Ocrelizumab Treatment Induces a Sustained Blood NfL Reduction in Patients with PPMS and RMS

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Disclosures

A Bar-Or has served on scientific advisory boards for Biogen, F. Hoffmann-La Roche Ltd, Genentech, Inc., GSK, Guthy-Jackson/GGF, MedImmune, Merck, EMD Serono, Mitsubishi Tanabe, Ono, Receptos and Sanofi Genzyme and has received research support from Biogen, Novartis and Sanofi Genzyme.

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AH Cross has, in the past year, received fees or honoraria for consulting from Biogen, Celgene/Bristol Myers Squibb, EMD Serono, F. Hoffmann-La Roche Ltd, Genentech, Inc., and Novartis and received fees for serving on scientific advisory boards and reviewing grants for the Conrad N. Hilton Foundation and Race to Erase MS.

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SL Hauser serves on the board of trustees for Neurona and on scientific advisory boards for Annexon, Alector, Bionure, Molecular Stethoscope and Symbiotix and has received travel reimbursement and writing assistance from F. Hoffmann-La Roche Ltd for CD20-related meetings and presentations.

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Introduction

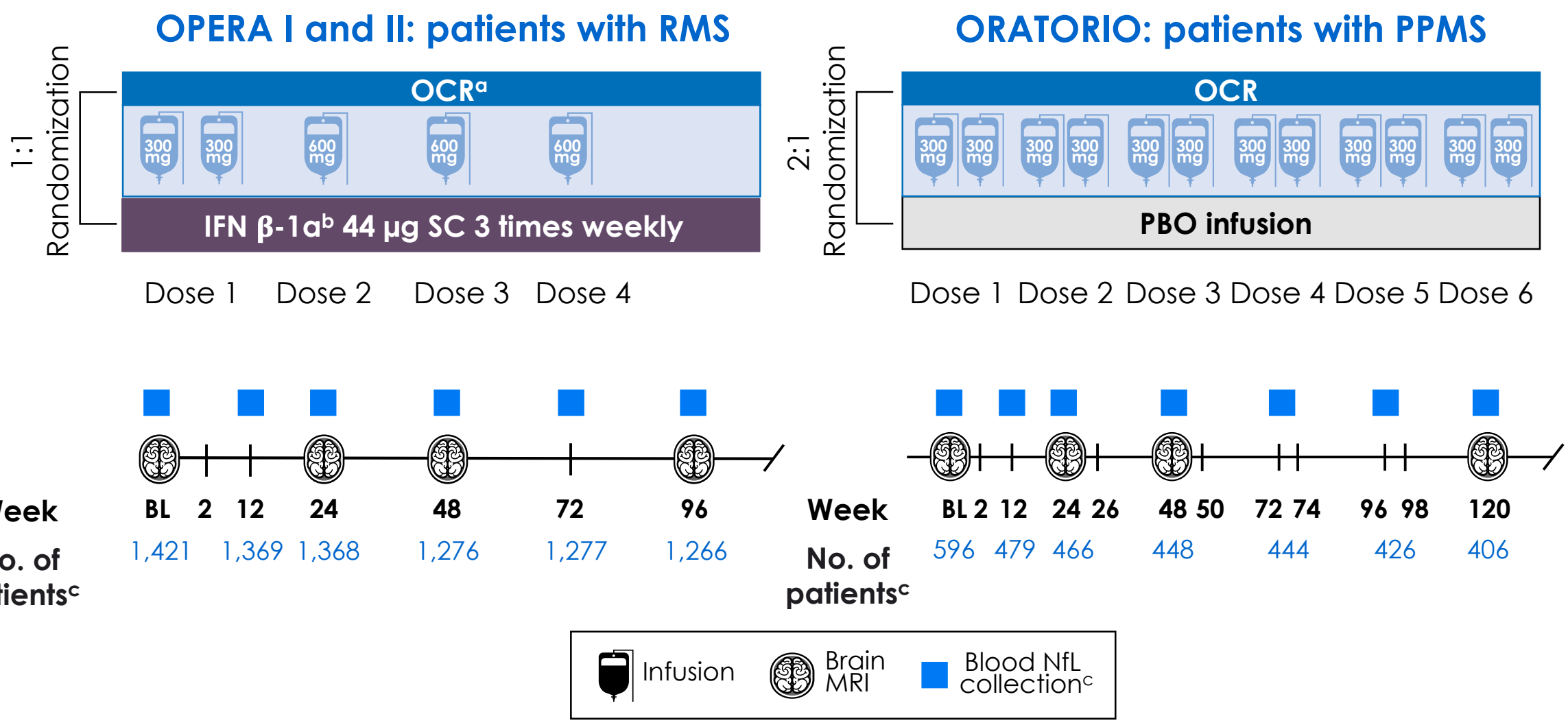
- Neurofilament light chain (NfL) is a cytoskeletal protein that is released into the blood on neuroaxonal injury and may represent a biomarker for disease activity and treatment response in multiple sclerosis (MS)[1,2]
- Ocrelizumab (OCR)[a] is the first monoclonal antibody approved for the treatment of relapsing MS (RMS) and primary progressive MS (PPMS); it remains the only approved treatment for PPMS.[3,4]

