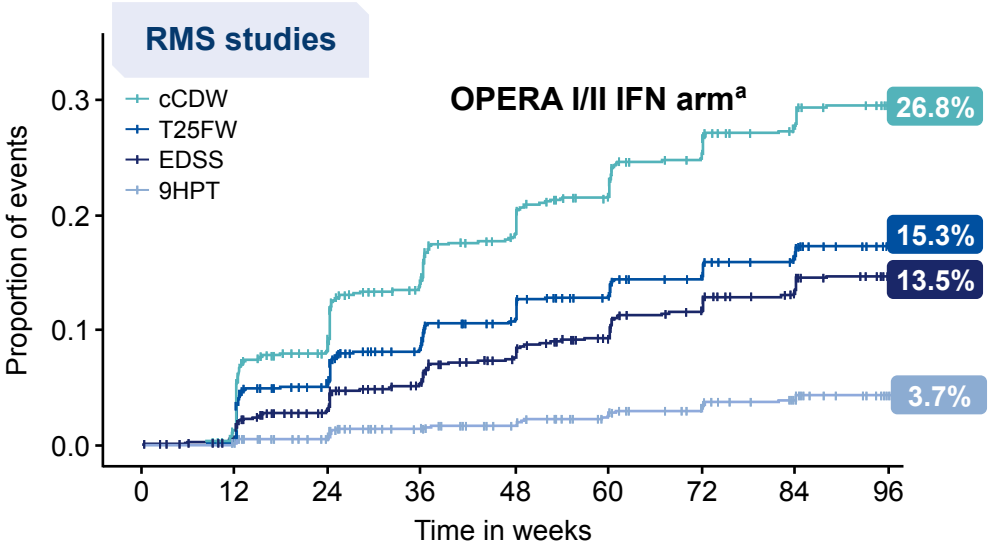
Results

RMS – Frequency of CDW on T25FW, 9HPT, EDSS and cCDW

cCDW and CDW–T25FW occurred more frequently than CDW–EDSS



Study	Proportion of patients with events (%)	
	cCDW	CDW–EDSS
ENSEMBLE	28.1	13.9



These findings were consistent across all RMS studies (see Supplementary Materials for details)



cCDW and CDW–T25FW yield a greater number of events than CDW–EDSS

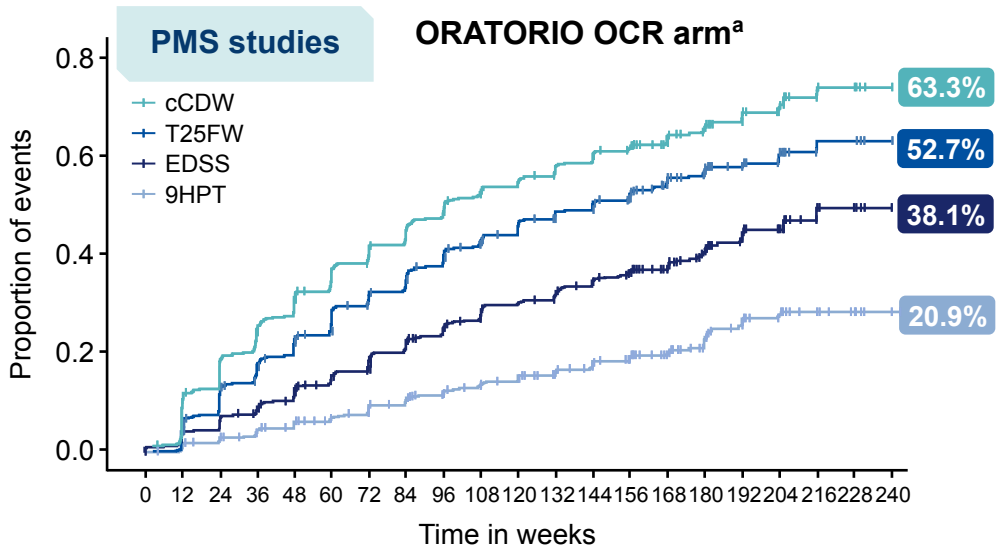
9HPT, Nine-Hole Peg Test; cCDW, composite confirmed disability worsening; CDW, confirmed disability worsening; EDSS, Expanded Disability Status Scale; IFN, interferon; OCR, ocrelizumab; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; T25FW, Timed 25-Foot Walk.

^aData also shown for proportion (%) of patients with an event over the duration of the study based on the number of patients at risk at baseline; see Supplementary Materials for the number of patients at risk in the individual RMS studies (ENSEMBLE, OPERA I/II) and PPMS studies (CONSONANCE, ORATORIO, OLYMPUS).

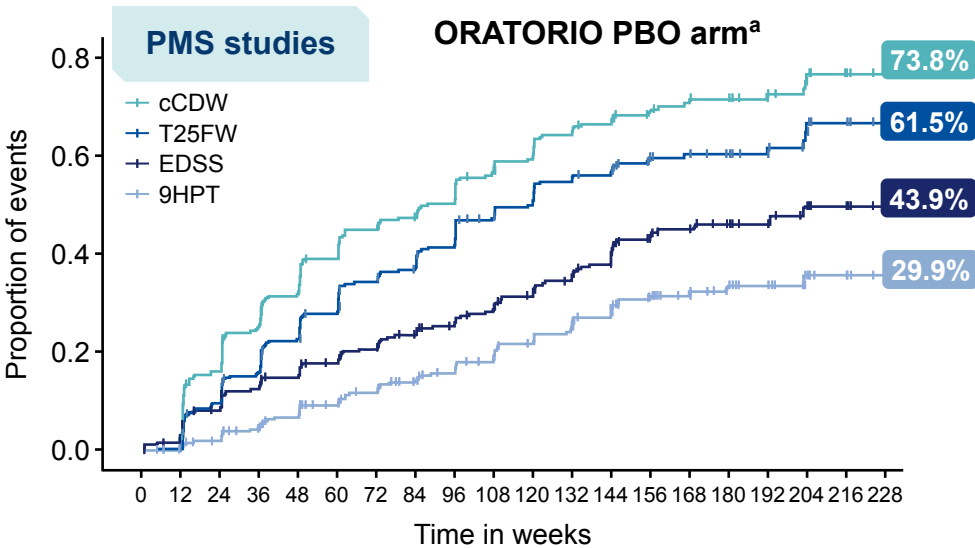
Results

PMS – Frequency of CDW on T25FW, 9HPT, EDSS and cCDW

cCDW and CDW–T25FW occurred more frequently than CDW–EDSS



Study	Proportion of patients with events (%)	
	cCDW	CDW–EDSS
CONSONANCE	41.5	20.3
OLYMPUS RTX	54.5	28.4
OLYMPUS PBO	66.0	39.5



These findings were consistent across all PMS studies (see Supplementary Materials for details)



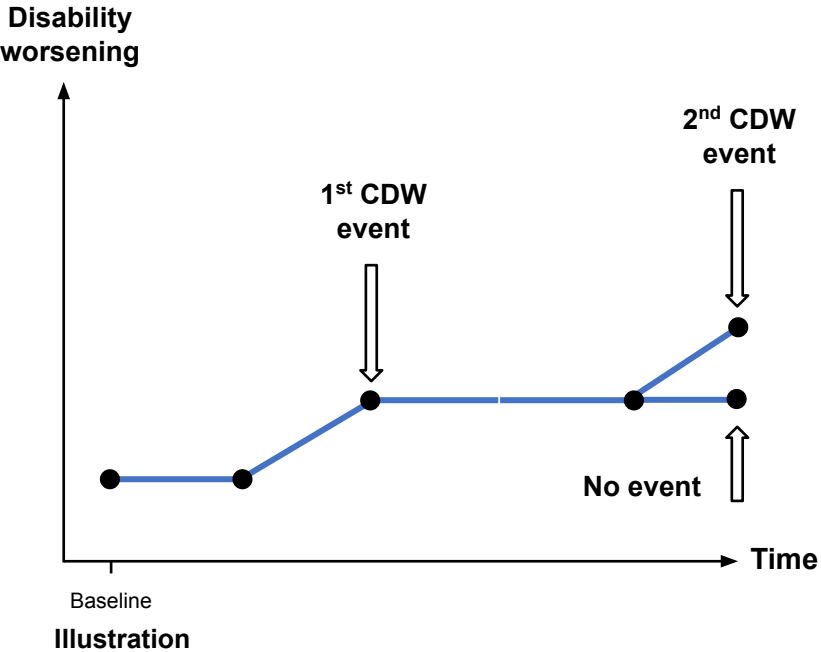
cCDW and CDW–T25FW yield a greater number of events than CDW–EDSS. PMS studies have higher event rates vs RMS studies, including CDW–9HPT

9HPT, Nine-Hole Peg Test; cCDW, composite confirmed disability worsening; CDW, confirmed disability worsening; EDSS, Expanded Disability Status Scale; OCR, ocrelizumab; PBO, placebo; PMS, progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; RTX, rituximab; T25FW, Timed 25-Foot Walk.
^aData also shown for proportion (%) of patients with an event over the duration of the study based on the number of patients at risk at baseline; see Supplementary Materials for the number of patients at risk over the study duration in the individual RMS studies (ENSEMBLE, OPERA I/II) and PPMS studies (CONSONANCE, ORATORIO, OLYMPUS).

Results

cCDW and CDW–T25FW Often Occur Prior to CDW–EDSS; 9HPT Contributes More in PMS

cCDW and CDW–T25FW events occurred earlier than CDW–EDSS.
CDW–9HPT contributes to worsening events primarily if baseline EDSS score is ≥4, where gait-driven changes have long transition times



	RMS studies ^a		PMS studies ^a	
1st CDW event, % (n/N):	OPERA I/II RCTs	ENSEMBLE open-label study	ORATORIO OLYMPUS RCTs	CONSONANCE open-label study
with CDW–T25FW before ^b CDW–EDSS	57.5% (199/346)	55.8% (178/319)	65.7% (433/659)	63.2% (203/321)
with CDW–EDSS before ^b CDW–T25FW	39.6% (133/346)	39.5% (126/319)	26.3% (173/659)	31.8% (102/321)
with CDW–9HPT before ^b CDW–EDSS*	41.3% (19/46)	N/A	30.7% (109/355)	39.2% (74/189)

*Where the proportion of patients is in the range of EDSS where changes are primarily driven by the ambulation score with baseline EDSS ≥4.



CDW–T25FW and cCDW analyses can lead to earlier identification of disability worsening than CDW–EDSS, and CDW–9HPT relevantly contributes to cCDW

9HPT, Nine-Hole Peg Test; cCDW, composite confirmed disability worsening; CDW, confirmed disability worsening; EDSS, Expanded Disability Status Scale; N/A, not applicable; PMS, progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; RCT, randomised controlled trial; RMS, relapsing multiple sclerosis; T25FW, Timed 25-Foot Walk.
^aData from the individual RMS studies (ENSEMBLE, OPERA I/II) and PPMS studies (CONSONANCE, ORATORIO, OLYMPUS) are provided in the Supplementary Materials. Data are expressed as a percent of patients who experienced any CDW event; ^bOr with the first CDW event without a subsequent CDW event.

Results

Impact of CDW–T25FW and CDW–9HPT on Risk of Future CDW–EDSS

On-study CDW–T25FW and CDW–9HPT were positively associated with an increased risk of CDW–EDSS in all study arms. The strong associations between CDW–T25FW and CDW–EDSS were not entirely driven by changes in the ambulation score

CDW–T25FW significantly increases risk of subsequent CDW–EDSS in RMS and PMS studies

CDW–9HPT^b significantly increases risk of subsequent CDW–EDSS in RMS and PMS studies

RMS studies^a

CDW–EDSS
2x as likely

following onset of CDW–T25FW
HR range: 2.11–2.56;
p-values: 0.07–<0.001

CDW–EDSS
2x as likely^b

following onset of CDW–9HPT
HR range: 0.62–2.48;
p-values: 0.77–0.05

PMS studies^a

CDW–EDSS
3–5x as likely

following onset of CDW–T25FW
HR range: 2.99–5.20;
p-values: all ≤0.001

CDW–EDSS
1.5–4x as likely

following onset of CDW–9HPT
HR range: 1.53–4.65;
p-values: 0.17–<0.001

Sensitivity analysis: The strong associations between CDW–T25FW and CDW–EDSS were still present in most studies when the ambulation score was removed in the definition of CDW–EDSS (see Supplementary Materials for results).



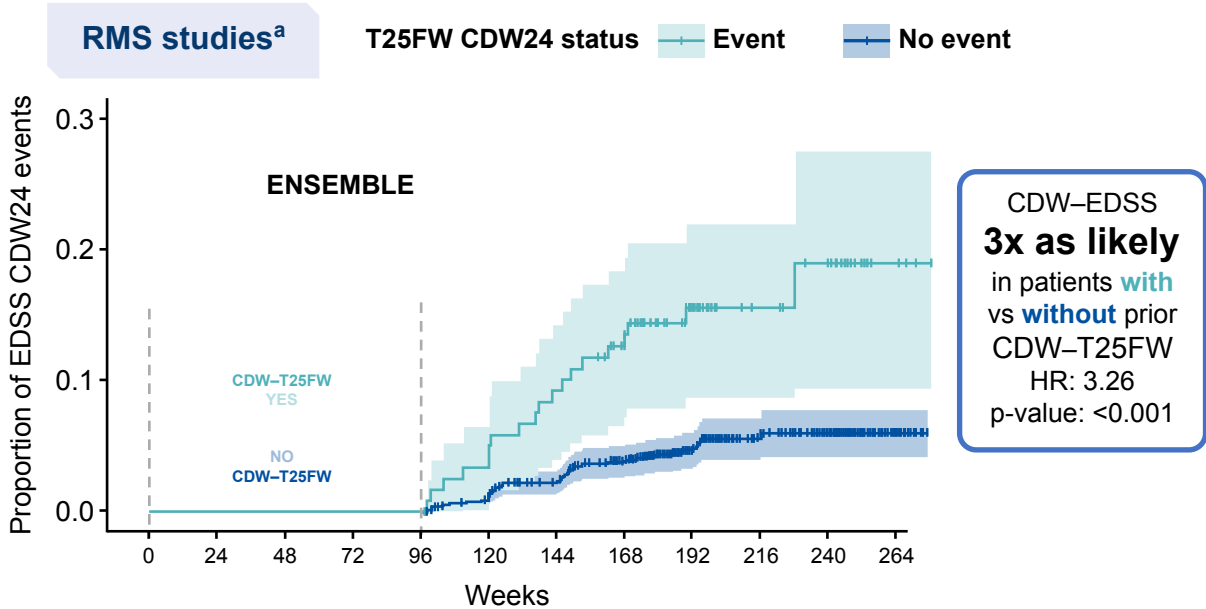
CDW–T25FW and CDW–9HPT were associated with an increased risk of future CDW–EDSS

9HPT, Nine-Hole Peg Test; CDW, confirmed disability worsening; EDSS, Expanded Disability Status Scale; HR, hazard ratio; OCR, ocrelizumab; PMS, progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; T25FW, Timed 25-Foot Walk.
^aData from the individual RMS studies (ENSEMBLE, OPERA I/II) and PPMS studies (CONSONANCE, ORATORIO, OLYMPUS) are provided in the Supplementary Materials. HR based on comparison of with vs without the prior event (CDW–T25FW or CDW–9HPT); ^bApart from in ENSEMBLE and the OPERA I/II OCR arm where CDW–9HPT events were infrequent.

Results

Patients With/Without CDW–T25FW in the First 96 Weeks and the Risk of Future CDW–EDSS

CDW–T25FW in the first 96 weeks was associated with an increased risk of CDW–EDSS after 96 weeks in PwRMS and PwPMS; similar trends were seen for CDW–9HPT



Study	CDW–EDSS in in patients with vs without prior CDW–T25FW; HR (p-value)
ENSEMBLE	3.26 (p<0.001)
OPERA I/II OCR	1.74 (p=0.01)
OPERA I/II IFN	2.02 (p<0.001)



Worsening on CDW–T25FW was predictive of future CDW–EDSS in PwRMS and PwPMS

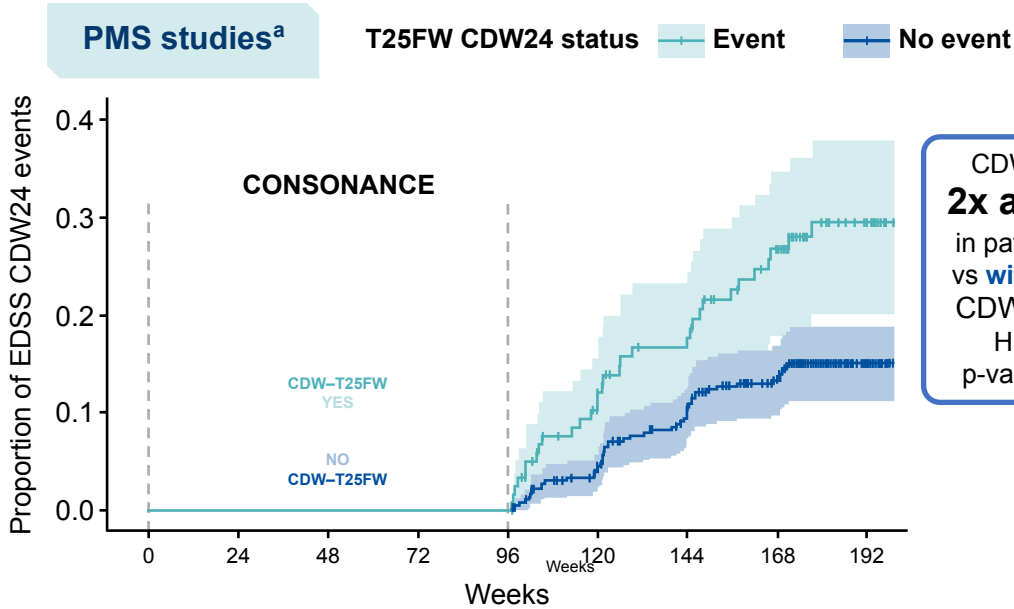
9HPT, Nine-Hole Peg Test; CDW24, confirmed disability worsening at 24 weeks; CDW, confirmed disability worsening; EDSS, Expanded Disability Status Scale; HR, hazard ratio; IFN, interferon; OCR, ocrelizumab; PMS, progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; PwPMS, people with progressive multiple sclerosis; PwRMS, people with relapsing multiple sclerosis; RMS, relapsing multiple sclerosis; T25FW, Timed 25-Foot Walk.

