Supplementary Material

Van Wijmeersch B, Singer BA, Boster A, et al. Efficacy of alemtuzumab over 6 years in relapsing-remitting multiple sclerosis patients who relapsed between Courses 1 and 2: Post hoc analysis of the CARE-MS studies.

This supplementary material has been provided by the authors to give readers additional information about their work.

MRI methodology.

Details on the MRI methodology for the CARE-MS I and II core studies and the CARE-MS extension have been described previously.[1-5]

Briefly, standardized cranial MRI scans were obtained at baseline and annually and the following sequences were collected: T1-weighted pre-contrast and post-contrast, T2-weighted and proton density (Dual Echo) pre-contrast, fluid-attenuated inversion recovery (FLAIR) pre-contrast, and 3D Gradient Echo post-contrast. A standard dosage of gadolinium (Gd)-contrast medium was used, with a wait time of 5 minutes before commencing post-contrast T1-weighted scans. Scans were analysed by neuroradiologists at Cleveland Clinic Foundation (for Brain Parenchymal Fraction [BPF]) and NeuroRx Research (for all other imaging endpoints), who were masked to treatment-group assignment.

New MRI lesion outcomes included proportions of early relapsers and early non-relapsers with Gd-enhancing, new/enlarging T2 hyperintense, and new nonenhancing T1 hypointense lesions examined over Years 0–6. Freedom from MRI disease activity was defined as absence of new Gd-enhancing and new/enlarging T2 lesions.

Brain volume loss was measured as changes in the BPF, calculated from proton density/T2-weighted dual-echo images using brain segmentation software developed at the Cleveland Clinic.

<u>References.</u>

1. Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: A randomised controlled phase 3 trial. *Lancet* 2012; 380: 1819–1828.

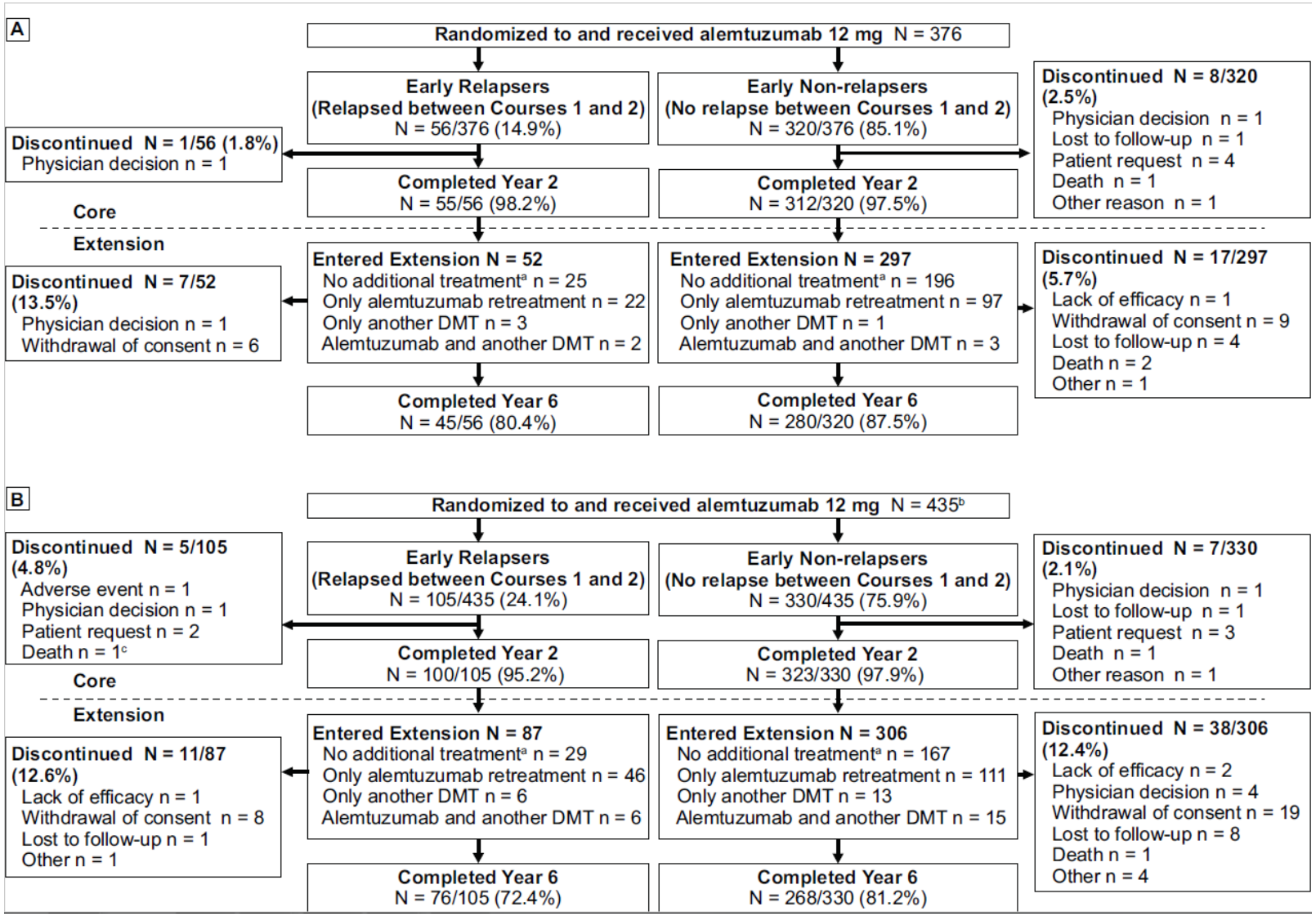
2. Coles AJ, Twyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: A randomised controlled phase 3 trial. *Lancet* 2012; 380: 1829–1839.