Objective: To assess the effect of ocrelizumab treatment on NfL levels in patients with RMS and PPMS

[a]OCR is approved at a dose of 600 mg intravenous (IV) twice yearly. OCR demonstrated significant benefit on 12/24-week confirmed disability progression, annualized relapse rate and MRI measures in pivotal Phase III studies in patients with RMS[5] or PPMS,[6] with sustained efficacy in the respective open-label extension periods.[7,8]

1. Kuhle J, *et al. Neurology* 2019;92:e1007–e1015; 2. Disanto G, *et al*. *Ann Neurol* 2017;81:857–870; 3. Ocrevus (ocrelizumab) [full prescribing information]. Genentech, Inc.; 2020; 4. Ocrevus (ocrelizumab) [summary of product characteristics]. Roche Pharma AG; 2020; 5. Hauser SL, *et al*. *N Engl J Med* 2017;376:221–234; 6. Montalban X, et al. *N Engl J Med* 2017;376:209–220; 7. Hauser SL, *et al. Neurology* 2020; ePub ahead of print: DOI: 10.1212/WNL.0000000000010376; 8. Wolinsky J, et al. *ECTRIMS* 2019:Presentation 159.

Methods:
OPERA and ORATORIO double-blind treatment period—study design



[a]Patients received a matching SC PBO; [b]Patients received a matching IV PBO; [c]Serum NfL was measured at baseline in consenting OPERA and ORATORIO patients and during the controlled treatment period in OPERA. Plasma NfL was measured during the controlled treatment period in ORATORIO.
BL, baseline; IFN, interferon; IV, intravenous; NfL, neurofilament light chain; OCR, ocrelizumab; PBO, placebo; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; SC, subcutaneous.

Results: Baseline characteristics were comparable between the NfL study population[a] and ITT population