^aSubgroup analyses were performed in the subset of patients who have long-term CDW24–EDSS, i.e. outside of the first 96 weeks of the study; data from the individual RMS studies (ENSEMBLE, OPERA I/II) and PPMS studies (CONSONANCE, ORATORIO) are provided in the Supplementary Materials. Positive associations between presence of CDW–9HPT during the first 96 weeks of the study and an increased risk of long-term CDW24–EDSS were also observed for all eligible study arms (except the OCR arm of OPERA I/II): Across RMS studies, risk of CDW–EDSS in patients with/without CDW–9HPT: HRs 1.45–2.14; p-values: 0.35–0.45; across PMS studies, risk of CDW–EDSS in patients with/without CDW–T25FW: HRs 2.03–3.08; p-values: 0.02–<0.001.

Results

Patients With/Without CDW–T25FW in the First 96 Weeks and the Risk of Future CDW–EDSS

CDW–T25FW in the first 96 weeks was associated with an increased risk of CDW–EDSS after 96 weeks in PwRMS and PwPMS; similar trends were seen for CDW–9HPT



CDW–EDSS
2x as likely
in patients **with**
vs **without** prior
CDW–T25FW
HR: 2.13
p-value: 0.001

Study	CDW–EDSS in patients with vs without prior CDW–T25FW; HR (p-value)
CONSONANCE	2.13 (p=0.001)
ORATORIO OCR	2.29 (p<0.001)
ORATORIO PBO	3.03 (p<0.001)



Worsening on CDW–T25FW was predictive of future CDW–EDSS in PwRMS and PwPMS

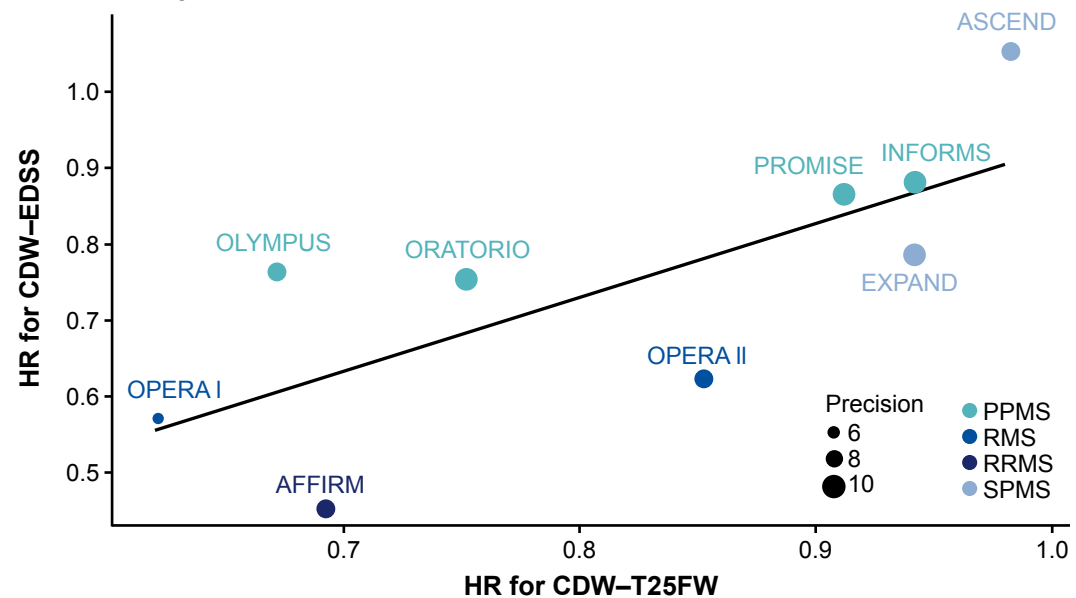
9HPT, Nine-Hole Peg Test; CDW24, confirmed disability worsening at 24 weeks; CDW, confirmed disability worsening; EDSS, Expanded Disability Status Scale; HR, hazard ratio; OCR, ocrelizumab; PBO, placebo; PMS, progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; PwPMS, people with progressive multiple sclerosis; PwRMS, people with relapsing multiple sclerosis; RMS, relapsing multiple sclerosis; T25FW, Timed 25-Foot Walk.
^aSubgroup analyses were performed in the subset of patients who have long-term CDW24–EDSS, i.e. outside of the first 96 weeks of the study; data from the individual RMS studies (ENSEMBLE, OPERA I/II) and PPMS studies (CONSONANCE, ORATORIO) are provided in the Supplementary Materials. Positive associations between presence of CDW–9HPT during the first 96 weeks of the study and an increased risk of long-term CDW24–EDSS were also observed for all eligible study arms (except the OCR arm of OPERA I/II): Across RMS studies, risk of CDW–EDSS in patients with/without CDW–9HPT: HRs 1.45–2.14; p-values: 0.35–0.45; across PMS studies, risk of CDW–EDSS in patients with/without CDW–T25FW: HRs 2.03–3.08; p-values: 0.02–<0.001.

Results

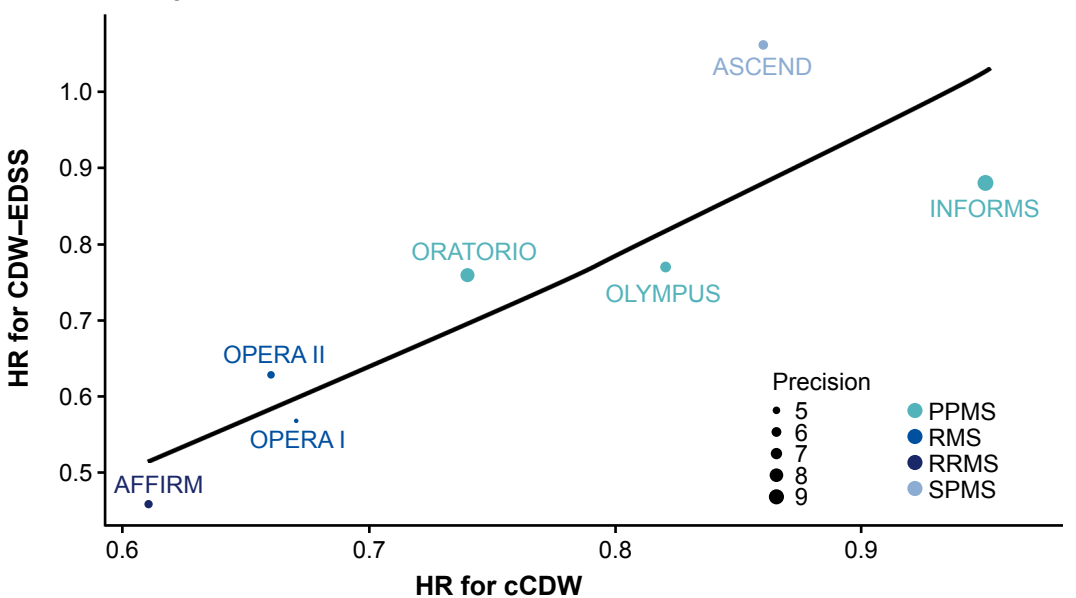
Relationship Between Treatment Effects on CDW–T25FW and cCDW with Treatment Effects on CDW–EDSS from a Literature Review of Nine MS Clinical Studies

High correlations were seen between treatment effects on CDW–T25FW and cCDW with treatment effects on CDW–EDSS

Treatment effects on: CDW–T25FW and CDW–EDSS
Spearman’s correlation between log HR: 0.82
(Analysis based on nine studies)



Treatment effects on: cCDW and CDW–EDSS
Spearman’s correlation between log HR: 0.93
(Analysis based on seven studies)



In RMS and PMS, treatment effects on cCDW and CDW–T25FW were highly correlated with treatment effects on CDW–EDSS

9HPT, Nine-Hole Peg Test; cCDW, composite confirmed disability worsening; CDW12, confirmed disability worsening at 12 weeks; CDW24, confirmed disability worsening at 24 weeks; CDW, confirmed disability worsening; EDSS, Expanded Disability Status Scale; HR, hazard ratio; MS, multiple sclerosis; PMS, progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; T25FW, Timed 25-Foot Walk.
NB: Treatment effects for AFFIRM are based on CDW24, and treatment effect on T25FW CDW for PROMISE are based on a composite between T25FW and 9HPT. Otherwise, all other treatment effects are based on T25FW and EDSS CDW12.

Conclusions

cCDW is a more sensitive measure of disability worsening than CDW–EDSS

CDW–T25FW and CDW–9HPT were demonstrated to be harbingers of subsequent CDW–EDSS in six studies spanning MS phenotypes and a wide range of disability status

The harbinger effect of prior CDW–T25FW on CDW–EDSS did not appear to be entirely driven by changes in the ambulation score

Treatment effects on CDW–T25FW and cCDW were highly correlated with treatment effects on CDW–EDSS based on a literature review of nine and seven MS clinical studies, respectively

The predictive validity of CDW on the performance tests as harbingers of subsequent CDW–EDSS greatly enhances their clinical relevance and supports cCDW as a key outcome measure for MS worsening in clinical trials

Supplementary Materials

Methods

Patient populations

ENSEMBLE PATIENT POPULATION

RRMS diagnosis
(McDonald 2010)¹

Age 18–55 years,
inclusive

Disease duration ≤ 3
years (early-stage MS)

EDSS^a 0.0–3.5 inclusive

≥ 1 relapse
or MRI activity in
prior 12 months

Treatment naive

OPERA I/II PATIENT POPULATION

RMS diagnosis
(McDonald 2010)¹

Age 18–55 years,
inclusive

MRI activity consistent
with MS

EDSS 0.0–5.5 inclusive

≥ 2 relapses in the
previous 2 years or
one relapse in prior
12 months

Treatment naive or
previously treated^b

CONSONANCE PATIENT POPULATION

PMS diagnosis
(McDonald 2010;
Lublin 2014)^{1,2}

Age 18–65 years,
inclusive

PMS disease duration
 ≤ 10 years if EDSS ≤ 5.0 ,
 ≤ 15 years if EDSS > 5.0

EDSS ≤ 6.5

PIRA during prior 2 years^c
Fulfil ≥ 1 criteria of PIRA in
prior 2 years per disability
rating system checklist

Treatment naive or
previously treated^b

ORATORIO PATIENT POPULATION

PPMS diagnosis
(McDonald 2005)³

Age 18–55 years,
inclusive

MS disease duration < 10
years if EDSS ≤ 5.0 , < 15
years if EDSS > 5.0

EDSS 3.0–6.5 inclusive

Documented history or
presence of elevated
IgG index or $\geq$ IgG OCB

Treatment naive or
previously treated^b

OLYMPUS PATIENT POPULATION

PPMS diagnosis
(McDonald 2001)⁴

Age 18–55 years,
inclusive

Disease duration ≥ 1
year; FSS ≥ 2.0 for
pyramidal system or
gait impairment^d

EDSS 2.0–6.5 inclusive

IgG OCB and/or elevated
CSF IgG index, at
screening or prior
24 months

Treatment naive or
previously treated^b

CSF, cerebrospinal fluid; EDSS, Expanded Disability Status Scale; IgG, immunoglobulin G; MS, multiple sclerosis; OCR, ocrelizumab; PMS, progressive multiple sclerosis; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

^aBaseline EDSS is defined as the average of the EDSS scores at screening and baseline visit. ^bSee original publication for additional details. ^cDisability progression was considered as independent of relapse activity as per treating physician's judgment. ^dGait impairment due to lower extremity dysfunction.

1. Polman CH, *et al. Ann Neurol* 2011;69:292–302. 2. Lublin FD, *et al. Neurology* 2014;83:278–86. 3. Polman CH, *et al. Ann Neurol* 2005;58:840–846. 4. McDonald WI, *et al. Ann Neurol* 2001;50:121–127.

Results

Baseline demographics and disease characteristics

	ENSEMBLE RRMS (N=1225)	OPERA I/II RMS (OCR; N=827)	OPERA I/II RMS (IFN; N=829)	CONSONANCE PMS (N=629; SPMS 48.5%, PPMS 51.5%)	ORATORIO PPMS (OCR; N=488)	ORATORIO PPMS (PBO; N=244)	OLYMPUS PPMS (RTX; N=292)	OLYMPUS PPMS (PBO; N=147)
Age years mean $\pm$ SD	32.8 $\pm$ 9.1	37.1 $\pm$ 9.2	37.2 $\pm$ 9.2	48.5 $\pm$ 9.2	44.7 $\pm$ 7.9	44.4 $\pm$ 8.3	50.1 $\pm$ 9.0	49.6 $\pm$ 8.7
Female Number (%)	784 (64.0%)	541 (65.4%)	552 (66.6%)	329 (52.3%)	237 (48.6%)	124 (50.8%)	140 (47.9%)	81 (55.1%)
Time since symptom onset years, mean $\pm$ SD	1.1 $\pm$ 0.9	6.7 $\pm$ 6.2	6.5 $\pm$ 6.1	11.7 $\pm$ 8.0	6.7 $\pm$ 4.0	6.1 $\pm$ 3.6	9.5 $\pm$ 6.5	9.4 $\pm$ 6.9
EDSS score	1.8 $\pm$ 0.9	2.8 $\pm$ 1.3	2.8 $\pm$ 1.3	5.0 $\pm$ 1.3	4.7 $\pm$ 1.2	4.7 $\pm$ 1.2	4.8 $\pm$ 1.3	4.7 $\pm$ 1.4
T25FWT seconds, mean $\pm$ SD	6.3 $\pm$ 5.9	7.9 $\pm$ 9.9	7.2 $\pm$ 9.2	15.1 $\pm$ 18.1	14.8 $\pm$ 21.2	12.9 $\pm$ 15.5	13.5 $\pm$ 21.1	12.5 $\pm$ 18.9
9HPT seconds, mean $\pm$ SD	22.0 $\pm$ 7.5	24.5 $\pm$ 13.1	24.0 $\pm$ 8.3	32.6 $\pm$ 15.7	31.9 $\pm$ 23.3	30.6 $\pm$ 13.4	31.4 $\pm$ 27.3	28.9 $\pm$ 11.2

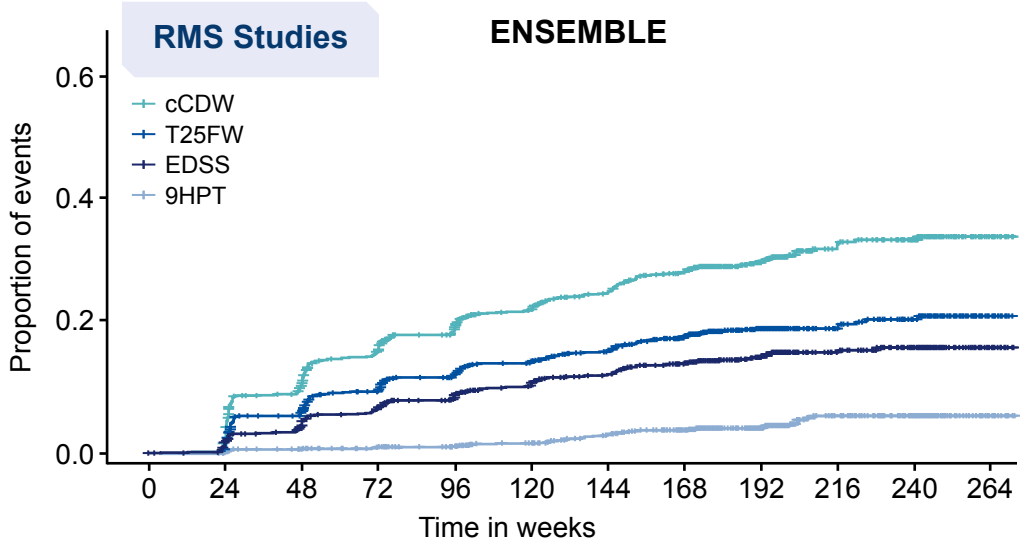


Baseline demographics and disease characteristics were representative of the spectrum of MS disease

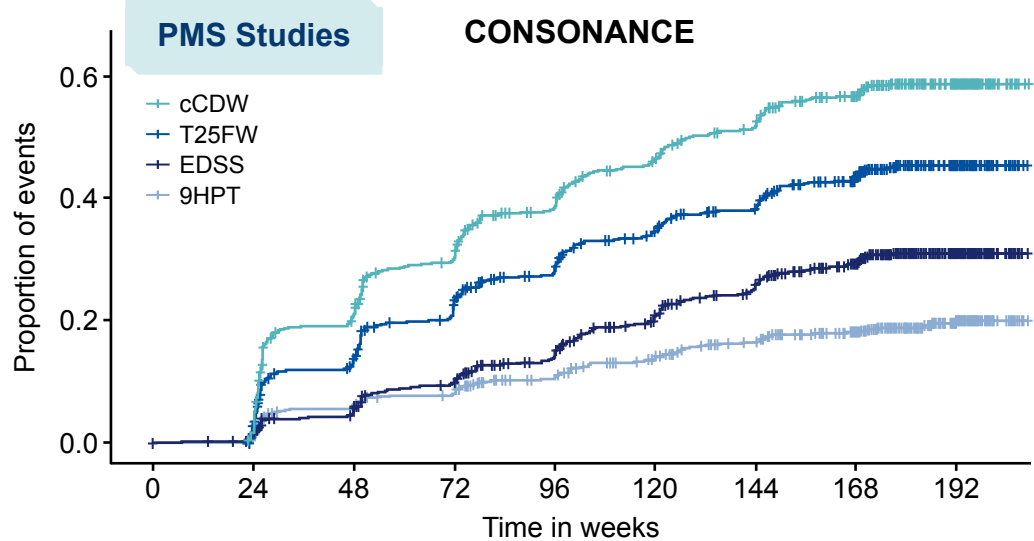
Results

Frequency of CDW on T25FW, 9HPT, EDSS and cCDW – RMS/PMS studies

Composite-CDW and CDW-T25FWT occurred more frequently than CDW-EDSS



ENSEMBLE open-label study, proportion of patients with events:
cCDW 28.1% vs CDW-EDSS 13.9%