3. Coles AJ, Cohen JA, Fox EJ, et al. Alemtuzumab CARE-MS II 5-year follow-up: Efficacy and safety findings. *Neurology* 2017; 89: 1117–1126.

4. Havrdova E, Arnold DL, Cohen JA, et al. Alemtuzumab CARE-MS I 5-year follow-up: Durable efficacy in the absence of continuous MS therapy. *Neurology* 2017; 89: 1107–1116.

5. Arnold DL, Fisher E, Brinar VV, et al. Superior MRI outcomes with alemtuzumab compared with subcutaneous interferon b-1a in MS. *Neurology* 2016; 87: 1464–1472.

eFigure 1. Disposition by subgroup. (A) CARE-MS I patients and (B) CARE-MS II patients.



The disposition schematic includes participation of patients with and without relapse between Courses 1 and 2 in the core CARE-MS I (A) or CARE-MS II (B) studies, who enrolled in the extension study. [a]Patients who received no additional alemtuzumab courses or another DMT in the extension study through Year 6. [b]The as-treated CARE-MS II population (n = 435) consisted of 426 patients originally randomized to alemtuzumab 12 mg, and an additional 9 patients who were randomized to alemtuzumab 24 mg but who received alemtuzumab 12 mg/day in the core study. [c]One death of an early relapsing patient occurred in the CARE-MS II core study and was deemed not related to treatment. CARE-MS: Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis; DMT: disease-modifying therapy.

eTable 1. Proportions of early relapsers free of new MRI lesions and achieving NEDA annually through 6 years.

Annual Assessments[a]	CARE-MS I						CARE-MS II					
	Early Relapsers (*n*=56)						Early Relapsers (*n*=105)					
MRI Lesion Activity	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**
Free of Gd-enhancing T1 lesions, % (95% CI)	82 (72.1, 92.2)	94 (84.3, 98.8)	86 (76.4, 95.6)	90 (81.3, 98.3)	85 (74.9, 95.3)	84 (73.3, 94.9)	79 (71.6, 87.3)	86 (79.0, 92.7)	81 (72.5, 90.2)	89 (81.9, 96.2)	93 (87.8, 99.0)	94 (88.4, 99.7)
Free of new/enlarging T2 hyperintense lesions, % (95% CI)	54 (40.5, 66.6)	72 (59.6, 83.8)	77 (64.5, 88.7)	74 (62.0, 86.9)	73 (60.4, 86.3)	71 (56.8, 84.7)	56 (46.7, 65.9)	71 (61.7, 79.7)	64 (53.1, 74.9)	71 (60.3, 81.3)	72 (61.4, 81.9)	68 (56.3, 79.1)
Free of T1 hypointense lesions, % (95% CI)	71 (59.6, 83.3)	94 (84.3, 98.8)	85 (74.9, 95.3)	89 (80.5, 98.2)	89 (79.7, 98.1)	90 (81.2, 99.3)	80 (71.8, 87.4)	88 (81.5, 94.3)	85 (77.3, 93.3)	85 (76.1, 92.9)	86 (78.4, 94.2)	89 (81.4, 96.7)
NEDA[b]	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**
Patients with NEDA, % (95% CI)	0	53 (39.2, 66.6)	55 (41.1, 69.5)	48 (33.8, 62.0)	59 (44.5, 72.9)	48 (32.5, 62.7)	0	38 (28.2, 47.4)	41 (30.2, 52.5)	49 (37.1, 60.2)	54 (42.7, 65.4)	58 (46.5, 70.4)

[a]Proportions of patients free of MRI lesions or achieving NEDA are expressed as annual percentages within the relevant year. [b]NEDA was defined as absence of clinical disease activity (relapses and 6-month CDW) and MRI disease activity (new Gd-enhancing T1 and new/enlarging T2 hyperintense lesions). CARE-MS: Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis; CDW: confirmed disability worsening; CI: confidence interval; Gd: gadolinium; NEDA: no evidence of disease activity.

eTable 2. Efficacy outcomes of early non-relapsers and early relapsers through 6 years.