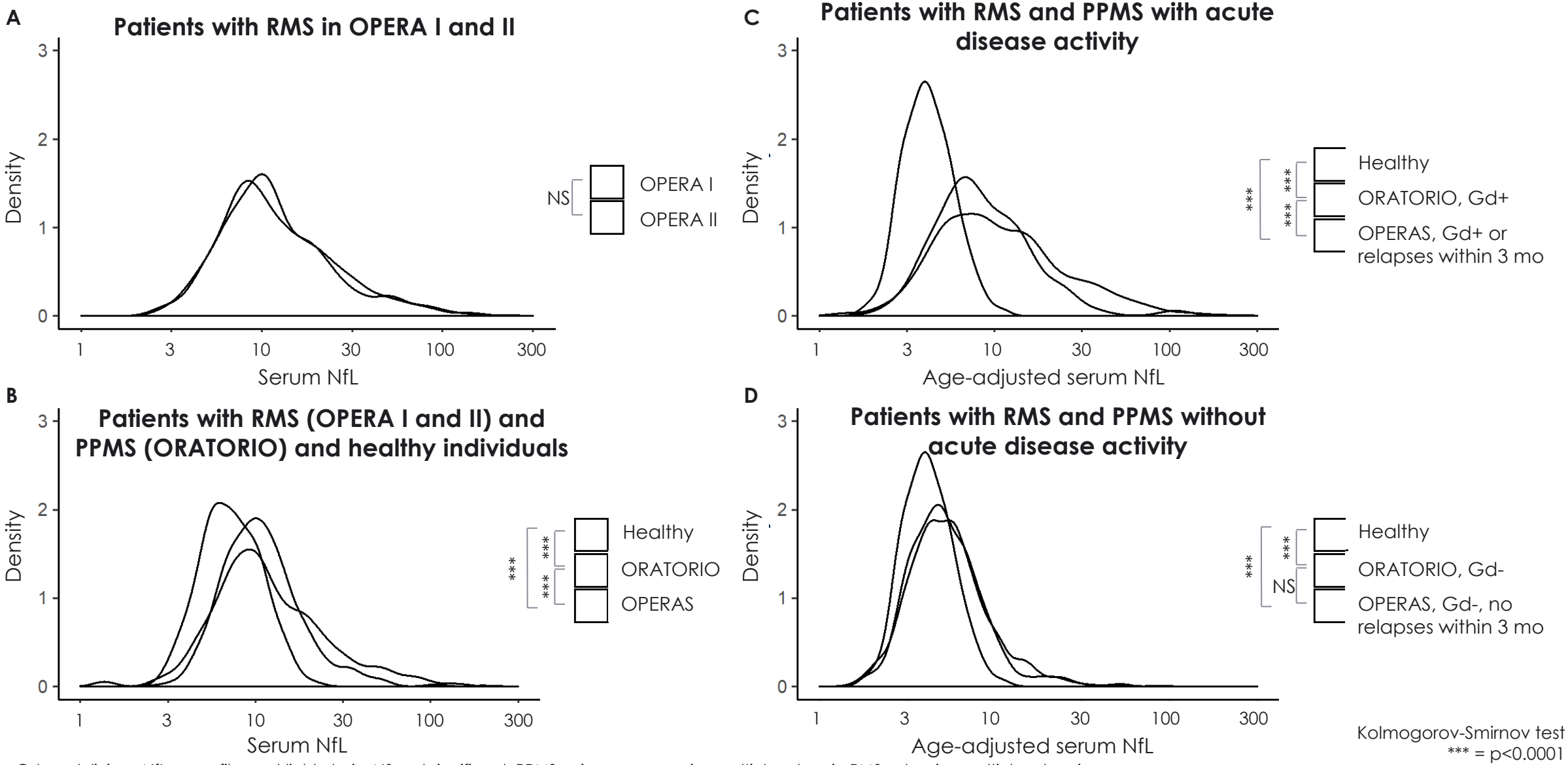
Baseline characteristics	OPERA I and II (NfL study population)[a]		OPERA I and II (ITT population)[1,2]		ORATORIO (NfL study population)[a]		ORATORIO (ITT population)[2,3]	
	IFN β-1a (n=701)	OCR (n=720)	IFN β-1a (n=829)	OCR (n=827)	PBO (n=205)	OCR (n=391)	PBO (n=244)	OCR (n=488)
Age, median (range), years	38 (18–55)	38 (18–56)	37 (18–55)	38 (18–56)	46 (19–56)	47 (20–56)	46 (18–56)	45 (20–56)
Female, n (%)	447 (63.8)	476 (66.1)	552 (66.6)	541 (65.4)	100 (48.8)	196 (50.1)	124 (50.8)	237 (48.6)
Weight, median (range), kg	75 (42.1–163.6)	75 (38–170)	75 (42.1–163.6)	75 (38–170)	74 (45–136)	72 (40.2–135)	72 (45.0–136.0)	72 (40.2–135.9)
Years since MS diagnosis, median (range)	1.6 (0.1–28.5)	1.8 (0–28.9)	1.7 (0.1–28.5)	1.8 (0–28.9)	1.2 (0.1–13.8)	1.5 (0.1–16.8)	1.3 (0.1–23.8)	1.6 (0.1–16.8)
Years since last relapse, median (range)	0.4 (0.1–1.9)	0.4 (0.1–2)	0.4 (0.1–2)	0.4 (0.1–2)	NA	NA	NA	NA
Patients with T1 Gd-enhancing lesions, n (%)	273 (39.3)	289 (40.6)	327 (39.8)	333 (40.7)	50 (24.4)	93 (24)	60 (24.7)	133 (27.5)