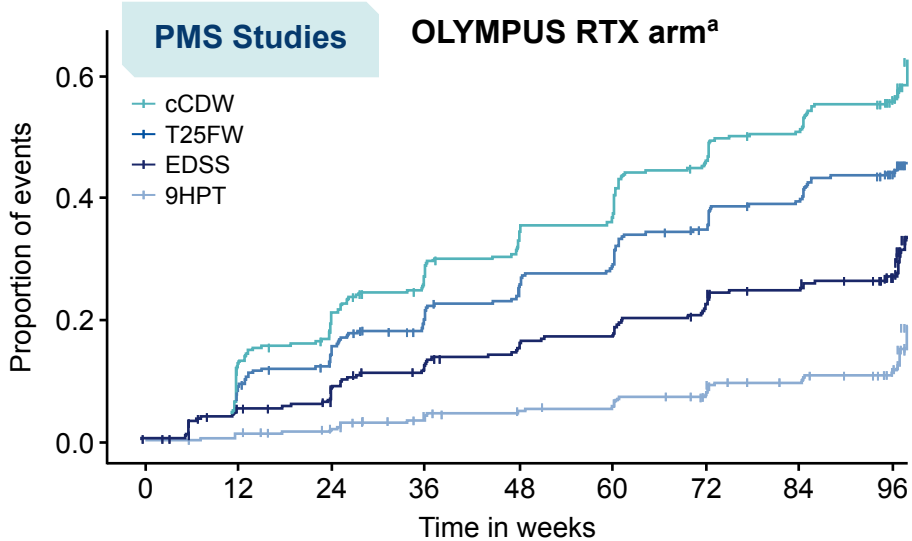
CONSONANCE open-label study, proportion of patients with events:
cCDW 54.2% vs CDW-EDSS 27.7%

cCDW and CDW-T25FWT yield a greater number of events than CDW-EDSS
PMS studies have higher event rates vs RMS studies, including CDW-9HPT

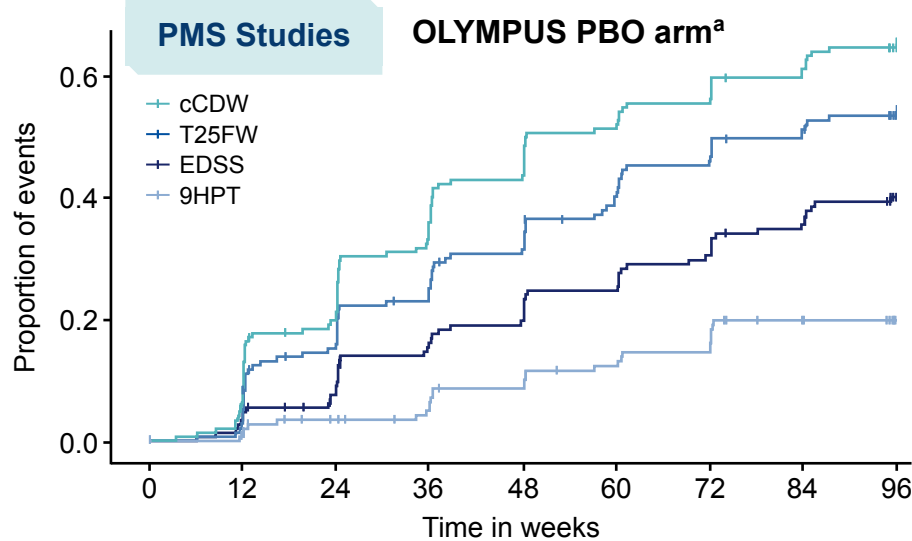
Results

Frequency of CDW on T25FW, 9HPT, EDSS and cCDW – PMS study

Composite-CDW and CDW-T25FWT occurred more frequently than CDW-EDSS



OLYMPUS RTX, proportion of patients with events:
cCDW 54.5% vs 28.4% CDW-EDSS



OLYMPUS PBO, proportion of patients with events:
cCDW 66.0% vs 39.5% CDW-EDSS

cCDW and CDW-T25FWT yield a greater number of events than CDW-EDSS
PMS studies have higher event rates vs RMS studies, including CDW-9HPT

9HPT, 9-Hole Peg Test; cCDW; composite CDW; CDW, confirmed disability worsening; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; PMS, progressive multiple sclerosis; T25FWT, Timed 25-Foot Walk test.

Results

Frequency of CDW on T25FWT, 9HPT, EDSS and cCDW – numbers of patients at risk (RMS/PMS studies)

OPERA I/II OCR arm

Number of patients at risk	Time (weeks)									
	0	12	24	36	48	60	72	84	96	
T25FW	827	794	754	727	703	679	656	627	532	
9HPT	827	797	773	752	741	728	718	700	592	
Composite	827	788	737	699	662	638	617	594	533	
EDSS	827	796	767	738	718	702	691	675	604	

ENSEMBLE

Number of patients at risk	Time (weeks)													
	0	24	48	72	96	120	144	168	192	216	240	264		
T25FW	1225	1198	1115	1053	1004	960	914	851	544	243	185	21		
9HPT	1225	1210	1184	1157	1130	1100	1056	999	659	286	216	30		
Composite	1225	1186	1071	991	932	875	823	757	493	201	156	20		
EDSS	1225	1198	1145	1096	1051	1007	965	908	593	250	199	28		

ORATORIO OCR arm

Number of patients at risk	Time (weeks)																							
	0	12	24	36	48	60	72	84	96	108	120	132	144	156	168	180	192	204	216	228	240			
T25FW	488	467	432	391	370	342	315	300	277	251	242	224	217	189	127	109	63	54	18	15	2			
9HPT	488	472	459	447	437	417	408	396	383	371	364	352	341	312	213	185	107	88	28	21	3			
Composite	488	456	412	366	339	308	282	263	241	217	209	196	184	159	109	92	52	42	15	12	2			
EDSS	488	463	451	432	432	392	377	356	339	320	305	296	284	256	175	147	89	71	22	18	2			

OLYMPUS RTX arm

Number of patients at risk	Time (weeks)									
	0	12	24	36	48	60	72	84	96	
T25FW	292	279	243	217	204	190	171	157	114	
9HPT	292	282	272	259	252	247	236	227	172	
Composite	292	269	232	203	185	172	146	131	90	
EDSS	292	271	260	240	228	222	206	196	147	

OPERA I/II IFN arm

Number of patients at risk	Time (weeks)									
	0	12	24	36	48	60	72	84	96	
T25FW	829	791	724	667	637	604	581	548	468	
9HPT	829	793	763	721	701	672	657	628	542	
Composite	829	786	700	631	589	549	517	486	430	
EDSS	829	789	744	698	666	633	610	584	512	

CONSONANCE

Number of patients at risk	Time (weeks)													
	0	24	48	72	96	120	144	168	192					
T25FW	629	598	504	446	389	340	305	248	118					
9HPT	629	609	562	536	497	463	432	382	188					
Composite	629	608	479	412	347	294	256	210	99					
EDSS	629	615	579	538	491	436	392	336	161					

ORATORIO PBO arm

Number of patients at risk	Time (weeks)																							
	0	12	24	36	48	60	72	84	96	108	120	132	144	156	168	180	192	204	216	228	240			
T25FW	244	236	211	193	174	159	141	132	120	103	95	86	82	58	44	36	28	19	6	1	-			
9HPT	244	238	229	219	207	197	186	176	167	158	149	140	131	95	70	51	39	24	8	2	-			
Composite	244	230	195	169	151	133	118	110	102	85	78	67	61	42	30	26	22	15	4	1	-			
EDSS	244	232	212	169	189	180	172	162	153	145	136	124	114	81	60	44	35	21	7	2	-			

OLYMPUS PBO arm

Number of patients at risk	Time (weeks)									
	0	12	24	36	48	60	72	84	96	
T25FW	147	141	120	105	95	81	73	65	45	
9HPT	147	144	135	129	123	116	113	102	75	
Composite	147	137	114	91	80	69	63	54	37	
EDSS	147	141	130	116	111	104	96	88	58	

Results

Impact of CDW–T25FW and CDW–9HPT on Risk of Future CDW–EDSS

Study	HR (with vs without prior CDW-T25FWT)	HR (with vs without prior CDW-9HPT)
RMS studies		
OPERA I/II OCR DBT	2.11 (p=0.07)	0.62 (p = 0.66)
OPERA I/II IFN DBT	2.56 (p<0.001)	2.48 (p = 0.05)
ENSEMBLE ^a	2.29 (p<0.001)	1.23 (p=0.77)
PMS studies		
ORATORIO OCR DBT	5.20 (p<0.001)	3.04 (p<0.001)
ORATORIO OCR DBT + OLE	4.33 (p<0.001)	2.52 (p<0.001)
ORATORIO PBO DBT	3.44 (p<0.001)	1.53 (p=0.17)
ORATORIO PBO DBT + OLE	4.03 (p<0.001)	1.58 (p=0.04)
OLYMPUS RTX DBT	3.67 (p<0.001)	4.65 (p=0.002)
OLYMPUS PBO DBT	3.29 (p=0.001)	2.14 (p=0.07)
CONSONANCE ^a	2.99 (p<0.001)	1.87 (p=0.008)

Hazard ratios quantifying the change in risk of CDW-EDSS following CDW-T25FWT and CDW-9HPT

CDW-T25FWT and CDW-9HPT were associated with an increased risk of CDW-EDSS in RMS and PMS



On-study CDW-T25FWT and CDW-9HPT were associated with an increased risk of future CDW-EDSS in all study arms except one where CDW-9HPT was extremely rare

9HPT, 9-Hole Peg Test; CDW, confirmed disability worsening; DBT, double-blind treatment period; EDSS, Expanded Disability Status Scale; IFN, interferon β -1a; OCR, ocrelizumab; OLE, open-label extension period; PBO, placebo; RTX, rituximab; T25FWT, Timed 25-Foot Walk test.

^aThe confirmation period for CDW was at least 6 (as opposed to 3) months for these study arms. 24W-CDW, 24-week confirmed disability worsening; OCR, ocrelizumab.

Results

Impact of CDW–T25FW and CDW–9HPT on Risk of Future CDW–EDSS; Sensitivity Analysis

Study	HR for CDW-EDSS without ambulation (with vs without CDW-T25FW)
RMS studies	
OPERA I/II OCR DBT	0.85 (p=0.79)
OPERA I/II IFN DBT	1.74 (p=0.10)
ENSEMBLE ^a	2.51 (p<0.001)
PMS studies	
ORATORIO OCR DBT	4.34 (p<0.001)
ORATORIO OCR DBT + OLE	4.31 (p<0.001)
ORATORIO PBO DBT	2.39 (p=0.03)
ORATORIO PBO DBT + OLE	4.17 (p<0.001)
OLYMPUS RTX DBT	5.81 (p<0.001)
OLYMPUS PBO DBT	0.68 (p=0.75)
CONSONANCE ^a	2.60 (p<0.001)

Hazard ratios quantifying the change in risk of CDW-EDSS without the ambulation score following CDW-T25FWT and CDW-9HPT

The strong associations between CDW–T25FW and CDW–EDSS were still present in most studies when the ambulation score was removed in the definition of CDW–EDSS



On-study CDW-T25FWT and CDW-9HPT were associated with an increased risk of future CDW-EDSS in all study arms except one where CDW-9HPT was extremely rare

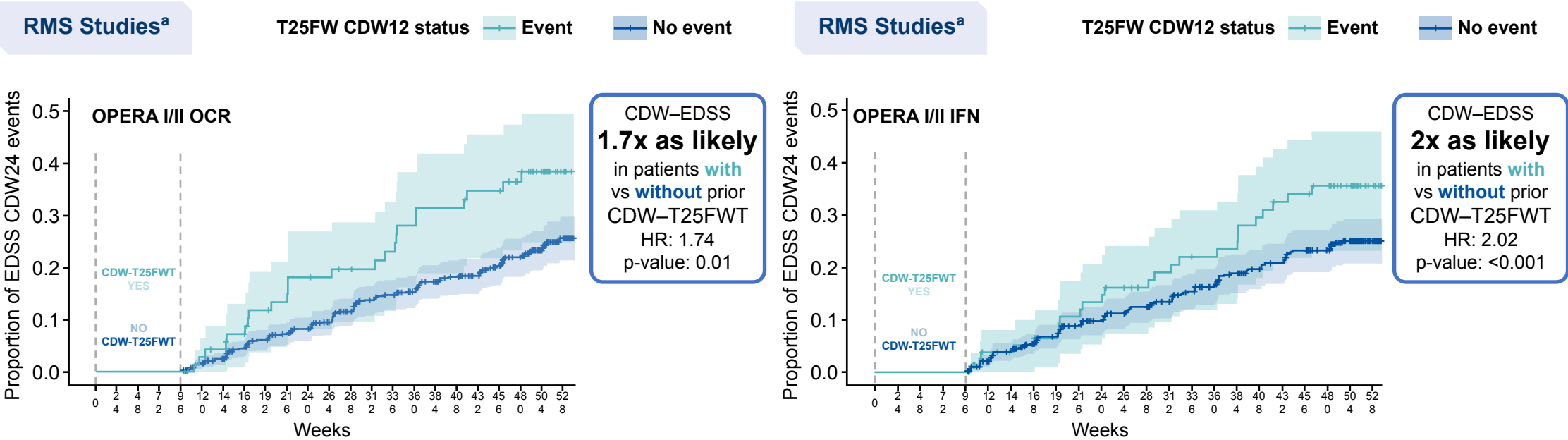
9HPT, 9-Hole Peg Test; CDW, confirmed disability worsening; DBT, double-blind treatment period; EDSS, Expanded Disability Status Scale; IFN, interferon β-1a; OCR, ocrelizumab; OLE, open-label extension period; PBO, placebo; RTX, rituximab; T25FWT, Timed 25-Foot Walk test.

^aThe confirmation period for CDW was at least 6 (as opposed to 3) months for these study arms. 24W-CDW, 24-week confirmed disability worsening; OCR, ocrelizumab.

Results

Patients With/Without CDW–T25FW in the First 96 Weeks and the Risk of Future CDW–EDSS

T25FW in the first 96 weeks was associated with an increased risk of CDW–EDSS after 96 weeks in PwRMS; similar trends were seen for CDW–9HPT



Worsening on CDW-T25FW was predictive of future CDW-EDSS in PwRMS

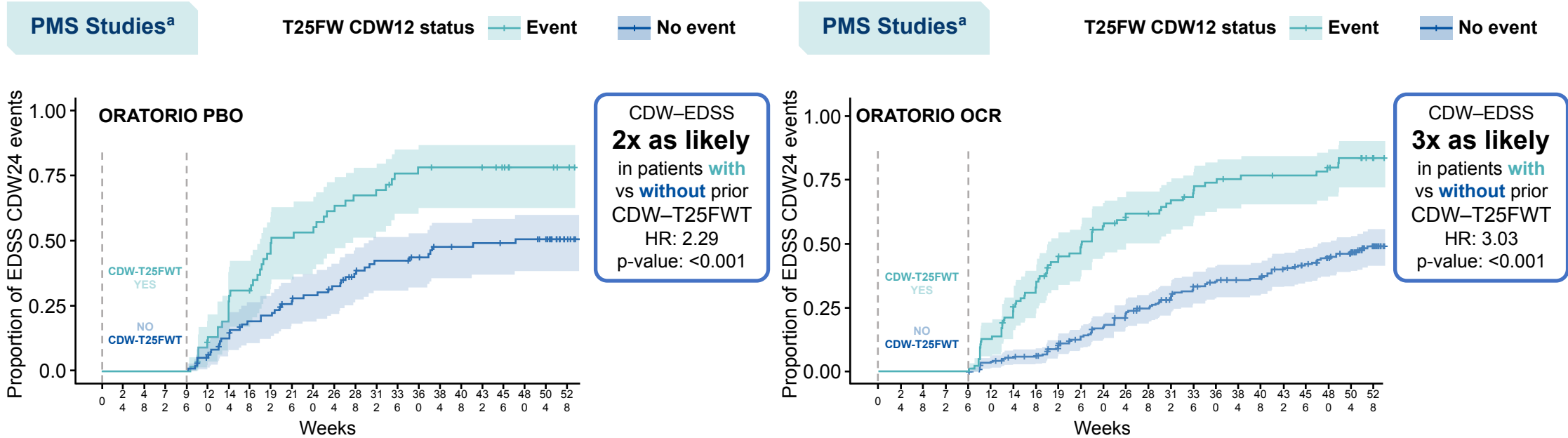
9HPT, 9-Hole Peg Test; CDW; CDW, confirmed disability worsening; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; PwRMS, patients with progressive multiple sclerosis; T25FWT, Timed 25-Foot Walk test.

^aSubgroup analyses were performed in the subset of patients who have long-term CDW24-EDSS, i.e., outside of the first 96 weeks of the study. Positive associations between presence of CDW-9HPT during the first 96 weeks of the study and an increased risk of long-term CDW24-EDSS were also observed for all eligible study arms (except the OCR arm of OPERA I/II: across RMS studies, risk of CDW-EDSS in patients w/wo CDW-9HPT: HRs 1.45-2.14 p values: 0.35-0.45; across PMS studies, risk of CDW-EDSS in patients w/wo CDW-T25FWT: HRs 2.03-3.08 p values: 0.02-<0.001.