CARE-MS I Early non-relapsers	(*n*=320)	(*n*=320)	(*n*=297)	(*n*=291)	(*n*=289)	(*n*=285)	CARE-MS I Early Relapsers (*n*=50)
CARE-MS II Early non-relapsers	(*n*=330)	(*n*=329)	(*n*=306)	(*n*=304)	(*n*=289)	(*n*=279)	CARE-MS II Early Relapsers (*n*=78)
Annual Assessments[a]	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**	**Year 6**
ARR, mean (95% CI)	0	0.09 (0.06, 0.14)	0.14 (0.10, 0.19)	0.11 (0.08, 0.15)	0.12 (0.09, 0.17)	0.10 (0.07, 0.15)	0.26 (0.15, 0.47)
	0	0.16 (0.12, 0.22)	0.18 (0.14, 0.23)	0.20 (0.15, 0.26)	0.16 (0.12, 0.22)	0.15 (0.10, 0.21)	0.15 (0.08, 0.28)
Patients free of MRI disease activity, % (95% CI)[b]	61 (55.7, 66.4)	78 (73.6, 82.9)	71 (66.0, 76.6)	70 (64.1, 75.0)	69 (63.8, 74.7)	65 (59.5, 71.0)	69 (55.1, 83.0)
	63 (57.1, 67.9)	78 (72.9, 82.3)	70 (64.2, 74.9)	70 (64.2, 75.2)	67 (61.3, 72.9)	69 (63.2, 74.9)	68 (56.3, 79.1)
Yearly BPF change, median % (95% CI)	–0.57 (–0.75, –0.51)	–0.27 (–0.36, –0.18)	–0.19 (–0.29, –0.08)	–0.17 (–0.26, –0.08)	–0.18 (–0.31, –0.10)	–0.16 (–0.25, –0.09)	–0.24 (–0.39, 0.12)
	–0.49 (–0.58, –0.39)	–0.27 (–0.36, –0.19)	–0.12 (–0.27, –0.03)	–0.19 (–0.24, –0.06)	–0.01 (–0.11, 0.12)	–0.10 (–0.19, 0)	–0.13 (–0.37, 0.02)
Patients with NEDA, % (95% CI)[c]	59 (53.7, 64.6)	70 (64.8, 75.1)	63 (57.1, 68.4)	62 (56.6, 68.0)	63 (57.3, 68.7)	59 (52.8, 64.7)	48 (32.5, 62.7)
	58 (52.9, 63.8)	64 (58.8, 69.5)	56 (50.2, 61.7)	56 (50.1, 62.0)	59 (53.1, 65.2)	60 (53.6, 66.0)	58 (46.5, 70.4)

eTable 2. Efficacy outcomes of early non-relapsers and early relapsers through 6 years (continued).

Cumulative Assessments	**Years 0–1**	**Years 0–2**	**Years 0–3**	**Years 0–4**	**Years 0–5**	**Years 0–6**	**Years 0–6**
Patients free of 6-month CDW, % (95% CI)[d,e]	97 (93.8, 98.2)	94 (91.0, 96.4)	91 (86.6, 93.4)	86 (81.5, 89.5)	83 (77.7, 86.5)	80 (75.1, 84.3)	60 (45.0, 71.4)
	94 (90.8, 96.3)	91 (87.0, 93.6)	86 (81.5, 89.4)	80 (74.9, 84.0)	78 (72.7, 82.1)	75 (69.5, 79.4)	60 (48.4, 69.3)
Patients with 6-month CDI, % (95% CI)[d,f]	17 (12.0, 23.2)	27 (20.6, 33.8)	30 (23.8, 37.5)	32 (26.0, 40.0)	36 (28.9, 43.2)	36 (29.4, 43.8)	24 (13.9, 40.6)
	20 (15.0, 25.3)	31 (25.3, 37.3)	37 (30.7, 43.2)	43 (36.8, 49.7)	44 (38.2, 51.1)	45 (39.1, 52.1)	34 (24.4, 47.1)

[a]ARR, proportions of patients free of MRI disease activity, yearly percentage BPF changes, and proportion of patients achieving NEDA are expressed as annual outcomes within the relevant year. [b]Freedom from MRI disease activity was defined as the absence of new Gd-enhancing T1 and new/enlarging T2 hyperintense lesions. [c]NEDA was defined as absence of clinical disease activity (relapses and 6-month CDW) and MRI disease activity (new Gd-enhancing T1 and new/enlarging T2 hyperintense lesions). [d]Kaplan-Meier estimates. [e]CDW is defined as ≥1-point EDSS increase (or ≥1.5 points if baseline EDSS = 0) confirmed over 6 months. [f]CDI is defined as ≥1-point EDSS decrease from baseline confirmed over 6 months (CDI is assessed only in patients with baseline EDSS score ≥2.0). ARR: annualized relapse rate; BPF: brain parenchymal fraction; CARE-MS: Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis; CDI: confirmed disability improvement; CDW: confirmed disability worsening; CI: confidence interval; EDSS: Expanded Disability Status Scale; Gd: gadolinium; NEDA: no evidence of disease activity.