No. of T1 Gd-enhancing lesions, median (range)	0 (0–54)	0 (0–56)	0 (0–54)	0 (0–56)	0 (0–10)	0 (0–18)	0 (0–50)	0 (0–77)
No. of T2 lesions, median (range)	42 (0–226)	39 (1–209)	42 (0–226)	40 (1–233)	42 (0–208)	41 (0–226)	43 (0–208)	42 (0–249)
T2 lesion volume, median (range), mL	6.2 (0–76.1)	5.2 (0–96)	6.2 (0–76.1)	5.4 (0–96)	6.2 (0–59.2)	6.9 (0–89.4)	6.2 (0–81.1)	7.3 (0–90.3)
EDSS score, median (range)	2.5 (0–6)	2.5 (0–6)	2.5 (0–6)	2.5 (0–6)	4.5 (2.5–6.5)	4.5 (2.5–6.5)	4.5 (2.5–6.5)	4.5 (2.5–6.8)
9HPT score, median (range)	22.4 (11.5–149.1)	22.4 (10–300)	22.2 (11.3–149.1)	22.2 (10–300)	26.4 (13.2–120.7)	26.6 (13.3–300)	26.9 (11.1–120.7)	26.8 (12.3–300)
T25FW score, median (range)	5.5 (2.7–116.3)	5.6 (2.6–149.8)	5.5 (2.7–180)	5.6 (2.6–149.8)	7.3 (2.6–145)	7.8 (3.3–180)	7.4 (2.6–145.0)	7.8 (3.3–180)
Serum NfL level, median (range), pg/mL	10.4 (2.7–339)	10.7 (2.7–230.7)	10.4 (2.7–339)	10.7 (2.7–230.7)	10.3 (3.3–102)	10.3 (2.7–198.9)	10.3 (2.7–198.9)	10.3 (2.7–198.9)
Clinical outcomes								
Annualized relapse rate	0.30	0.17	0.30	0.16	NA	NA	NA	NA
Pts with 12-week CDP, %	13.1	9.2	13.6	9.1	41.0	33.5	39.3	32.8
Pts with 24-week CDP, %	10.1	7.1	10.5	6.9	36.6	30.2	35.7	29.5