Results

Patients With/Without CDW–T25FW in the First 96 Weeks and the Risk of Future CDW–EDSS

T25FW in the first 96 weeks was associated with an increased risk of CDW–EDSS after 96 weeks in PwPMS; similar trends were seen for CDW–9HPT



Worsening on CDW-T25FW was predictive of future CDW-EDSS in PwRMS

9HPT, 9-Hole Peg Test; CDW; CDW, confirmed disability worsening; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; OCR, ocrelizumab; PwPMS, patients with progressive multiple sclerosis; T25FWT, Timed 25-Foot Walk test.

^aSubgroup analyses were performed in the subset of patients who have long-term CDW24-EDSS, i.e., outside of the first 96 weeks of the study. Positive associations between presence of CDW-9HPT during the first 96 weeks of the study and an increased risk of long-term CDW24-EDSS were also observed for all eligible study arms (except the OCR arm of OPERA I/II: across RMS studies, risk of CDW-EDSS in patients w/wo CDW-9HPT: HRs 1.45-2.14 p values: 0.35-0.45; across PMS studies, risk of CDW-EDSS in patients w/wo CDW-T25FWT: HRs 2.03-3.08 p values: 0.02-<0.001

Results

Patients With/Without CDW–T25FW in the First 96 Weeks and the Risk of Future CDW–EDSS – patients at risk (RMS/PMS studies)

OPERA I/II OCR arm

Number of patients at risk	Time (weeks)																							
	0	24	48	72	96	120	144	168	192	216	240	264	288	312	336	360	384	408	432	465	480	504	528	
CDW-T25FW status: No event	584	584	584	584	584	563	544	519	505	491	479	459	441	421	412	395	378	368	356	332	314	236	99	
CDW-T25FW status: Event	74	74	74	74	74	69	66	62	57	55	52	51	49	48	46	43	41	41	38	38	33	25	7	

ENSEMBLE

Number of patients at risk	Time (weeks)												
	0	24	48	72	96	120	144	168	192	216	240	264	288
CDW-T25FW status: No event	919	919	919	919	919	892	857	809	528	223	176	24	0
CDW-T25FW status: Event	120	120	120	120	120	115	108	99	65	27	23	4	0

ORATORIO OCR arm

Number of patients at risk	Time (weeks)																							
	0	24	48	72	96	120	144	168	192	216	240	264	288	312	336	360	384	408	432	465	480	504	528	
CDW-T25FW status: No event	99	99	99	99	99	91	82	74	72	65	62	58	51	46	46	43	38	37	36	35	34	31	22	
CDW-T25FW status: Event	55	55	55	55	55	48	41	34	27	24	23	19	16	16	11	11	9	9	9	6	4	4	2	

OPERA I/II IFN arm

Number of patients at risk	Time (weeks)																							
	0	24	48	72	96	120	144	168	192	216	240	264	288	312	336	360	384	408	432	465	480	504	528	
CDW-T25FW status: No event	478	478	478	478	478	450	436	418	405	386	373	362	355	340	326	316	302	293	287	276	263	206	81	
CDW-T25FW status: Event	81	81	81	81	81	74	72	71	68	65	63	60	57	55	53	52	51	47	44	43	40	31	8	

CONSONANCE

Number of patients at risk	Time (weeks)										
	0	24	48	72	96	120	144	168	192	216	
CDW-T25FW status: No event	362	362	362	362	362	336	306	267	131	1	
CDW-T25FW status: Event	119	119	119	119	119	100	86	69	30	0	

ORATORIO PBO arm

Number of patients at risk	Time (weeks)																							
	0	24	48	72	96	120	144	168	192	216	240	264	288	312	336	360	384	408	432	465	480	504	528	
CDW-T25FW status: No event	248	248	248	248	248	234	226	223	209	194	183	172	159	149	140	130	126	125	113	106	97	90	58	
CDW-T25FW status: Event	95	95	95	95	95	83	74	64	51	45	36	33	30	26	23	19	17	16	15	15	13	9	6	

Identified studies from a literature review where treatment effects on CDW-T25FWT and CDW-EDSS could be obtained

Study	Phase	Design	Population phenotype	Treatments	N (total) (active treatment /comparator)	Source for treatment effects
AFFIRM [NCT00027300]	3	Multicenter, randomized, double-blind, parallel group, placebo controlled,	RRMS	Natalizumab, placebo	942 (627/315)	Dong et al. 2014 ¹
ASCEND [NCT01416181]	3b	Multicenter, randomized, double-Blind, placebo-controlled	SPMS	natalizumab, placebo	889 (440/449)	Kapoor et al. 2018 ²
EXPAND [NCT01665144]	3	Multicenter, randomized, double-blind, parallel group, placebo controlled,	SPMS	Siponimod, placebo	1652 (1105/546)	Kappos et al. 2018 ³
INFORMS [NCT00731692]	3	Multicenter, randomized, double-blind, parallel group, placebo controlled,	PPMS	Fingolimod, placebo	970 cohort 1/2: (147/133)/(336/354)	Lublin et al. 2016 ⁴
OLYMPUS [NCT00087529]	3	Multicenter, randomized, double-blind, parallel group, placebo controlled,	PPMS	Rituximab, placebo	439 (292/147)	Hawker et al. 2009 ⁵
OPERA I [NCT01247324]	3	Multicenter, randomized, double-blind, double-dummy, parallel-group plus long-term extension	RMS	Ocrelizumab, IFN β -1a	821 (410/411)	Roche database
OPERA II [NCT01412333]	3	Multicenter, randomized, double-blind, double-dummy, parallel-group plus long-term extension	RMS	Ocrelizumab, IFN β -1a	835 (417/418)	Roche database
ORATORIO [NCT01194570]	3	Multicenter, randomized, parallel-group, double-blind, placebo-controlled plus long-term extension	PPMS	Ocrelizumab, placebo	732 (488/244)	Roche database
PROMISE [NA]	Unavailable	Multicenter, randomized, double-Blind, placebo-controlled	PPMS	Glatiramer acetate, placebo	943 (627/316)	Wolinsky et al. 2007 ⁶

9HPT, 9-Hole Peg Test; CDW; CDW, confirmed disability worsening; EDSS, Expanded Disability Status Scale; IFN, interferon; MS, multiple sclerosis; OCR, ocrelizumab; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

1. Dong Q, et al. *Mult Scler* 2014;20:118. 2. Kapoor R, et al. *Lancet Neurol* 2018;17:405–415. 3. Kappos L, et al. *Lancet* 2018;391:1263–1273. 4. Lublin F, et al. *Lancet* 2016;387:1075-1084. 5. Hawker K, et al. *Ann Neurol* 2009;66:460–71. 6. Wolinsky JS, et al. *Ann Neurol* 2007;61:14–24



<https://ter.li/l8gook>

Fenebrutinib, a Noncovalent, Reversible, Bruton's Tyrosine Kinase Inhibitor, Potently Blocks Neuroinflammation Induced by FcγR Activation in Human Microglial Systems: Implications for MS Treatment

Julie Langlois,¹ Simona Lange,¹ Jonathan DeGeer,¹ Will Macnair,¹ Martin Ebeling,¹ Roland Schmucki,¹ Christopher Harp,² Yun-An Shen,² Ludovic Collin,¹ Jacqueline A Nicholas,³ Jiwon Oh,⁴ James Keaney¹

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Thursday, 12 October 2023

Disclosures

J Langlois, S Lange, J DeGeer, W Macnair, M Ebeling, R Schmucki, L Collin and J Keaney are employees and shareholders of F. Hoffmann-La Roche Ltd. **C Harp** and **Y-A Shen** are employees of Genentech, Inc. and shareholders of F. Hoffmann-La Roche Ltd. **JA Nicholas** has received research grants from Biogen, Novartis, PCORI, Genentech, Inc., University of Buffalo; she has received compensation for consulting from EMD Serono, Genentech, Inc., Greenwich Biosciences, Novartis, TG Therapeutics and Sanofi and speaking honoraria from BMS, EMD Serono, Horizon, TG Therapeutics. **J Oh** has received personal compensation for serving as a consultant from Biogen, Bristol-Myers Squibb, Eli Lilly, Novartis AG, EMD Serono, F. Hoffmann-La Roche Ltd and Sanofi. The institution of Dr Oh has received research support from Biogen, EMD Serono and F. Hoffmann-La Roche Ltd.

Objective



To evaluate the pharmacological and functional properties of the BTKi FEN in human microglial systems

Introduction



Neuroinflammation driven by detrimental microglial activation may contribute to progressive disease biology in **multiple sclerosis** (MS)



In the periphery, **Bruton's tyrosine kinase** (BTK) is expressed in both **adaptive** (B cells) and **innate** (monocytes, macrophages) immune cells,¹ whereas in the central nervous system (CNS), BTK is expressed primarily in **microglia**²



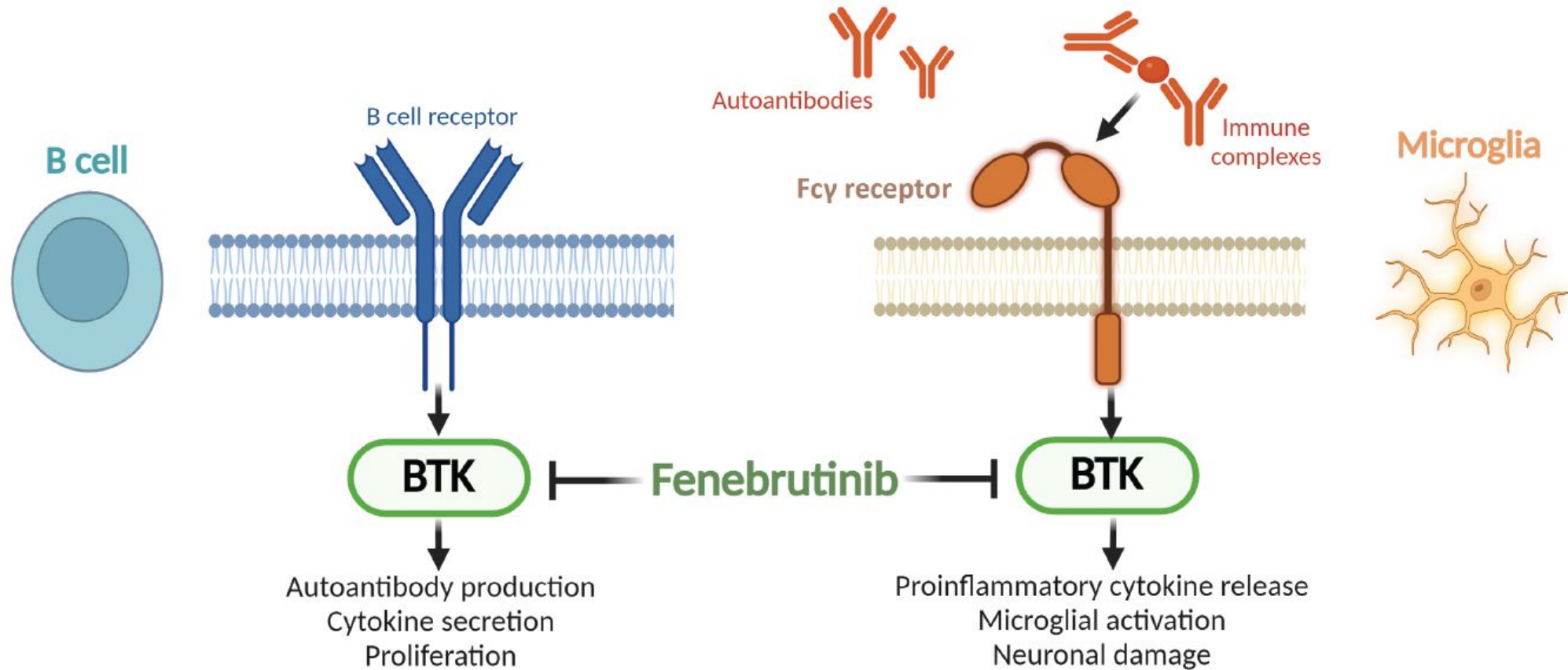
Fenebrutinib (FEN) is a **potent, highly selective, noncovalent, reversible BTK inhibitor** (BTKi)³ that may address MS disease progression by targeting multiple pathogenic mechanisms in both the peripheral and CNS arms of the immune system



Much research to date has investigated the effects of BTKis using rodent disease models. Here, we characterise the impact of FEN in blocking BTK-mediated, **disease-associated Fcγ receptor (FcγR) activation** in **human microglia and complex human brain cell systems** to enhance translatability to people with MS

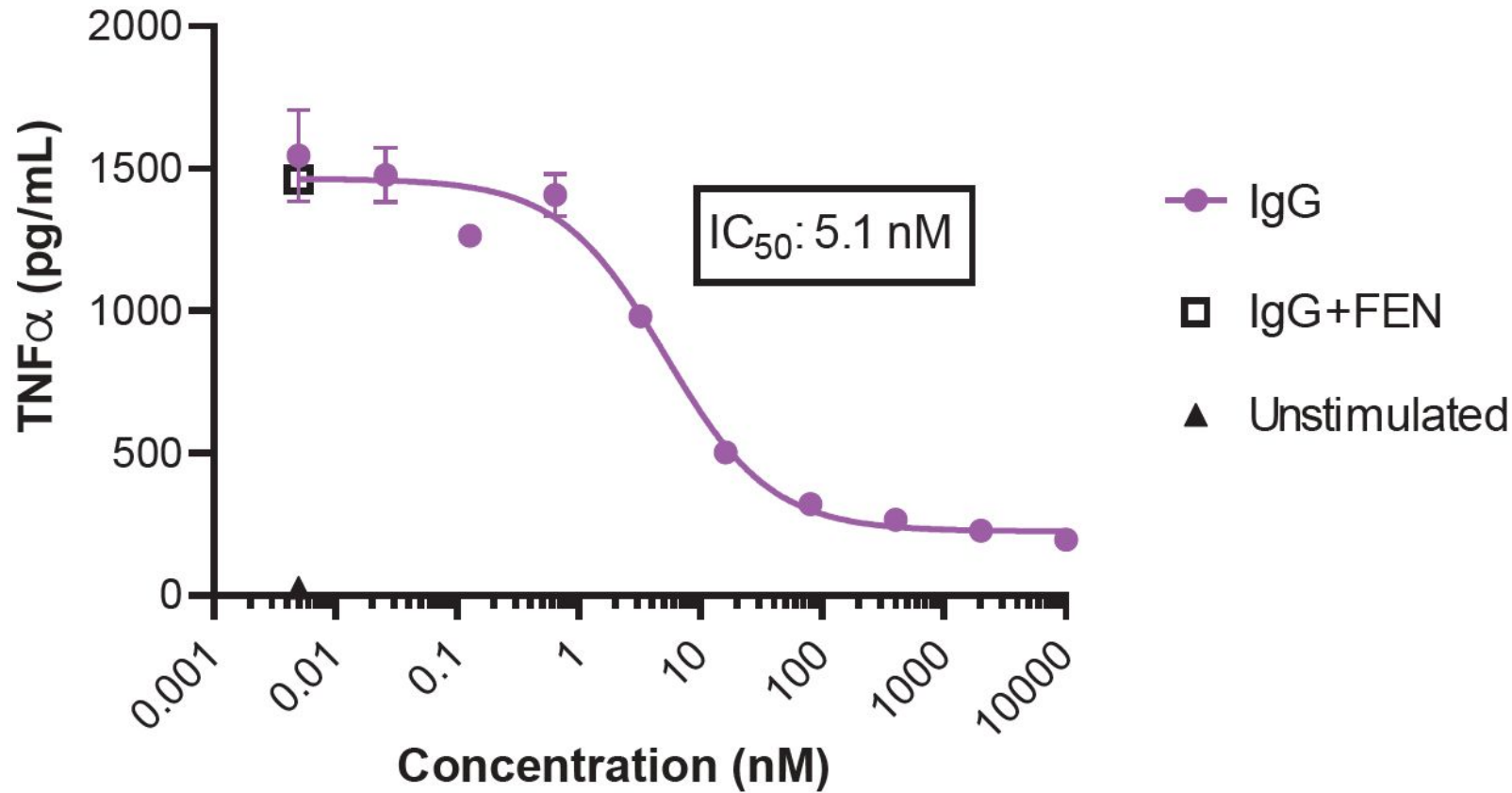
Introduction

Fenebrutinib Proposed Mechanism of Action



Results

FEN Potently Blocked FcγR-Induced Activation in Human Microglia



- FEN showed similar high potency in microglia to B cells and monocytes

Results

FEN Acts on Human Microglia to Attenuate the Release of Multiple Pro-Inflammatory Cytokines and Chemokines Linked to MS Pathogenesis

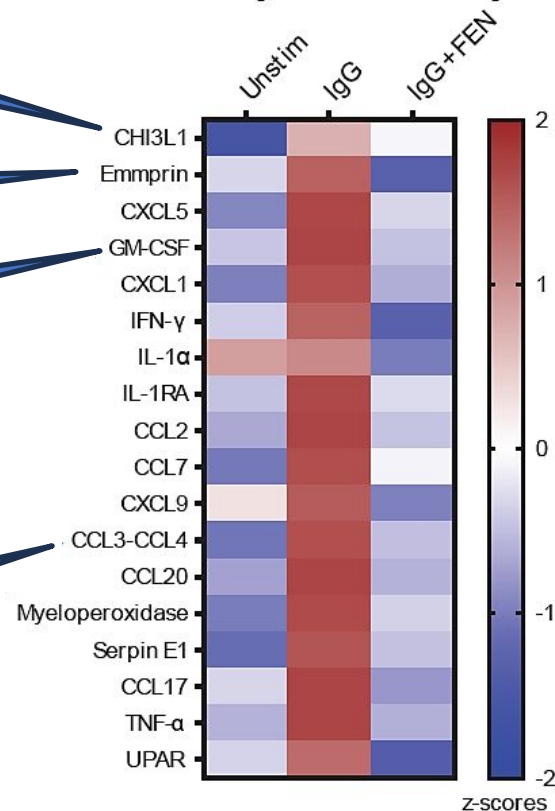
CHI3L1 (YKL-40) levels in CSF are associated with disability in progressive MS.⁴

Emmprin/BSG is elevated in CSF of people with MS and regulates leucocyte transmigration.^{5,6}

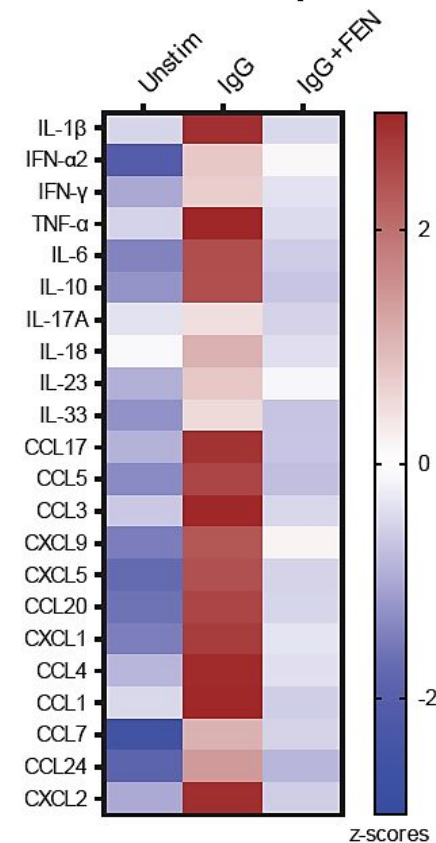
Pro-inflammatory cytokines like GM-CSF and TNF- α induce loss of neurite integrity.⁷

Chemokines (e.g. CCL3, CCL4) mediate leucocyte migration and activation.⁸

Cytokine Array



LEGENDplex

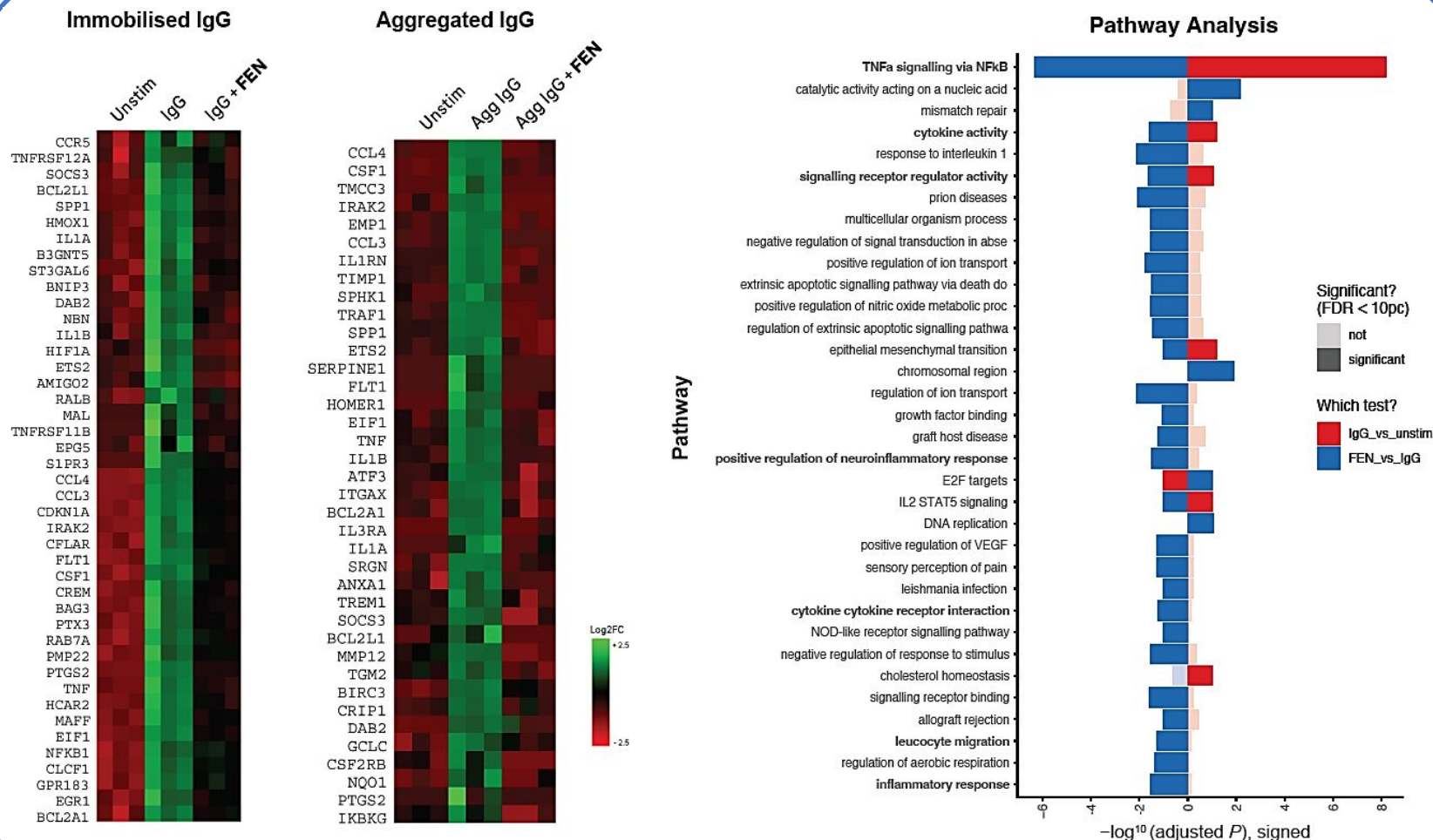


BSG, basigin; CCL, C-C motif chemokine ligand; CHI3L1, chitinase 3 like 1; CSF, cerebrospinal fluid; FEN, fenebrutinib; CXCL, C-X-C chemokine ligand; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN, interferon; IgG, immunoglobulin G; IL, interleukin; MS, multiple sclerosis; TNF- α , tumour necrosis factor α ; UPAR, urokinase plasminogen activator receptor.

4. Pérez-Miralles et al. 2020 *Neurol Neuroimmunol Neuroinflamm* PMID: 32611760. 5. Kaushik et al. 2016 *PLoS One* PMID: 27727297. 6. Agrawal et al. 2011 *J Neurosci* PMID: 21228176. 7. Meyer-Arndt et al. 2023 *J Neuroimmune Pharmacol* PMID: 36862362. 8. Cui et al. 2020 *Int Immunopharmacol* PMID: 32197226.

Results

Gene Expression Analyses Identified Microglial Genes and Pathways Linked to Neuroinflammation and Cytokine Signalling Modulated by FEN

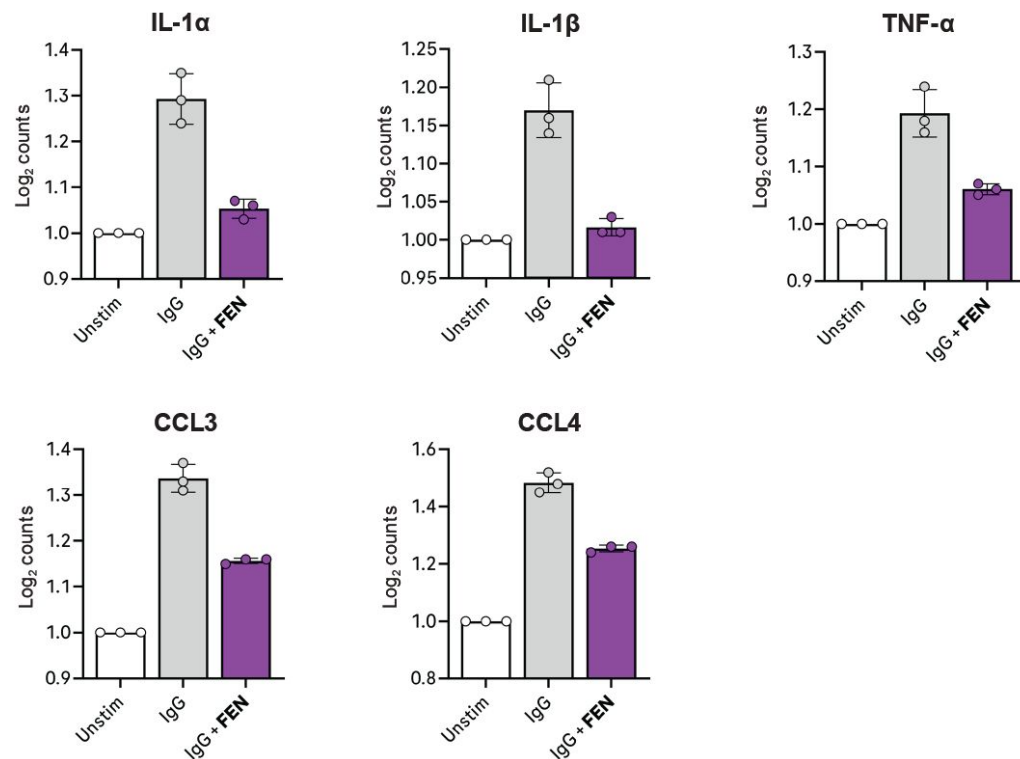


- FEN reversed gene expression changes induced by Fc γ R signalling in microglia
- Transcriptional signatures of FEN activity included pathways linked to neuroinflammation and cytokine signalling

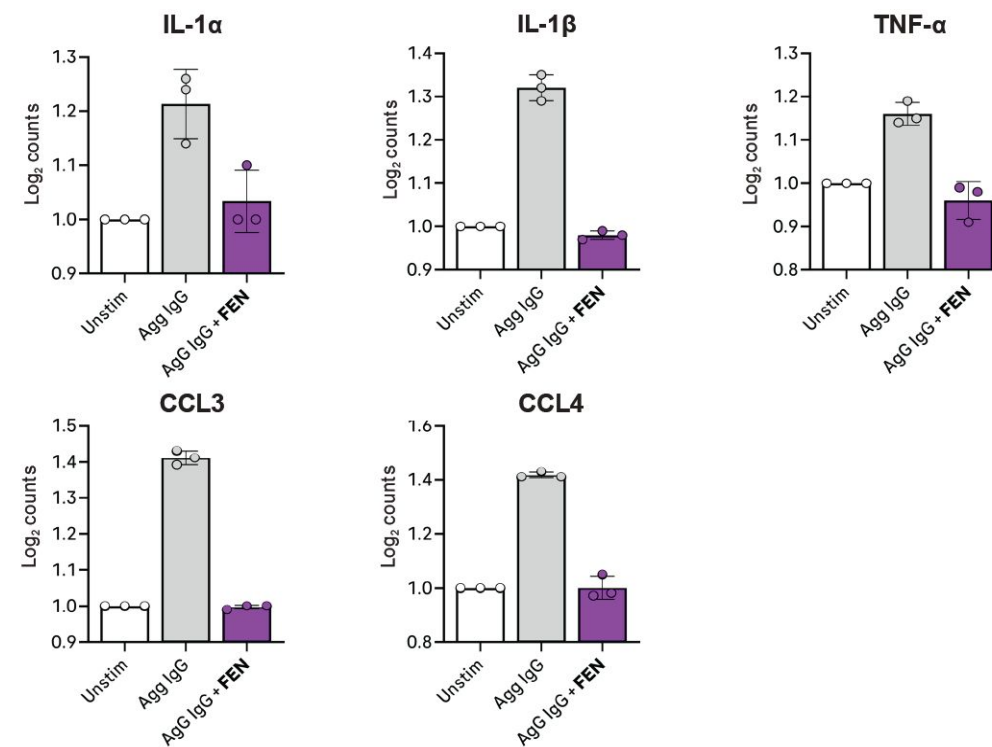
Results

Gene Expression Analyses Identified Microglial Genes and Pathways Linked to Neuroinflammation and Cytokine Signalling Modulated by FEN

Immobilized IgG



Aggregated IgG



Consistent effects of FEN on cytokine (IL-1 α , IL-1 β , TNF- α) and chemokine (CCL3, CCL4) genes were observed

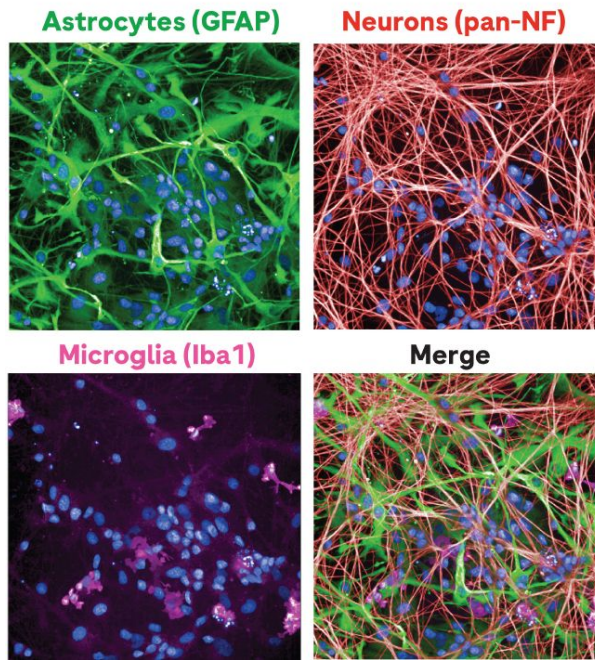
Results

FEN Blocks FcγR-Mediated Activation of Basigin and Matrix Metalloproteinase Pathways in Human Brain Tri-Culture System

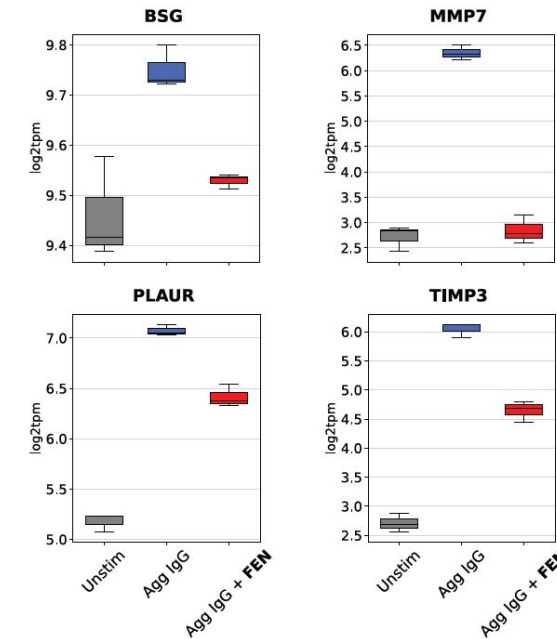


- BSG (an MMP inducer) and MMP are elevated in MS plaques, and BSG blockade attenuates the severity of experimental autoimmune encephalomyelitis, an animal model of MS⁹
- BBB damage by MMPs mediates transmigration of leukocytes into CNS¹⁰

Human Brain Tri-Cultures



Targets of BSG



Agg, aggregated; BSG, basigin; GFAP, glial fibrillary acidic protein; Iba1, ionized calcium binding adaptor molecule 1; IgG, immunoglobulin G; MMP, matrix metalloproteinase; NF, neurofilament; PLAUR, plasminogen activator, urokinase receptor; TIMP3, TIMP metalloproteinase inhibitor 3.

9. Agrawal et al. 2011 *J Neurosci* PMID: 21228176. 10. Rempe et al. 2016 *J Cereb Blood Flow Metab* PMID: 27323783.

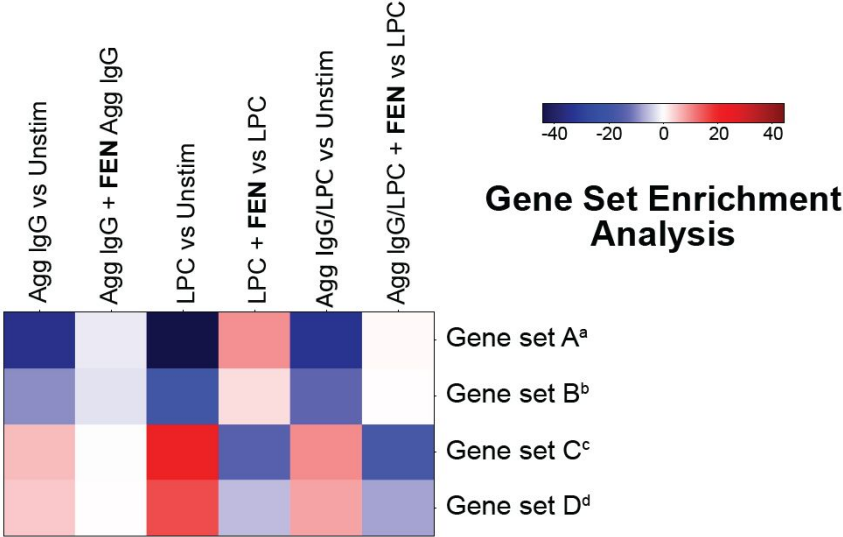
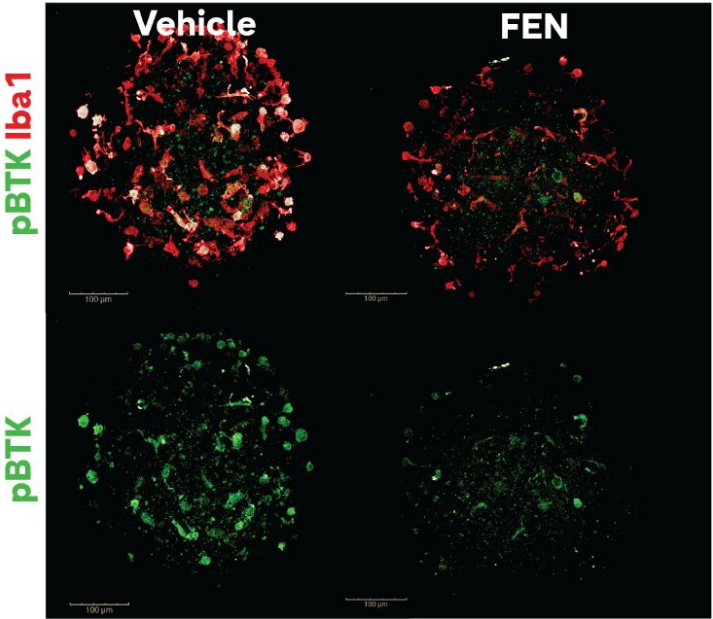
Results

Treatment of Immunocompetent Human Brain Organoids With FEN Blocked FcγR-Mediated Inflammatory Signalling



- FEN reversed FcγR- and lysolecithin (LPC)-mediated effects on cholesterol metabolism and toll-like receptor (TLR) inflammatory signalling pathways

Microglia-Containing Human Brain Organoids



Agg, aggregated; BTK, Bruton's tyrosine kinase; FEN, fenebrutinib; Iba1, ionized calcium binding adaptor molecule 1; IgG, immunoglobulin G.
^aGene set A = cholesterol_biosynthesis_REACTOME. ^bGene set B = activation_of_gene_expression_by_SREBF_SREBP_REACTOME. ^cGene set C = enriched_in_monocytes_(II)_(M11.0).
^dGene set D = TLR_and_inflammatory_signalling_(M16).