[a]Patients in safety assessment population who completed baseline serum collection in OPERA and ORATORIO.

9HPT, nine-hole peg test; CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; Gd, gadolinium; IFN, interferon; ITT, intention to treat; MS, multiple sclerosis; NA, not applicable; NfL, neurofilament light chain; OCR, ocrelizumab; PBO, placebo; pt, patient; T25FW, timed 25-foot walk.

1. Hauser SL, *et al. N Engl J Med* 2017;376:221–234. 2. F. Hoffmann-La Roche Ltd/Genentech, Inc. Data on file (March 2016). 3. Montalban X, *et al. N Engl J Med* 2017;376:209–220.

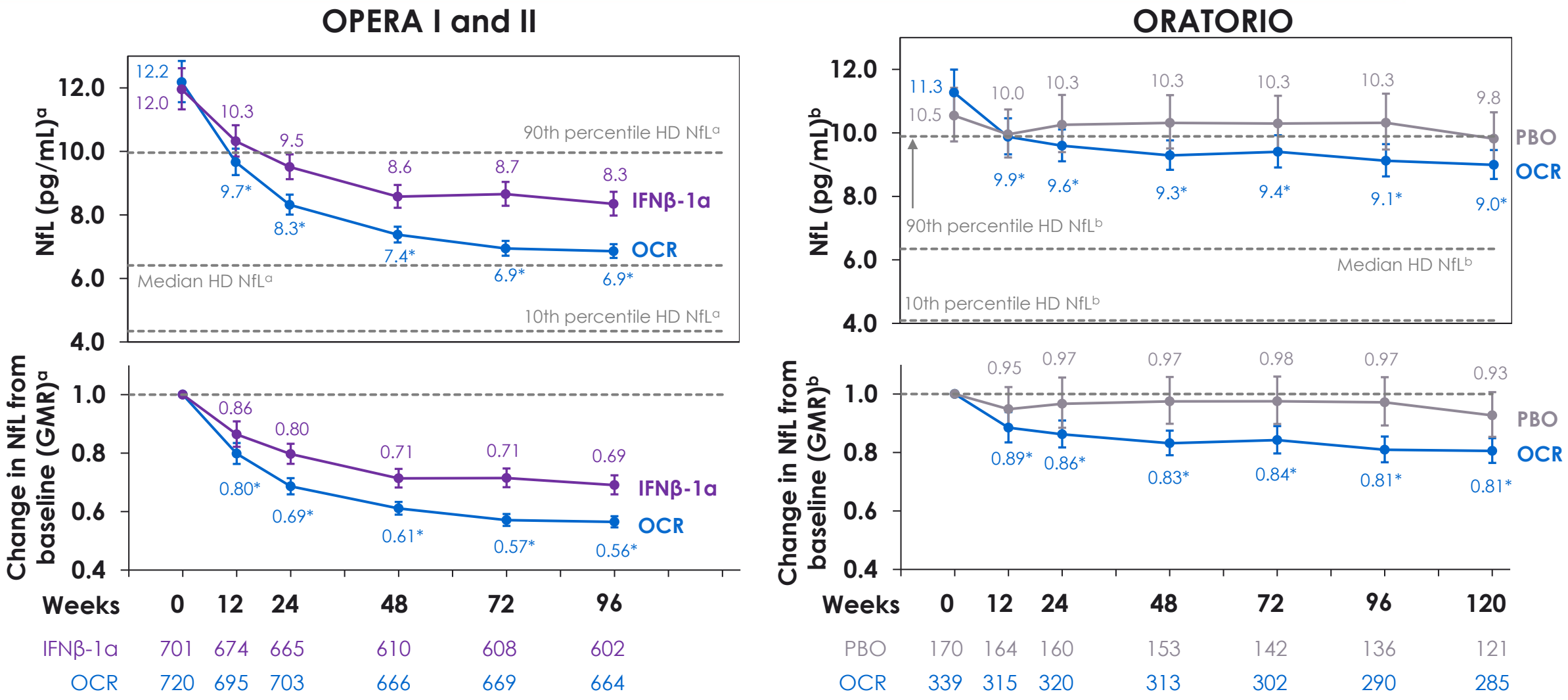
Results:
Baseline serum NfL distribution in the pooled OPERA and ORATORIO studies