Conclusions



FEN acts on microglia to ameliorate pathogenic neuroinflammation resulting from FcγR activation. In people with MS, this effect may reduce progressive neurodegeneration resulting from chronic CNS inflammation in MS



Further biomarker and efficacy assessments in clinical trials may help to confirm the clinical relevance of this observed effect on microglia

Supplementary Material

Methods



- Efficacy and potency of fenebrutinib (FEN) was assessed in human-induced pluripotent stem cell (iPSC)–derived microglia by measuring tumour necrosis factor α (TNF- α) release following Fc γ receptor (Fc γ R) activation
- Two different immunoassay methods were used to detect a broad range of cytokines and chemokines modulated by FEN treatment
- Two different methods to activate Fc γ R signaling in human microglia were used: immobilized immunoglobulin G (IgG) and aggregated IgG
- NanoString gene expression profiling and RNA-sequencing was used to capture transcriptional signatures associated with FEN treatment in iPSC-derived microglia, human brain tri-cultures and human brain organoids



<https://ter.li/p8wdfo>

Cerebrospinal Fluid and MRI Analyses of Fenebrutinib Treatment in Multiple Sclerosis Reveal Brain Penetration and Early Reduction of New Lesion Activity: Results From the Phase II FENopta Study

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Mario Habek,⁵ Le H. Hua,⁶ Martin S. Weber,⁷ Pija Thomas,⁸ Julie Napieralski,⁸
David Clayton,⁸ Denison Kuruvilla,⁸ Qi Qi,⁸ Yan Xu,⁸ Alexandra Goodyear,⁸ Jiwon Oh⁹

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Session 22: LBAs; Oral

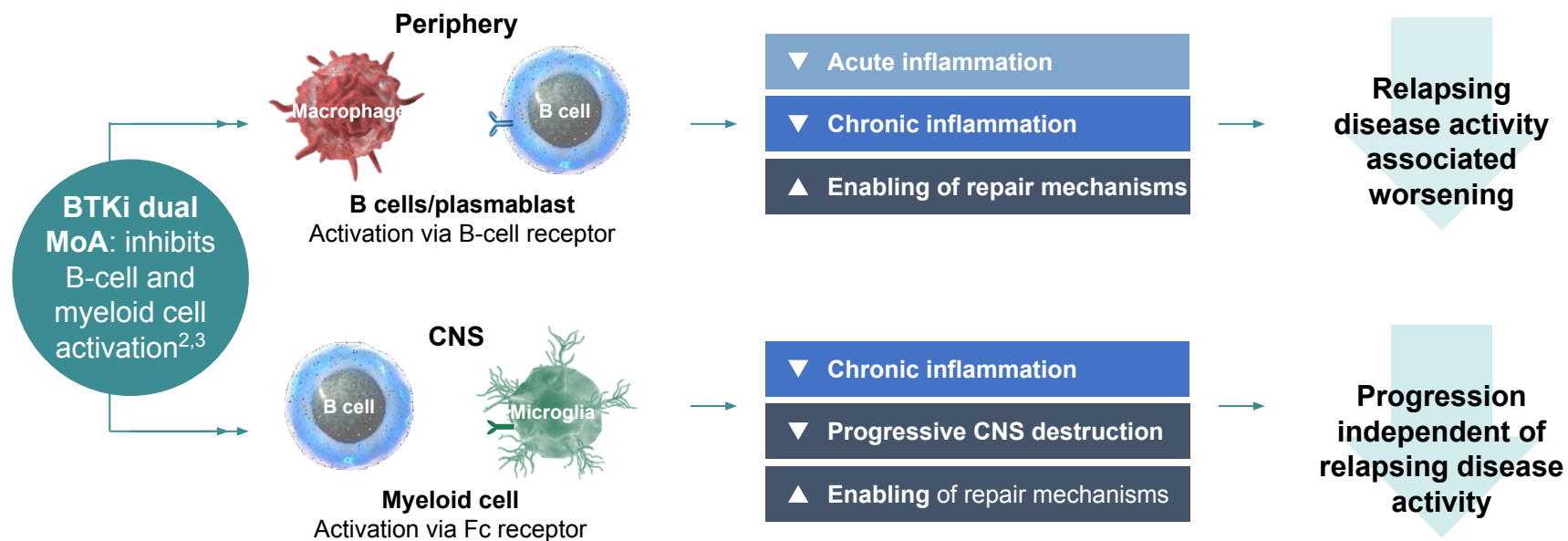
Friday, 13 October 2023

Disclosures

A Bar-Or reports consulting fees from Gossamer, Janssen/Actelion, Atara Biotherapeutics, Biogen, BMS/Celgene/Receptos, F. Hoffmann-La Roche Ltd, Genentech, Inc., Mapi, MedImmune, Merck/EMD Serono, Novartis, Sanofi Genzyme and GSK; contracted research for Genentech, Inc., Novartis and Biogen; salary from the University of Pennsylvania Perelman School of Medicine. **M Dufek** and **H Budincevic** have nothing to disclose. **J Drulovic** reports research support from Merck and Roche; personal honoraria for speaking or serving on advisory boards from Amicus, Bayer Schering Pharma, Biogen, Hemofarm, Janssen, Medis, Merck Serono, Novartis, Roche, Sanofi Genzyme and Teva. **M Habek** reports speaker/consultant fees from Biogen, Merck, Novartis, Pliva/Teva, Roche and Sanofi Genzyme. LH Hua reports personal fees for speaking, consulting and advisory board activities from Alexion, BMS, EMD Serono, Genentech, Inc., Genzyme, Greenwich Biosciences, Horizon and Novartis; research salary support paid to her institution from Biogen. **MS Weber** reports research support from the Deutsche Forschungsgemeinschaft (DFG; WE3547/5-1), Novartis, Teva, Biogen, Roche, Merck and the ProFutura Programme of the Universitätsmedizin Göttingen; serving as editor for PLoS One; travel funding and/or speaker honoraria from Biogen, Merck Serono, Novartis, Roche, Teva, Bayer and Genzyme. **P Thomas, J Napieralski, D Clayton, D Kuruvilla, Q Qi, Y Xu** and **A Goodyear** are employees of Genentech, Inc., and shareholders of F. Hoffmann-La Roche Ltd **J Oh** has received compensation for consulting/speaking from Biogen, BMS, Eli Lilly, EMD Serono, Novartis, Roche, and Sanofi Genzyme and research funding from Biogen and Roche.

Background and Study Objective

- **Inflammatory and neurodegenerative processes** begin early in MS and **may drive progressive disease biology**¹
- **BTK** is implicated in peripheral and CNS inflammation in MS and **is a therapeutic target for relapsing and progressive disease**²⁻⁴
- **Fenebrutinib is a potent, highly selective, noncovalent, reversible BTK inhibitor** under investigation for MS



Study Objective



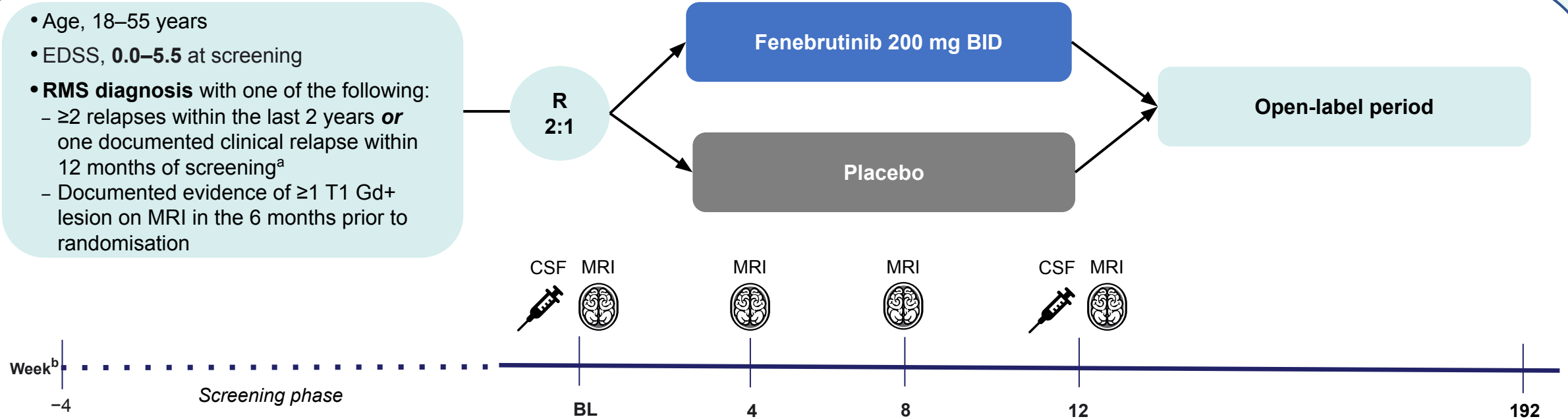
To evaluate the efficacy and safety of fenebrutinib in RMS and its early impact on MRI outcomes and soluble markers of disease activity and progression

BTK, Bruton's tyrosine kinase; BTKi, Bruton's tyrosine kinase inhibitor; CNS, central nervous system; MoA, mechanism of action; MS, multiple sclerosis; RMS, relapsing multiple sclerosis.

1. Filippi M, et al. Nat Rev Dis Primers 2018;4:43. 2. Whang JA, Chang BY. Drug Discov Today 2014;19:1200–1204. 3. Crawford J, et al. J Med Chem 2018;61:2227–2245. 4. Weber MS, et al. AAN 2021; Oral presentation P15.091.

Methods

Study Design: FENopta—a Randomised, Double-Blind, Placebo-Controlled Trial (NCT05119569)



Primary endpoint

- Total number of new T1 Gd+ lesions on MRI at Weeks 4, 8 and 12

Secondary endpoints

- Total number of new/enlarging T2-weighted lesions on MRI at Weeks 4, 8 and 12^c
- Proportion of patients free from any new T1 Gd+ and new/enlarging T2-weighted lesions on MRI at Weeks 4, 8 and 12^c
- Safety

Exploratory endpoints

- Fenebrutinib CSF concentration at baseline and/or after Week 12 (optional substudy)
- Plasma pharmacokinetics
- Total number of new T1 hypointense lesions on MRI at Weeks 4, 8 and 12

Results

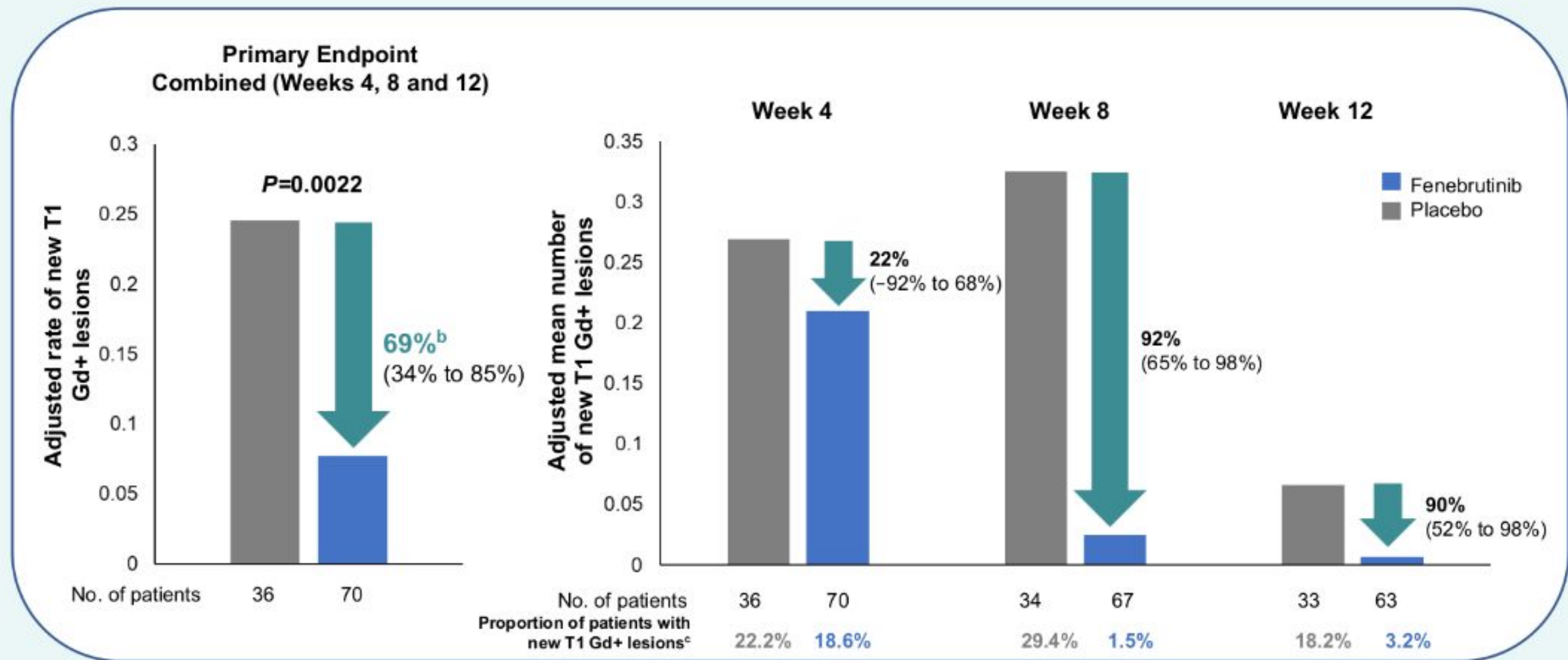
Baseline Demographics and Disease Characteristics Were Balanced Between Arms

	Fenebrutinib n=73	Placebo n=36	All patients N=109
Age, mean (SD), years	38.6 (8.5)	39.8 (7.7)	39.0 (8.2)
Female, n (%)	52 (71.2)	26 (72.2)	78 (71.6)
Time since diagnosis, mean (SD), years	4.9 (5.9)	5.9 (7.1)	5.2 (6.3)
Prior DMT use, n (%)	18 (24.7)	17 (47.2)	35 (32.1)
EDSS score, median (min–max)	2.5 (0.0–5.5)	3.0 (0.0–5.5)	2.5 (0.0–5.5)
No. of T1 Gd+ lesions, mean (SD)	0.74 (2.26)	0.72 (2.31)	0.73 (2.27)
Patients with T1 Gd+ lesions, n (%)	14 (19.2)	7 (19.4)	21 (19.3)
No. of T2-weighted lesions, mean (SD)	45.03 (28.46)	52.22 (33.09)	47.40 (30.11)
No. of T1 hypointense lesions, mean (SD)	21.1 (21.7)	26.2 (28.4)	22.8 (24.1)

T1 Gd+ lesions at baseline were balanced between the fenebrutinib and placebo arms

Results

Fenebrutinib Reduced T1 Gd+ Lesions, and Few Patients Had New Lesions After Week 4 of Treatment^a

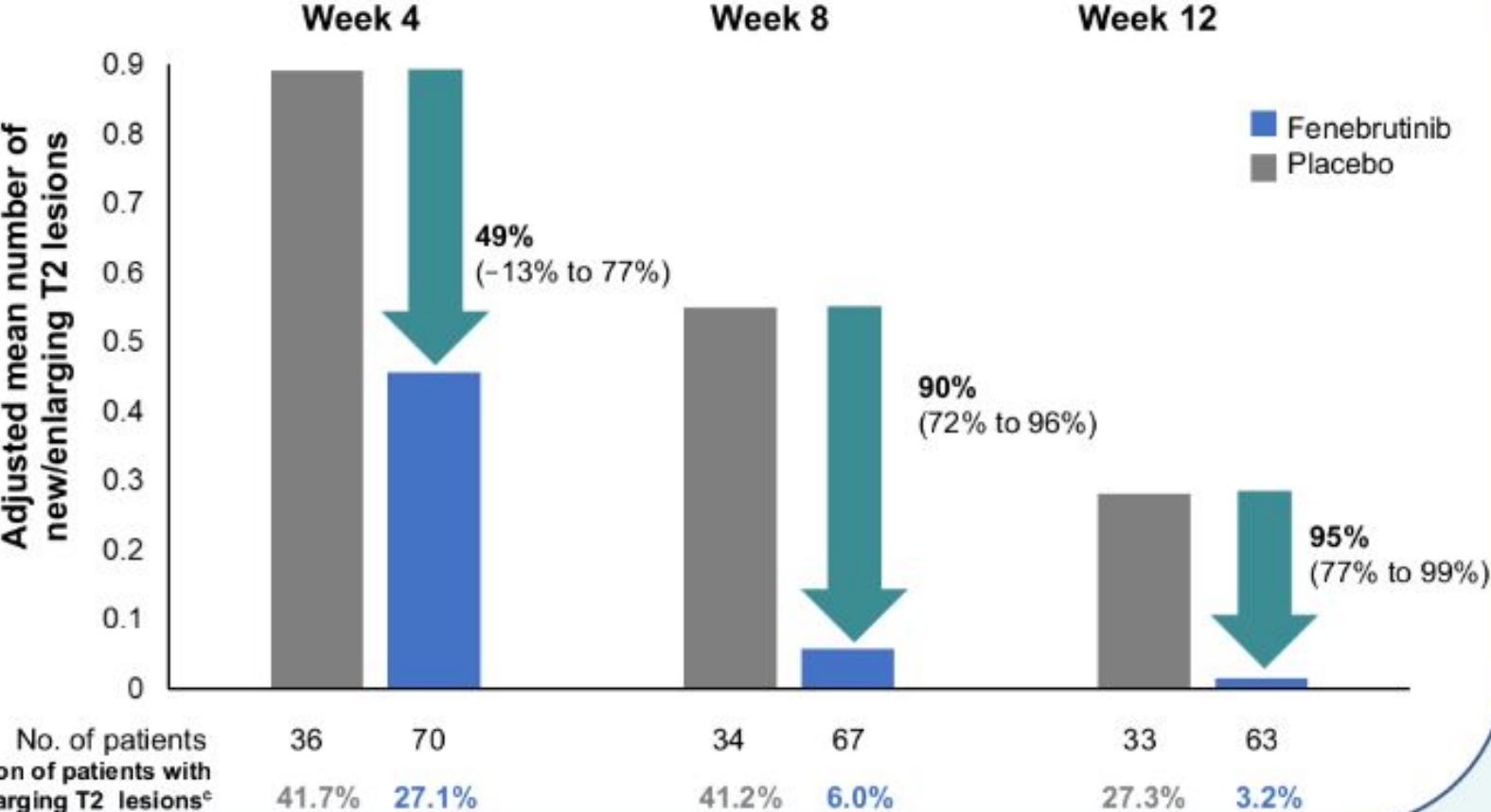
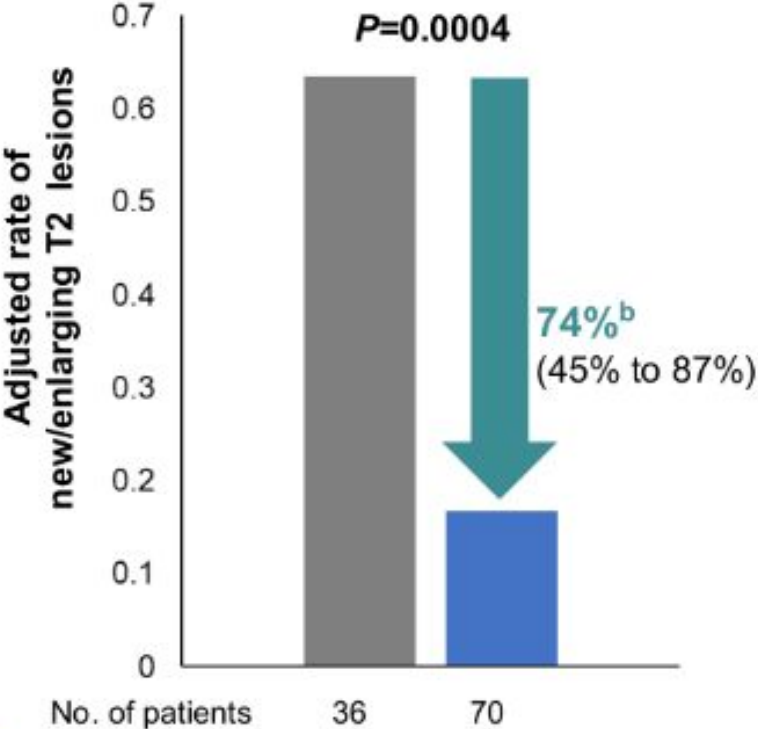


Gd+, gadolinium enhancing.
^aResults were estimated from a negative binomial model controlling for baseline T1 Gd+ lesion status (presence or absence) and included log number of scans as an offset. ^bTeal arrows indicate relative reduction (95% CI) of lesions. ^cNumber of patients who have a new lesion at that specific visit alone divided by the number of patients with a scan at that specific visit alone at Week X.

Results

Fenebrutinib Reduced T2-Weighted Lesions, and Few Patients Had New Lesions After Week 4 of Treatment^a

Secondary Endpoint
Combined (Weeks 4, 8 and 12)

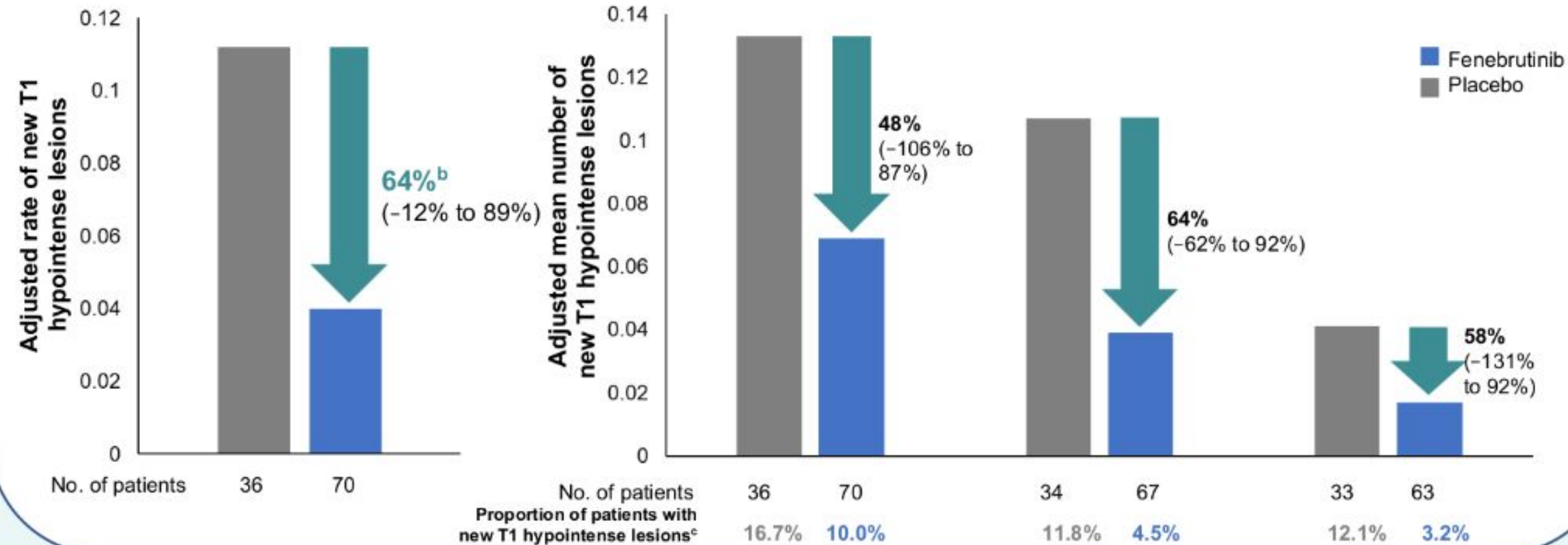


^aResults were estimated from a negative binomial model controlling for baseline T1 Gd+ lesion status (presence or absence) and included log number of scans as an offset. ^bTeal arrows indicate relative reduction (95% CI) of lesions. ^cNumber of patients who have a new lesion at that specific visit alone divided by the number of patients with a scan at that specific visit alone at Week X.

Results

Fenebrutinib Reduced T1 Hypointense Lesions, and Few Patients Had New Lesions After Week 4 of Treatment^{a,b}

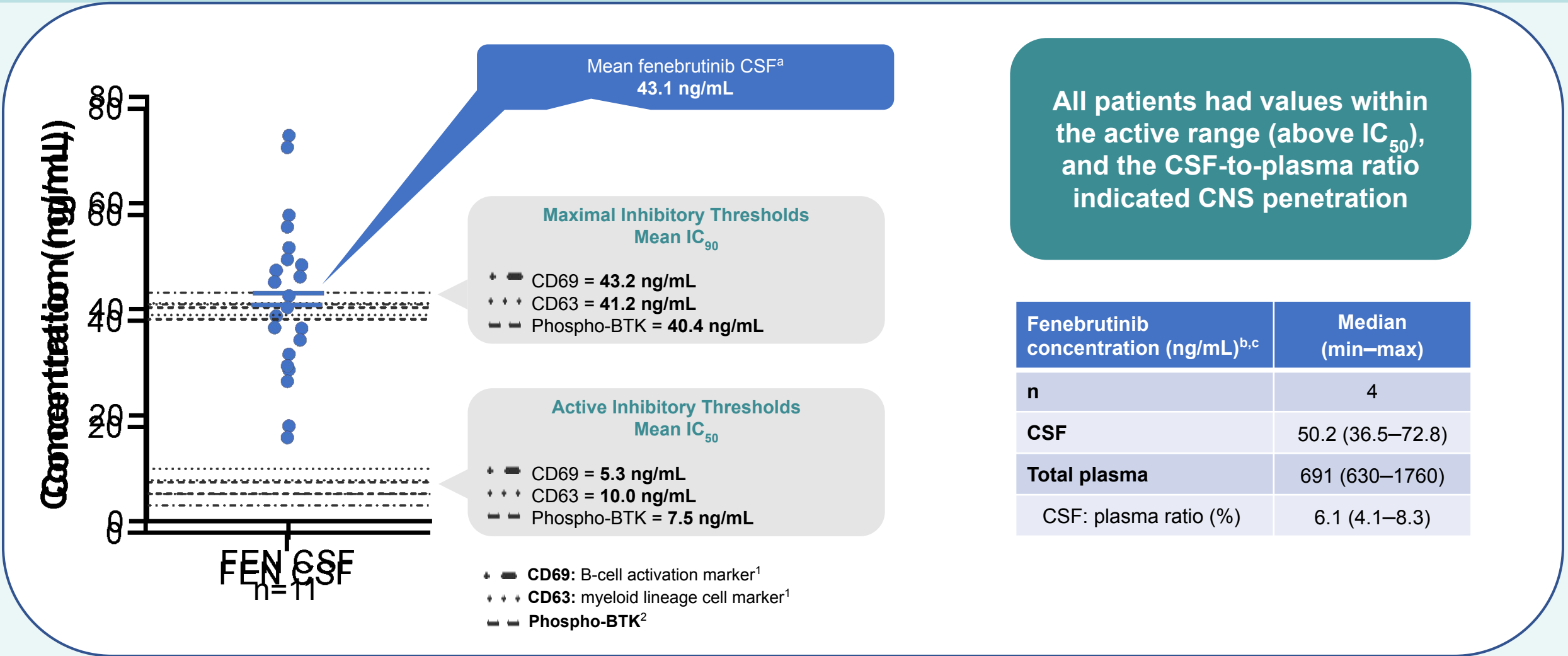
Exploratory Endpoint
Combined (Weeks 4, 8 and 12)



^aResults were estimated from a negative binomial model controlling for baseline T1 Gd+ lesion status (presence or absence) and included log number of scans as an offset. ^bNot Type I error controlled. ^cTeal arrows indicate relative reduction (95% CI) of lesions. ^dNumber of patients who have a new lesion at that specific visit alone divided by the number of patients with a scan at that specific visit alone at Week X.

Results

Fenebrutinib Was Detected in the CSF at Clinically Relevant Concentrations to Impact Mechanisms Underlying Chronic Progressive Disease Biology in MS



BTK, Bruton's tyrosine kinase; CNS, central nervous system; CSF, cerebrospinal fluid; FEN, fenebrutinib; IC₅₀, half maximal inhibitory concentration; IC₉₀, 90% inhibitory concentration.

^aFollowing 12 weeks of continuous FEN administration. ^bData from Week 12 presented. ^c4 patients with matching CSF to plasma samples were included.

1. Weber MS, et al. AAN 2021; Oral presentation P15.091. 2. Crawford JJ, et al. J Med Chem 2018;61:2227–2245.

Results

Safety Summary

	Fenebrutinib (n=73)	Placebo (n=36)
Patients with ≥1 AE, n (%)	28 (38.4)	12 (33.3)
Total no. of AEs	40	19
Patients with ≥1, n (%)		
AE with fatal outcome	0	0
SAE	0	0
AE leading to dose interruption	0	0
Related AE	10 (13.7)	2 (5.6)
Grade 3 AE	2 (2.7) ^a	0
Patients withdrawn from study due to an AE, n (%)	7 (9.6) ^b	0
Most common AEs, n (%)		
Abnormal hepatic enzyme levels	4 (5.5)	0
Urinary tract infection	4 (5.5)	2 (5.6)
Headache	3 (4.1)	1 (2.8)
Nasopharyngitis	2 (2.7)	0
Nausea	2 (2.7)	1 (2.8)
Pharyngitis	2 (2.7)	1 (2.8)
Upper abdominal pain	2 (2.7)	0

No SAEs were reported

All AEs were Grade 1 or 2, except for two Grade 3 asymptomatic liver transaminase level elevations

Rate of infections was balanced between the fenebrutinib and placebo arms

AE, adverse event; SAE, serious adverse event.
^aTwo Grade 3 AEs of abnormal hepatic enzyme levels (asymptomatic).
^bAEs leading to withdrawal: 4 abnormal hepatic transaminase levels (discontinuation required by protocol); 1 upper abdominal pain; nausea and headache; 1 upper abdominal pain; and 1 hypersensitivity.

Conclusions

1

Fenebrutinib was present in the CSF at levels sufficient to reduce activation of B cells and microglia in vitro,¹ suggesting that fenebrutinib may impact mechanisms underlying chronic progressive disease biology in MS

2

The primary endpoint was met with a **69% reduction** in the total number of new T1 Gd+ lesions at Weeks 4, 8 and 12 (combined) of treatment with fenebrutinib, and a rapid onset of lesion reduction was observed by Week 4, with relative **reductions of 92% and 90% in T1 Gd+ lesions** and relative **reductions of 90% and 95% in T2 lesions** at Week 8 and 12, respectively

3

No new safety concerns were identified, consistent with previous studies demonstrating a potentially favourable benefit-risk profile



<https://ter.li/hcpbwr>

Smartphone-Based Passive Monitoring of Gait in People with Progressive Multiple Sclerosis

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Disclosures

M Ganzetti is a contractor for F. Hoffmann-La Roche Ltd. **L Kriara** is an employee of F. Hoffmann-La Roche Ltd. **M Zanon** is an employee of and shareholder in F. Hoffmann-La Roche Ltd. **MD Rinderknecht** is a contractor for F. Hoffmann-La Roche Ltd. **S Hubeaux** is an employee of and shareholder in F. Hoffmann-La Roche Ltd. **F Lipsmeier** is an employee of F. Hoffmann-La Roche Ltd. **L Leocani** has received compensation for consulting services from Almirall, EXCEMED, F. Hoffmann-La Roche Ltd, Merck, Novartis, Biogen, Janssen-Cilag and Bristol Myers Squibb. **MP McGinley** has served on scientific advisory boards for Genzyme and Genentech; received research support from Novartis; and receiving funding from a KL2 (KL2TR002547) grant from Clinical and Translational Science Collaborative of Cleveland, from the National Center for Advancing Translational Sciences component of the National Institutes of Health. **MP Sormani** has received personal compensation for serving as a consultant for Biogen, F. Hoffmann-La Roche Ltd, Sanofi, Merck, Celgene, Novartis, GeNeuro and Immunic; and for serving on a scientific advisory or data safety monitoring board for MedDay, Sanofi and F. Hoffmann-La Roche Ltd. **G Comi** has received compensation for consulting services from Almirall, Chugai, EXCEMED, F. Hoffmann-La Roche Ltd, Forward Pharma, Genzyme, Merck, Novartis, Receptos, Sanofi and Teva Pharmaceuticals; and compensation for speaking activities from Almirall, EXCEMED, F. Hoffmann-La Roche Ltd, Genzyme, Merck, Novartis, Receptos, Sanofi and Teva Pharmaceuticals. **H Butzkueven's** institution (Monash University) has received funding from Biogen, F. Hoffmann-La Roche Ltd, Merck and Novartis; has carried out contracted research for Novartis, Merck, F. Hoffmann-La Roche Ltd and Biogen; has taken part in speaker's bureaus for Biogen, Genzyme, F. Hoffmann-La Roche Ltd and Merck; and has received personal grants from Oxford Pharmagenesis and Biogen. **L Craveiro** is an employee of and shareholder in F. Hoffmann-La Roche Ltd.

Background and Objectives



Daily activity is an important indicator of quality of life and disease-related impairment in PwPMS¹



Digital health solutions, including passive monitoring, could help to monitor gait in the home environment, outside of clinical settings, potentially providing data that are more representative of abilities during daily life²



Sustained adherence to the use of digital health solutions, including smartphone-based assessments, remains a challenge, especially for active tests (i.e. tests that require active input or interaction from the user)^{3,4}



Passively collected smartphone data could, therefore, offer a lower burden method of data collection as well as providing valuable insights into daily activity^{2,5} and disease state



To evaluate adherence to passive monitoring

To investigate the extent of maximum capacity gait in daily life gait

To explore whether clinically relevant measures can be extracted from passive monitoring

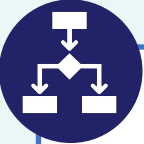
PwPMS, people with progressive multiple sclerosis.