Kolmogorov-Smirnov test
*** = p<0.0001

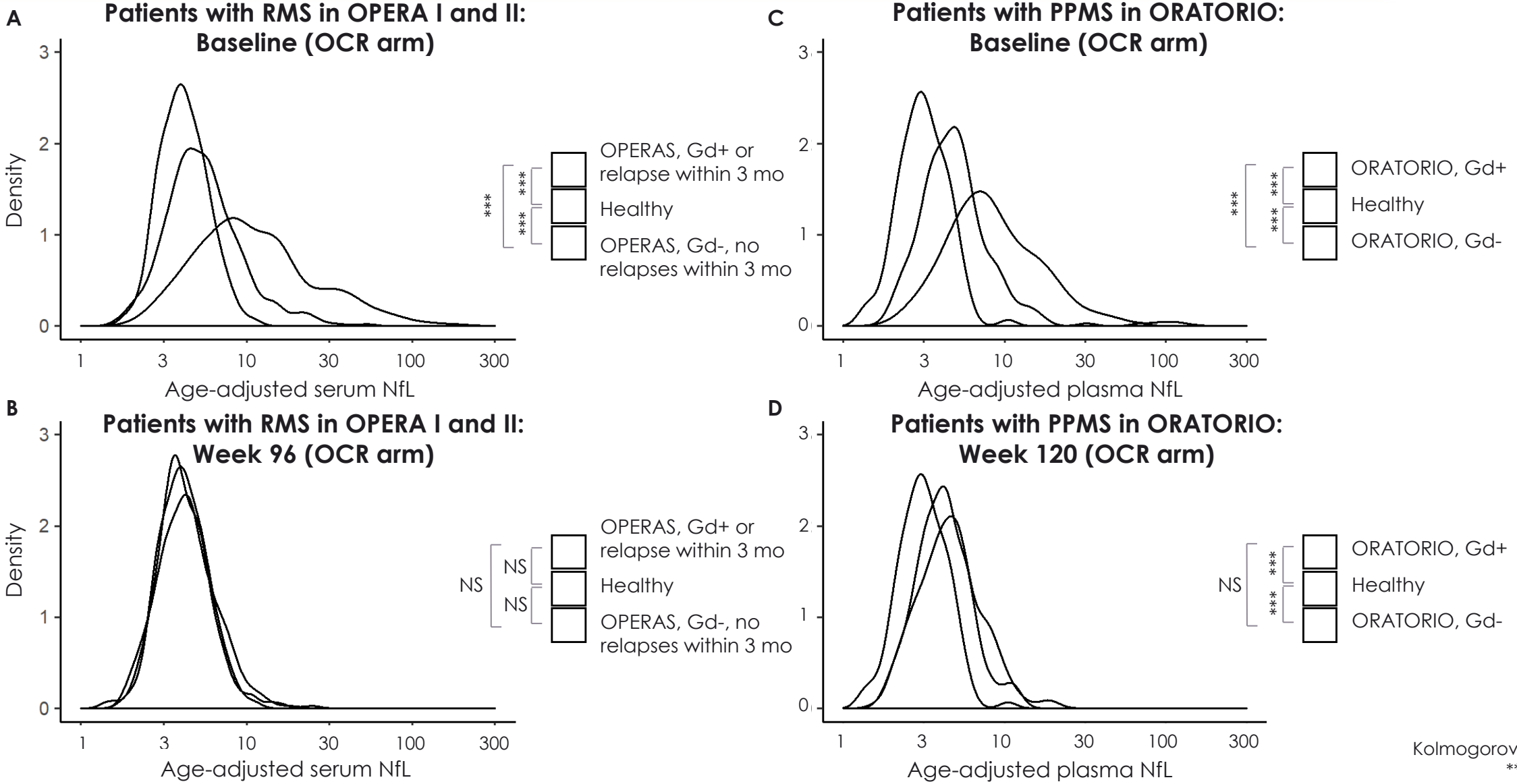
Gd, gadolinium; NfL, neurofilament light chain; NS, not significant; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis.

Results: NfL levels were significantly reduced in patients with RMS and PPMS following treatment with OCR vs comparator



[a]Serum NfL; [b]Plasma NfL; *Significant reduction in NfL following treatment with OCR vs baseline. Plots show geometric means of blood NfL and 95% CIs. Future work may apply a model that accounts for minor differences in NfL level at baseline. [a]NfL levels from GNE healthy donor cohort were adjusted to median ages in OPERA (38) and ORATORIO (47) to determine median, 10th percentile and 90th percentile levels. GMR, geometric mean ratio; GNE, Genentech; HD, healthy donor; IFN, interferon; NfL, neurofilament light chain; OCR, ocrelizumab; PBO, placebo; pNfL, plasma neurofilament light chain; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; sNfL, serum neurofilament light chain.

Results: OCR reduced NfL levels in patients with RMS and PPMS with and without acute disease activity (ie, presence of T1 Gd-enhancing lesions on baseline brain MRI and/or clinical relapse within prior 3 months)



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Gd, gadolinium; NfL, neurofilament light chain; NS, not significant; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis.

Conclusions

- NfL levels are highly elevated in patients with acute MS disease activity
- However, a more subtle elevation is observed in patients with RMS and PPMS without detectable disease activity.
- This is consistent with the possibility that even mild elevations in NfL might reflect insidious neuroaxonal injury that occurs in both RMS and PPMS
- Ocrelizumab significantly reduced NfL levels in patients with RMS and PPMS with and without detectable disease activity
- In ocrelizumab-treated patients with RMS, age-adjusted serum NfL levels after 96 weeks approached those of a healthy donor cohort

[a]RMS, GMR=0.80, PPMS, GMR=0.89; [b]RMS[96 weeks], GMR=0.56; PPMS[120 weeks], GMR=0.81.
GMR, geometric mean ratio; HD; healthy donors; NfL, neurofilament light chain; MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis.

Doing now what patients need next