1. Mayo CD, et al. *J Clin Exp Neuropsychol* 2019;41:715–722; 2. Montalban X, et al. *Mult Scler J* 2022;28:654–664; 3. Pratap A, et al. *NPJ Digit Med* 2020;3:1–10;

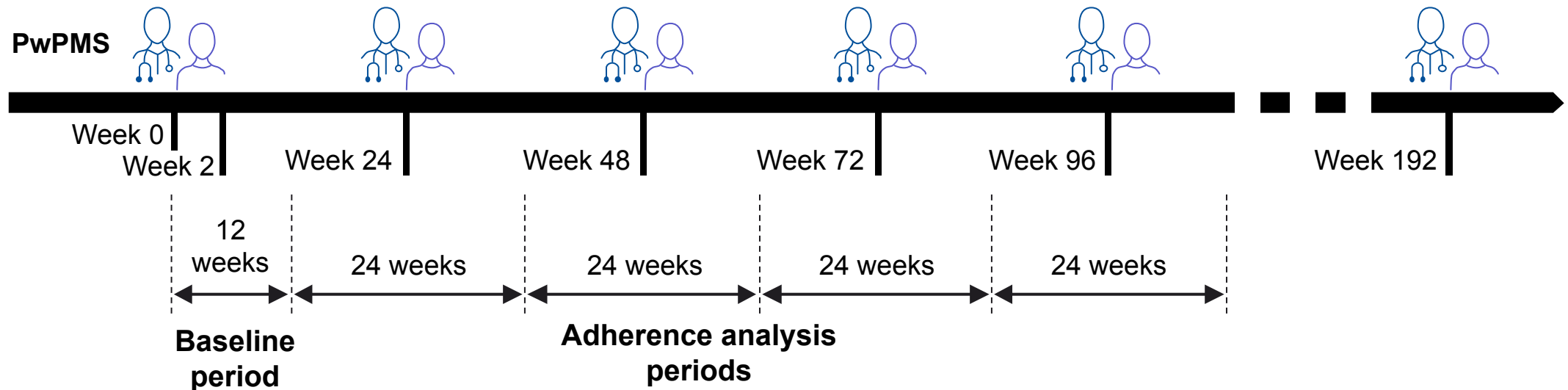
4. Midaglia L, et al. *J Med Internet Res* 2019;21:e14863; 5. Usdin M, et al. ECTRIMS 2022;Poster P522.

Methods

Study Design



- CONSONANCE (NCT03523858) is a Phase IIIb, 4-year, open-label study assessing the effectiveness and safety of ocrelizumab in PwPMS
- PwPMS were instructed to carry a provisioned Samsung Galaxy smartphone with a pre-installed precursor of the Floodlight™ MS app, for ~4 hours per day
- Sensor data were collected on a daily basis, while the phone was on and not charging, from June 2018 to November 2021 (the cut-off date for this analysis)





Adherence

- Mean adherence was calculated for the 12-week baseline and 24-week periods around clinic visits
 - Adherence was defined as number of days with passive monitoring data / number of days in the analysis period

Association between measures of gait in daily life (passive monitoring) vs maximum capacity (digital 2MWT)

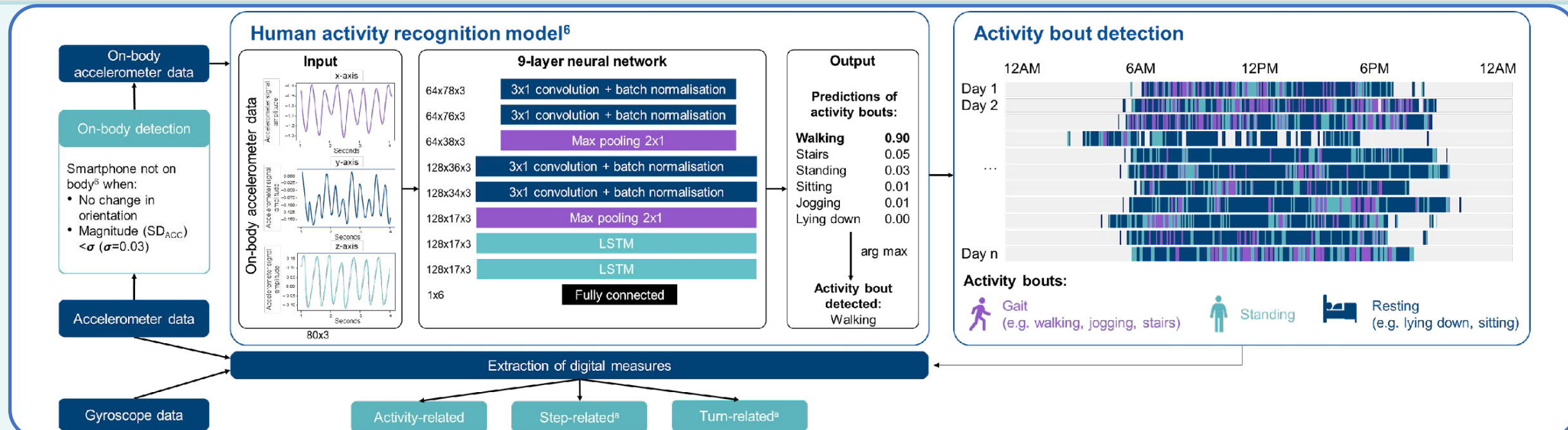
- Digital measures obtained from passive monitoring were correlated (Spearman's rank correlation) against those obtained from a digital 2MWT, using data from the baseline period

Association between passive monitoring and clinical measures

- Digital measures obtained from passive monitoring were correlated (Spearman's rank correlation) against demographics, clinical (T25FW) and patient-reported (MSWS-12) measures of gait, and overall disability (EDSS, including FSSs), using data from the baseline period

Methods

Passive Monitoring Digital Measures Extraction Workflow; Inclusion Criteria and Data Aggregation



Inclusion criteria

- ≥ 7 days per analysis period with valid passive monitoring data
 - ≥ 1 hour on-body coverage per day
 - ≥ 3 sec gait bout length
 - ≥ 1 turn with a turn angle $\geq 90^\circ$ (for turn-related measures)

Data aggregation

- Within-day aggregation: Median across all activity bouts
- Within-period aggregation: E.g. for the baseline period, median of within-day aggregated measures across the 12-week baseline period

LSTM, long short-term memory networks; SD_{ACC} , standard deviation of acceleration.

^aComputed only on gait bouts.

6. Cheng W-Y, et al. *MobiHealth* 2017;Conference paper:pp 12–19.

Results

Baseline Characteristics

	Participants on study ^a n=423	Participants who fulfilled the criteria for inclusion in the analysis ^b n=370
 Female, n (%)	218 (52)	199 (54)
 Age, years, mean (SD)	48.5 (9.4)	48.4 (9.4)
 Diagnosis (PPMS; SPMS), n (%)	201 (48); 222 (52)	172 (46); 198 (54)
 EDSS, mean (SD)	5 (1.3)	5 (1.3)
 Ambulation score, mean (SD)	4.1 (3.0)	4.2 (3.0)
 T25FW, mean (SD)	14.8 (16.8)	15.0 (17.0)

EDSS, Expanded Disability Status Scale; PPMS, primary progressive multiple sclerosis; SD, standard deviation; SPMS, secondary progressive multiple sclerosis; T25FW, Timed 25-Foot Walk.
^aTwo independent datasets were set up in the CONSONANCE study, for model development purposes, termed the Build and Test cohorts. The Build cohort was comprised of the first 450 enrolled PwPMS and the Test cohort by the last 450 enrolled PwPMS. Blinding procedures were applied to the Test cohort; ^bPwPMS with clinical, passive monitoring and active test data.

Results

Adherence



- Adherence was defined as number of days with passive monitoring data / number of days in the analysis period
- A relatively high number of days with passive monitoring data was preserved despite the initial decrease in adherence from baseline to Week 48

	Participants on study, n	Participants who fulfilled the criteria for inclusion in the analysis, n	Mean adherence, % (days of passive monitoring data)
Baseline	423	370	86 (72)
Week 24	404	336	73 (123)
Week 48	379	289	56 (94)
Week 72	353	236	53 (89)
Week 96	336	197	58 (97)

Results

Gait Bouts Per On-Body Coverage Hour

Ambulation score groups ^a				T25FW groups ^b				MSWS-12 groups ^c								
		Fully ambulatory	Without assistance	With assistance			Healthy	Mild	Moderate	Severe			<25%	25–50%	50–75%	75–100%
		Median on-body coverage, hours					Median on-body coverage, hours						Median on-body coverage, hours			
		5.40	5.24	5.17			11.60	5.34	5.51	5.03			7.20	4.10	6.20	4.90
		Median number of gait bouts per on-body coverage hour					Median number of gait bouts per on-body coverage hour						Median number of gait bouts per on-body coverage hour			
Gait bout duration	<5 s	3.43	2.88	1.69 <th rowspan="5">Gait bout duration</th> <th><5 s</th> <td>4.81</td> <td>3.31</td> <td>3.52</td> <td>1.92<th rowspan="5">Gait bout duration</th><th><5 s</th><td>3.56</td><td>3.09</td><td>3.01</td><td>1.86</td></td>	Gait bout duration	<5 s	4.81	3.31	3.52	1.92 <th rowspan="5">Gait bout duration</th> <th><5 s</th> <td>3.56</td> <td>3.09</td> <td>3.01</td> <td>1.86</td>	Gait bout duration	<5 s	3.56	3.09	3.01	1.86
	5–10 s	7.55	6.21	3.09 <th>5–10 s</th> <td>10.00</td> <td>7.55</td> <td>7.29</td> <td>3.90<th>5–10 s</th><td>7.42</td><td>6.73</td><td>6.70</td><td>3.62</td></td>		5–10 s	10.00	7.55	7.29	3.90 <th>5–10 s</th> <td>7.42</td> <td>6.73</td> <td>6.70</td> <td>3.62</td>		5–10 s	7.42	6.73	6.70	3.62
	10–30 s	4.42	3.05	1.46 <th>10–30 s</th> <td>4.98</td> <td>4.29</td> <td>4.26</td> <td>1.96<th>10–30 s</th><td>4.43</td><td>4.05</td><td>3.17</td><td>1.93</td></td>		10–30 s	4.98	4.29	4.26	1.96 <th>10–30 s</th> <td>4.43</td> <td>4.05</td> <td>3.17</td> <td>1.93</td>		10–30 s	4.43	4.05	3.17	1.93
	30–60 s	0.66	0.47	0.33 <th>30–60 s</th> <td>0.64</td> <td>0.66</td> <td>0.55</td> <td>0.39<th>30–60 s</th><td>0.62</td><td>0.64</td><td>0.47</td><td>0.38</td></td>		30–60 s	0.64	0.66	0.55	0.39 <th>30–60 s</th> <td>0.62</td> <td>0.64</td> <td>0.47</td> <td>0.38</td>		30–60 s	0.62	0.64	0.47	0.38
	>60 s	0.37	0.30	0.22 <th>>60 s</th> <td>0.28</td> <td>0.37</td> <td>0.32</td> <td>0.26<th>>60 s</th><td>0.33</td><td>0.40</td><td>0.29</td><td>0.26</td></td>		>60 s	0.28	0.37	0.32	0.26 <th>>60 s</th> <td>0.33</td> <td>0.40</td> <td>0.29</td> <td>0.26</td>		>60 s	0.33	0.40	0.29	0.26

MSWS-12, Multiple Sclerosis Walking Scale; T25FW, Timed 25-Foot Walk.

^aAmbulation score (based on a neurological examination by a clinician): Fully ambulatory (0–1); without assistance (2–5); with assistance (6–9);⁷ ^bT25FW (quantitative mobility and leg function performance test): <4 s healthy;⁸ 4–<6 s mild; 6–8 s moderate; >8 s severe;⁹ ^cMSWS-12 (self-report measure of the impact of MS on the individual's walking ability): 0.00–24.99 was associated with working outside the home and assistance-free mobility; 25.00–49.99 was associated with gait disability and difficulty doing housework; 50.00–74.99 was associated with unemployment, government healthcare, cane use and difficulty performing IADLs; 75.00–100.00 was associated with change in occupation due to walking, mobility impairment requiring bilateral assistance and inability to perform IADLs.¹⁰

7. Kurtzke JF. *Neurology* 1983;33:1444–1452; 8. Hvid LG, et al. *Neurorehabil Neural Repair* 2020;34:360–369. 9. Kalinowski A, et al. *Mult Scler J* 2021;28:13524585211017013.

10. Goldman MD, et al. *Mult Scler J* 2017;23:1405–1414.

Results

What is the Association Between Passive Monitoring and a Digital 2MWT?



- Statistically significant correlations were observed across **all gait bout durations** ($p < 0.05$)
- As expected, **correlations increased in strength for medium and long bouts compared with very short and short bouts**

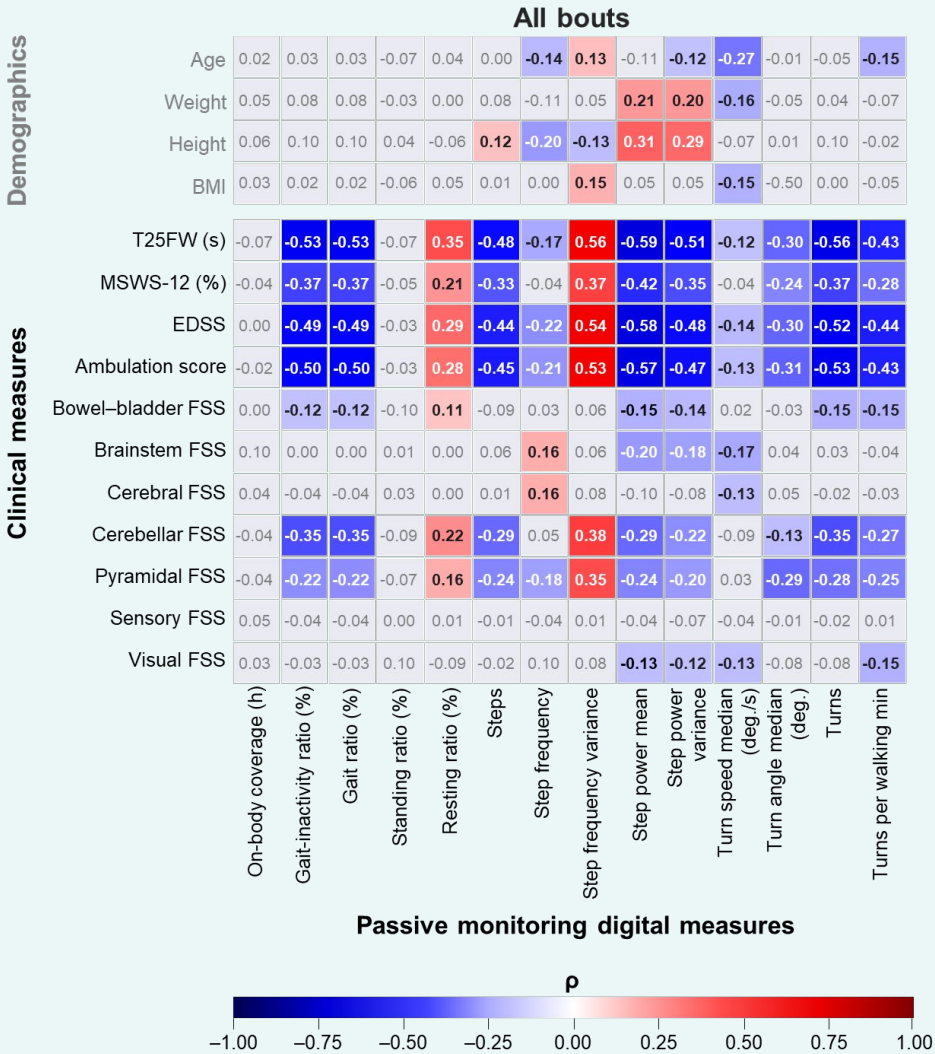
Digital measures		Correlations per gait bout length					
2MWT	Passive monitoring	All bouts, ρ	Very short (<5 s), ρ	Short (5–10 s), ρ	Medium (10–30 s), ρ	Long (30–60 s), ρ	Very long (>60 s), ρ
Step power mean	Step power mean	0.82	0.76	0.79	0.84	0.84	0.83
Step power variance	Step power variance	0.80	0.75	0.77	0.83	0.79	0.79
Step frequency mean	Step frequency mean	0.51	0.41	0.46	0.54	0.57	0.56
Step frequency variance	Step frequency variance	0.75	0.58	0.70	0.79	0.77	0.73

Results

What is the Association Between Passive Monitoring and Clinical Measures/Demographics?



- There were **statistically significant correlations** between **passive monitoring digital measures** and most **clinical measures** ($p < 0.05$)
- The **strongest** correlations were observed between **passive monitoring digital measures** and **T25FW, MSWS-12, EDSS** and **Ambulation score**
- **Statistically significant correlations** were also found between **passive monitoring digital measures** and **pyramidal FSS** (measuring muscle weakness or difficulty moving limbs) and **cerebellar FSS** (measuring ataxia, loss of balance, coordination or tremor; $p < 0.05$)



Conclusions



- Passive monitoring may offer a low burden assessment of gait in PwPMS. Importantly, passive monitoring data can be collected frequently over the course of 96 weeks without PwPMS needing to find a time and place to perform a gait test
- Statistically significant correlations were observed between passive monitoring digital measures and clinical measures, as well as digital measures obtained from the 2MWT (complementary smartphone-based active test; to explore concordance)
 - The imperfect correlations between passive monitoring and the digital 2MWT may suggest that they provide complementary information: performance in daily life (passive monitoring) vs maximum capacity (digital 2MWT)